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Chronic Pulmonary Aspergillosis: Prevalence, favouring pulmonary diseases and prognosis

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Abstract

Chronic pulmonary aspergillosis (CPA) is an emerging disease in patients with common chronic pulmonary diseases (CPD). While its prevalence is linked to tuberculosis (TB) in endemic countries, epidemiologic and prognostic data are lacking in low TB incidence countries. The aim of this study was to describe these features in CPA patients hospitalized in France between 2009 and 2018.

We estimated the prevalence and mortality of hospitalized CPA patients using the French nationwide administrative hospital database. We also assessed the association with CPDs, thoracic interventions, and malnutrition.

From 2009 to 2018, 17,290 patients were hospitalized in France for CPA, with an increasing prevalence during this period. Most patients were male (63.5%) with a median age of 65 years at CPA diagnosis, living in farming regions and large cities. The proportion of underlying chronic obstructive pulmonary disease (COPD) and emphysema during the previous 5 years was 44% and 22%, respectively, whereas it was only 3% for both TB and non-TB mycobacterial (NTM) infections. The mortality rates during the first hospitalization, at 1 year, and at 5 years were 17%, 32%, and 45%, respectively. In multivariate analysis, mortality rates were increased in patients aged over 65 years, males and patients with malnutrition, diabetes, or lung cancer history. The risk of mortality in patients with COPD or emphysema was higher compared to those with previous mycobacterial lung infection.

In France CPA is an emerging infection commonly associated with non-mycobacterial CPD. This shift in the distribution profile of underlying CPD will likely worsen CPA mortality.

Introduction

Chronic pulmonary aspergillosis (CPA) occurs in immunocompetent patients with respiratory tracts weakened by underlying chronic pulmonary disease (CPD). Though CPA has been relatively overlooked for some time, it has been the subject of recent interest [1–5]. The high mortality and morbidity associated with CPA leads to substantial financial costs [6, 7], which have been subject of recent reviews [2, 8, 9]. Mortality rates vary from 17% to 80% depending on the study [10–12]. The rates should thus be specified according to the type of underlying CPD, favouring factors or comorbidities, the surgical options and the use of antifungal treatments. Although, epidemiologic data for CPA are lacking worldwide, tuberculosis (TB) [13, 14] and non-tuberculous mycobacterial (NTM) lung infections are classically considered to be the diseases that pose the most risk of subsequent CPA [15]. The residual cavities in the lung parenchyma left by these infections are colonized by *Aspergillus* spp. and finally responsible for CPA [16]. Therefore, CPA rates correlate with the prevalence of TB [17]. Its incidence was prospectively assessed in a large TB cohort, revealing a 6.5% annual incidence rate of CPA in patients with post-TB cavitation over 2 years of follow-up [14]. Although CPA is a classical complication of mycobacterial lung infections, nowadays a wide variety of other CPD have been shown to put patients at risk of CPA, including chronic obstructive pulmonary diseases (COPD), emphysema, sarcoidosis, and even post-surgical residual thoracic cavities [18–22]. Finally, there is a lack of European epidemiological data based on large cohorts of CPA patients. Studies are therefore needed to determine the prevalence of CPA, the underlying CPD, and patient outcomes. In an attempt to improve current knowledge, we used medical and administrative data collected from the French national administrative database for hospitalized patients (PMSI) [23–25], which gathers exploitable epidemiological data on CPA.

Methods

The national administrative database

Inspired by the US diagnosis-related group model, the French hospital discharge abstract database (PMSI) contains individual, exhaustive and linkable but anonymous data on healthcare for the entire hospitalized population in France, and collects main and associated diagnoses. The data are encoded using the *International Classification of Diseases, 10th Revision* (ICD-10), and procedures performed during all hospital stays are encoded with the French common classification system for medical

procedures. The very good performance of the French hospital database has previously been evaluated, and we have published several epidemiological and health service-related research studies on hospitalized patients in France [23–25]. The National Commission for Data Protection approved the use of PMSI data for this study (CNIL 1576793). As the database is anonymous, written consent was not required. This study conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh in 2000). The PMSI data were transmitted by the Technical Agency for Information on Hospital Care (ATIH 2015-111111-47-33).

Study design

This study was based on the French nationwide collection of PMSI data, including more than 20 million hospital stays per year over the last 10 years. We collected the diagnosis justifying hospitalization, main or associated diagnoses coded according to ICD-10, from the medical data. All CPA patients⩾18 years of age hospitalized from 2009 to 2018 were included.

Identification of CPA

There is no specific ICD-10 diagnosis coding for all CPAs. In order to collect all CPAs, we defined two populations (A and B). Population A corresponded to patients hospitalized from 2009 to 2018 with a diagnosis of ICD-10 code B441 (other forms of aspergillosis), excluding patients with a diagnosis of ICD-10 code J458-459 (asthma), J679 (hypersensitivity pneumonitis), J998 (allergic bronchopulmonary aspergillosis), E84 (cystic fibrosis), or Z94 (only if coded in main diagnosis) (organ or tissue transplants) in the same year. Since B441 is not coded in all hospitals, we also had to consider population B whose CPA was differently coded. Population B was defined as patients hospitalized from 2009 to 2018 with a diagnosis code B440 (invasive aspergillosis) excluding patients with the following ICD-10 codes: B20, B21, B22, B24, Z21 (HIV infection), D848, D849 (other immune deficiencies), T451, D898, T509, Y434 (immunosuppressive treatments), D619, D70 (neutropenia), Z949, T860, Z948, T869, T864, T861, Z943, Z942, Z941, Z940, Z944 (organ transplants + stem cells), C81, C82, C83, C84, C85, C86, C88 (lymphomas), C90 (myeloma), C91, C92, C93, C94, C95 (leukaemia), E84 (cystic fibrosis). We had to exclude all diagnoses relative to immunosuppression in order to exclude truly invasive pulmonary aspergillosis from our study population. These diagnoses were identified in main diagnosis and/or associated diagnoses for the population and for the events studied, and were considered over the same year. We thus selected a population of CPA, defined as

recommended by the latest guidelines [9]. Deleting duplicates, the sum of populations A and B provides an estimation of the prevalence of hospitalized CPA patients between 2009 and 2018. Incidence of CPA was estimated from 2013 to 2018, excluding patients who were hospitalized with a diagnosis of CPA during the four previous years.

The accuracy of the algorithm that we used to select CPA patients was assessed with a review of the medical records of 150 CPA patients (99 from population A and 51 from population B) (data not shown). This analysis was performed for the French department of Côte d'Or. We deliberately chose this department because the prevalence CPA is particularly low and thus the potential risk of miscoding is the highest.

Variables collected

In the population of individuals hospitalized in France with CPA from 2009 to 2018, age, sex, zip-code of residence, and the hospital location were extracted from the administrative data.

The following diseases and medical acts were extracted from the medical data, coded as main or associated diagnosis (supplementary material 1): pulmonary TB, pulmonary TB scarring, NTM lung infection, lung cancer, bronchiectasis, COPD, emphysema, lung fibrosis, lung sarcoidosis, pneumothorax, thoracic surgery acts, radiotherapy acts, chronic respiratory failure (CRF), malnutrition, diabetes, and haemoptysis. We also identified hospital mortality.

Statistical analysis

Qualitative variables were expressed as percentages and quantitative variables as medians and interquartile ranges. The Cochran-Armitage test was used to evaluate the trends over time for qualitative variables, and we used Poisson's regression for qualitative values. For hospitalized cases of prevalent and incident CPA, hospital mortality, associated diagnoses were collected for the same year as the diagnosis of CPA. We studied the geographical distribution of prevalent CPA patients hospitalized in France from 2009 to 2018 to determine whether there were regional differences. The rate of CPA prevalence was adjusted on age and sex according to the structure of the population for each department of France, per 100,000 inhabitants, using 2013 French census data from INSEE as a reference. We also assessed the geographical distribution of the relative proportion of in-hospital mortality the same year as the CPA diagnosis. The distribution of rural and agricultural lands in France

were defined using government reference data [26]. For CPA incident patients hospitalized from 2014 to 2018, we studied underlying CPD or conditions in the 5 years preceding the diagnosis of CPA. Concerning in-hospital mortality, we studied the effect of the underlying CPD or conditions (TB or NTM, lung sarcoidosis, and COPD or emphysema) on one-year survival (for incident cases from 2013 to 2017) and five-year survival (for incident cases from 2013). We first used a Kaplan-Meier curve and then a multivariate analysis using a Cox model adjusting for age, malnutrition, diabetes, history of lung cancer and other CPD (pneumothorax, bronchiectasis or lung fibrosis). Since the prognostic factors were expected to vary according to the underlying CPD, multivariate analysis was limited to the following mutually exclusive CPD subgroups: 1) COPD or emphysema, 2) TB or NTM lung infection and 3) pulmonary sarcoidosis. Hazard ratios (HR) and 95% confidence intervals (95%CI) were calculated. SAS version 9.3 (SAS Institute, Carry, NC, USA) was used for data analysis. All assumptions were tested with an α risk of 0.05. Geographic Information System (GIS) MapInfo 11.0 was used for cartography.

Results

A 10-year overview of hospitalized CPA cases in France

From 2009 to 2018, a total of 17,290 patients were hospitalized for CPA in France. There were 22,637 associated hospital stays during this period. The geographic distribution of CPA by department of residence is presented in Figure 1. Departments with CPA prevalence rates higher than 34 per 100,000 inhabitants were mainly rural departments. Nevertheless, the CPA prevalence rates were also high in the 3 biggest French cities: Paris 30.8 per 100,000, Lyon 32.6 per 100,000, and Marseille 27.3 per 100,000. Most CPA cases were male (63.5%), with a median age of 65 [56-75] at diagnosis. For 1,814 patients (10.5%), haemoptysis was associated to the diagnosis of CPA, and haemoptysis was the main diagnosis in 624 patients (3.6%). Within one year of diagnosis, 4,272 CPA cases had died (24.7%). Considerable regional disparities were observed in CPA mortality, which ranged from 12.2 to 48.6% (Figure 2a).

The main known risk factors observed during the same year as the CPA diagnosis were classified into CPD and thoracic interventions (supplemental material 2). COPD was diagnosed in 6,301 patients (36.4%), emphysema in 2,447 (14.2%), bronchiectasis in 2,577 (14.9%), lung cancer in 1,852 (10.7%), lung TB in 1,428 (8.2%), lung TB scarring in 1,061 (6.1%), NTM lung infection in 406 (2.3%), lung

sarcoidosis in 261 (1.5%) and lung fibrosis in 882 (5.1%). The proportion of underlying COPD or emphysema, TB, and NTM lung infections according to department of residence are presented in Figures 2b, 2c and 2d, respectively. Globally, COPD and emphysema were more common in CPA cases living in Northern France, NTM lung infection those living in the French coastal areas and both NTM and TB lung infections were more common in those living around Paris. Finally, CRF, which indicates severe CPD, was diagnosed in 7,780 patients (45.0%). During the same year as CPA diagnosis, pneumothorax was diagnosed in 848 patients (4.9%) and thoracic surgeries were performed in 1,656 patients (9.6%). Diabetes and malnutrition were observed in 2,397 (13.9%) and 5,778 (33.4%) patients, respectively. Males were predominant among CPA cases with known risk factors, except for bronchiectasis (49% of males). In CPA patients with sarcoidosis, median age was lower than in the other groups (55 [45-65] *vs*. 66 [56-65]; p<0.01).

Change in annual incidence of CPA hospitalized in France

We were able to estimate the annual incidence of patients hospitalized for CPA from 2013 to 2018. This incidence increased in France from 3.41 per 100,000 inhabitants in 2013 to 3.97 per 100,000 inhabitants in 2018 (p=0.04) (Table 1 and Figure 3) with a rate of change of +16.4%. The proportion of males decreased from 63.6% in 2013 to 62.2% in 2017 (p<0.01), but the median age (65 years (56-75) globally) did not vary with time. The annual mortality rate (24.6%) and the association of a diagnosis of haemoptysis (10.6%) were also constant. The same tendencies were observed in prevalent CPA (Table 1 and Figure 3), with a considerable increase in annual prevalence from 2013 to 2018 (rate of change of +14.4%). Finally, incident cases represented more than 75% of prevalent cases (Table 1).

Change in known risk factors 5 years before CPA diagnosis

Changes in the rates of previous underlying CPD, thoracic surgery, diabetes and malnutrition in incident CPA cases (2014 to 2018) are shown in Table 2. Among the 2,022 incident CPA cases diagnosed in 2018, 43.9% had a diagnosis of COPD in the 5 previous years. The other most frequent underlying CPD were emphysema (22.2%) and bronchiectasis (17.5%), while previous TB and NTM were observed in only 2.9% of incident CPA. Finally, sarcoidosis was associated with CPA in only 1.3% of cases. From 2014 to 2018, the proportion of COPD, emphysema and lung cancer increased (p=0.05, p<0.01, and p=0.05, respectively) while the proportion of lung TB and lung TB scarring

decreased (p<0.01 and p=0.01, respectively) and other CPD did not vary. Thoracic interventions that occurred in the 5 years before CPA diagnosis were thoracic surgery, pneumothorax, and radiotherapy in 10.9, 7.5, and 2.8% of cases, respectively. Their proportions did not vary significantly from 2014 to 2018. Diabetes (15.6%) and malnutrition (44.2%), which contribute to morbidity, were frequent in the 5 years before CPA diagnosis. The proportion of malnutrition increased from 2014 to 2018, while the proportion of diabetes remained stable.

Factors associated with mortality during the first hospitalization, at 1 year and at 5 years following CPA diagnosis

- Univariate analysis of prognostic factors associated with mortality in 2013 incident CPA cases

In the 1,705 incident CPA cases hospitalized in 2013, the mortality rates for the first hospitalization, at 1 year, and 5 years of follow-up were 16.7%, 32.1%, and 44.8%, respectively (Figure 4a). In univariate analysis, older age, male gender, malnutrition, lung cancer history and type of CPD (COPD *vs*. TB and NTM lung infections *vs.* sarcoidosis) significantly affected the 5-year mortality rate (Figures 4b, 4c, and 5). All of these variables were included in the multivariate analysis.

- Multivariate analysis of mortality during the first hospitalization and at 1 year, in 2013 to 2017 pooled CPA incident cases

During the first hospitalization, the risk of mortality was higher in patients older than 65 years (HR=1.62 CI95% [1.32-1.98]), males (HR=1.51 [1.21-1.89]), and those with malnutrition (HR=2.49 [2.05-3.04]), diabetes (HR=1.78 [1.37-2.30]), lung cancer history (HR=2.01 [1.51-2.68]), and in patients with COPD or emphysema compared to those with TB or NTM lung infection (HR=2.37 [1.61-3.48]) (Figure 6).

Factors associated with the risk of 1-year mortality were the same, but there was a marked increase in patients with COPD or emphysema compared to patients with TB or NTM lung infection (HR=1.66 [1.28-2.14]) (Figure 6).

- Multivariate analysis of mortality at 5 years in 2013 CPA incident cases

Apart from diabetes, all of the previously mentioned factors were associated with mortality at 5 years. The risk was increased in patients with COPD or emphysema compared to patients with TB or NTM lung infection (HR=1.72 [1.13-2.62]), (Figure 6).

Discussion

This study is, to the best of our knowledge, the largest published cohort of CPA cases hospitalized in a country with a low TB incidence. This work is also unique in that it uses a nationwide database, providing a 10-year overview of CPA prevalence. We found that in France, CPA was more commonly associated with COPD, emphysema, lung cancer, or lung fibrosis than the more typical mycobacterial lung diseases. CPA mortality was related to the distribution profile of underlying CPD.

The prevalent rate of CPA in France was consistent with the limited data available for other low TB incidence countries [17]. We can note that the CPA prevalence rate in the present study was slightly lower than another French study by Gangneux *et al*. [27] (4.30 *vs*. 5.24/100,000 population in 2014), which was predictable since our study was limited to patients admitted to hospital. The increase in CPA prevalence and incidence rates from 2009 to 2018 confirms the urgent need to focus more resources on this long-neglected infection, which is the cause of considerable mortality, morbidity and financial cost [6, 7]. Globally, incident cases represent three quarters of the population with prevalent CPA. This proportion was constant from 2013 to 2018, highlighting two challenges: the early mortality of CPA patients and the lack of follow-up. Seeing as the change in prevalence (14.4%) is close to the change in incidence (16.4%), it can be assumed that the duration of the disease did not change over the period. Indeed, the one-year mortality rate was stable, which supports this hypothesis.

The use of the PMSI database may have led to an over-estimation of CPA prevalence, notably by including patients with invasive aspergillosis associated or not with severe influenza or long-term use of corticosteroids, in patient with ABPA or *Aspergillus* colonization. Nevertheless, coding quality was checked in a standardized manner by medical information professionals in each hospital to correct diagnoses and improve the level of comorbidity recording (PMSI internal quality assessment).

Moreover, the medical record revision we performed in 150 CPA patients found miscoding in less than 8% of cases (data not shown). The only comparison we could make in the literature is with the French study by Gangneux *et al*. [27], and it was reassuring to see that the difference in the prevalence of CPA in 2014 between our study and Gangneux *et al.* does not suggest the over-estimation of in CPA our work. Finally, the increase of CPA incidence and prevalence during our study period could also reflect the better recognition and thus screening of CPA. The better recognition is a result of the studies [21, 28–30], reviews [1, 31, 32] and guidelines [9, 33] published in the last 10 years.

Hospitalized CPA cases were mainly found in French departments with intensive farming activity [26], confirming the theory that *Aspergillus* spp. contamination occurs in a person's living environment [34]. Nonetheless, CPA cases, particularly those complicating mycobacterial infections, also occurred around cities. Notably, the three largest French cities had significant rates of prevalent CPA, higher than 27 per 100,000 inhabitants. Indoor *Aspergillus* spp. exposure has been shown in urban environments [35], and high temperatures and demolition activities increase the risk of spore inhalation [36]. The variation observed in the geographic distribution of mortality rates revealed an important regional disparity in access to healthcare, penalizing rural departments in France. It may also be partly explained by the different geographic distribution of underlying CPD. As expected, TB and NTM lung infections were more frequent around the French capital [37] and coastlines [38] respectively, whereas COPD and emphysema were more frequent in Northern France where smoking prevalence is the highest [39].

In the current study, CPA clearly occurred as a complication of CPD or conditions weakening respiratory tracts. Contrary to previous studies performed in high TB incidence countries [13, 14], French cases of CPA more commonly complicated non-mycobacterial lung diseases. For instance, in CPA incident cases hospitalized in 2018, the proportions of COPD, emphysema, and bronchiectasis during the five previous years were 44%, 22% and 17% respectively. On the contrary, only 3% of CPA patients had been previously diagnosed with TB or NTM lung infections. The low proportion of mycobacterial diseases and its decrease in underlying CPD in our study may be explained by the falling incidence of TB in France.

Our study highlighted the alarmingly high mortality rate of CPA patients, that is to say a 5-year mortality rate of 45% among incident CPA cases hospitalized in 2013. Surprisingly, 17% of incident

cases died during the first hospitalization for CPA, highlighting that this disease is often diagnosed too late. Previously diagnosed CPD also significantly influenced mortality rates, since nearly half of CPA cases secondary to emphysema or COPD (49%) and sarcoidosis (44%) died five years after CPA diagnosis, compared with only 27% when CPA occurred secondary to mycobacterial lung infection. The follow-up and the specific treatment for certain CPD, such as inhaled corticosteroids, may also explain the differences in prognosis. Unfortunately, the PMSI database does not provide data relative to patient medications, but this important aspect will be explored in an upcoming study.

In a cohort of 387 CPA patients, Lowes *et al*. also demonstrated the poor prognosis of CPA (38% mortality at 5 years), and the negative impact of age and previous COPD [30]. Our study highlighted the impact of patient history, particularly age, sex, malnutrition and history of lung cancer, as independent risk factors for death at different times. Lowes *et al*. also identified malnutrition and age as risk factors for death. Moreover, CPA led to considerable morbidity in the 5 years of follow-up. We were not able to access to information in the PMSI concerning spirometry, which would have been useful for the evaluation of CPD severity. We therefore included the ICD-10 diagnosis of CRF to estimate the severity of CPA and CPD, and the ICD-10 diagnosis of malnutrition to assess the overall health condition more globally than with CRF. Considering that nearly half of the patients were previously affected by CRF when CPA was diagnosed, morbidity increased further over the following five years. Notably, one third developed malnutrition, which contributed to their poor prognosis. Hence, given the level of morbidity before and after CPA diagnosis, including CPD and their specific treatments, malnutrition, and diabetes [19, 30], the alarming mortality rate could also be due to underlying conditions in addition to aspergillosis. This hypothesis is supported by Uzunhan *et al.*, who found that the death due to CPA complicating sarcoidosis was due more to the underlying sarcoidosis than CPA [19]. In any event, high mortality and morbidity rates should justify specific screening for CPA, particularly in COPD and emphysema patients. This screening could reflect the approach used by Page *et al.* in treated TB patients with residual cavitation [14], which was based on thoracic imagery, mycology culture of good quality respiratory samples, and anti-*Aspergillus* IgG detection. The aim is to start CPA management earlier and to limit morbidity and mortality from all causes.

The use of PMSI database may have led to an underestimation of lung diseases such as COPD, emphysema, bronchiectasis, which can be managed in non-hospital settings. Since our study population was an exclusively hospitalized population, our results cannot be generalized to all CPA,

but only to hospitalized CPA. The worrying results in the epidemiology of hospitalized CPA cases described in our study only represent the visible part of the iceberg without taking into account non-hospitalized nor non-diagnosed CPA. We have deliberately chosen to not include the very specific population of cystic-fibrosis (CF) patients among our CPA population in order to limit the risk of CPA miscoding in CF patients with ABPA. The CPA prevalence we report among bronchiectasis patients may be underestimated.

This novel 10-year nationwide study of hospitalized CPA cases presents data for 17,290 patients hospitalized for CPA in a low TB incidence country. Our results suggest that CPA is on the rise in France, and it was more commonly associated with COPD, emphysema, and lung cancer than with mycobacterial lung infections. Underlying CPD such as COPD or emphysema worsen CPA prognosis. The alarming morbidity and mortality rates associated with CPA justify specific screening for CPA in some CPD. The absence of specific ICD-10 diagnosis for CPA reveals a lack of knowledge of this emerging disease. This omission must be corrected in order to facilitate worldwide epidemiological surveillance of each aspergillosis disease.

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Conflict of Interest

Cendrine Godet received consultancy or speaker fees, travel support from Pfizer, Astellas, Gilead, MSD, SOS Oxygene, Elivie, Pulmatrix and ISIS Medical. Thomas Maitre, Jonathan Cottenet, Adrien Roussot, Nafiz Abdoul Carime, Vichita Ok, Antoine Parrot, Philippe Bonniaud, Catherine Quantin, and Jacques Cadranel report no conflict of interest.

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TABLE 1: Annual prevalence and incidence rate of Chronic Pulmonary Aspergillosis in France

		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	p
Prevalence	**Population A**	1,451	1,537	1,733	1,794	1,842	1,821	1,951	1,922	2,045	2,100	<0.01
	Population B	388	393	458	499	445	455	464	470	511	587	<0.01
	Prevalent cases*	1,759	1,857	2,091	2,174	2,190	2,156	2,318	2,280	2,421	2,558	<0.01
	Prevalence rate (per 100,000 population)	3.59	3.77	4.23	4.38	4.39	4.30	4.60	4.51	4.77	5.02	<0.01
	Male (%)	63.2	65.6	64.1	63.1	62.5	62.2	61.7	61.9	61.3	63.2	0.02
	Age, median [IQ]	64 [54-74]	64 [54-75]	64 [55-74]	65 [55-75]	65 [55-74]	65 [56-75]	65 [56-75]	66 [57-75]	66 [57-75]	66 [57-75]	<0.01
	Haemoptysis associated to CPA ** n (%)	177 (10.06)	192 (10.34)	243 (11.62)	237 (10.90)	230 (10.50)	218 (10.11)	250 (10.79)	277 (12.15)	275 (11.36)	275 (10.75)	0.25
	Haemoptysis in main diagnosis ** n (%)	72 (4.09)	78 (4.20)	88 (4.21)	92 (4.23)	84 (3.84)	89 (4.13)	84 (3.62)	110 (4.82)	86 (3.55)	95 (3.71)	0.37
	In-hospital mortality n (%)**	399 (22.68)	407 (21.92)	490 (23.43)	525 (24.15)	520 (23.74)	465 (21.57)	523 (22.56)	513 (22.50)	512 (21.15)	574 (22.44)	0.19
	In-hospital mortality during the first hospitalization n (%)	263 (14.95)	254 (13.68)	335 (16.02)	342 (15.73)	335 (15.30)	311 (14.42)	363 (15.66)	330 (14.47)	339 (14.00)	407 (15.91)	0.93
Incidence	**Incident cases**					1,705	1,642	1,792	1,755	1,910	2,022	<0.01
	Incidence rate (per 100,000 population)					3.41	3.27	3.56	3.47	3.76	3.97	0.04
	Male (%)					63.6	62.9	63.0	62.5	62.2	63.5	<0.01
	Age, median [IQ]					65 [55-74]	65 [56-75]	66 [57-75]	66 [57-76]	67 [57-75]	66 [58-75]	0.76
	Haemoptysis associated to CPA ** n (%)					167 (9.79)	154 (9.38)	191 (10.66)	205 (11.68)	216 (11.31)	213 (10.53)	0.97
	Haemoptysis in main diagnosis ** n (%)					53 (3.11)	62 (3.78)	62 (3.46)	73 (4.16)	64 (3.35)	68 (3.36)	0.10
	In-hospital mortality n (%)**					438 (25.69)	389 (23.69)	461 (25.73)	428 (24.39)	447 (23.40)	498 (24.63)	0.01
	In-hospital mortality during the first					295 (17.30)	277 (16.97)	333 (18.58)	293 (16.7)	304 (15.92)	367 (18.15)	0.37

	hospitalization n (%)

* Duplicates were deleted

**The same year as CPA diagnosis

Population A corresponded to patients hospitalized with an ICD-10 diagnosis B441 (other forms of aspergillosis), excluding patients with an ICD-10 diagnosis J458-459 (asthma) or J679 (hyper-sensitive lung disease) or J998 (ABPA), or E84 (cystic fibrosis), or Z94 (only if coded in DP) (organ or tissue transplants) in the same year.

Population B correspond patients hospitalized with an ICD-10 diagnosis B440 (invasive aspergillosis) excluding patients with an ICD-10 diagnosis: B20, B21, B22, B24, Z21 (HIV infection), D848, D849 (other immune deficiencies), T451, D898, T509, Y434 (immunosuppressive treatments), D619, D70 (neutropenia), Z949, T860, Z948, T869, T864, T861, Z943, Z942, Z941, Z940, Z944 (organ transplants + stem cells), C81, C82, C83, C84, C85, C86, C88 (lymphomas), C90 (myeloma), C91, C92, C93, C94, C95 (leukaemia), E84 (cystic fibrosis)

CPA: Chronic Pulmonary Aspergillosis

TABLE 2: Proportion of incident cases of underlying Chronic Pulmonary Diseases or conditions in the 5 years preceding the diagnosis of Chronic Pulmonary Aspergillosis

		2014	2015	2016	2017	2018	p
CPA incident cases		1,642	1,792	1,755	1,910	2,022	<0.01
		Prevalence of CPD and conditions 5 years before CPA diagnosis, n (%)					
Underlying CPD	**COPD**	689 (42.0)	729 (40.7)	689 (39.3)	833 (43.6)	888 (43.9)	0.05
	Emphysema	290 (17.7)	286 (16.0)	298 (17.0)	401 (21.0)	449 (22.2)	<0.01
	Bronchiectasis	300 (18.3)	325 (18.1)	313 (17.8)	361 (18.9)	354 (17.5)	0.77
	Lung cancer	171 (10.4)	204 (11.4)	208 (11.9)	226 (11.8)	254 (12.6)	0.05
	Lung TB	99 (6.0)	63 (3.5)	75 (4.3)	68 (3.6)	59 (2.9)	<0.01
	Lung TB scarring	132 (8.0)	104 (5.8)	122 (7.0)	125 (6.5)	104 (5.1)	0.01
	NTM lung infection	48 (2.9)	46 (2.6)	48 (2.7)	57 (3.0)	59 (2.9)	0.72
	Lung Sarcoidosis	24 (1.5)	21 (1.2)	35 (2.0)	36 (1.9)	27 (1.3)	0.67
	Lung fibrosis	112 (6.8)	102 (5.7)	118 (6.7)	117 (6.1)	120 (5.9)	0.47
Interventions in the thorax	**Pneumothorax**	110 (6.7)	105 (5.9)	128 (7.3)	159 (8.3)	151 (7.5)	0.06
	Thoracic surgery	199 (12.1)	202 (11.3)	196 (11.2)	229 (12.0)	221 (10.9)	0.49
	Radiotherapy	36 (2.2)	41 (2.3)	35 (2.0)	55 (2.9)	57 (2.8)	0.10
CRF		792 (48.2)	848 (47.3)	837 (47.7)	919 (48.1)	1044 (51.6)	0.03
Diabetes		271 (16.5)	283 (15.8)	268 (15.3)	294 (15.4)	316 (15.6)	0.45
Malnutrition		621 (37.8)	696 (38.8)	785 (44.7)	862 (45.1)	894 (44.2)	<0.01

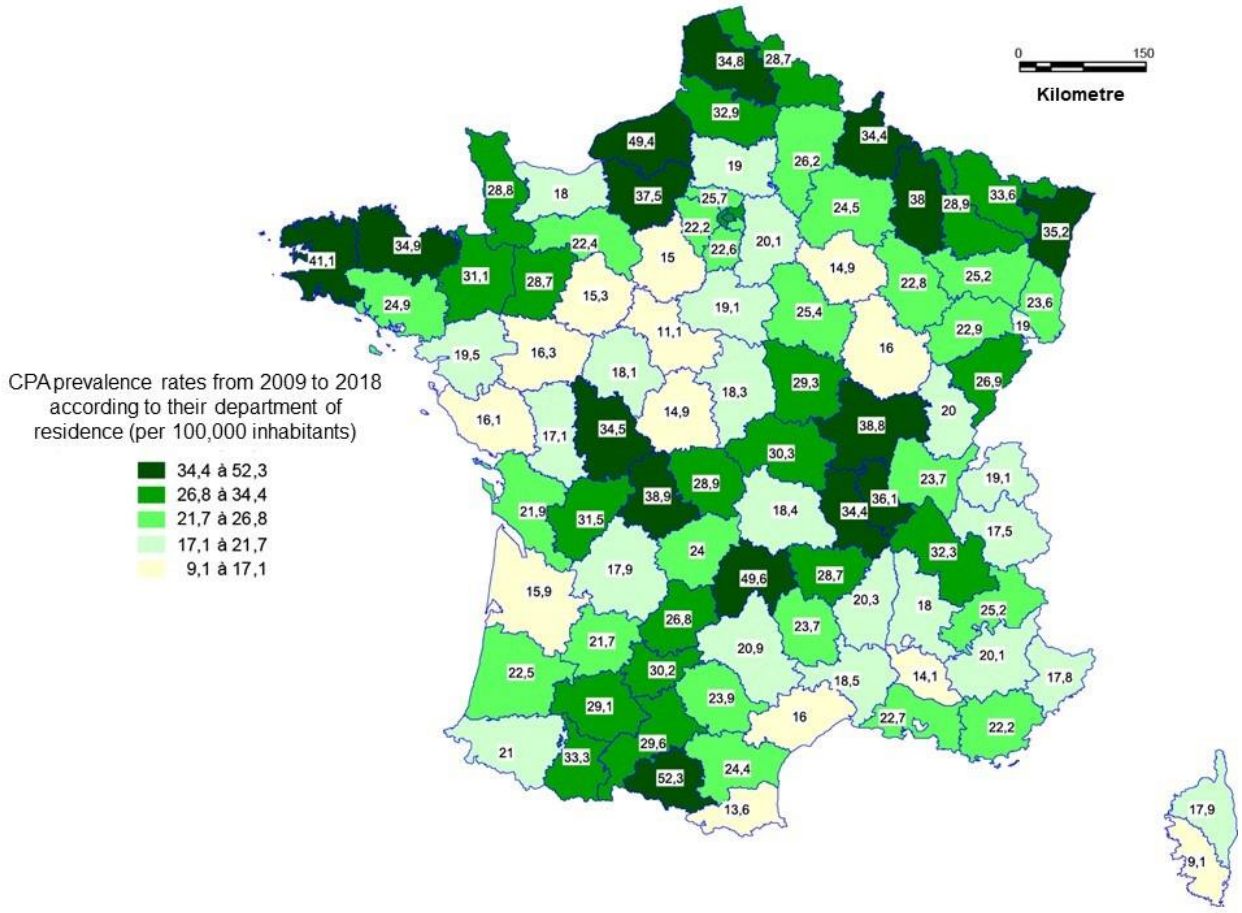
NTM: Non-Tuberculosis Mycobacteria

TB: Tuberculosis

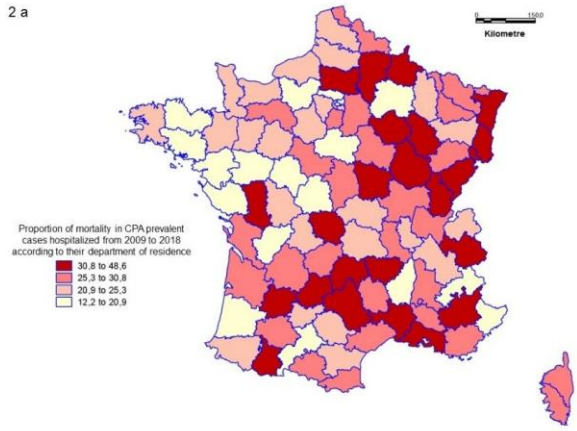
CRF: Chronic Respiratory Failure

CPA: Chronic Pulmonary Aspergillosis

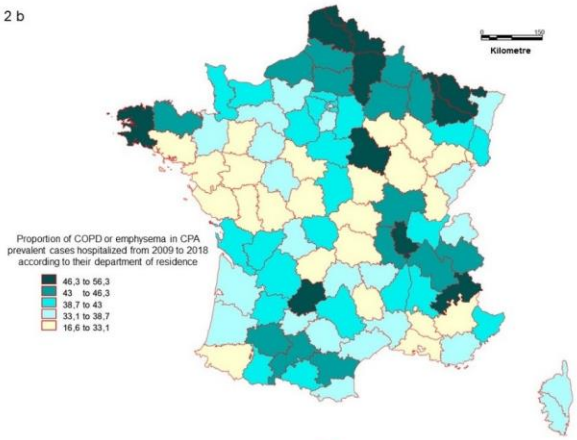
CPD: Chronic Pulmonary Disea


CPA prevalence rates from 2009 to 2018 according to their department of residence (per 100,000 inhabitants)
34,4 à 52,3
26,8 à 34,4
21,7 à 26,8
17,1 à 21,7
9,1 à 17,1
0
150
Kilometre
34,8
28,7
32,9
49,4
19
26,2
34,4
28,8
18
37,5
25,7
24,5
38
28,9
33,6
35,2
22,4
22,2
20,1
34,9
41,1
15
22,6
14,9
31,1
28,7
22,8
25,2
15,3
19,1
25,4
23,6
24,9
11,1
22,9
19
19,5
16,3
16
18,1
29,3
26,9
18,3
14,9
20
16,1
17,1
34,5
38,8
30,3
23,7
19,1
21,9
38,9
28,9
36,1
31,5
18,4
34,4
17,5
24
32,3
17,9
49,6
28,7
15,9
20,3
18
25,2
26,8
23,7
21,7
20,9
20,1
22,5
30,2
18,5
14,1
17,8
29,1
23,9
16
22,7
22,2
21
29,6
33,3
24,4
52,3
13,6
17,9
9,1

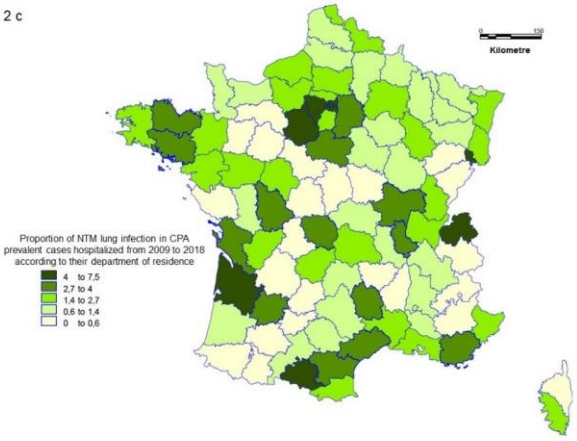
2 a


0 1500
Kilometre
Proportion of mortality in CPA prevalent cases hospitalized from 2009 to 2018 according to their department of residence
30,8 to 48,6
25,3 to 30,8
20,9 to 25,3
12,2 to 20,9

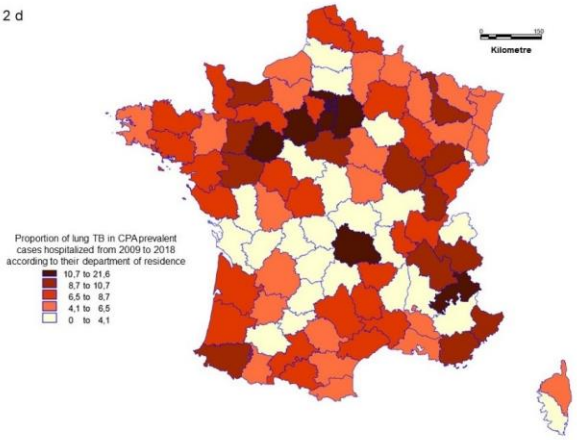
2 b

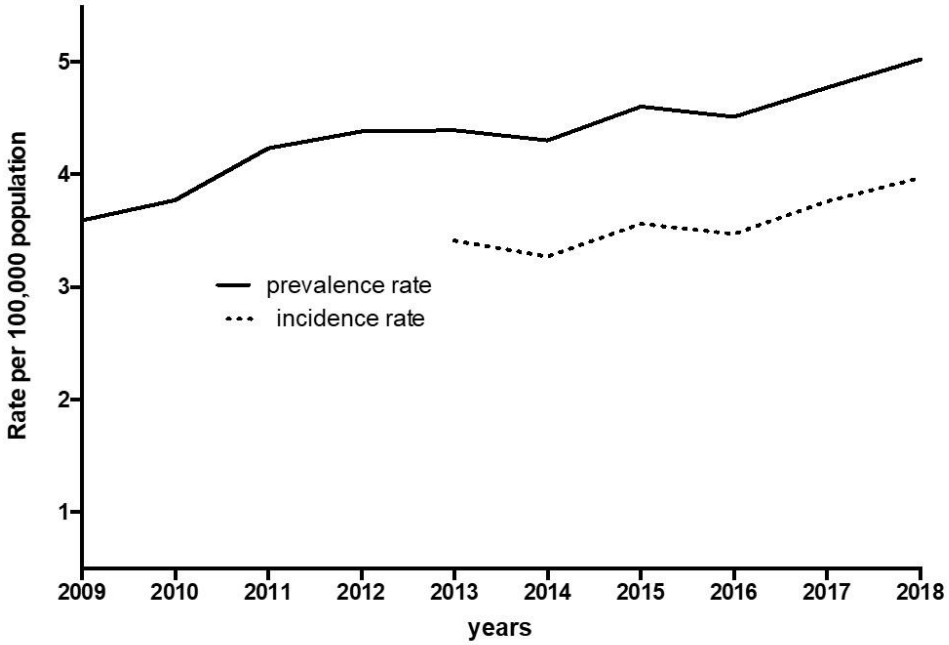

0 150
Kilometre
Proportion of COPD or emphysema in CPA prevalent cases hospitalized from 2009 to 2018 according to their department of residence
46,3 to 56,3
43 to 46,3
38,7 to 43
33,1 to 38,7
16,6 to 33,1

2 c

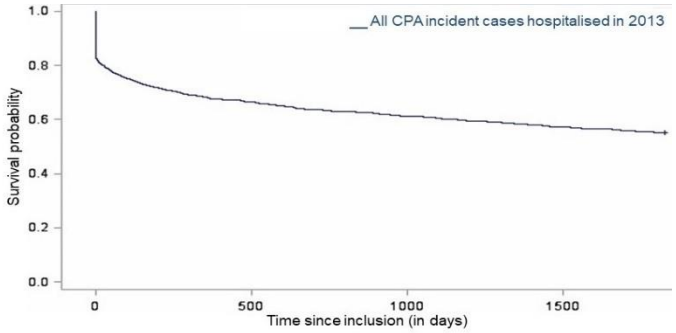

0 150
Kilometre
Proportion of NTM lung infection in CPA prevalent cases hospitalized from 2009 to 2018 according to their department of residence
4 to 7,5
2,7 to 4
1,4 to 2,7
0,6 to 1,4
0 to 0,6

2 d


0 150
Kilometre
Proportion of lung TB in CPA prevalent cases hospitalized from 2009 to 2018 according to their department of residence
10,7 to 21,6
8,7 to 10,7
6,5 to 8,7
4,1 to 6,5
0 to 4,1


Rate per 100,000 population
5
4
3
2
1
prevalence rate
incidence rate
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
years

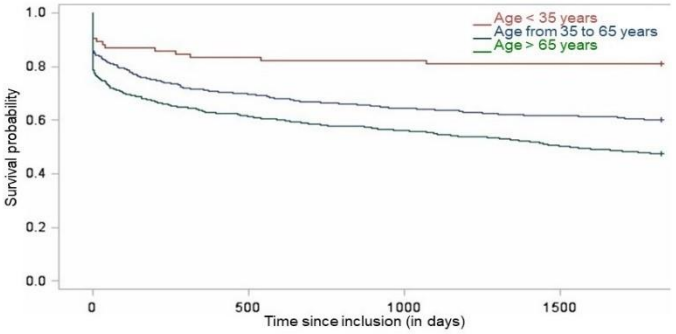
4 a



Number at risk

All CPA cases	1705	1133	1045	976

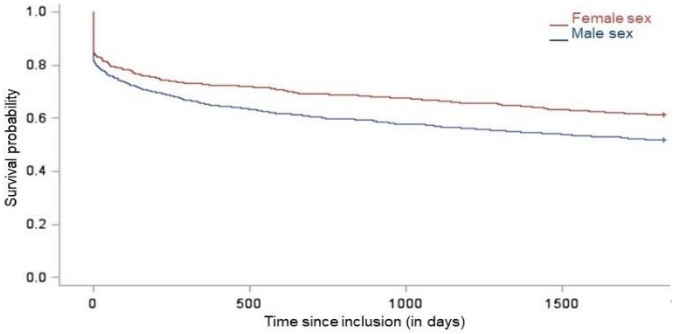
4 b



Number at risk

Age < 35 years	85	71	70	69
Age from 35 to 65 years	811	565	522	499
Age > 65 years	809	497	453	408

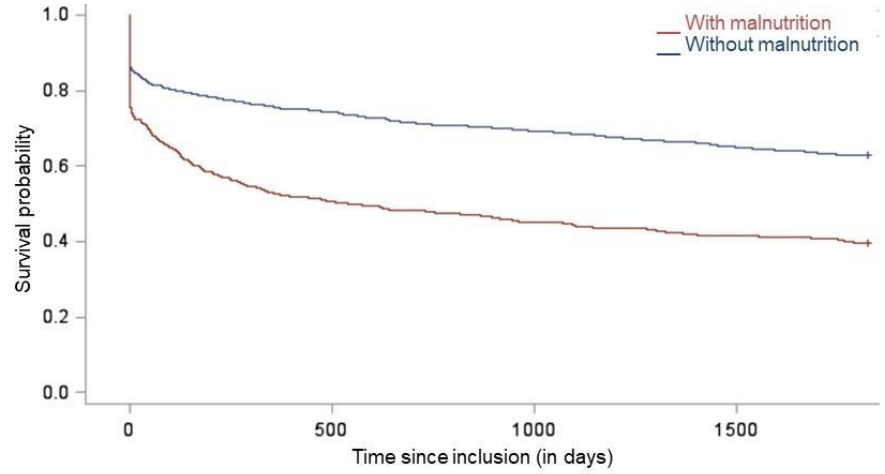
4 c



Number at risk

Female sex	620	446	418	392
Male sex	1085	687	627	584

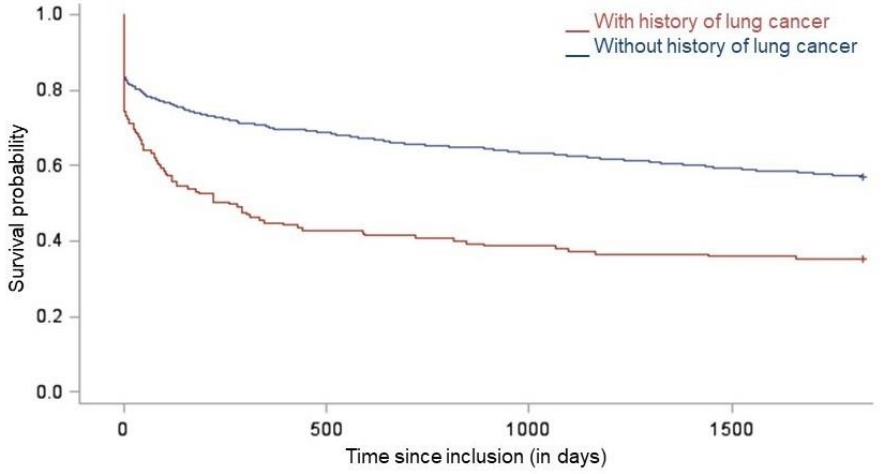
5 a



Number at risk

With malnutrition	1141	848	791	742
Without malnutrition	564	285	254	234

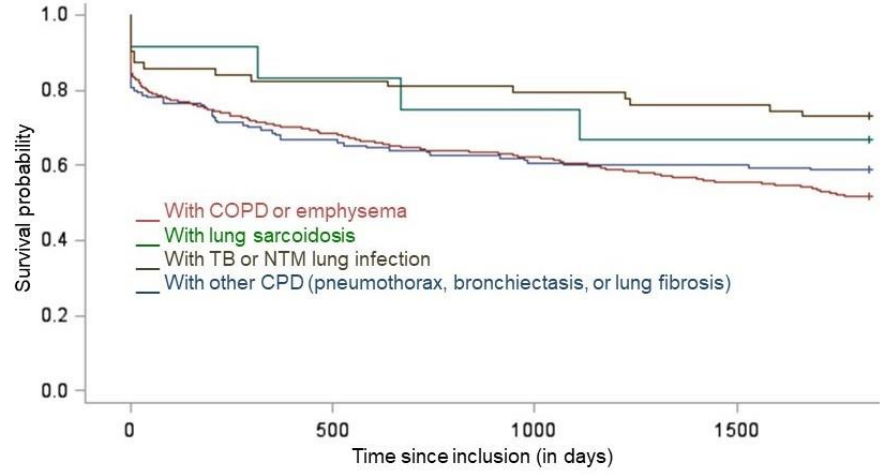
5 b



Number at risk

With history of lung cancer	145	62	56	52
Without history of lung cancer	1560	1071	989	924

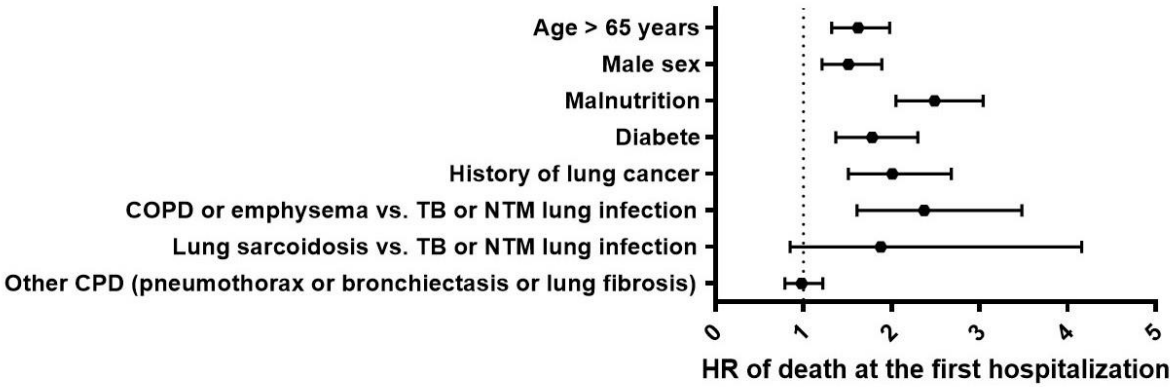
5 c



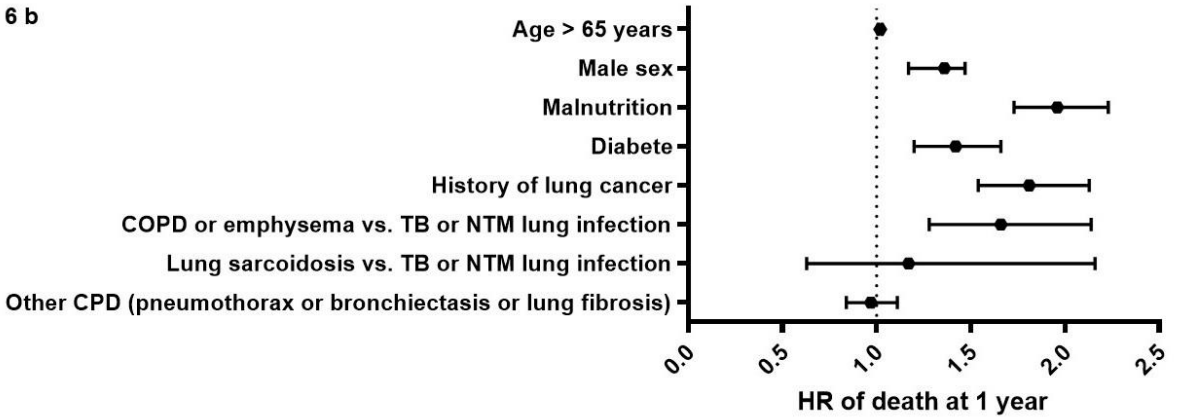
Number at risk

With COPD or emphysema	444	304	276	246
With lung sarcoidosis	12	10	9	8
With TB or NTM lung infection	63	52	50	48
With other CPD	150	100	91	90

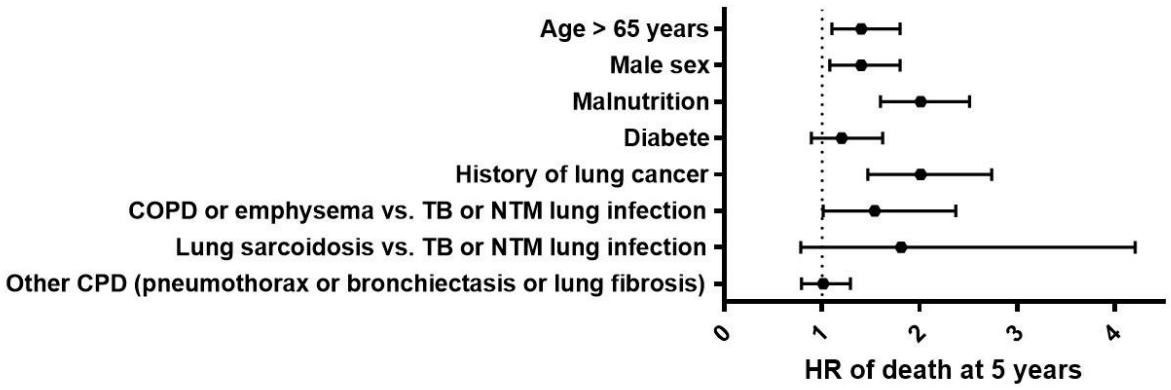
6 a


Age > 65 years
Male sex
Malnutrition
Diabete
History of lung cancer
COPD or emphysema vs. TB or NTM lung infection
Lung sarcoidosis vs. TB or NTM lung infection
Other CPD (pneumothorax or bronchiectasis or lung fibrosis)
0
1
2
3
4
5
HR of death at the first hospitalization

6 b


Age > 65 years
Male sex
Malnutrition
Diabete
History of lung cancer
COPD or emphysema vs. TB or NTM lung infection
Lung sarcoidosis vs. TB or NTM lung infection
Other CPD (pneumothorax or bronchiectasis or lung fibrosis)
0.0
0.5
1.0
1.5
2.0
2.5
HR of death at 1 year

6 c


Age > 65 years
Male sex
Malnutrition
Diabete
History of lung cancer
COPD or emphysema vs. TB or NTM lung infection
Lung sarcoidosis vs. TB or NTM lung infection
Other CPD (pneumothorax or bronchiectasis or lung fibrosis)
0
1
2
3
4
HR of death at 5 years

Supplementary Material

TABLE S1: Disease and respective ICD-10 codes identified in main or related diagnosis

Lung diseases	ICD-10 codes
Lung tuberculosis (TB)	A15, A16, and A19
Lung tuberculosis scarring	B909
Non-tuberculosis mycobacterial (NTM) lung infection	A310, A318, and A319
Lung cancer	C34
Bronchiectasis	J47
Chronic obstructive pulmonary disease (COPD)	J40, J41, J42, and J44
Emphysema	J43, and J982
Lung fibrosis	J841
Lung sarcoidosis	D860, D862, and D869
Chronic respiratory failure	J96
Pneumothorax	J93 and S270
Thoracic surgery acts	GFFC002, GFFCA017, GFFA021, GFFC006, GFFC005, GFFA05, GFFA032, GFBA004, GFBA002, GFBA001, GFBA003, GFFA014, GFFA029, GFFA009, GFFA013, GFFA026, GFFA004, GFFA027, GFFA016, GFFA006, GFFA022, GFFA008, GFFA030, GFFA033, GFFA019, GFFA018, GFFA023, GFFA010, GFFA031, GFFA015, GFFA034, GFFA012, GFFA024, GFFA011, GFFA001, GFFA025, GFFA028, GFFA002, and GFFA007
Radiotherapy acts	Z51.01 and C34
Diabetes	E10, E11, E12, E13, and E14
Malnutrition	E46, E40, E41, E42, E43, E440, and E441
Haemoptysis	R042

TABLE S2: Main known risk factors diagnosed in the same year as the diagnosis of the 17,290 CPA cases

Main known risk factors of CPA diagnosed in the same year as CPA		n (%)	Age, median [IQ]	Male (%)
Underlying CPD	COPD	6,301 (36.4)	68 [61-77]	70.4
	Emphysema	2,447 (14.2)	65 [58-73]	78.1
	Bronchiectasis	2,577 (14.9)	68 [58-77]	49.3
	Lung cancer	1,852 (10.7)	65 [58-72]	78.8
	Lung TB	1,428 (8.2)	63 [49-75]	68.8
	Lung TB scarring	1,061 (6.1)	64 [50-76]	67.1
	NTM lung infection	406 (2.3)	64 [54-73]	59.1
	Lung Sarcoidosis	261 (1.5)	55 [45-65]	59.0
	Lung fibrosis	882 (5.1)	69 [60-76]	71.2
Interventions in the thorax	Pneumothorax	848 (4.9)	60 [50-69]	73.2
	Thoracic surgery	1,656 (9.6)	57 [47-66]	70.1
	Radiotherapy	241 (1.4)	64 [58-70]	76.8
CRF		7,780 (45.0)	67 [58-76]	67.2
Diabetes		2,397 (13.9)	68 [60-76]	70.9
Malnutrition		5,778 (33.4)	66 [57-76]	66.1

NTM: Non-Tuberculosis Mycobacteria

TB: Tuberculosis

CRF: Chronic Respiratory Failure

CPA: Chronic Pulmonary Aspergillosis

CPD: Chronic Pulmonary Disease