Original research

Epidemiology and prognostic factors of pleural empyema

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2020-215267).

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Received 11 May 2020
Revised 22 February 2021
Accepted 1 March 2021

To cite: Bobbio A, Bouam S, Frenkiel J, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2020-215267

ABSTRACT

Background Infection of the pleural cavity invariably leads to hospitalisation, and a fatal outcome is not uncommon. Our aim was to study the epidemiology of pleural empyema on a nationwide basis in the whole population and in three subgroups of patients, namely post-lung resection, associated cancer and those with no surgery and no cancer.

Methods Data from patients aged ≥18 years hospitalised with a diagnosis of pleural infection in France between January 2013 and December 2017 were retrieved from the medical-administrative national hospitalisation database and retrospectively analysed. Mortality, length of stay and costs were assessed.

Results There were 25 512 hospitalisations for pleural empyema. The annual rate was 7.15 cases per 100 000 habitants in 2013 and increased to 7.75 cases per 100 000 inhabitants in 2017. The mean age of patients was 62.4±15.6 years and 71.7% were men. Post-lung resection, associated cancer and no surgery–no cancer cases accounted for 9.8%, 30.1% and 60.1% of patients, respectively. These groups were significantly different in terms of clinical characteristics, mortality and risk factors for length of stay, costs and mortality. Mortality was 17.1% in the whole population, 29.5% in the associated cancer group, 17.7% in the post-lung resection group and 10.7% in the no surgery–no cancer group. In the whole population, age, presence of fistula, higher Charlson Comorbidity Index (≥3), alcohol abuse, arterial hypertension, hyperlipidaemia, atheroma, atrial fibrillation, performance status ≥3 and three subgroups of pleural empyema independently predicted mortality.

Conclusions Empyema is increasing in incidence. Factors associated with mortality are recent lung resection and associated diagnosis of cancer.

Key messages

What is the key question?
► Is pleural empyema a single nosological entity, or can it be attributed to underlying conditions?

What is the bottom line?
► Previous lung resection and an associated diagnosis of cancer represent specific subgroups of patients with increased length of stay, costs and mortality as compared to non-lung resection and non-associated cancer subgroups.

Why read on?
► Previous lung resection and associated diagnosis of cancer are strong determinants in the course of pleural empyema with specific characteristics.

INTRODUCTION

Pleural infection is an old topic handed down since the ancient Greek civilisation, but modern memory has been tremendously marked by the peak of incidence and related mortality observed during the influenza pandemic in 1918–1919.[1 2] In the 10th International Classification of Diseases (ICD-10), infection of the pleural cavity is indifferently named as pleural empyema or pyothorax and coded as J86 or J86.9 when associated with bronchopleural fistula.[3]

Although antibiotics in the mid-20th century radically changed the picture of pleural empyema,[4] recent epidemiological studies have reported an increasing incidence of the disease.[5–8] A database registry of the whole population in Taiwan found an increase in annual incidence from 5.2 to 9.6 cases per 100 000 habitants between 1997 and 2008.[5] A study of the USA Nationwide Inpatient Sample found an incidence of 3.04 cases per 100 000 inhabitants in 1996 and nearly double that (5.98 cases per 100 000) in 2006.[6] An increasing incidence in the paediatric and adult patient populations during the period between 1995 and 2003 was reported in a study using the Discharge Abstract Database of the Canadian Institute for Health Information.[7] In registries of all Danish hospitals from 1997 to 2011, the incidence increased from 8.7 to 11.8 per 100 000 person-years, and increased most among people aged ≥80 years.[8] Diagnosis of pleural space infections in the Washington statewide administrative database increased over the period between 1987 and 2004, as did the proportion of patients undergoing operative management.[9] All these previous studies focused on incidence and on time trends, and most on length of hospital stay and on mortality, however, risk factors associated with unfavourable outcome, specific subpopulations and cost of hospitalisation were scantly explored.[10]

Pleural empyema is better termed parapneumonic empyema when it is the result of complicated pneumonia. However, recent studies have shown that surgery could account for a relevant percentage of cases and, in this setting, because of the involvement of different etiologic mechanisms, the term of 'post-surgical empyema' could be employed.[7 11] Post-lung resection pleural empyema should be considered

among these latter cases, because of the challenge faced by the remaining lung to fill the pleural cavity, in the case of segmental or lobar resection, or sterilisation and obliteration of an infected space in the case of pneumonectomy.[12] A recent European Association of Cardio-Thoracic Surgery expert consensus statement for surgical management of pleural empyema pointed out the similarities of parapneumonic and postsurgical empyema, but stressed the peculiarity in presentation and management of post-resectional empyema, as in the case of post-pneumonectomy empyema with or without bronchopleural fistula.[13]

On the other hand, in Western countries, apart from ageing and related comorbidities, which logically are risk factors of malignancies, the presence of a concurrent cancer has scarcely been explored in terms of its role in defining specific characteristics of a subpopulation of patients and in determining the outcome of empyema.[10]

In the present study, we investigated the epidemiologic characteristics of patients hospitalised with a diagnosis of pleural empyema on a nationwide scale during a 5-year period. In particular, we explored the clinical characteristics of patients with post-lung resection empyema, and those presenting with an associated diagnosis of cancer other than resected lung cancer. Analysed outcome measures in the whole population and in the subgroups were length of hospital stay, mortality and costs of hospitalisation.

METHODS

Study design and database structure

The study is based on 2012–2017 exhaustive data from the 'Programme de Médicalisation des Systèmes d'Information' database (Programme for Medicalisation of Information Systems, PMSI) of the national healthcare system, which collects data on all hospital stays, regardless of duration, in French public and private hospitals. In addition to its administrative purpose (monitoring of hospital activity based on the diagnostic-related groups (DRGs) model, to inform pricing and strategic decisions by payers and policy-makers), the database is also used for epidemiological purposes in several areas.[14 15]

Data in the PMSI database are collected on a real-time basis and analysed yearly, and include the encrypted patient identification number, the main diagnosis leading to the hospitalisation, associated comorbidities and hospital-related complications, as well as other administrative and medical information, including some treatment modalities. Diagnostic coding relies on ICD-10 and follows its updates (ICD-10, WHO). Coding of medical and surgical procedures is based on the French 'Classification Commune des Actes Médicaux' (Common Classification of Medical Procedures, CCAM). The main diagnosis is given by treating clinicians in charge of the patients immediately after discharge.

The data were anonymously collected and analysed. Because of the retrospective analysis of anonymised data, no informed consent was possible, and institutional review board approval was unnecessary according to French biomedical research law.

Retrieved data

All hospital stays in the period 2013–2017 presenting the codes J86.0 (ie, pleural empyema) or J86.9 (ie, pyothotax with fistula) were retrieved. ICD definition of fistula includes both peripheral and more proximal leak. Being under the age of majority (<18 years) and duration of stay less than 1 day were considered as exclusion criteria. As intensive care or thoracic surgery facilities are frequently unavailable in several first-level and second-level hospitals, in the case of two or more hospitalisations for a single patient the data of the hospitalisations were merged and a single hospital stay was considered, provided that the modality of discharge from the first one was 'referral to another hospital'. In the remaining cases, if the interval between two hospitalisations was less than 1 month, the second episode was considered as early recurrence within the same disease process. The modality of readmission was recorded (in particular through the emergency room).

All patients who had a lung resection in the 3 months before the hospitalisation for pleural empyema were identified by searching for previous hospitalisation in computer files where a surgical procedure encoded as GFFA* (ie, lung resection in French CCAM) was recorded.

The data obtained from each hospital stay included age, sex, comorbidities (in particular alcohol abuse (F10*), malnutrition and/or cachexia (E43; E44*; R64), WHO Performance Status (PS) ≥3 (R26.30), arterial hypertension (I10), atherosclerosis (I25*), hyperlipidaemia (E78.0–2; E78.4–5), atrial fibrillation (I48*), COPD (J44*; J47; J96.1*), obstructive sleep apnoea (G47.3), ascites (R18)), those allowing calculation of Charlson Comorbidity Index (CCI)).[16] When bacteriological documentation was coded, data were collected, in particular with respect to isolation of *Escherichia coli* (B96.2), *Klebsiella pneumoniae* (B96.1), *Pseudomonas aeruginosa* (B96.5), *Streptococcus* spp (B95.0–5) and *Staphylococcus* spp (B95.6–8). The duration of hospital stay and the type of hospital unit(s) in which the patient was hospitalised (emergency/medicine/surgery/Intensive Care Unit (ICU) were collected and, for patients admitted to the ICU, the Simplified Acute Physiology Score II (SAPS II) at admission was collected.[17] The modality of discharge was recorded: (1) home, (2) referral to another hospital, (3) death. Thanks to the medical-administrative character of the database, there was no missing data.

Finally, as an outcome measure, we collected mortality, length of stay and costs. For each hospitalisation, the whole cost was estimated by a particular method which consisted of a modulation of the statistical cost, provided by the National Cost Study and based on 171 DRGs cost categories grouped into five main compartments, according to the following specificities of each stay: performance index (length of stay based), fixed charges, clinical loads for critical care, clinical expenses excluding critical care, structural loads. The microcost elements are added or substituted to an existing bucket, if any.[18–21]

Statistics

Continuous variables were presented as mean and SD or median and IQR if their distribution was skewed, and categorical variables were summarised as numbers and percentages. For continuous variables, one-way analysis of variance (for age) or Kruskal-Wallis tests (for all other variables that had a skewed distribution) were used to compare the differences between groups, and for categorical variables, Pearson's χ^2 test was used. Two-by-two subgroup comparisons were added, with the Holm correction for multiplicity. To emphasise the association of baseline characteristics with the study subgroup, a multinomial regression taking the no cancer–no surgery subgroup as reference was used. Relative risk ratios for each between-subgroup comparison quantified the strength of the association with baseline characteristics, and are presented with the Holm adjusted 99% CI. We assessed which characteristics were associated with (1) mortality in the whole population and in subgroups, (2) length of stay >median, (3) costs >median using logistic regression, both in the whole population and in the subgroups. No data-driven variable selection was

Table 1 Prevalence of pleural empyema (per 100 000 inhabitants)

Year	Number of patients	French population	Prevalence (100 000)
2013	4685	65 564 756	7.15
2014	4554	66 129 671	6.89
2015	4863	66 420 595	7.32
2016	5066	66 694 863	7.60
2017	5192	66 953 638	7.75

performed, and both quantitative (ie, a difference in magnitude of association on the log OR scale) and qualitative (ie, a difference in the direction of association) interactions were tested.[22] For multivariable regression models, ORs are presented with their 99% CI, as an informal mean to account for the many associations studied. Analyses were performed using SAS (V.7.15 HF7, SAS Institute) and R (V.3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We retrieved from the PMSI national database 25 512 stays corresponding to 23 509 patients hospitalised for pleural empyema in the period from January 2013 to December 2017. The incidence of the disease was 7.15 per 100 000 inhabitants in 2013 and increased to 7.75 per 100 000 in 2017. The increase in incidence seems slowly progressive in the timespan of the study, but the exception of the year 2014 (when it was at 6.89 per 100 000 inhabitants) led us to consider the increase likely but uncertain (table 1).

Whole dataset

Seventy-two per cent of patients in the whole period were men, and mean age was 62.4±15.6 years; occurrence of pleural empyema increased with age (table 2).

Concurrent diseases included mainly malnutrition (33.7% of cases), arterial hypertension (26.6%), atrial fibrillation (16.2%) and COPD (15.4%); median CCI was 5. Concurrent cancer other than resected lung cancer was present in as many as 30% of cases (n=7074) and was represented mainly by non-resected lung cancer (n=2129) and cancer of the oesophagus or cardia (n=2196). Ten per cent of patients of the whole dataset (n=2299) had undergone major lung resection for lung cancer during the same hospitalisation as that necessary for pleural empyema, or in the 3 months before it. Thus, only 60% of patients had neither cancer nor a recent history of lung resection. We therefore present our results in the following three subpopulations: post-lung resection, associated cancer and no surgery–no cancer patients (figure 1).

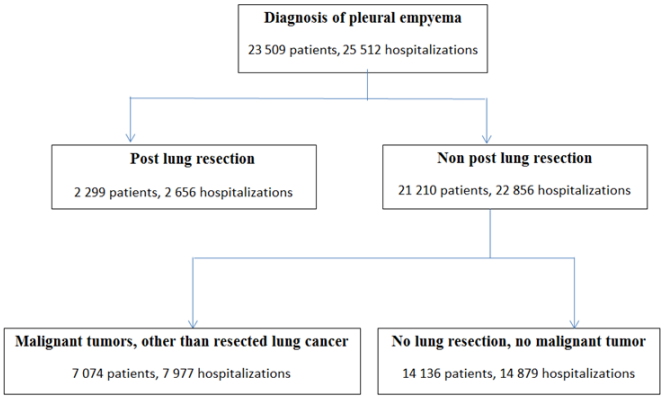
Characteristics of the three groups

Patients in the post-lung resection group were more frequently men, and had a more frequent history of heavy smoking, COPD, sleep apnoea, arterial hypertension, atheroma, hyperlipidaemia and atrial

Table 2 Characteristics of the whole population and of the three subgroups

Characteristics	Whole population	Post-lung resection	Associated cancer no previous lung surgery	No surgery no cancer	P value
Patients, no. (%)	23 509	2299 (9.8)	7074 (30.1)	14 136 (60.1)	—
Gender, male (%)	16 858 (71.7)	1805 (78.5)	5259 (74.3)	9794 (69.3)	<0.0001
Age, mean (SD), years	62.4 (15.6)	61.2 (12.5)	65.0 (11.4)	61.3 (17.6)	<0.0001
Age classes, no. (%)					<0.0001
18–40 years	2187 (9.3)	151 (6.6)	131 (1.9)	1905 (13.4)	
41–60 years	7761 (33.0)	826 (35.9)	2308 (32.6)	4627 (32.7)	
61–80 years	10 592 (45.0)	1244 (54.1)	3990 (56.4)	5358 (37.9)	
>80 years	2969 (12.6)	78 (3.4)	645 (9.1)	2246 (15.8)	
Charlson Comorbidity Index, median (IQR)	5 (2–5)	5 (3–8)	7 (4–10)	3 (1– 4)	<0.0001
Alcohol abuse (F10*), no. (%)	2297 (9.8)	222 (9.7)	578 (8.2)	1497 (10.6)	<0.0001
Smoking (F17*), no. (%)	3719 (15.8)	608 (26.5)	899 (12.7)	2212 (15.7)	<0.0001
Malnutrition and/or cachexia (E43; E44*; R64), no. (%)	7931 (33.7)	804 (35)	3172 (44.8)	3955 (28.0)	<0.0001
Performance status ≥3 (R26.30), no. (%)	746 (3.2)	20 (0.9)	223 (3.2)	503 (3.6)	<0.0001
Arterial hypertension (I10), no. (%)	6256 (26.6)	701 (30.5)	1784 (25.2)	3771 (26.7)	<0.0001
Atherosclerosis (I25*), no. (%)	1597 (6.8)	194 (8.4)	455 (6.4)	948 (6.7)	0.0033
Hyperlipidaemia (E78.0–2; E78.4–5), no. (%)	1467 (6.2)	216 (9.4)	449 (6.3)	802 (5.7)	<0.0001
Atrial fibrillation (I48*), no. (%)	3807 (16.2)	449 (19.5)	1135 (16.0)	2223 (15.7)	<0.0001
COPD (J44*; J47; J96.1*), no. (%)	3621 (15.4)	627 (27.3)	1004 (14.2)	1990 (14.1)	<0.0001
Sleep apnoea (G47.3), no. (%)	706 (3.0)	87 (3.8)	173 (2.4)	446 (3.2)	0.0012
Ascites (R18), no. (%)	637 (2.7)	16 (0.7)	221 (3.1)	400 (2.8)	<0.0001
Pleural empyema with fistula (J860), no. (%)	7425 (31.6)	1222 (53.2)	3748 (53.0)	2455 (17.4)	<0.0001
SAPS II, median (IQR)	0 (0–32)	21 (0–37)	0 (0–33)	0 (0–30)	<0.0001
ICU, no. (%)	3908 (16.6)	397 (17.3)	880 (12.4)	2631 (18.6)	<0.0001
Length of stay, median (IQR) days	19 (11–35)	25 (15– 46)	22 (11– 39)	17 (10–30)	<0.0001
Cost, median (IQR) ×1000 €	12.6 (6.6–25.3)	24.7 (13.7–43.4)	13.6 (6.9–27.1)	11.1 (6.2–21.5)	<0.0001
Fatal outcome, no. (%)	4010 (17.1)	407 (17.7)	2090 (29.5)	1513 (10.7)	<0.0001

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score.



	patients	hospitalizations
Malignant Tumors	7 074	7 977
Lung	2 129	2 435
Esophagus, cardia	2 196	2 541
Digestive	643	689
ORL - Tracheal	564	654
Hematologic	419	458
Metastasis*	271	292
Other tumors	852	908

** metastasis with no primitive tumor code*

Figure 1 Flow chart.

fibrillation, but had a better PS and lower incidence of malnutrition. Patients in the associated cancer group were older, and had higher CCI, and increased incidence of malnutrition/cachexia (45% of cases); ascites was often more frequently encountered among them. In the no surgery–no cancer group, patients more frequently had a history of alcohol abuse; they more frequently had a PS >3 in spite of lower CCI; a higher percentage of younger patients was seen in this group (13% <40 years) (table 2 and online supplemental table 1).

Fistula

Overall, there were 16 084 cases without fistula (68.4%) and 7425 cases with fistula (31.6%). The presence of fistula identified subpopulations in the whole dataset and in the three subpopulation groups (online supplemental table 2). Patients with fistula were more frequently men and had higher CCI in the whole population and in the post-lung resection and associated cancer groups, but not in the no surgery–no cancer group. Cachexia and PS ≥3 were more frequent in all three groups in the case of fistula, whereas COPD was more frequent in the post-lung resection and no surgery–no cancer groups in the case of fistula. Lastly, for patients admitted to the ICU, the SAPS II score was significantly higher in the case of fistula, irrespective of groups.

Bacteriological documentation

Bacteriological documentation was available in PMSI files in 10,643 cases (45%), with *Streptococcus* spp and *Staphylococcus* spp being more frequent (18% and 14%, respectively), followed by *E. coli* and *P. aeruginosa*, which accounted for 9% and 7% of cases, respectively. In the post-lung resection group, infection with *Staphylococcus* spp, and, to a lesser extent, *Streptococcus* spp, and *P. aeruginosa* was more frequent than in other groups. Every bacteriological species was retrieved more frequently in pleural empyema with fistula in the no surgery–no cancer group, with the exception of *Streptococcus* spp, whereas in the post-lung resection group *Staphylococcus* spp were found more frequently in pleural empyema without fistula, with all remaining germs found more frequently in the case of fistula. *Streptococcus* spp and *Staphylococcus* spp were found more frequently in pleural empyema without fistula in the associated cancer group, with all remaining germs being found more frequently in cases of fistula in this subgroup (online supplemental table 2).

Length of hospital stay

Mean hospital stay was 28 days (median 19, IQR 11–35). Length of hospitalisation was higher in the post-lung resection group (median 25, IQR 15–46), followed by the associated cancer group (median 22, IQR 11–39) and by the no surgery–no cancer group (median 17, IQR 10–30) (table 2).

Factors independently associated with hospital stay are shown in online supplemental table 3). Multivariable analysis (including deceased and non-deceased patients) showed that the presence of fistula (OR 1.47 (99% CI 1.35 to 1.60)), need for the ICU (OR 2.33 (99% CI 2.10 to 2.58)), malnutrition and cachexia (OR 3.01 (99% CI 2.77 to 3.26)), COPD (OR 1.29 (99% CI 1.16 to 1.43)) and atrial fibrillation (OR 1.81 (99% CI 1.63 to 2.02)) predicted hospital stay in the whole population. The same factors independently predicted hospital stay in the three subgroups as well (online supplemental table 3). In particular, like alcohol abuse, higher CCI had a negative impact on hospital stay in the no surgery–no cancer and in post-lung resection subgroups, but not in the associated cancer subgroup.

Mortality

The mortality rate was 17.1% (4010 out of 23 509 patients), with significant differences between groups: 29.5% in the associated cancer group, 17.7% in the post-lung resection group and 10.7% in the no surgery–no cancer group. In the case of fistula, mortality was higher (36.9% vs 14.2%, p<0.0001). Factors associated with fatal outcome in each group in univariate analysis are shown in table 3. Factors independently associated with mortality are displayed in table 4. In particular, in the whole population, multivariable analysis showed that increasing age (OR: 18–40 years: ref.; 41–60 years: 1.83 (99% CI 1.34 to 2.48); 61–80 years: 1.88 (99% CI 1.37 to 2.57); >80 years: 2.54 (99% CI 1.81 to 3.56)) and CCI (OR: 0–2: ref.; 3–4: 2.11 (99% CI 1.75 to 2.54); 5–6: 2.84 (99% CI 2.30 to 3.50); >6: 3.65 (99% CI 2.96 to 4.49)), PS ≥3 (OR 3.31 (99% CI 2.66 to 4.10)), alcohol abuse (OR 1.23 (99% CI 1.02 to 1.48)), atheroma (OR 1.14 (99% CI 0.96 to 1.36)), atrial fibrillation (OR 1.60 (99% CI 1.42 to 1.80)), ascites (OR 2.37 (99% CI 1.86 to 3.02)), fistula (OR 2.09 (99% CI 1.88 to 2.32)) and, also, each of the three groups (OR: no surgery–no cancer: ref.; post-lung resection: 1.17 (99% CI 0.98 to 1.40); associated cancer: 1.72 (99% CI 1.51 to 1.97), independently predicted mortality.

In the post-lung resection group, age >60 years, male sex, CCI >5, atrial fibrillation, ascites and presence of fistula independently predicted mortality, whereas in the associated cancer subgroup, CCI >6, PS ≥3, arterial hypertension, hyperlipidaemia, atrial fibrillation, COPD, obstructive sleep apnoea, ascites and presence of fistula were independently associated with fatal outcome. In the no surgery–no cancer group, death was independently associated with increasing age, higher CCI, alcohol abuse, arterial hypertension, atheroma, hyperlipidaemia, ascites, atrial fibrillation, PS≥3 and presence of fistula.

Mortality in patients requiring invasive mechanical ventilation

In the whole population, mortality rate was 30.4% in patients requiring invasive mechanical ventilation (1930 out of 6404), as compared with 12.1% (2080 out of 17 105) in non-intubated patients (p<0.001). The difference was statistically significant in the three subgroups (always p<0.001): in the post-lung resection subgroup, mortality rates were 36.9% (345/934) and 4.5% (62/1365) in intubated and non-intubated patients, respectively; in the associated cancer–no previous lung cancer subgroup, the mortality rate was

Table 3 Fatal outcome: univariate analysis in overall population and in the three subgroups.

	Overall		Post-lung resection		Associated cancer no previous lung surgery		No surgery no cancer	
Characteristics	Fatal outcome n (%)/mean (SD)/ median (IQR)	P value	Fatal outcome n (%)/mean (SD) /median (IQR)	P value	Fatal outcome n (%)/mean (SD) /median (IQR)	P value	Fatal outcome N(%)/mean(SD) /median(IQ range)	P value
Patients, number	4010 (20.57%)		407 (21.51%)		2090 (41.93%)		1513 (11.99%)	
Male sex	2947 (21.18%)		353 (24.31%)		1582 (43.02%)		1012 (11.52%)	
Female sex	1063 (19.02%)	0.0059	54 (12.27%)	<0.0001	508 (38.87%)	0.0920	501 (13.04%)	0.0324
Age classes								
18–40 years	90 (4.29%)	<0.0001	8 (5.59%)	<0.0001	26 (24.76%)	0.0712	56 (3.03%)	<0.0001
41–60 years	1090 (16.34%)		106 (14.72%)		670 (40.9%)		314 (7.28%)	
61–80 years	2109 (24.86%)		269 (27.59%)		1196 (42.81%)		644 (13.66%)	
>80 years	721 (32.07%)		24 (44.44%)		198 (44.3%)		499 (28.56%)	
Alcohol abuse No	3637 (20.69%)	0.2721	366 (21.39%)	0.7534	1920 (41.96%)	0.9417	1351 (11.97%)	0.8754
Alcohol abuse Yes	373 (19.39%)		41 (22.65%)		170 (41.67%)		162 (12.13%)	
Smoking No	3561 (21.94%)	<0.0001	321 (23.43%)	0.0073	1836 (42.31%)	0.3638	1404 (13.35%)	<0.0001
Smoking Yes	449 (13.73%)		86 (16.48%)		254 (39.38%)		109 (5.18%)	
Malnutrition and/or cachexia No	2352 (17.78%)	<0.0001	257 (20.76%)	0.3800	1107 (39.61%)	0.0163	988 (10.75%)	<0.0001
Malnutrition and/or cachexia Yes	1658 (26.43%)		150 (22.94%)		983 (44.91%)		525 (15.31%)	
Performance status ≥3 No	3711 (19.48%)	<0.0001	400 (21.29%)	0.0418	1957 (39.99%)	<0.0001	1354 (11.03%)	<0.0001
Performance status ≥3 Yes	299 (66.89%)		7 (53.85%)		133 (147.78%)		159 (46.22%)	
Arterial hypertension No	2907 (20.26%)	0.1590	263 (19.7%)	0.0182	1593 (43.09%)	0.0711	1051 (11.28%)	0.0003
Arterial hypertension Yes	1103 (21.41%)		144 (25.85%)		497 (38.62%)		462 (13.96%)	
Atherosclerosis No	3633 (19.88%)	<0.0001	357 (20.42%)	0.0021	1950 (41.76%)	0.5540	1326 (11.18%)	<0.0001
Atherosclerosis Yes	377 (30.9%)		50 (34.72%)		140 (44.44%)		187 (24.57%)	
Hyperlipidaemia No	3787 (20.75%)	0.0509	361 (20.96%)	0.1461	1979 (42.6%)	0.0206	1447 (12.17%)	0.0196
Hyperlipidaemia Yes	223 (17.93%)		46 (27.06%)		111 (32.84%)		66 (8.97%)	
Atrial fibrillation No	3003 (17.98%)	<0.0001	272 (17.24%)	<0.0001	1668 (39.05%)	<0.0001	1063 (9.8%)	<0.0001
Atrial fibrillation Yes	1007 (35.96%)		135 (42.99%)		422 (59.19%)		450 (25.38%)	
COPD No	3264 (19.63%)	<0.0001	282 (20.29%)	0.0859	1740 (40.18%)	<0.0001	1242 (11.39%)	<0.0001
COPD Yes	746 (25.95%)		125 (24.9%)		350 (53.52%)		271 (15.76%)	
Sleep apnoea No	3903 (20.65%)	0.1726	390 (21.41%)	0.6474	2052 (42.32%)	0.0269	1461 (11.95%)	0.5070
Sleep apnoea Yes	107 (17.86%)		17 (24.29%)		38 (28.15%)		52 (13.2%)	
Ascites No	3799 (19.92%)	<0.0001	400 (21.24%)	0.0061	2006 (41.39%)	0.0051	1393 (11.29%)	<0.0001
Ascites Yes	211 (49.53%)		7 (77.78%)		84 (61.31%)		120 (42.86%)	
Fistula No	2007 (14.26%)	<0.0001	105 (10.8%)	<0.0001	817 (32.56%)	<0.0001	1085 (10.24%)	<0.0001
Fistula Yes	2003 (36.94%)		302 (32.83%)		1273 (51.43%)		428 (21.11%)	
ICU No	2882 (17.24%)	<0.0001	260 (15.83%)	<0.0001	1701 (37.86%)	<0.0001	921 (8.7%)	<0.0001
ICU Yes	1128 (40.58%)		147 (58.8%)		389 (79.23%)		592 (29.03%)	
Charlson Comorbidity Index, mean (SD)	6.4 (±3.4)	<0.0001	6.6 (±3.47)	<0.0001	7.8 (±3.27)	<0.0001	4.4 (±2.3)	<0.0001
SAPS II, median (IQR)	30 (0–52)	<0.0001	43 (30–57)	<0.0001	0 (0–43)	<0.0001	40 (0–59)	<0.0001
Length of stay, median (IQR) days	21 (10–39.8)	<0.0001	30 (16–55.5)	<0.0001	21 (10–38)	0.1383	19 (9–37)	<0.0001

ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score.

40.7% (733/1802) and 25.7% (1357/5272) in intubated and non-intubated patients, respectively, whereas in the no surgery–no cancer group the mortality rate was 23.2% (852/3668) and 6.3% (661/10 468) in intubated and non-intubated patients, respectively.

Costs: reimbursements by national health system

The mean hospitalisation reimbursement for the whole population was 21 822 € (median 12 627, IQR 6616–25 553). Reimbursement was higher ($p<0.0001$ for each pairwise comparison after correction for multiple testing) in the post-lung resection group (median 24 724 €, IQR 13 741–43 435), followed by the associated cancer group (13 586 €, 6896–27 090) and the no surgery–no cancer group (11 066 €, 6206–21 463) (table 2).

Multivariable analysis (including deceased and non-deceased patients) showed that higher CCI (ORs: 0–2: ref; 3–4: 1.26 (99% CI 1.12 to 1.43); 5–6: 1.65 (99% CI 1.42 to 1.93); >6: 1.61 (99% CI 1.38 to 1.89)), fistula (OR 1.59 (99% CI 1.46 to 1.74)), malnutrition or cachexia (OR 2.36 (99% CI 2.17 to 2.56)), PS ≥3 (OR 1.16 (99% CI 0.93 to 1.44)), alcohol abuse (OR 1.39 (99% CI 1.21 to 1.61)), atrial fibrillation (OR 2.06

Table 4 Fatal outcome: multivariable analysis in the whole population and in the three subgroups. Models were adjusted for all variables presented in the table, including study subgroup for the analysis of the whole sample

	All patients		Post-lung resection		Associated cancer no previous lung surgery		No surgery no cancer		Quantitative interaction	Qualitative interaction
Characteristic	OR (99% CI)	P value	OR (99% CI)	P value	OR (99% CI)	P value	OR (99% CI)	P value	P value	P value
Male gender	1.06 (0.95 to 1.19)	0.14	1.60 (1.04 to 2.45)	0.005	1.10 (0.93 to 1.29)	0.14	0.96 (0.82 to 1.13)	0.56	0.013	0.49
Age (year)										
18–40	1		1		1		1			
41–60	1.83 (1.34 to 2.48)	<0.0001	1.71 (0.61 to 4.78)	0.18	1.48 (0.81 to 2.72)	0.093	1.90 (1.29 to 2.81)	<0.0001	0.67	0.75
61–80	1.88 (1.37 to 2.57)	<0.0001	2.33 (0.82 to 6.62)	0.036	1.47 (0.80 to 2.70)	0.10	2.15 (1.43 to 3.24)	<0.0001	0.37	0.75
>80	2.54 (1.81 to 3.56)	<0.0001	3.43 (0.99 to 11.8)	0.010	1.47 (0.77 to 2.81)	0.12	3.19 (2.06 to 4.96)	<0.0001	0.032	0.75
Charlson Comorbidity Index										
0–2	1		1		1		1			
3–4	2.11 (1.75 to 2.54)	<0.0001	1.43 (0.81 to 2.50)	0.10	1.27 (0.77 to 2.09)	0.21	2.01 (1.57 to 2.58)	<0.0001	0.060	0.75
5–6	2.84 (2.30 to 3.50)	<0.0001	1.85 (1.02 to 3.35)	0.007	1.42 (0.85 to 2.37)	0.080	3.01 (2.27 to 4.00)	<0.0001	0.002	0.75
>6	3.65 (2.96 to 4.49)	<0.0001	2.45 (1.41 to 4.26)	<0.0001	1.92 (1.18 to 3.14)	0.0006	4.06 (2.93 to 5.62)	<0.0001	0.002	0.54
Alcohol abuse	1.23 (1.02 to 1.48)	0.004	1.26 (0.74 to 2.14)	0.26	0.95 (0.71 to 1.26)	0.63	1.52 (1.15 to 2.00)	<0.0001	0.009	0.75
Smoking	0.68 (0.58 to 0.80)	<0.0001	0.59 (0.40 to 0.87)	0.0005	0.90 (0.71 to 1.15)	0.28	0.51 (0.38 to 0.69)	<0.0001	0.0003	0.63
Malnutrition or cachexia	1.00 (0.91 to 1.11)	0.95	0.90 (0.66 to 1.23)	0.39	1.01 (0.88 to 1.17)	0.79	1.00 (0.85 to 1.17)	0.98	0.67	0.75
Performance status ≥3	3.31 (2.66 to 4.10)	<0.0001	2.49 (0.68 to 9.10)	0.069	3.73 (2.58 to 5.39)	<0.0001	3.06 (2.32 to 4.05)	<0.0001	0.47	0.75
Hypertension	0.80 (0.72 to 0.90)	<0.0001	0.91 (0.64 to 1.28)	0.46	0.85 (0.72 to 1.01)	0.017	0.74 (0.62 to 0.88)	<0.0001	0.22	0.75
Atherosclerosis	1.14 (0.96 to 1.36)	0.046	1.14 (0.70 to 1.86)	0.48	0.95 (0.72 to 1.27)	0.68	1.28 (1.00 to 1.64)	0.011	0.14	0.57
Hyperlipidaemia	0.74 (0.60 to 0.91)	0.0002	1.00 (0.61 to 1.65)	>0.99	0.78 (0.57 to 1.06)	0.040	0.59 (0.41 to 0.85)	0.0002	0.075	0.75
Atrial fibrillation	1.60 (1.42 to 1.80)	<0.0001	1.79 (1.27 to 2.51)	<0.0001	1.53 (1.27 to 1.84)	<0.0001	1.56 (1.31 to 1.86)	<0.0001	0.58	0.75
COPD	1.12 (0.98 to 1.27)	0.027	1.00 (0.71 to 1.40)	0.99	1.28 (1.05 to 1.56)	0.001	1.01 (0.83 to 1.24)	0.86	0.063	0.74
Sleep apnoea	0.80 (0.60 to 1.07)	0.051	0.90 (0.42 to 1.95)	0.73	0.61 (0.37 to 1.01)	0.011	0.91 (0.60 to 1.38)	0.56	0.26	0.75
Ascites	2.37 (1.86 to 3.02)	<0.0001	3.83 (0.91 to 16.0)	0.016	1.53 (1.05 to 2.23)	0.004	3.08 (2.22 to 4.28)	<0.0001	0.001	0.75
Fistula	2.09 (1.88 to 2.32)	<0.0001	2.73 (1.96 to 3.79)	<0.0001	1.71 (1.48 to 1.97)	<0.0001	2.41 (2.03 to 2.87)	<0.0001	<0.0001	0.75
Study subgroup										
No surgery, no cancer	1									
Lung resection	1.17 (0.98 to 1.40)	0.026								
Associated cancer	1.72 (1.51 to 1.97)	<0.0001								

(99% CI 1.84 to 2.31)), arterial hypertension (OR 1.45 (99% CI 1.32 to 1.60)), hyperlipidaemia (OR 1.24 (99% CI 1.05 to 1.47)), COPD (OR 1.37 (99% CI 1.22 to 1.53)), obstructive sleep apnoea (OR 1.29 (99% CI 1.02 to 1.62)), ascites (OR 1.96 (99% CI 1.52 to 2.51)) and need for ICU admission (OR 5.75 (99% CI 5.10 to 6.48)) were independently associated with costs in the whole population (online supplemental table 4).

The subgroup results are shown in online supplemental table 4. In particular, increasing age, higher CCI, alcohol abuse, malnutrition, arterial hypertension, atheroma and atrial fibrillation were independently associated with increased costs in the whole population and in all subgroups, together with the presence of fistula (online supplemental table 4).

DISCUSSION

In the present database study, we measured the adult incidence of pleural empyema in a nationwide population. The yearly rate ranging from 6.8 to 7.7 cases for 100 000 habitants is in line with previous reported data, though it should be noted that we included postsurgical cases and excluded the paediatric population (age <18 years).[5–10] Like previous studies, but over a shorter period, we noted a slight increase in the incidence of the disease.

The main originality of our study is the identification of three distinct subpopulations: no surgery–no cancer, associated cancer and post-lung resection. This last group accounted for 9% of the whole population, an original finding never reported previously to our knowledge: in an epidemiologic study from Canada, 20% of patients had previous surgery, although all kinds of thoracic surgery (including heart, mediastinal and oesophageal).[7]

The three groups of our study are different with respect to demographics and comorbidities, as well as to outcomes, in terms of mortality, length of stay and costs. For example, in a recent meta-analysis of previous studies on pleural empyema, a prevalence of 20% of respiratory illness has been reported[10]; in our study, COPD was found in 15% of the whole population, but in 27% of patients with previous lung resection. We would like to underline that our large-scale dataset enabled us to demonstrate that differences between groups related not only to comorbidities (ie, COPD or CCI) expected to have an impact

on either the occurrence or outcome of pleural empyema, but also other concurrent illnesses or conditions (age class, PS, atrial fibrillation hyperlipidaemia, alcohol abuse, sleep apnoea), which probably reflect the overall fitness of people.

Bacterial isolation (a topic never investigated in studies based on medical-administrative records) was also different among groups, and, within groups, in the case of concurrent fistula or not, underlying the different pathophysiological mechanisms. For example, *Staphylococcus* spp were isolated more frequently in the post-lung resection group, and, among these patients, in those without fistula, in agreement with the concept that post-lung resection empyema without fistula often results from contamination of the operative field during surgery.[12] These data when combined with recent knowledge on the microbiological pattern of pleural empyema, as well as the use of the RAPID clinical score at the time of hospitalisation, are useful tools in the treatment of patients admitted with pleural infection.[23–25]

Empyema is a severe condition whose fatality rate is high, especially after lung resection and, even more, in the case of associated cancer, but the disease frequently affects severely ill patients: CCI was on average 7 in the associated cancer group, and 5 and 3 in the post-lung resection and no surgery–no cancer groups, respectively, and malnutrition occurred as frequently as in 45% of associated cancer cases, 35% of post-lung resection patients and even 11% of no surgery–no cancer patients.

As previously reported in the Taiwanese[5] and Danish population studies,[8] CCI was an excellent predictor of outcome, in particular fatality, in the whole population; we observed that it maintained its prognostic significance in all subgroups. Fistula also determined the outcome: fistula is associated with infected space, difficulties in mechanical ventilation (when needed), inhalation, and may require additional surgical/endoscopic procedures which can per se worsen prognosis in severely ill patients.

The mean cost of hospitalisation in our study was 21 822±28 745 €, which is higher in comparison with that reported from Taiwan (upper mean cost 4400 US$) and lower than the mean cost of 27 368 US$ found in the study in the Washington State Comprehensive Hospital Abstract Reporting System database.[5 6] Unfortunately, methods to estimate costs are rare in previous studies and different policy payment providers are applied, precluding detailed comparisons.

Our study has limitations related to the retrospective analysis of an administrative database[26 27]: in particular, it is not possible to discriminate fistulas with respect to their topography. Furthermore, the design does not allow all patients with different cancer types to be followed up over time, so as to assess the subsequent incidence of empyema and relative outcome. Similarly, it is impossible to discriminate clearly among cancer patients those insufficiently fit to undergo specific surgery. Also, fatal outcome was recorded as a dichotomous endpoint (alive/dead) with no time to event modelled, because of the lack of precision of date of the event (only the month of discharge is available in the database). Finally, multivariable analysis showed that smoking, hypertension, hyperlipidaemia and sleep apnoea could somehow be protective: this unexpected result is difficult to explain and may be the consequence of multiple comparators.

In spite of these limitations, our study provides important information on the epidemiology of pleural empyema. Furthermore, it outlines the differences in clinical presentation and course between patients with previous lung resection surgery and those with a concurrent diagnosis of cancer.

Contributors AB, SB and MA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LF and EC contributed to the study design. PI, RP, KZ and JF contributed to data analysis, and performed revision of the manuscript. AB and MA are responsible for study conception and design and contributed to manuscript writing and revision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data are available upon reasonable request

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