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Impact of the COVID-19 pandemic on lung cancer diagnoses and mortality: A nationwide study in France

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ABSTRACT

Background: During the first wave of the COVID-19 pandemic, a reduction in the number of newly diagnosed cases of lung cancer has been reported worldwide, often associated with a higher proportion of cases diagnosed at an advanced stage compared with previous years.

Methods: Using the French National Hospital Database, we investigated incident lung cancer cases and their mortality during pandemic years 2020 and 2021, compared to predictions based on pre-pandemic years 2013–2019. Mortality was assessed up to 24 months following incidence date. Expected numbers of incident cases and all-cause deaths during the pandemic were estimated using Poisson regression models and survival was analyzed using Cox regressions.

Results: The database included 397,092 incident lung cancer cases in total, 20 % of whom underwent thoracic surgery. During the first pandemic wave (March–June 2020), there were 12 % i.e., 1940 fewer incident lung cancer cases than the expected figure (16,325), while no significant difference was found thereafter. Survival at 6 and 24 months improved steadily from 2013 to 2019 and continued to improve during pandemic years 2020–2021. However, during the first wave, a slight excess mortality was observed compared with predictions based on pre-pandemic trends.

Conclusions: The lower incidence observed during the first wave with no catch-up in the following periods could be explained by deaths among yet undiagnosed patients, either from COVID-19 or as a result of barriers to accessing healthcare. The excess mortality observed for both operated and non-operated patients may be attributable to delayed diagnosis, as well as to COVID-19-related deaths.

1. Introduction

Lung cancer is the most common cancer, and the leading cause of death by cancer worldwide, with 2.5 million new cases and 1.8 million deaths in 2022 [1]. Patients with lung cancer have an increased risk of death from COVID-19 compared to patients with other cancers and to the rest of the population [2–7]. Around 40 % of non-small-cell lung

cancer (NSCLC) are diagnosed at early or locally advanced stage [8]. In those patients, surgical resection is the recommended treatment as it provides the highest overall survival [9]. In recent years, lung cancer treatment methods have evolved considerably, with the development of immunotherapy and targeted therapies, which could significantly improve patient survival [10–12].

During the COVID-19 pandemic, healthcare systems were

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; HR, hazard ratio; ICD, international classification of diseases; IQR, interquartile range; PMSI, program de médicalisation des systèmes d'information; NSCLC, non-small cell lung cancer; SNDS, système national des données de santé.

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reorganized to manage patients with severe COVID-19 complications, leading to a reduction in scheduled hospitalizations for other diseases. A decrease in the number of lung cancer diagnoses – or first hospitalizations for lung cancer – has been observed worldwide during the first wave of the pandemic, to a variable extent depending on the country and period of observation [13–22]. In the months following the first wave, lung cancer incidence remained below pre-pandemic levels in some countries, including Italy, Hungary and Northern Ireland [13,15,20], while it returned to normal in England and France, with no catch-up [16, 21].

Among patients newly diagnosed with lung cancer, the risk of being diagnosed at an advanced stage was reportedly greater in 2020 compared to previous years in most studies. In South Korea, the proportion of patients with stage III–IV NSCLC increased from 58–67 % in 2017–2019 to 75 % in 2020 [23]. Findings from Italy, Ireland, Poland and Japan were similar [13,14,24–27]. Other studies, including in France, found no difference in the lung cancer stage in patients diagnosed in 2020 compared with previous years [7,21].

The impact of the pandemic on the mortality of lung cancer patients has been little explored to date. Studies based on pre-pandemic data have anticipated that possible delays in diagnosis or surgical treatment during the pandemic could lead to excess mortality at 5 years [28–30]. Among the observational studies carried out to date, a meta-analysis of studies from several countries worldwide did not find any excess mortality for patients diagnosed in 2020 compared with pre-pandemic years 2018–2019 [7]. In another study conducted in the Paris region covering the same period, no excess mortality was observed, except for the sub-population of patients in palliative care [21]. However, these studies had a limited time coverage and did not integrate longer-term mortality trends.

In the present study, we investigated the direct and indirect effects of the COVID-19 pandemic on lung cancer diagnoses and on patient mortality in France. The specific objectives were (1) to analyze trends in lung cancer incidence and all-cause mortality in France between 2013 and 2021 and (2) to explore the specific effects of the pandemic on the number of lung cancer diagnoses and on the mortality of diagnosed cases, taking into account pre-pandemic trends.

2. Materials and methods

This observational study was conducted according to STROBE guidelines [31].

2.1. Database: National health data system

The study was based on the French National Hospital Database (*Programme de médicalisation des systèmes d'information*, PMSI), from the National Health Data System (*Système National des Données de Santé*, SNDS), an exhaustive and nationwide administrative health claims database, covering 99 % of the French population, i.e., over 66 million people [32]. The PMSI covers all private and public hospitalizations [33]. All hospital stays are assigned a primary diagnosis and possibly one or more related diagnoses, coded according to the International Classification of Diseases, 10th revision (ICD10). In the PMSI, hospitalizations encompass both inpatient and outpatient admissions. Medical procedures, such as surgery carried out during hospitalization are coded according to the French medical classification for clinical procedures. A detailed presentation of the French healthcare system can be found in the 2023 Health system review by the European Observatory on Health Systems and Policies [34].

No missing data had to be processed, as all variables of interest were complete.

2.2. Design of the study

Individuals with incident lung cancer identified between January 1,

2013 and December 31, 2021 were included in the study. Mortality was assessed during the 24 months following incidence date. Incidence periods were classified as follows: a pre-pandemic period from January 1, 2013 to February 29, 2020, and three pandemic periods: from March 1 to June 30, 2020 (first wave); from July 1 to December 31, 2020; and from January 1, 2021 to December 31, 2021.

2.3. Identification of incident lung cancer patients

The population of incident lung cancer patients included all individuals aged 18 years or older, with a first hospitalization for lung cancer (ICD-10 codes C33, C34, D021 or D022) as a primary or related diagnosis during the study period. Individuals hospitalized for lung cancer in the previous 5 years were excluded in order to retain only incident cases of lung cancer. However, individuals previously hospitalized for another cancer were included.

Patients with incident lung cancer were then separated into two groups, depending on their type of treatment. Surgical treatment was identified from hospital stays with a clinical procedure relating to thoracic cancer surgery during the 3 months following their first hospitalization for lung cancer. The detailed procedure codes are presented in [supplementary material](#) (Appendix A). This categorization was used as a proxy for distinguishing early-stage from advanced-stage patients, as early-stage patients can benefit from lung surgery shortly after diagnosis, whereas this procedure is not indicated for advanced-stage patients. The population was also divided into five age groups: 18–49 years, 50–59, 60–69, 70–79, and 80 or older.

2.4. Statistical analyses

The variables of interest were the number of lung cancer diagnoses and of deaths from all causes, and the survival of incident lung cancer cases. Probabilities of dying within 6 and 24 months after diagnosis were calculated. Expected numbers of incident cases and all-cause deaths in patients diagnosed during the pandemic periods were estimated based on trends observed during the pre-pandemic period. This was done using Poisson regression models, adjusting on sex, age groups, and with a sinusoidal component to account for seasonality. National census data were used as offset for modeling the number of incident cases, and incident cases were used as offset for modeling the number of all-cause deaths. Excess deaths were estimated as the difference between observed and expected deaths in patients diagnosed in 2020–2021.

Survival analyses were computed using Cox regressions to model the risk of death at 6 and 24 months from the incidence date, adjusting on sex, age, incidence year and incidence period. The incidence period coefficients (pre-pandemic period vs. pandemic periods) were used to assess the specific effect of the three pandemic periods on mortality, taking into account the time trend. The year of diagnosis was used as a time variable, assuming a linear trend. Complementary models were run with the same adjustment variables, adding the occurrence of a first COVID-19 related hospitalization as a time-dependent covariate. Hospitalizations for COVID-19 were identified as stays with a primary or related diagnosis of COVID-19, using the ICD-10 code U07.1. Patients diagnosed between September 30, 2021 and December 31, 2021 were censored to September 30, 2023, date until which mortality data were documented in the SNDS database at the time of the analysis.

3. Results

3.1. Description of the population

Between January 1, 2013 and December 31, 2021, a total of 397,092 individuals experienced a first hospitalization for lung cancer, among whom 243,779 (61 %) deaths were observed at 24 months. The median age was 68 years (interquartile range (IQR): 61–76), and 67 % of individuals were men. Among the incident lung cancer population, 81,283

(20 %) patients underwent thoracic cancer surgery within three months of their first hospital admission. For operated patients, the average time between first hospitalization for lung cancer and initiation of surgery was 14 days. Compared to non-operated patients, those who underwent surgery were slightly younger (median age [IQR]: 66 [60–73] vs. 69 [61–77] years), with a slightly higher proportion of women (36 % vs. 32 %), and a much better survival (84 % vs. 27 % at 24 months).

3.2. Time trends in lung cancer diagnoses (2013–2021)

Over the study period, the number of incident lung cancer cases rose by 17 %, from 40,476 in 2013 to 47,217 in 2021 (Fig. 1). Women experienced a significantly greater increase than men (+43 % vs. +6 %). The number of cases rose each year until 2019, before declining slightly in 2020 and rising again in 2021.

The median age increased slightly between 2013 and 2021 (from 67 [59–76] to 69 [62–76]), as well as the proportion of operated patients (from 19 % to 22 %), whereas the time between diagnosis and initiation of surgery remained stable.

3.3. Effects of the pandemic on the number of lung cancer diagnoses

During the first wave of the pandemic (March–June 2020), the number of lung cancer diagnoses was significantly lower than would have been expected, with 1940 [95 % confidence interval (CI) 1459; 2463] fewer cases, corresponding to a deficit of 12 % [9 %; 15 %] (Table 1). This shortfall affected all age groups, but unevenly: incidence was 20 % [95 % CI: 15 %; 24 %] lower than expected in individuals aged 18–49 years, 22 % [19 %; 26 %] lower in those aged 50–59, 10 % [7 %; 13 %] lower in those aged 60–69, 7 % [4 %; 10 %] lower in those aged 70–79, and 13 % [9 %; 16 %] lower in those aged 80 or over. In the second half of 2020 and in 2021, the number of incident cases remained slightly lower than expected, but the difference was not statistically significant.

3.4. Time trends in mortality among incident lung cancer cases (2013–2021)

Survival of incident lung cancer cases improved between 2013 and 2021. Overall, the probability of dying within 6 months decreased by three percentage points in patients diagnosed in 2021 compared with those diagnosed in 2013, in both operated (from 6 % to 3 %) and non-operated patients (from 46 % to 43 %, Fig. 2). Over the same period, probability of dying within 24 months fell by eight percentage points for

Table 1

Observed and expected numbers of incident lung cancer patients during the pandemic, based on pre-pandemic trends (France, 2013–2021).

Period	Observed incident lung cancer cases	Expected incident lung cancer cases [95 % CI]	Observed - expected cases [95 % CI]	Difference in % [95 % CI]
Mar–June 2020	14,385	16,325 [15,844; 16,848]	-1940 [-2463; -1459]	-12 % [-15 %; -9 %]
July–Dec 2020	22,945	23,108 [22,495; 23,725]	-163 [-780; +450]	-1 % [-3 %; +2 %]
Jan–Dec 2021	47,217	48,197 [46,985; 49,473]	-980 [-2256; +232]	-2 % [-5 %; +0 %]

Abbreviations: CI, confidence interval

operated patients (from 20 % to 12 %) and by ten percentage points for non-operated patients (from 78 % to 68 %).

In terms of survival, we find that the 24-month survival probability improved each year from 2013 to 2019, and the trend continued in 2020 and 2021 in both sub-populations (Fig. 3). Among operated cases, the 24-month survival probability rose from 0.80 in patients diagnosed in 2013–2015 to 0.83 in those diagnosed in 2016–2017, 0.85 in 2018–2019, 0.86 in 2020, and 0.89 in 2021. Among non-operated cases, it increased from 0.22 in patients diagnosed in 2013–2015 to 0.25 in those diagnosed in 2016–2017, 0.30 in 2018–2019, 0.32 in 2020, and 0.33 in 2021.

3.5. Effects of the pandemic on mortality in patients with incident lung cancer

As shown in Table 2, non-operated lung cancer patients diagnosed between March and June 2020 experienced a slight excess mortality at 6 months post-diagnosis compared with what would be expected (hazard ratio (HR) 1.04 [95 % CI 1.01; 1.07], model 1). This excess mortality remained significant after adjusting for COVID-19 hospitalizations (model 2). Over this period, we estimated that 204 excess deaths occurred. We observed a similar excess mortality at 24 months (HR 1.04 [1.02; 1.07], model 1), with 141 estimated excess deaths. Operated lung cancer patients with an incidence date between March and June 2020 also experienced an excess mortality, at 6 months only (HR 1.22 [1.02; 1.47], model 1), with 30 estimated excess deaths.

Non-operated patients diagnosed between July and December 2020 experienced a slight excess mortality at 6 months, which was no longer significant after adjusting for COVID-19 hospitalizations (model 2), and no excess mortality at 24 months (model 1 & 2).

Among patients diagnosed between January and December 2021, those who received surgery had a lower mortality at 24 months than expected (HR 0.91 [0.84; 0.98]), while patients without surgery had a slight excess mortality, which was no longer significant after adjusting for COVID-19 hospitalizations (model 2).

4. Discussion

This population-based study analyzes the changes in the incidence of lung cancer cases and their mortality during the first two years of the COVID-19 pandemic. Based on exhaustive national patient cohorts, we demonstrate (1) an upward trend in the number of incident cases of lung cancer between 2013 and 2021, with a dip in 2020; (2) a notable deficit in the number of cases diagnosed during the first pandemic wave compared with predictions based on pre-pandemic trends, with no catch-up in the following months; (3) a steady decline in mortality for incident lung cancer cases in the pre-pandemic years 2013–2019, continuing in 2020 and 2021 despite the pandemic; and (4) a slight excess mortality for patients diagnosed during the first wave compared

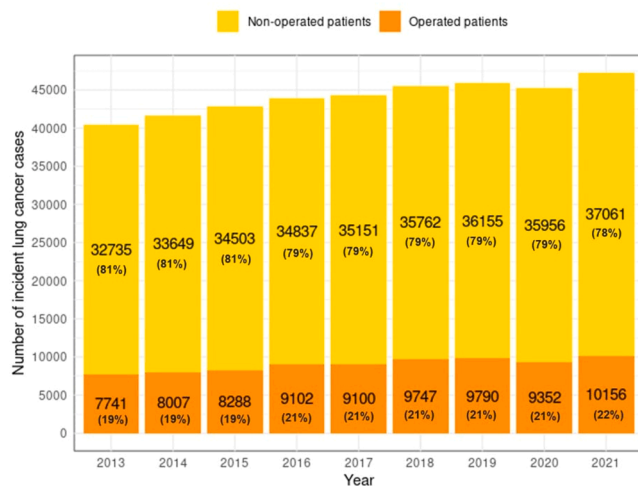


Fig. 1. Trends in the number of incident lung cancer patients (France, 2013–2021).

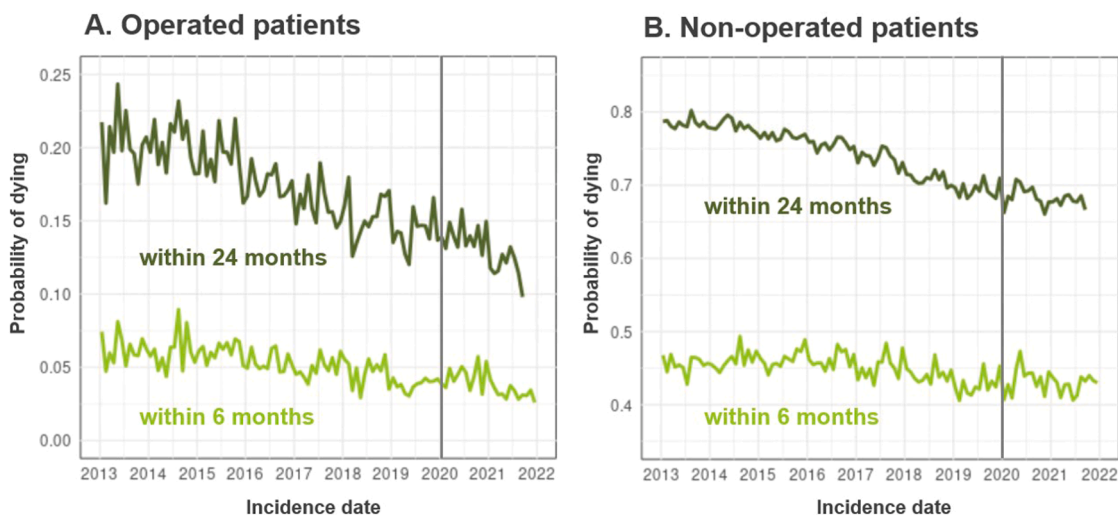
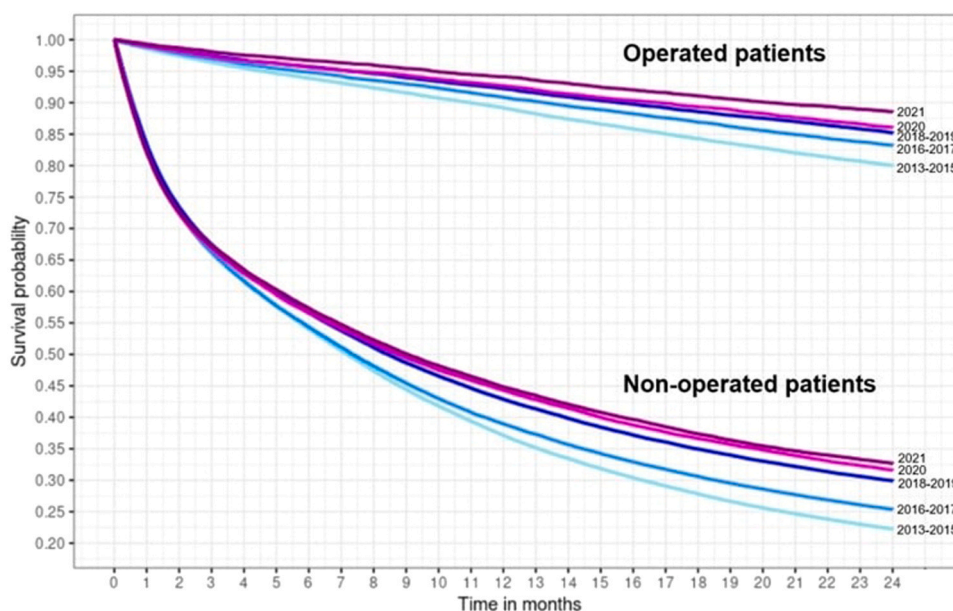


Fig. 2. Trends in the probability of dying from all causes within 6 and 24 months for (A) operated and (B) non-operated incident lung cancer patients, by year and month of incidence (France, 2013–2021). Note that the scale of the y-axis is different on each graph.



Year of incidence	Operated patients					Non-operated patients				
	0 month	6 months	12 months	18 months	24 months	0 month	6 months	12 months	18 months	24 months
2013-2015	24,036	22,564	21,430	20,260	19,227	100,887	54,509	37,423	28,071	22,434
2016-2017	18,202	17,266	16,535	15,820	15,145	69,988	38,047	27,245	21,419	17,752
2018-2019	19,537	18,702	18,020	17,305	16,645	71,917	40,711	30,807	25,140	21,501
2020	9,352	8,942	8,668	8,353	8,048	35,956	20,362	15,921	13,167	11,355
2021	10,156	9,823	9,558	9,249	9,008	37,061	21,249	16,604	13,848	12,198

Corresponding numbers of at-risk patients at 0, 6, 12, 18 and 24 months after the incidence date

Fig. 3. Kaplan-Meier 24-month survival curves for incident lung cancer patients, by year of incidence (France, 2013–2021). To optimize the graph readability, the years 2013–2015, 2016–2017 and 2018–2019 have been grouped together.

with predictions based on pre-pandemic trends, slowing the pace of the mortality decline.

The incidence of lung cancer has risen sharply in recent decades, in France as in many other countries [35,36]. In this study, we observe an upward trend in the number of patients diagnosed between 2013 and 2021, despite a dip in 2020 compared with 2019. Consistent with studies in the literature showing a narrowing of the incidence gap between men

and women in recent years [35,36], we observed a greater increase in women (+43 %) than in men (+6 %) between 2013 and 2021.

A number of studies have shown a decrease in the number of newly diagnosed lung cancer patients during the first year of the pandemic, varying in scale and duration between countries [13–21]. In this study, we observed a decline concentrated during the first wave of the pandemic. In line with studies carried out in several European countries

Table 2

Specific effect of the COVID-19 pandemic on lung cancer patient mortality at 6 and 24 months, taking time trends into account, by period of incidence (France, 2013–2021).

Incidence period ^a	6-month mortality				24-month mortality			
	Model 1 ^b HR [95 % IC]	Model 2 ^c HR [95 % IC]	Expected deaths [IC 95 %]	Observed - expected deaths HR [IC 95 %]	Model 1 ^b HR [95 % IC]	Model 2 ^c HR [95 % IC]	Expected deaths [IC 95 %]	Observed - expected deaths HR [IC 95 %]
Operated patients								
Mar–June 2020	1.22 [1.02; 1.47] *	1.21 [1.00; 1.45] *	105 [96; 114]	+30 [+21; +39]	1.10 [0.99; 1.22]	1.08 [0.97; 1.19]	385 [369; 401]	+36 [+20; +52]
July–Dec 2020	1.17 [1.00; 1.36]	1.07 [0.92; 1.25]	192 [177; 207]	+20 [+5; +35]	1.03 [0.95; 1.13]	0.98 [0.90; 1.07]	645 [619; 671]	+11 [−15; +37]
Jan–Dec 2021	0.92 [0.80; 1.05]	0.89 [0.77; 1.02]	363 [332; 395]	−30 [−62; +1]	0.91 [0.84; 0.98] *	0.89 [0.82; 0.96]**	983 [940; 1025]	−62 [−104; −19]
Non-operated patients								
Mar–June 2020	1.04 [1.01; 1.07]**	1.03 [1.00; 1.07] *	4869 [4803; 4937]	+204 [+136; +270]	1.04 [1.02; 1.07]**	1.03 [1.00; 1.05] *	7842 [7787; 7896]	+141 [+87; +196]
July–Dec 2020	1.03 [1.00; 1.05] *	1.01 [0.98; 1.03]	7898 [7797; 8003]	−4 [−109; +97]	1.01 [0.99; 1.03]	0.98 [0.96; 1.00]	12,411 [12,329; 12,493]	−35 [−117; +47]
Jan–Dec 2021	1.02 [0.99; 1.04]	1.00 [0.98; 1.03]	15,731 [15,509; 15,966]	+81 [−154; +303]	1.02 [1.01; 1.04]**	1.01 [0.99; 1.02]	18,803 [18,663; 18,940]	+257 [+120; +397]

Abbreviations: HR, hazard ratio; CI, confidence interval

Significance levels: *p<0.05, **p<0.01

^a Reference period: 01/2013–02/2020 (pre-pandemic period)

^b Cox regression models, adjustment variables: sex, age group, incidence year, incidence period (coefficient shown in the table)

^c Cox regression models, adjustment variables: sex, age group, incidence year, incidence period (coefficient shown in the table), COVID-19 hospitalization

[13,15,16,20,21], we did not observe any catch-up in the following months, as the number of incident cases remained slightly lower than expected. As the incidence of lung cancer is mainly determined by cumulated exposure to tobacco over decades and has no reason to change abruptly, this finding suggests that a number of lung cancer cases may have died before being diagnosed [20]. Some may have died of COVID-19, as lung cancer patients have an increased risk of death once infected, compared with the rest of the population [2–7]. In addition, undiagnosed cases, being unaware of their disease, may have been less vigilant in applying preventive measures than diagnosed cases. Other cases may have died of other causes, possibly due to reduced access to care during the first wave.

Secondly, we found a substantial improvement in lung cancer patient survival over the period extending from 2013 and 2019, and the trend has continued in 2020 and 2021 despite the pandemic. Overall, between 2013 and 2021, there was a slight decrease in the probability of dying within 6 months, and a greater decrease in the probability of dying within 24 months, for both operated and non-operated patients. This finding is consistent with the literature [37–40], and the decline can be explained primarily by recent therapeutic improvements, including immunotherapy and targeted therapies, which were shown to considerably improve patient survival. Preliminary results from a French study showed a rise in the two-year survival from 21 % to 48 % between 2000 and 2020, attributable to therapeutic advances including immunotherapy [41,42]. Another study in the United States showed a reduction in NSCLC mortality of 6 % per year between 2013 and 2016, linked to the development of targeted therapies [37].

The pandemic did not reverse the downward trend in mortality among patients with incident lung cancer, but it slowed it down. This is highlighted by the slight excess mortality observed among patients diagnosed between March and June 2020, compared with what would have been expected. Delays in diagnosis or treatment are likely to explain this excess mortality, as the strain on the healthcare system during the first wave of the pandemic has impacted the care trajectories of lung cancer patients, with the postponement of screening and lung nodule investigations [43]. In the literature, the link between early

treatment and the prognosis of lung cancer patients has been well established [44–46]. A number of studies have observed a higher proportion of patients diagnosed with stage III or IV lung cancer during the first wave of the pandemic compared with pre-pandemic years [13,14, 23,24,26,27]. In our study, however, the proportion of patients undergoing surgery did not fall during the pandemic, indicating a relative stability in the proportion of early stage patients. After the first wave, we observed a slight excess mortality at 6 months in non-operated patients diagnosed in the second half of 2020, and at 24 months in non-operated patients diagnosed in 2021, but this was no longer significant after adjusting for COVID-19 hospitalizations, suggesting that the excess mortality was directly related to COVID-19 deaths.

This study has several limitations. First, as the database does not contain clinical data at the individual level, we were unable to identify patients' tumor stage. However, categorizing patients according to whether or not they had received thoracic surgery seems to be a good marker of the severity of their disease, as shown by the difference in the probability of survival at 24 months between the two groups. Second, we used hospitalizations as a proxy for severe COVID-19 episodes, which is imperfect, as some individuals may have died from COVID-19 without having been hospitalized. This could therefore lead to an underestimation of the direct impact of COVID-19.

In conclusion, this study provides robust findings on lung cancer diagnoses and mortality, highlighting both direct and indirect impacts of the COVID-19 pandemic. Incident lung cancer patient mortality has declined steadily in recent years in France, and the pandemic has not reversed this trend, despite a slight excess mortality compared to what would have been expected in patients diagnosed between March and June 2020, possibly due to delays in diagnosis. However, the substantial shortfall in the number of patients with newly diagnosed lung cancer during the first wave could illustrate an important effect of the pandemic, as some patients may have died before being diagnosed with lung cancer, as a direct or indirect consequence of the COVID-19 pandemic. This work reminds the importance of early diagnosis and treatment of lung cancer, and, shedding light on the vulnerability of lung cancer patients to COVID-19, calls for greater emphasis on measures to

prevent respiratory infections in individuals at risk of lung cancer, such as heavy smokers.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the Local Legislation and Institutional Requirements. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements. In accordance with European and French regulations on data protection and Ethics, the French Institute for Demographic Studies (INED) has carried out the required compliance formalities for access to administrative health databases. The French decree no. 2016–1871 of December 26, 2016 on the processing of personal data known as the “Système National des Données de Santé” (SNDS) has granted INED permanent access to the SNDS databases. All data of the SNDS are pseudonymized. Researchers and engineers affiliated with INED benefit from simplified access to data, on the condition that they follow the necessary training, respect the security measures outlined in the order of March 22, 2017 on the security framework applicable to the SNDS and accomplish any necessary procedures related to data protection compliance. JP received authorization to access SNDS databases in 2021. The research was approved by INED’s Data Protection Officer and registered in INED’s records of processing activities under references 2021-DPD-0007. JP’s processing of SNDS data is considered compliant in terms of personal data protection and ethical research.

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CRedit authorship contribution statement

Nathanaël Lapidus: Writing – review & editing, Software, Methodology. **Myriam Khlal:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition. **Maude Espagnacq:** Writing – review & editing, Methodology. **Christos Chouaid:** Writing – review & editing, Methodology, Conceptualization. **Sophie Le Cœur:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition. **Tristan Delory:** Writing – review & editing, Project administration, Methodology, Funding acquisition. **Jonas Poucineau:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Author Christos Chouaid received payments from: AZ, BI, GSK, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis, Pfizer, Takeda, Bayer, Janssen, and Amgen. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.canep.2024.102679](https://doi.org/10.1016/j.canep.2024.102679).

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