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Analyse de l'impact de la polymédication et des comorbidités chez les patients hospitalisés porteurs d'un cancer broncho-pulmonaire

Hélène Pluchart

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THÈSE

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Présentée par

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préparée au sein du **Laboratoire Translational Innovation in Medicine and Complexity**
dans l'**École Doctorale Ingénierie pour la Santé la Cognition et l'Environnement**

Analyse de l'impact de la polymédication et des comorbidités chez les patients hospitalisés porteurs d'un cancer broncho-pulmonaire

Analysis of the impact of polymedication and comorbidities in hospitalized patients with bronchopulmonary cancer

Thèse soutenue publiquement le **15 décembre 2021**,
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A mon Papa

*« Un pessimiste voit la difficulté dans chaque opportunité,
Un optimiste voit l'opportunité dans chaque difficulté »*

Winston Churchill

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Abréviations

ATC : Anatomique, Thérapeutique et Chimique

CIM-10 : Classification internationale des maladies, 10e révision (CIM-10)

PMSI : Programme de Médicalisation des Systèmes d'Information

PREDIMED : Plateforme de Recueil et d'Exploitation de Données Biomédicales

RCP : Réunion de concertation pluridisciplinaire

SNIIRAM : Système national d'information inter-régimes de l'Assurance maladie

SNDS : Système national des données de santé

TNM : Tumeur, Nodes et Metastasis

Résumé

Impact de la polymédication et des comorbidités chez les patients hospitalisés porteurs d'un cancer bronchopulmonaire

Les patients ayant un cancer bronchopulmonaire peuvent avoir des comorbidités préexistantes au diagnostic ou qui apparaissent après réalisation du traitement antitumoral. Ces comorbidités peuvent avoir un impact sur la décision de traitement antitumoral ainsi que sur la survie des patients. De plus, ces comorbidités apparues avant ou après le diagnostic peuvent entraîner de la polymédication. Cette polymédication peut potentiellement engendrer des interactions médicamenteuses avec le traitement antitumoral, et ainsi avoir une conséquence sur la prise en charge du patient.

Dans ce travail, nous nous sommes intéressés au lien entre le cancer bronchopulmonaire, les comorbidités, la polymédication, et leurs conséquences sur la réalisation du traitement systémique et sur la survie des patients. Dans une première partie, une revue narrative de la littérature a été faite et propose une synthèse des connaissances actuelles sur le lien entre ces entités, et notamment sur ce qui a déjà été décrit dans le cancer du poumon. Dans la deuxième partie, le protocole de cette étude qui est originale de par son design mais également de par son analyse statistique a été décrit. Par la suite dans une troisième partie, nous nous sommes focalisés sur les comorbidités et le calcul des scores de comorbidités. Une étude de comparaison de scores de comorbidités a été réalisée afin de choisir le score qui prédit le mieux la mortalité dans la cohorte de patients. Enfin, l'impact de la polymédication et des comorbidités sur la réalisation du traitement systémique et sur la survie médiane des patients a été étudié.

Mots-clés : Cancer bronchopulmonaire, comorbidités, polymédication, médicament, modèles de survie

Abstract

Impact of polypharmacy and comorbidities in hospitalized patients having lung cancer

Patients with lung cancer may have comorbidities that are pre-existing at diagnosis or that appear after anticancer treatment. These comorbidities may have an impact on the decision to treat with anticancer treatment as well as on the survival of patients. In addition, these comorbidities that appear before or after diagnosis can lead to polypharmacy. This polypharmacy can potentially lead to drug interactions with the anticancer treatment, and thus have an impact on the patient's management.

In this work, we assessed the link between lung cancer, comorbidities, polymedication, and their consequences on the performance of systemic treatment and on patient survival. In the first part, a narrative review of the literature was performed and we proposed a synthesis of current knowledge on the link between these entities, and in particular on what has already been described in lung cancer. In the second part, the protocol of this study, which is complex in terms of its design but also in terms of its statistical analysis has been described. Then in the third part, we focused on comorbidities and the calculation of comorbidity scores. A comparison study of comorbidity scores was carried out in order to choose the score that best predicted mortality in the patient cohort. Finally, the impact of polypharmacy and comorbidities on systemic treatment completion and median survival of patients was studied.

Keywords: Lung cancer, comorbidities, polypharmacy, medication, survival models

1. Introduction

1.1. Contexte

Au diagnostic, la médiane d'âge des patients ayant un cancer du poumon est de 70 ans [1] et 50 à 70% de ces patients ont au moins une comorbidité [2,3]. Cette forte proportion de comorbidités préexistantes au diagnostic est expliquée en partie par l'exposition au tabac, responsable de 90% des cancers du poumon [4]. Des médicaments peuvent être prescrits pour équilibrer ces comorbidités. Le questionnement sur l'impact de ces traitements et comorbidités sur la prise en charge des patients ayant un cancer bronchopulmonaire est le point de départ de la réflexion de ce travail.

1.1.1. Comorbidités

Une première définition de comorbidité a été proposée par Alvan Feinstein en 1970 qui définit le terme comme étant : « l'existence d'une entité clinique supplémentaire distincte » [5]. En cancérologie, il a été décrit que les comorbidités ont un impact sur la survie des patients, notamment car cela influence la stratégie thérapeutique [2,6,7]. En effet, les patients ayant des comorbidités sont susceptibles de moins bien supporter les cures de chimiothérapie, ou sont plus à risque de présenter une altération de l'état général ce qui peut potentiellement retarder le traitement anti-tumoral des patients et/ou altérer leur survie. Cette notion est déjà décrite dans des études sur le cancer colorectal, du sein ou de la vessie où le poids des comorbidités entraîne moins de prescription de chimiothérapie ou d'un autre traitement systémique [8–10]. Peu d'études existent dans le cancer du poumon, mais relatent également le lien inverse entre comorbidités lourdes au diagnostic et prescription de chimiothérapie [11–13].

Dans les études, la notion de comorbidité est souvent traduite sous forme de score afin d'estimer le poids de ces comorbidités sur le patient, et de faciliter l'utilisation de cette variable dans les modèles statistiques. Les différentes comorbidités sont donc résumées en un score. De très nombreux scores existent et ont été développés au fur et à mesure des années dans la littérature [14–16]. Le score de Charlson est le plus utilisé [17,18].

1.1.2. Polymédication

De ces comorbidités découlent la prescription de médicaments avec un risque de polymédication. Celle-ci est généralement définie par un seuil de 5 à 6 médicaments prescrits [19–21]. Le phénomène de polymédication a été largement décrit chez les patients ayant un cancer, et notamment chez la personne âgée [22–28]. Dans des populations de patients ayant un cancer du poumon, quelques publications récentes rapportent un nombre médian variant de 6 à 11 médicaments par patient, et 33% à 60% de patients polymédiqués [24,27,28].

Certaines molécules auraient des effets négatifs sur la carcinogénèse comme la metformine [29], ou les anti-inflammatoires non stéroïdiens [30]. Le risque d'interactions médicamenteuses avec la polymédication et le traitement anti-tumoral est discuté dans la littérature [24,31] car cela peut augmenter le risque d'effets indésirables [32] tout comme diminuer l'efficacité du traitement antitumoral [33]. La polymédication peut avoir un impact sur la stratégie thérapeutique des patients, sur l'état général du patient [34], être associée à un risque élevé d'effets indésirables après administration de chimiothérapie [35], ce qui peut entraîner des ré-hospitalisations [28,36]. Hakozaki a également décrit l'impact négatif de la polymédication sur la survie des patients ayant un cancer du poumon et recevant de l'immunothérapie [27].

1.1.3. Traitements anti-tumoraux

Les traitements peuvent quant à eux induire une toxicité et des comorbidités secondaires tout en aggravant les comorbidités préexistantes au diagnostic [37–41]. Il a été également décrit que les comorbidités peuvent favoriser la carcinogénèse [42–44], être liées à l'histologie [42,45] ou au stade selon la classification Tumor, Nodes et Metastasis (TNM) au diagnostic [46–48]. A l'inverse, le cancer du poumon et son traitement peuvent impacter les comorbidités préexistantes ou en entraîner de nouvelles [49–53].

1.2. Objectifs

En partant de la littérature, nous avons émis l'hypothèse que la polymédication et les comorbidités ont un impact sur l'administration de traitement systémique et sur la survie des patients.

Dans un premier temps, une revue de la littérature a été réalisée. Elle a pour objectif de décrire les liens entre les trois entités que sont le patient/le cancer, les comorbidités et la polymédication.

Ensuite, une étude rétrospective a inclus des patients avec un cancer broncho-pulmonaire hospitalisés entre 2011 et 2015 au CHU Grenoble Alpes. L'objectif était de décrire l'impact des comorbidités et de la polymédication sur la réalisation du traitement systémique et sur la survie.

Un article décrivant le protocole a été rédigé.

Puis nous avons recherché le score de comorbidité le plus associé à la survie à 4 mois.

Enfin, nous avons mené à bien l'étude principale qui a pour objectif de décrire, l'impact de la polymédication et des comorbidités sur la réalisation du traitement systémique, et la survie.

2. Liens entre polymédication, comorbidités et cancer

Le premier objectif de cette thèse a donc été de faire une revue exhaustive sur le sujet. Nous avons décrit les liens rapportés entre le patient/le cancer, ses comorbidités et ses traitements médicamenteux.

Ce travail est réparti en 4 parties :

- Conséquences des comorbidités sur le patient et son cancer.
- Conséquences du traitement anticancéreux sur les comorbidités.
- Conséquences du traitement médicamenteux sur le patient et son cancer.
- Conséquences du cancer sur les traitements médicamenteux.

Publication n°1

Lung cancer, comorbidities, and medication: the infernal trio

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Christos CHOUAID, Gil FREY, Julie VILLA, Bruno DEGANNO,

Matteo GIAJ LEVRA, Pierrick BEDOUCH, Anne-Claire TOFFART

Soumis

Lung cancer, comorbidities, and medication: the infernal trio

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Highlights

Comorbidities and lung cancer, which intricately affect each other, need to be considered by clinicians. Comorbidities can lead to the prescription of medication that can influence lung cancer course. Their potential impact has to be known by physicians.

Abstract

Most patients with lung cancer are smokers and are of advanced age. They are therefore at high risk of having age- and lifestyle-related comorbidities. These comorbidities are subject to treatment or even polypharmacy.

There is growing evidence of a link between lung cancer, comorbidities and medications. The relationships between these entities are complex. The presence of comorbidities and their treatments influence the time of cancer diagnosis, as well as the diagnostic and treatment strategy. On the other hand, cancer treatment may have an impact on the patient's comorbidities such as renal failure, pneumonitis or endocrinopathies.

This review highlights how some comorbidities may have an impact on lung cancer presentation and may require treatment adjustments. Reciprocal influences between the treatment of comorbidities and anticancer therapy will also be discussed.

Keywords

Lung cancer, comorbidities, medication, survival

Background

Lung cancer is often diagnosed at an advanced stage of the disease (1,2), at a median age of 70 years (3). At this age, 65% of the general population has at least two comorbidities (4). The prevalence of comorbidities for lung cancer patients is higher than that of other cancer patients, approximately 50 to 70% at diagnosis (5,6). However, little is known about lung cancer in elderly patients with comorbidities because they are excluded from most clinical trials (7).

On the one hand, comorbidities can have an impact on cancer survival (5,8,9) by influencing the therapeutic strategy. They could be responsible to an alteration of the general condition or a worse tolerance of anticancer treatments. In addition anticancer treatments can worsen or induce comorbidities (10–14).

On the other hand, comorbidities generally imply the addition of medication to the symptomatic treatment intrinsically related to lung cancer. Such medication is likely to have consequences on drug-drug interactions or non-adherence or be responsible for adverse drug reactions (15,16). Such multiple prescriptions can lead to polypharmacy (PP) (generally defined as a threshold of five medications) (17) and the administration of potentially inappropriate medications, which has been described for cancer patients, in particular, the elderly (18–20).

This paradigm concerns all cancers, and we have chosen to focus on lung cancer. Here, we review the existing literature concerning the impact of both comorbidities and medication on lung cancer patients, as well as the consequences of anticancer treatments on comorbidities (Figure 1).

A. Lung cancer and comorbidities

Comorbidity was first defined as the existence of any distinct additional clinical entity by Alvan Feinstein in 1970 (21). Comorbidity can be scored by several means. The most used in lung cancer is the Charlson Comorbidity Index (CCI), which assesses the impact of comorbidities (22). More than half (50 to 70%) of lung cancer patients have comorbidities at diagnosis (5,23). In 90% of cases (24), lung cancer is associated with tobacco consumption, which can lead to lung injury, cardiovascular diseases, and diabetes mellitus (25–27). Most lung cancer patients are over 65 years of age (3). Ageing can be associated with a decline in renal function and cardiovascular and metabolic disorders (28–30). The most frequent comorbidity of

lung cancer patients is chronic obstructive pulmonary disease (COPD) (30 to 50% of lung cancer patients), followed by diabetes (15%), congestive heart failure (12%), peripheral vascular disease (7-8%), cerebrovascular disease (7%), and renal disease (from 2 to 6%) (5,23).

We first discuss the impact of comorbidities on lung cancer and the impact of lung cancer on comorbidities.

1. Impact of comorbidities on lung cancer features (Table 1)

Certain comorbidities taken separately are reported as independent poor prognostic factors for the survival of lung cancer patients (8), such as COPD, tuberculosis, interstitial lung disease, cardiovascular diseases, and renal insufficiency. Obesity is described as a favorable prognostic factor, within the framework of “obesity paradox” described in lung cancer (31,32). While low body mass index is associated with lower survival, patients with obesity have improved survival.

Furthermore, comorbidities could induce carcinogenesis, such as COPD (33), infections (34,35), diabetes mellitus (although still debated (36)) and obstructive sleep apnea through hypoxia (37,38). Several mechanisms have been proposed, mostly oxidative damage and chronic inflammation. Comorbidities can affect various lung cancer characteristics such as histology, stage at diagnosis, and anticancer treatment.

1.1. Impact of comorbidities on histology

COPD increases the frequency of squamous cell carcinoma by four fold (33,39), whereas asthma increases the frequency of this histological subtype or of small-cell lung cancer (SCLC) by two fold (40,41). The mechanism is still unclear but may involve an altered inflammatory response and fibrogenesis. Lung cancer patients who had prior tuberculosis show a higher frequency of adenocarcinoma (approximately two-fold higher) (42), probably also due to fibrosis and inflammation (8).

Tobacco smoke has been shown to be strongly associated with SCLC and squamous cell carcinoma (proximal localization) (43). The relationship between histology and the size of inhaled smoke particles was already described in 1989, supporting the hypothesis that the biggest particles settle on cells of the epidermal bronchi and the smallest in peripheral tissue near glandular cells (44). In addition,

different molecular profiles have been described between smokers and never-smokers with non-small-cell lung cancer (NSCLC). Barlesi et al. (45) reported that nearly 44% of patients who were never smokers had a mutation in the epidermal growth factor receptor (EGFR) gene (vs. 11% in the overall population). The carcinogens contained in tobacco smoke induce, instead, loss-of-function mutations in tumor suppressor genes, such as p53 (46).

1.2. Impact of comorbidities on stage at diagnosis

Several studies have investigated how comorbidities affect the stage at diagnosis of lung cancer. However, most showed only a trend towards earlier stages for patients with more comorbidities (47–49). For 402 patients with advanced NSCLC, a significantly higher proportion of stage IIIb than stage IV was observed at diagnosis for patients with severe comorbidities (50). Dalton et al. reported similar results, showing that a higher CCI correlated with an earlier stage at diagnosis (51). However, these findings are still debated (52,53).

Lung cancer screening of smokers or COPD patients with emphysema was investigated in the NELSON, NLST, and AIR trials (54–56). These studies aimed to diagnose lung cancer at an early stage, when they are eligible for radical treatment that could improve patient survival. For example, lung cancer-specific mortality (primary outcome) was significantly lower in the screening group in the NELSON study (54).

1.3. Impact of comorbidities on treatment strategy

Surgery: Studies clearly show that surgery is preferred for patients with no or few comorbidities (47,57). For example, in the Swedish Lung Cancer Data Base (58), surgery was performed less for patients in early stages of NSCLC with a CCI ≥ 3 than those without a comorbidity. In addition, the number of comorbidities has been shown to be associated with morbi-mortality for surgically treated NSCLC patients. A CCI score of 3 to 4 was predictive of major complications (59) and a CCI of 2 to 4 with higher 90-day mortality after surgery (60). In the European Respiratory Society and European Society of Thoracic Surgery guidelines, indications for surgery depend on the morbi-mortality risk, which takes into account comorbidities (61,62). Patients can

be considered to have a low (< 1%), moderate, or high (> 10 %) risk of mortality, depending on their respiratory and cardio-vascular status. The French Society of Thoracic and Cardio-Vascular Surgery developed a risk model to predict in-hospital mortality for patients undergoing lung surgery. The most frequent comorbidities were evaluated: COPD, arterial hypertension, smoking, heart disease, peripheral vascular disease, history of cancer, and diabetes mellitus (63). Having at least three comorbid conditions was associated with lower in-hospital survival. The revised cardiac risk index is a widely used tool for cardiac risk stratification before major lung resection (64). It relies on four variables that were identified to be predictive risk factors of major cardiac morbidity (cerebrovascular disease, cardiac ischemia, renal disease, and pneumonectomy) and allows the selection of patients who need further cardiac testing. The burden of comorbidities also has an impact on the choice of surgical strategy. Patients with COPD, a history of cardiovascular disease, or a CCI ≥ 2 preferentially benefit from sub-lobar surgery rather than lobectomy (65). For patients with few comorbidities, lobectomy is preferentially offered over sub-lobar resection, because it is associated with higher overall survival (66). Video-assisted thoracoscopic surgery is preferred to open surgery for patients with severe comorbidities (67).

Radiotherapy: In early stages, stereotactic radiotherapy is more likely to be proposed for patients with severe comorbidities (CCI ≥ 3) (58). The decision to attempt curative radiotherapy increases with the CCI. However, no impact of the CCI on survival after radiotherapy has been reported (68). Radiation-induced lung injury is a common complication of radiotherapy. In 1998, Monson et al. found that pre-existing comorbid lung disease increases the risk of radiation pneumonitis (69) and that tobacco consumption is responsible for more extensive lung injury. Cardiac comorbidity has been found to be associated with a higher risk of radiation-induced lung injury than for patients with no prior cardiac comorbidity (70). However, the impact of these comorbidities on radiation-induced lung injury is also still debated (71).

Pharmacological treatment: In terms of chemotherapy-related toxicity, the choice of molecule should be very carefully made to not worsen patients' comorbidities. The number of comorbidities has an impact on pharmacological treatment (72) and chemotherapy in NSCLC is less prescribed as the number of comorbidities increases (50,67,73). Patients with high a comorbidity score are more likely to have

complications after chemotherapy. NSCLC patients with severe comorbidities have been shown to be more likely to have a higher frequency of thrombocytopenia, febrile neutropenia, or death after neutropenic infections than those without comorbidity (50). Another study reported that patients with comorbidities have a higher risk of developing grade 3 to 5 gastro-intestinal, cardiovascular, and infectious adverse events, rash, and nausea (74). In addition, cardiovascular disease and diabetes increase the risk of cisplatin-induced nephropathy (75).

Immune oncology treatments, such as immune-checkpoint inhibitors that target programmed cell death (PD)-1, PD-ligand (PD-L) 1, or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are routinely used in lung cancer. Given the protective role of PD-(L)1 signaling in immune tolerance (76), auto-immune diseases can appear or worsen with PD-(L)1 inhibitors. It is very important to identify the risk of dysimmunity before prescribing immune-checkpoint inhibitors (77). Patients with auto-immune diseases have been excluded from phase 3 clinical trials testing immune oncology therapies. Therefore, prescribing this therapeutic class in the context of a pre-existing auto-immune disease can only be considered after multidisciplinary consultation. It has been reported that preexisting interstitial lung disease is associated with higher incidence of immune-related pneumonitis (78). The indication of immune-checkpoint inhibitors in these patients should be discussed in a multidisciplinary setting.

While some cytotoxic drugs prescriptions such as platin salts are capped if body surface area is superior to 2 square meters, the question of obesity impact on flat doses for immune oncology treatments arises. In obesity, blood volume increases but less than proportional with the change in body weight. Given that monoclonal antibodies distribute only in the blood plasma and extracellular fluids, for some of them, body weight does not have a significant impact on the volume of distribution. In that situation, flat doses can be justified in this population, as described in the updated ASCO recommendations on therapy dosing in obese patients (79,80). More interestingly, in some studies obese patients receiving PD-1 inhibitors show better survival than nonobese patients, this may be due to increased PD-1 expression through leptin higher levels (81).

2. Impact of lung cancer treatment on comorbidities (Table 2)

After lung cancer treatment, it is important to distinguish temporary side effects from lasting comorbidities. This section will focus on the effect of lung cancer treatment in the exacerbation of pre-existing primary comorbidities or those that lead to irreversible secondary comorbidities.

2.1. Impact of surgery on comorbidities

Resection of lung cancer can have a consequence on pre-existing comorbidity. Indeed, reduction of lung parenchyma and altered pulmonary function can provoke acute exacerbation of interstitial pneumonia or phrenic nerve paralysis, leading to long-term decreased pulmonary function (82). Cardiovascular complications are also frequent such as myocardial infarction, atrial fibrillation can require antiplatelets or anticoagulants prescription (83,84). Principal risk factors identified for postoperative morbidity include decreased forced expiratory volume in one second, smoking, age and pre-existing cardiovascular disease (85–87).

2.2. Impact of radiotherapy on comorbidities

In the six months following lung irradiation, irreversible radiation pneumonitis appears in up to 25% of cases, potentially complicated by fibrosis (1 year after) (10). Glucocorticoids can be proposed for radiation pneumonitis, whereas patients with radiation pulmonary fibrosis should be given supportive care (10).

Cardiac toxicity has also been described with radiotherapy: effusion, unstable angina, myocardial infarction, and arrhythmias (88). In addition, chemoradiation has been reported to be an independent risk factor of conduction disorders, cardiac dysfunction, and heart failure (89).

2.3. Impact of chemotherapy on comorbidities

Patients with lung cancer have a high risk of venous (90,91) or arterial (92) thrombosis, which increases with chemotherapy (93). Furthermore, chemotherapy-related hepatotoxicity can lead to the activation of prothrombotic processes, as the liver is responsible for natural anticoagulant protein synthesis (94). Cisplatin, through the release of procoagulant endothelial microparticles (95), has been reported to be associated with thromboembolic events (96).

Chemotherapy can also induce chronic cardiac toxicity (97). Chemotherapy is an independent risk factor of ischemic heart disease, cardiac dysfunction, and heart failure in older NSCLC patients (89). Cisplatin is associated with arrhythmias and cardiomyopathy (98,99), which are probably related to electrolyte abnormalities subsequent to its nephrotoxicity (100,101). Vinka-alkaloids can lead to arrhythmias and acute myocardial infarction (99), which may be due to a direct effect on myocardial cells, leading to hypoxia and acute coronary artery spasm (99). Other anti-microtubule agents, such as paclitaxel, docetaxel, and etoposide, are also involved in chronic heart failure, acute myocardial infarction, bradycardia, and hypotension (99). Anthracyclines are less prescribed in lung cancer but their cardiac toxicity is the most described (102). They can induce heart failure, left ventricular dysfunction, pericarditis, and acute myocardial infarction (11,98,99).

Nephrotoxicity is another side effect. Half of patients require dose adjustment based on the alteration of renal function (103). Chronic kidney disease occurs in approximately 2/3 of lung cancer patients treated with chemotherapy. For example, 30% of lung cancer patients experience renal toxicity with cisplatin (101). Cisplatin and pemetrexed can induce acute tubular damage and tubulopathies (12,104), which can lead to irreversible chronic kidney disease. Gemcitabine induces glomerular toxicity (104), with only partial recovery of kidney function. Microangiopathy thrombosis has been described for patients treated with gemcitabine (endothelial injury and reduced ADAMTS-13 (von Willebrand factor protease (105)) or cisplatin (12).

2.4. Impact of anti-angiogenic therapies on comorbidities

Bevacizumab is associated with arterial thrombosis and venous thromboembolism (106,107). However, a recent meta-analysis reported possible overestimation of vascular adverse events of the anti-angiogenic therapies in open-label studies (108).

Bevacizumab can also induce glomerular toxicity, most often due to thrombotic microangiopathy (12,104). Epithelial renal cells produce vascular endothelial growth factor, which binds to its receptor localized on glomerular cells (109). Prevention of such binding induces hypertension and kidney-specific injury (proteinuria) (12). Proteinuria (any grade) occurred for 29 to 33% of patients with NSCLC treated with bevacizumab and chemotherapy and hypertension in 30% of patients (13).

2.5. Impact of oral targeted therapies on comorbidities

EGFR and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs), prescribed in stage IV NSCLC, are less responsible for chronic adverse events. The main adverse events of ALK TKIs are cardiovascular effects: QT prolongation (110), bradycardia (111), thrombotic events (112), or hypertension (111). Osimertinib (EGFR TKI) can also induce cardiac failure, atrial fibrillation, and QT prolongation (113). A common toxicity of all TKIs is interstitial lung disease (112), which may be a hypersensitivity pneumonitis (114).

2.6. Impact of immune checkpoint inhibitors on comorbidities

As discussed above, PD-1 or PD-L1 inhibitors can either provoke an auto-immune disease flare or lead to the onset of auto-immune diseases (115). The main adverse events that occur with immune oncology treatments are hypothyroidism, rash, colitis, arthritis, hepatitis, pneumonitis, and endocrine and musculoskeletal disorders (115). Depending on their severity, these immune-related adverse events can be managed with symptomatic treatment, corticosteroid therapy (or other immunosuppressive treatments), or discontinuation of the immune checkpoint inhibitor (116).

Endocrinopathies occur frequently in patients treated with immune checkpoint inhibitors, particularly hypothyroidism, which occurs for up to 40% of all tumor types (14,117), and may require hormone substitution (118). Hypophysitis (combination of hypothyroidism, adrenal insufficiency, and hypogonadism) (14) and type 1 diabetes mellitus have also been reported, although they are rare (117). Endocrinopathy often persists, even after discontinuation of the immune checkpoint inhibitor.

The incidence of pneumonitis related to immune checkpoint inhibitors has been reported to be approximately 4% (14), with no difference between monoclonal antibodies that target PD-1 and those that target PD-L1 (119).

Several cardiac complications, such as myocarditis, pericarditis, Takotsubo syndrome, acute coronary syndrome, and arrhythmias can occur with immune checkpoint inhibitors (98,120). Although rare (approximately 0.1%), myocarditis can be fatal (121).

B. Lung cancer and comorbidity-related medication (Figure 2)

1. Impact of comorbidity-related medications on lung cancer diagnosis

Performance of pulmonary diagnostic procedures (for example bronchial biopsies, transthoracic needle biopsy) can lead to complications such as minimal or severe bleeding (122). Concomitant use of antiplatelets or anticoagulant agents for cardiovascular comorbidities may increase this risk. The physician has to assess the risk of bleeding according to patient risk factor and adapt procedures and/or comorbidity-related medications to enable diagnosis to be carried out in safety. According to the level of procedure bleeding risk and the level of comorbidity severity, anticoagulants or antiplatelets are either stopped before the procedure or maintained according to guidelines, depending on diagnostic procedure (123,124).

2. Impact of comorbidity-related medications on lung cancer features

Comorbidities often lead to the prescription of medication, whereas support treatment is often proposed to counteract the side effects of anticancer treatment. This “prescribing cascade” increases the number of prescribed medications (125). Consequently, lung cancer patients are at a high risk of iatrogenic drug problems, such as drug-drug interactions, adverse drug reactions, or nonadherence (126). Medication can include both prescribed drugs and over-the-counter medication, including complementary and alternative medicines (CAM) (19). Of note, there are discrepancies in the definition of PP (127). Several studies have defined PP as two to nine medications (128,129), whereas others in the geriatric oncology population have used the threshold of five to six (20,130,131). Medication and PP in elderly cancer patients has been widely described in many studies (18,19,132–134). Nightingale et al. (20) reported a mean number of medications of 9, a prevalence of PP of 41%, and excessive PP of 43% (defined as more than 10 medications) in elderly cancer patients.

In the following section, we focus on the impact of medications for comorbidities in lung cancer and anticancer treatment, although some of data are not well described in the literature and were deduced from hypotheses based on physiopathology.

2.1. Impact of comorbidity-related medications on cancer history

Certain molecules used for the treatment of comorbidities have shown properties towards carcinogenesis or drug resistance.

It appears that AMP-activated kinase, a metformin target, is associated with the tumor suppressor TET2 (135). In a recent meta-analysis, metformin showed a possible positive effect in advanced NSCLC, both on overall and progression-free survival (136). The tendency of a favorable effect of statins in cancer has also been described (137–140), although the results have not been consistent between studies (141). There are several possible explanations for such an effect of statins (mevalonate pathway or the inhibition of cholesterol synthesis). Decreased activity of cyclin D1, cyclin-dependent kinase, and metallopeptidase 9 (involved in angiogenesis) by simvastatin would arrest the cell cycle and reduce metastatic potential (142). Even more surprisingly, simvastatin appears to reverse the resistance of tumors harboring the T790M mutation of the EGFR in NSCLC cell lines (143).

Non-steroidal anti-inflammatory drugs may play a positive role in carcinogenesis, the induction of apoptosis, and angiogenesis (144). For many years, the literature has suggested that aspirin may have a protective role against cancer, more specifically in colorectal cancer (145) and even lung cancer (146).

Lung cancer resistance is caused by various mechanisms (147), such as P-glycoprotein (P-gp), a protein highly expressed in multi-drug resistant lung cancer cells (148). P-gp is a drug efflux pump and can decrease antitumor drug concentrations. Verapamil, a calcium channel blocker that inhibits P-gp, may improve the survival of patients being treated with chemotherapy (149).

2.2. Impact of comorbidity-related medications on drug-drug interactions with anticancer treatment

PP is a risk factor for drug-drug interactions, which can have consequences on the patient, the cancer treatment, and the lung cancer prognosis. Given the narrow therapeutic index of cytotoxic antitumor treatment, it can lead to higher toxicity or therapeutic failure. Drug-drug interactions with antitumor treatment can be pharmacokinetic or involve pharmacodynamic interactions (16). PP, lung cancer diagnosis, and inpatient status are associated with severe drug-drug interactions

(133). Potential drug-drug interactions are common among cancer patients and most often involve medications related to comorbid conditions (150).

A drug-drug interaction with concomitant medication was detected as a potential problem in 32% of cases in a study of 112 cancer patients, of whom 103 were taking medication for a comorbidity, with a mean number of five medications (151). A larger study also reported a frequency of 35% of severe drug-drug interactions among patients (32% of PP), which required considering modification of their therapy or avoidance of the combination. Such potential drug-drug interactions have often been identified with chemotherapy, 14% with a potentially severe impact (15). In a large cohort of 7237 lung cancer patients with stage I/II disease, the most frequent and serious potential drug-drug interactions observed were warfarin associated with etoposide (14%) or gemcitabine (15%). Among the 302 patients treated with cisplatin, 34 (11%) had a concomitant furosemide prescription, which is considered to be a serious potential drug-drug interaction (132).

It is well established that TKIs can interact with treatments affecting cytochrome P450 (152) or with antacids (153). A recent review focused on the cardiovascular system and detailed all drug-drug interactions involving cancer treatment and cardiovascular drugs (154). Drug-drug interactions can occur between TKIs and drugs that prolong the QT interval, calcium-channel blockers, diuretics, and anticoagulants. Absorption of the EGFR TKI can be influenced by acid-reducing agents (with a reduced area under the curve) (155). A study recently reported that 507 NSCLC patients being concomitantly treated with erlotinib and acid-suppression drugs showed significantly lower progression-free and overall survival (156). The same results were found with the concomitant use of erlotinib (157) or gefitinib (158) and proton-pump inhibitors, with decreased overall survival. TKIs can be also be involved in metabolism-based interactions through cytochrome P450 activity (155).

2.3. Impact of the use of complementary and alternative medicines (CAMs) on efficacy of anticancer treatment

The use of CAMs has probably been underestimated in all studies, but 30 to 50% of patients with lung cancer probably use them (159,160), which is a higher proportion than for other cancer patients (161). CAMs must be thoroughly researched by the oncologist before (and during) the prescription of any treatment, particularly for TKIs. The use of CAMs could lead either to side-effects or decrease activity of the

antitumor treatment (162). For example, a pharmacokinetic drug-drug interaction was reported between crizotinib and ginger in a NSCLC patient, leading to higher plasma concentrations of crizotinib (via inhibition of the cytochrome P450 3A4 isoform, which metabolizes crizotinib), associated with hepatic cytolysis and discontinuation of the treatment (163).

2.4. Impact of comorbidity-related medications on adverse drug reactions

Concomitant medication is a risk factor for adverse drug reactions (164). Most studies have estimated a risk of adverse drug reactions, for which the search is inherent in the process of the pharmaceutical analysis of prescriptions. Taking five or more drugs and an age of over 76 years have been identified as potential factors associated with moderate/severe potential drug related problems (defined as drug interactions, additive toxicity, contraindications) (126,151). In 244 patients receiving chemotherapy taking a mean of 12 medications (15), the risk of severe non-hematological toxicity was almost doubled for each additional potential drug-drug interaction and tripled for each additional potential drug-drug interaction involving chemotherapeutics. No association between potential drug-drug interaction and hematological toxicity was found. Goh et al. also reported that PP leading to drug problems was frequent in elderly cancer patients receiving chemotherapy (126). Another study did not report any association between chemotherapy related toxicity and a higher number of medications (134). Interestingly, high concomitant medication does not predict adverse radiotherapy outcomes (165).

CAMs can lead to antitumor treatment adverse events through pharmacodynamic interactions (163), as discussed in section 1.3.

2.5. Impact of comorbidity-related medications on adherence and continuation of anticancer treatments

It is commonly accepted that concomitant medication increases the rate of non-adherence (166,167). There is much less data available for lung cancer patients than for breast cancer patients and oral therapy (168) and they do not report non-adherence. In 62 patients treated with erlotinib taking a mean of five co-medications (range from 1 to 13), no association was reported between incorrect intake of erlotinib under fasting conditions and the number of drugs (169). Similarly, Sud et al. (170) did

not identify any association between PP (defined as ≥ 6 medications) and toxicity-related discontinuation of chemotherapy.

2.6. Impact of comorbidity-related medications on utilization of healthcare resources

As medications can affect cancer and patient characteristics, they may lead to more utilization of healthcare resources. Taking a large number of medications has been shown to be associated with an increased risk of hospitalizations or emergency room visits (171,172) Among 298 unplanned admissions of cancer patients, 11% were considered to be associated with an adverse drug reaction and 2% with a drug-drug interaction (173). The most common drug-drug interactions involved warfarin, captopril, and anti-inflammatory agents, and the most frequent adverse drug reaction was neutropenic fever post-chemotherapy. Having a prescription of two or more psychotropic medication classes for at least 90 days in the first year after cancer diagnosis was reported to be associated with a higher number of outpatient visits, office visits, hospitalizations, and longer length of stay (174). However, these results are controversial (134).

2.7. Impact of comorbidity-related medications on general condition and survival

Medication can be associated with frailty (poor ECOG-performance status) or disability, which can have consequences on the administration and tolerance of antitumor treatment. In a cohort of 290 cancer patients, multiple medication was a risk factor of disability (175). This finding was supported by another study in which multiple medication was associated with pre-frailty or frailty and poor physical function (176). A cut-off between 6 and 9 medications was proposed for predicting the risk of frailty (129,177).

A recent meta-analysis of 47 studies (not focused on cancer patients) showed a significant association between PP and death. This association increased with the number of medications (178). In 289 cancer patients receiving palliative radiotherapy, neither PP nor the use of corticosteroids or opioid analgesics independently influenced overall survival (165). Although potential drug-drug interactions were significantly associated with lower overall survival in breast cancer, this was not true for NSCLC.

CAM use without anticancer treatment was independently associated with the risk of death in cancer patients (161).

3. Impact of lung cancer features on comorbidity-related medications

Although the impact of comorbidity-related medications on lung cancer is described in the literature, there are no data on the impact of lung cancer on concomitant medications. This raises the question of whether the treatment needs to be simplified to avoid known and unknown drug-drug interactions to improve therapeutic adherence with respect to the clinical benefit when the predicted survival is short. Medication should be re-evaluated on a case-by-case basis according to the type of tumor, its treatment, and the prognosis of the patient. These issues need to be addressed in large-scale studies.

Conclusion

Lung cancer is the cancer associated with the most comorbidities. These comorbidities and their related medications should be considered in lung cancer management, particularly in the choice of anticancer treatment. There are close relationships between these three entities. They are all intertwined and dependent on each other in lung cancer. Although several observational studies have been carried out, the impact of comorbidity-related medications on the care of cancer patients is less known. Further studies should assess the impact of both medications and comorbidities on lung cancer management and the prognosis of patients. There is a true need in the era of personalized medicine to better understand the impact of comorbidities on cancer and which drugs need to be avoided to optimize patient care.

Abbreviations

ALK: Anaplastic lymphoma kinase

CAM: Complementary and alternative medicine

CCI: Charlson comorbidity index

COPD: Chronic obstructive pulmonary disease

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4

EGFR: Epidermal growth factor receptor

NSCLC: Non-small cell lung cancer

PD-1: Programmed cell death 1

PD-L1: Programmed death-ligand 1

PP: Polypharmacy

SCLC: Small-cell lung cancer

TKI: Tyrosine kinase inhibitor

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Table 1. Impact of comorbidities on lung cancer features

Cancer characteristics or treatment	Comorbidities or risk factor exposure				
	Tobacco use	Chronic pulmonary diseases (or COPD)	Cardiovascular history	Diabetes mellitus	Increasing number or severity of comorbidities
Histology	high smoking intensity: ↗ the risk of SCLC (11-fold), 18-fold of SqCC (18-fold), and of ADC (4-fold) (43)	Tuberculosis ↗ (2-fold) the risk of ADC (42) COPD ↗ (4-fold) the risk of SqCC (33,39) Asthma ↗ (2-fold) the risk of SqCC or SCLC (40,41)			
Stage at diagnosis	Screening in smokers: earlier stage at diagnosis and ↗ survival (54–56)				Trend towards earlier stage at diagnosis (47–49)
Surgery		COPD: sub-lobar surgery preferred to lobectomy (65)	Preferentially sub-lobar surgery rather than lobectomy (65)		Less proposed (47) ↗ complications (59) ↘ survival (60) Video-assisted thoracoscopy preferred to open surgery (67)
Radiotherapy	↗ radiation pneumonitis (69)		↗ radiation pneumonitis (70)		Preferred to surgery in early stages (58)
Chemotherapy			↗ cisplatin nephropathy (75)	↗ cisplatin nephropathy (75)	Less prescribed (50,73) ↗ complications (50)
Immune oncology treatments		Interstitial lung disease ↗ incidence or immune-related pneumonitis			Less prescribed, particularly if concomitant auto-immune disease (77)

ADC: adenocarcinoma, COPD: chronic obstructive pulmonary disease, SCLC: small cell lung cancer, SqCC: squamous cell carcinoma

Table 2. Impact of lung cancer treatment on comorbidities

Comorbidities	Lung cancer treatment					
	Surgery	Radiotherapy	Chemotherapy	Anti-angiogenic therapy	Tyrosine kinase inhibitors	Immune oncology treatments
Cardiovascular comorbidities	Myocardial infarction, atrial fibrillation (83,84)	Pericarditis, acute coronary syndrome, rhythm and conduction disorders, heart failure (88,89)	Anthracyclines: Pericarditis, acute coronary syndrome, heart failure (11,98,99) Cisplatin: arrhythmias and cardiomyopathy (98,99) Anti-microtubule agents: heart failure, acute coronary syndrome, bradycardia, hypotension (99) Vinka-alkaloids: Arrhythmias, acute coronary syndrome (99)	Hypertension (13)	ALK TKI: QT prolongation, bradycardia, thrombotic events, hypertension (110–112) Osimertinib (EGFR TKI): cardiac failure, atrial fibrillation, QT prolongation (113)	Myocarditis, pericarditis, Takotsubo syndrome, acute coronary syndrome, arrhythmias (98,120)
Venous and arterial thromboembolism			Cisplatin (96)	Bevacizumab (107,179)		Pneumonitis (14)
Chest diseases	Acute exacerbation of interstitial diseases, phrenic nerve paralysis (82,83)	Radiation pneumonitis potentially complicated by fibrosis (10)			Interstitial lung disease (112)	
Renal failure			Cisplatin, pemetrexed, gemcitabine (12,104,105)	Bevacizumab (12,13,104)		
Endocrinopathies						Hypothyroidism (14,117) Hypophysitis (14) Type 1 diabetes mellitus (117)

ALK: anaplastic lymphoma kinase, EGFR: epithelial growth factor receptor, TKI: tyrosine kinase inhibitor

Figure legends

Figure 1. Lung cancer, medication, and comorbidities: an infernal trio

— → Potential links ← → Link proved → Existing intrinsically links

Figure 2. Consequences of concomitant medications in lung cancer patients

— → Proved consequences
- - - → Potential consequences

Figure 1. Lung cancer, medication, and comorbidities: an infernal trio

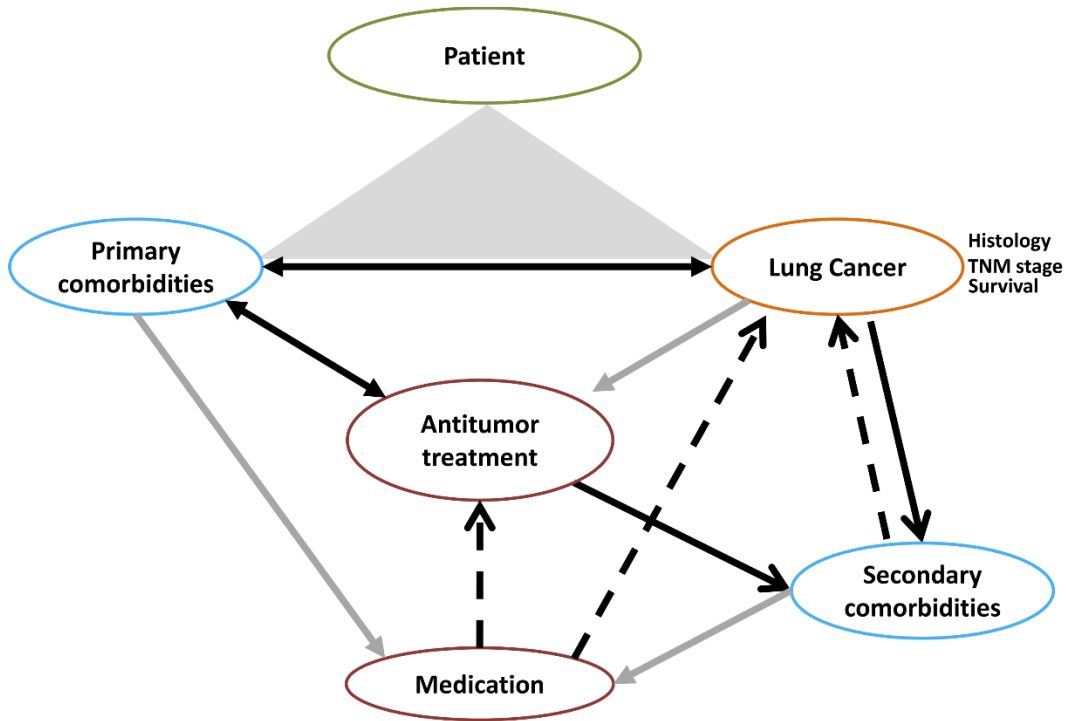
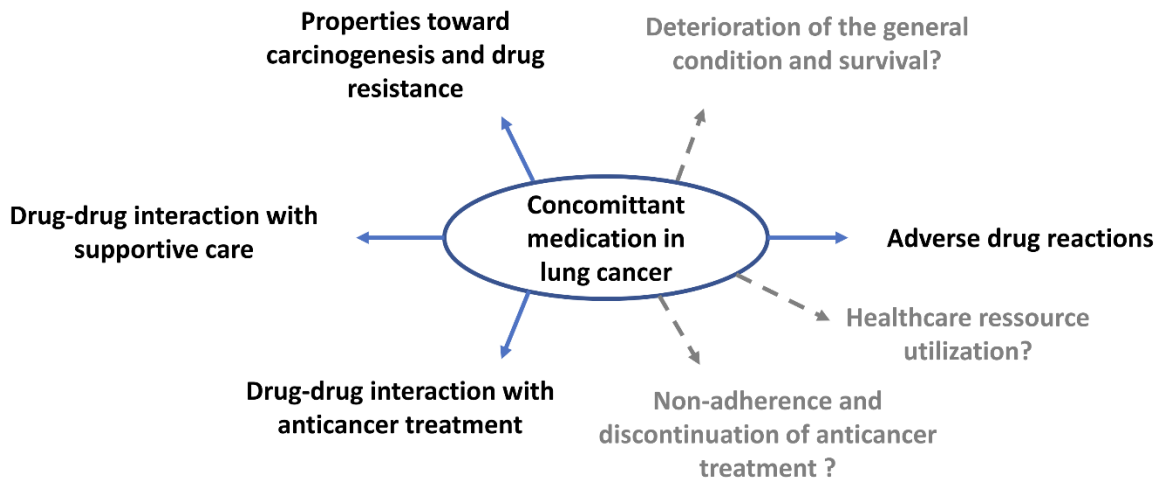


Figure 2. Consequences of concomitant medications in lung cancer patients



3. Protocole CBPMED: Impact de la polymédication et des comorbidités chez les patients hospitalisés porteurs d'un cancer bronchopulmonaire

Pour étudier à la fois, les caractéristiques des patients, de leur cancer, leurs comorbidités, et les traitements associés, nous avons mené à bien une étude rétrospective monocentrique au CHU Grenoble Alpes. En effet, différentes bases de données étaient disponibles. Pour obtenir les informations sur les comorbidités, il existe la base de la réunion de concertation pluridisciplinaire (RCP) du CHU Grenoble Alpes qui existe depuis 1980 et qui contient les données d'environ 10.000 patients présentés avec des informations précises notamment sur le performance status des patients. Les données sont contrôlées pour tous les patients mais il existe seulement 60% de concordance concernant les comorbidités avec ce qui est présent dans le dossier médical. Nous avons donc préféré utiliser les données de la base du Programme de Médicalisation des Systèmes d'Information (PMSI) qui fournit les comorbidités codées avec la classification internationale des maladies, 10ème révision (CIM-10), qui est mieux contrôlée. Sont présentes dans cette base seulement les comorbidités prises en charge durant l'hospitalisation ou en lien avec l'hospitalisation.

Le registre du cancer de l'Isère est un registre reprenant les données des patients ayant un cancer, domiciliés en Isère, comprenant des données robustes et exhaustives sur les caractéristiques des patients, les caractéristiques de leur cancer et le statut vivant ou décédé aux dates de dernières nouvelles.

Pour récupérer les informations sur les médicaments pris par les patients. Nous avons récupéré les prescriptions informatiques lors des séjours hospitaliers des patients, raison pour laquelle nous nous sommes intéressés aux patients hospitalisés, sans obtenir les données du Système national d'information inter-régimes de l'Assurance maladie (SNIIRAM).

Nous nous sommes intéressés à la période allant de 2011 à 2015 car ce travail a commencé en 2018 et la base du registre du cancer de l'Isère qui contient les informations exhaustives sur les patients, les caractéristiques du cancer, les données de survie étaient complètes jusqu'à la date du 31 décembre 2015.

Ainsi, 4 bases ont été utilisées :

- Base de la RCP.
- Base du PMSI.
- Base du registre du cancer de l'Isère qui fait partie des 27 registres de cancer qui alimentent la base Francim au niveau national.
- Base reprenant les prescriptions informatiques durant l'hospitalisation

Le projet a commencé en 2018. Les bases de données du PMSI, du registre du cancer de l'Isère et la RCP ont été rapidement récupérées. Cela a été plus difficile pour la base de données sur les médicaments (un an et demi). Un algorithme a dû être construit pour récupérer tous les médicaments pris par les patients durant leur hospitalisation. Ensuite, plusieurs appariements déterministes ont dû être faits, après un data management des données.

L'appariement déterministe de bases de données a l'avantage d'être utilisable quand des études prospectives seraient trop longues, ou trop difficiles à réaliser d'un point de vue organisationnel [54]. Cette méthode repose néanmoins sur la qualité des données, l'absence de données manquantes et sur l'absence d'erreur lors de l'appariement des bases [55,56]. De plus, dans le domaine de la cancérologie, lorsque l'on s'intéresse à un autre évènement que le décès, la prise en compte des risques compétitifs dans les modèles de survie doit être fait, par la méthode de Fine and Gray [57]. C'est pourquoi nous avons rédigé un protocole sous forme d'article afin de décrire méthodologie complexe de cette étude.

Publication n°2

Study protocol to assess polypharmacy and comorbidities in lung cancer

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Study protocol to assess polypharmacy and comorbidities in lung cancer

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Abstract

Background

At least half of patients with lung cancer have comorbidities, which can affect treatment decisions and survival. Associated with comorbidity, polypharmacy can also have consequences on patient care. This study will evaluate both polypharmacy and comorbidities in a cohort of hospitalized patients on the administration of chemotherapy and survival.

Methods

In this monocentric retrospective study, patients diagnosed with lung cancer during their first hospitalization in thoracic oncology were included between 2011 and 2015. Four datasets were obtained containing the variables of interest. Deterministic data linkage will be performed. The main objective will be to assess the impact of polypharmacy and comorbidities on chemotherapy administration within two months after the first hospitalization in thoracic oncology. The probability of chemotherapy administration will be estimated using the Kaplan Meier method. Prognostic factors will be identified using a Cox model. The Fine and Gray method will be used to analyze the competitive risk of death.

Expected results

We first aim to demonstrate the feasibility of working with real-life data and aggregate different databases. Then our goal is to assess impact of polypharmacy and comorbidities on chemotherapy administration and on the survival of lung cancer patients. This would help to understand the possibilities to aggregate several database for a protocol in view to help clinicians to rationalize treatment and define inappropriate medications for this population.

Keywords

Lung cancer, polypharmacy, comorbidities, survival analysis, competing risk

1.Introduction

The assessment of comorbidities is critical for the management of cancer patients. Indeed, it is well known that they have a negative impact on patient survival in lung cancer (1). This is important, as the prevalence of comorbidities in lung cancer is higher than that for other cancers (50 to 70% (2,3)), with patients having a median age at diagnosis of 70 years (4).

Comorbidity often implies polypharmacy, defined in the elderly in the literature as five or more medications (5–7) and as excessive polypharmacy for 10 or more prescribed medications (5,8). Polypharmacy has often been reported for cancer patients. In a cohort of 236 patients (5), 41% experienced polypharmacy, with a mean of nine medications. Among them, almost 20% had lung cancer. Although polypharmacy is well described among cancer patients, very few studies have focused on lung cancer.

In this study, we aim to evaluate the impact of polypharmacy and comorbidities on chemotherapy administration and overall survival. This protocol is original because it will require linkage of multiple datasets, which need to be collected in consideration of ethical issues. The four datasets will contain the variables of interest and will require complex data management for linkage to be feasible. There is no preliminary data on the feasibility of this study design on lung cancer patients. This is an original pharmacoepidemiology method based on multiple data sources. Such a study has not been published on lung cancer patients.

2.Objectives and methods

2.1. Study design

This is a retrospective single-center study on clinical and administrative datasets. Any patient over 18 years old with lung cancer (code C34.0 to 9 according to the Health Information Service Department) hospitalized in thoracic oncology at Grenoble University Hospital over the period from 2011 to 2015 will be included. They will be studied from their first hospitalization.

2.2. Objectives

The objectives, endpoints, and statistical analyses are summarized in Table 1. The main objective will be to assess the impact of polypharmacy and comorbidities on chemotherapy administration within two months after the first hospitalization in thoracic oncology. The secondary objectives will be to assess median survival, estimated in months, according to polypharmacy and comorbidities, identify any therapeutic classes associated with delayed administration of chemotherapy, describe the treatments received by the patients (excluding anticancer treatment), and assess the proportion of potentially inappropriate medication.

Datasets

Four datasets were obtained through a data collection process and will need to be merged into one database that will contain the data of interest (Table 2). The four datasets are:

Dataset A. Identification of patients' first hospitalization in thoracic oncology between 2011 and 2015. This dataset was provided by the Health Information Services Department and included comorbidities coded with the tenth revision of the International Statistical Classification of Diseases and Related Health Problems. Any comorbidities treated during or in connection with the hospitalization was included in this dataset"

Dataset B. Data from the district cancer registry based on the patient's identifying number provided following a request to the district cancer registry.

Dataset C. Data from multidisciplinary concertation meetings provided upon request.

Dataset D. Data concerning every chemotherapy and drug prescription for all hospitalizations, which will be separated into two sub-datasets, the first containing chemotherapy prescriptions and the second with all prescribed drugs. This dataset was provided by the Grenoble University Hospital computer system for the identified patients.

The data-linkage strategy is described in Figure 1. Dataset A (data from the Health Information Services department) will be merged with Dataset B (district cancer registry). Then this database will be merged with Dataset C (multidisciplinary concertation

meetings) based on the patient's family name, first name, and date of birth. The first sub-dataset of Dataset D will be merged with the patient's identifying number and hospitalization start date. Finally, the second sub-dataset from Dataset D will be merged into the overall database.

2.3. Statistical analyses

The primary endpoint (time to chemotherapy administration after the first day of hospitalization) will be assessed using the Fine and Gray method for competing risks with death (censored at two months) (Figure 2). Not taking competing risks into account may lead to overestimation of the probability of chemotherapy administration with the Kaplan Meier method (9).

Two months was chosen as the cut-off because it corresponds to the postponement of chemotherapy administration due to toxicity, and we will consider delays beyond this timepoint to be due to reasons other than chemotherapy-related toxicity. A multivariable model will be used to evaluate the risk depending on polypharmacy and comorbidities.

For the secondary endpoints, survival will be the time between the first day of first hospitalization and estimated median survival (in months) or death, estimated using the Kaplan Meier method. Survival curves between populations will be compared using a Log Rank test. A Cox model will be generated to identify prognostic factors. Statistical analyses to be used for the other secondary endpoints are described in Table 1.

In survival model, TNM stage, histological types, sex, age at hospitalization and at diagnosis will be used as covariates

Results of the descriptive analysis of associated treatments (excluding anticancer treatment) will be presented as medians and interquartile ranges for continuous variables and proportions (percentages) for qualitative variables.

All statistical analyses will be performed using SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA). A P-value < 0.05 will be considered significant.

2.4. Ethics

This study was approved by our institutional review board, respecting reference methodology No. 004 (MR004), which concerns research not involving human subjects (studies and evaluations in the health field). Study ethics approval was obtained on 01 september 2021 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB5891) An information and non-objection letter will be sent to living patients in the cohort.

3. Expected results

This original study on lung cancer patients aims to assess the impact of medication and comorbidities on chemotherapy administration and survival. Complex data linkage will be necessary and competitive risk analysis will be performed.

Data linkage allows the combining of individual-level information available in different datasets (10), enabling researchers to identify factors and associations that would otherwise be difficult to determine. Indeed, the strengths of this method include its utility in studies that require long-term follow-up (11) and those that would be very costly and organizationally difficult to undertake (12) . It can also be used for studies with large sample sizes to obtain detailed data on populations, with little loss to follow-up (13).

However, this approach can be challenging, as it relies on data quality and potentially poor-quality data and missing data. Linkage error can compromise the accuracy of the results (10,13). Other concerns include statistical issues, technical issues with permission to use datasets held by multiple units, and ethical issues (10). It can also be associated with multiple errors, such as non-matched data due to missing data (false negatives) or matched data between unrelated cases (false positives) (14). These two types of error determine overall linkage quality (15). Moreover, analysis is performed only on preexisting data available in datasets (16). Based on its retrospective monocenter design, this study has also limitations such as lack of intern validity, applicability and small sample. Some measurement biases concerning information towards comorbidity (only comorbidity treated or related to hospitalization are recorded) and medication prescription

(an estimation will be performed between chronic ambulatory medication and computer prescription during hospitalization) exist.

This study will use deterministic and probabilistic data linkage to account for potential biases. Adequate statistical analyses will be implemented, mainly by considering death as a competing event.

This study will lead to the identification of therapeutic classes that affect the administration of anticancer treatment or survival and will be of interest to clinicians seeking guidance for appropriate therapeutic use of such medications. Based on multidisciplinary teamwork, which ensures better healthcare, this original study will serve as a “case study” for our institution in the context of a feasibility study to create a data warehouse (17,18).

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Table 1. Primary and secondary objectives, their endpoints, and statistical analyses.

Primary objective	Primary endpoint	Statistical analyses
Assessment of the impact of polypharmacy and comorbidities on chemotherapy administration after the first hospitalization in thoracic oncology	Time to chemotherapy administration after the date of hospitalization (within 2 months)	-Kaplan Meier method to estimate the probability of chemotherapy administration -Log-rank method to compare the probability of the event (chemotherapy administration) between populations -Cox proportional hazards regression model to perform multivariate analyses of prognostic factors -Fine and Gray method to assess the competitive risk of "death" (19)
Secondary objectives	Secondary endpoints	Statistical analyses
Overall survival depending on polypharmacy and comorbidities	Time between the day of hospitalization and the date of last follow-up (cut off at survival median estimated in months)	- Kaplan Meier method to estimate the probability of survival -Log-rank method to compare the probability of the event (death) between populations -Cox proportional hazards regression model to perform multivariate analyses of prognostic factors
Identification of a therapeutic class associated with delayed administration of chemotherapy	Time to chemotherapy administration after the date of hospitalization for all therapeutic classes (cut off at 2 months)	- Kaplan Meier method to estimate the probability of chemotherapy administration -Log-rank method to compare the probability of the event (chemotherapy administration) between populations -Cox proportional hazards regression model to perform multivariate analyses of prognostic factors -Fine and Gray method to assess the competitive risk of "death" (19)
Description of treatments (excluding anticancer treatment) and assessment of the proportion of potentially inappropriate medications	Number of medications and classification with the Anatomical Therapeutic Chemical classification, number of potentially inappropriate medications	Descriptive analysis of associated treatments (excluding anticancer treatment)

Table 2. Description of the four datasets.

	Health information services department <u>Dataset A</u>	District cancer registry <u>Dataset B</u>	Multidisciplinary concertation meetings <u>Dataset C</u>	Computerized prescriptions <u>Dataset D</u>
Structure of origin	Grenoble University Hospital	District cancer registry	Grenoble University Hospital	Grenoble University Hospital
Data source	Grenoble University Hospital	Anatomopathological laboratory, long-term condition network, cancer network, hematology laboratories, and medical records	Grenoble University Hospital	Grenoble University Hospital
Objective	Collection and analysis of medical information on patients hospitalized in the establishment for epidemiology studies and the medical billing process	Contribute to the epidemiological surveillance of cancers by producing indicators of descriptive epidemiology, based on an active and exhaustive registration of cancer cases	To have a dataset with the characteristics of patients presented at the multidisciplinary concertation meetings	Date on the administration of medications during hospitalization and description of medications
Strengths	Data is complete, Homogeneous and standardized: comparability	Controlled and exhaustive data representative of the general population of Isère	Details on TNM status and each therapeutic line available ECOG-Performance Status data Vital status	Complete data on computerized prescriptions during hospital stay including chemotherapy, based on administered medications
Weaknesses	Medico-economic coding rule: less appropriate for epidemiological studies	Only people living in Isère are included Time frame of availability data	Only patients discussed at meetings are in the database and not all lung cancer patients treated in the center	Existence of old versions for data recovery

Figure legends

Figure 1. Dataset linkage method.

The highlighted data are the ones used for merging.

Figure 2. Statistical considerations for primary objective analyses.

Figure 1. Dataset linkage method

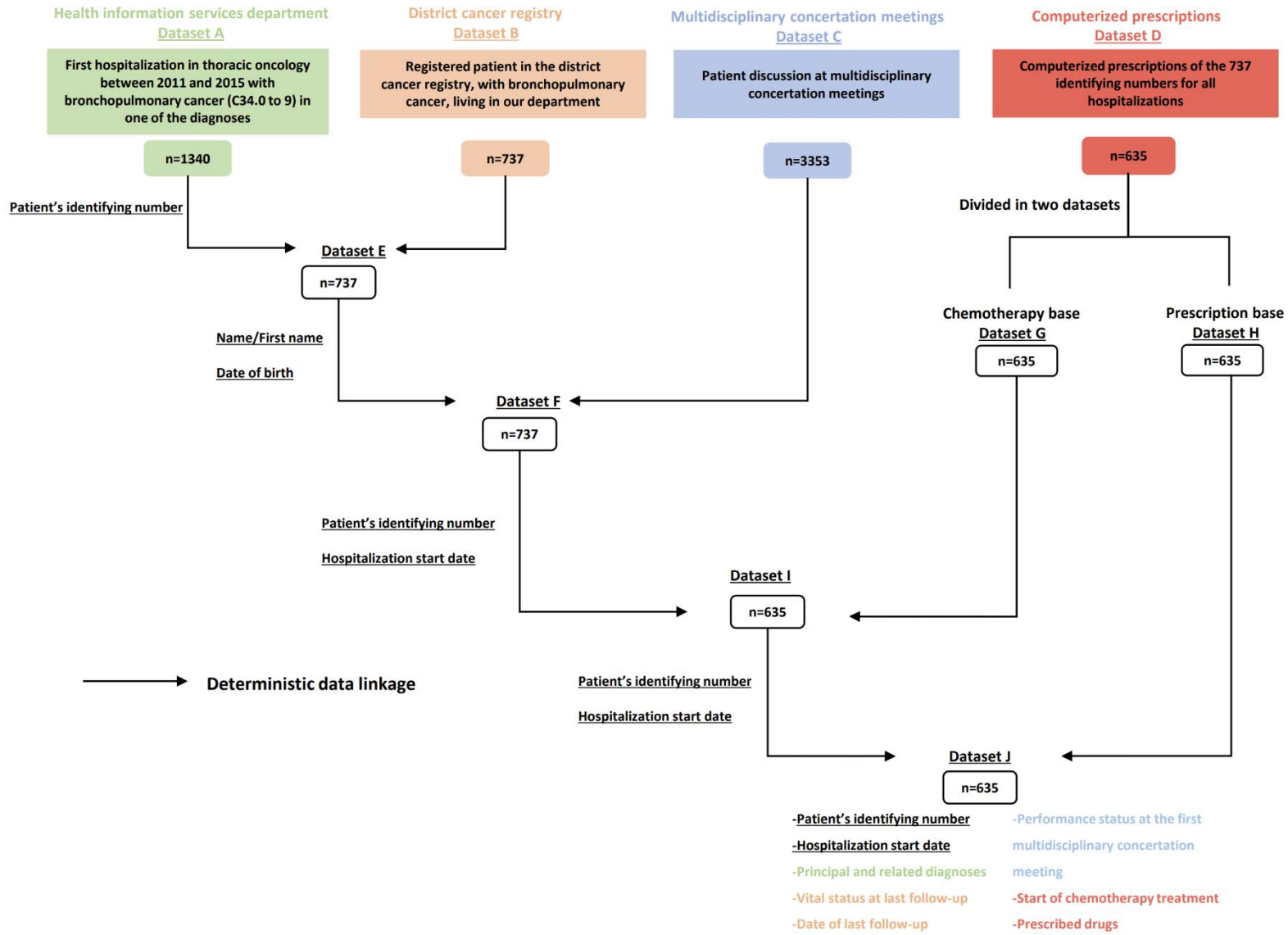
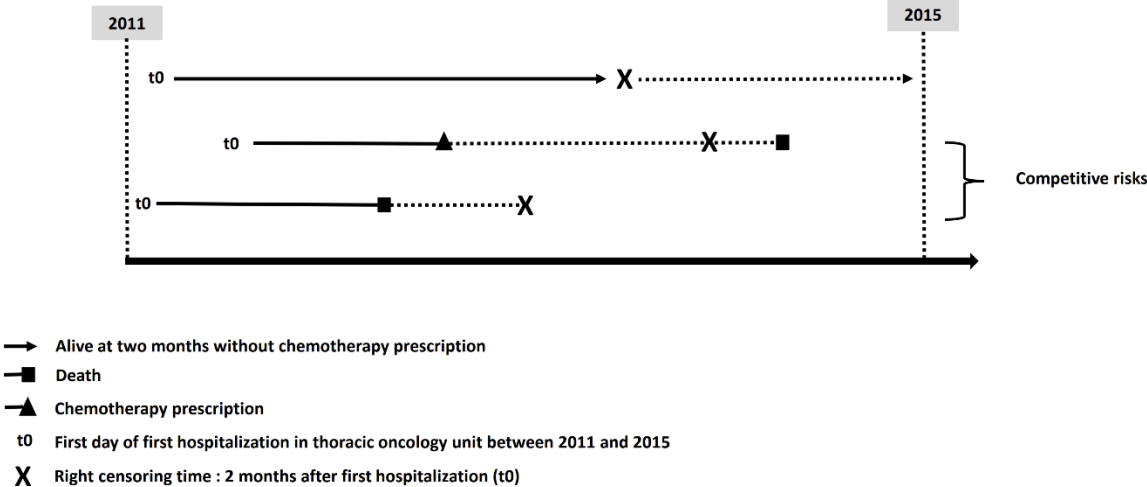


Figure 2. Statistical considerations for primary objective analyses.



4. Définition du score de comorbidité

Pour les objectifs de cette étude, nous avons besoin d'évaluer le poids porté par les comorbidités des patients. Nous avons commencé à nous intéresser aux deux entités que sont les comorbidités et la polymédication. Mais dans la littérature, il existe de très nombreux scores [18]. Ces scores se différencient selon le nombre de comorbidités prises en compte, la cohorte utilisée pour le construire, la méthode de calcul du score. Certains utilisent des poids assignés à chaque comorbidité (hazard ratio de chaque comorbidité prise séparément ou coefficient bêta de la régression logistique) quand d'autres utilisent le comptage du nombre de comorbidités. Enfin ils se distinguent par la méthode de recueil des comorbidités : d'après les déclarations des médecins ou par les données administratives. Comme dit précédemment, pour les recueillir, nous avons choisi de partir des données codées en CIM-10 fournies par le PMSI. Nous avons regardé quels scores dans la littérature étaient utilisables à partir des données administratives et nous avons, à partir des données codées en CIM-10, calculé chacun des scores.

Historiquement, c'est le score de Charlson qui est très utilisé dans la littérature, mais correspond-il au score qui prédit le mieux le décès dans cette cohorte ? C'est une question que nous avons soulevée et que nous avons souhaitée étudier en comparant le pouvoir de prédiction sur la mortalité à moyen terme de différents scores de comorbidités utilisables avec des données administratives.

Publication n°3

Comparison of seven comorbidity scores using administrative data in a cohort of hospitalized lung cancer patients

Hélène Pluchart, Sébastien Bailly, Sébastien Chanoine, Denis Moro-Sibilot,

Pierrick Bedouch, Anne-Claire Toffart

Soumis

Comparison of seven comorbidity scores on four-month survival of lung cancer patients

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Abstract

Background

The comorbidity burden has a negative impact on lung-cancer survival. Several comorbidity scores have been described and are currently used. The current challenge is to select the comorbidity score that best reflects their impact on survival. Here, we compared seven usable comorbidity scores (Charlson Comorbidity Index, Age adjusted Charlson Comorbidity Index, Charlson Comorbidity Index adapted to lung cancer, National Cancer Institute combined index, National Cancer Institute combined index adapted to lung cancer, Elixhauser score, and Elixhauser adapted to lung cancer) with coded administrative data according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems to select the best prognostic index for predicting four-month survival.

Methods

This cohort included every patient with a diagnosis of lung cancer hospitalized for the first time in the thoracic oncology unit of our institution between 2011 and 2015. The seven scores were calculated and used in a Cox regression method to model their association with four-month survival. Then, discrimination parameters (Akaike Information Criteria, Bayesian Information Criteria, the C-statistic and Harrell's c-statistic) were calculated. A sensitivity analysis of these parameters was finally performed using a bootstrap method based on 1,000 samples.

Results

In total, 633 patients were included. Male sex, histological type, TNM staging, CCI, CCI-lung, Elixhauser score, and Elixhauser-lung were associated with poorer four-month survival. The Elixhauser score had the lowest AIC and BIC and the highest c-statistic and Harrell's c-statistic. These results were confirmed in the sensitivity analysis, in which these discrimination parameters for the Elixhauser score were significantly different from the other scores.

Conclusions

Based on this cohort, the Elixhauser score is the best prognostic comorbidity score for predicting four-month survival for hospitalized lung cancer patients.

Keywords

Lung cancer, comorbidity, survival

Background

The median age at lung cancer diagnosis is 70 years (1). Given the increasing probability of developing comorbidities with age, the prevalence of comorbidity is higher in lung cancer than in other cancers, with at least 50 to 70% of patients having at least one comorbidity at diagnosis (2,3).

The negative affect of comorbidities on patient survival are well described (4,5) (6). Since the development of the Charlson Comorbidity Index (CCI) (7), several comorbidity scores have been developed and are currently used. They all differ by the origin of the initial data source (administrative data or physician-reported data), their purpose (measuring comorbidity, measuring the impact of comorbidity and physical function), and comorbidity measures (organ or system-based approaches, counts of individual conditions and weighted indices) (8) (Table S1 in Supplementary Materials). Some have been developed using lung cancer patient cohorts (9–11). Despite the large number of comorbidity scores available, The CCI is the most studied and used comorbidity index in the medical literature (12,13).

Certain comorbidity scores are based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10), as Quan et al. published ICD-10 codes relative to comorbidities in 2005 (14). They include the CCI (updated by Quan *et al.* in 2011 (7,15)), CCI for lung cancer (named later CCI-lung) (Klabunde et al. in 2007 (16)), age-adjusted CCI (ACCI) (17), Elixhauser score (updated in 2009 by Van Wallraven *et al.* (18,19)), Elixhauser for lung cancer (Elixhauser-lung) (Mehta *et al.* (20)), National Cancer Institute Combinex Index (NCI) (1), and NCI for lung cancer (NCI-lung) (Klabunde et al. in 2007 (16,21)). They differ in terms of the type of comorbidities considered, the cohort used for validation, and their initial purpose (22).

Yang et al. found that the ACCI was better at predicting three-year overall survival than the CCI and Elixhauser score in a cohort of resected lung-cancer patients (23) based on administrative data coded using the ICD-9. However, they only compared the ACCI,

CCI, and Elixhauser score. More recently, Mehta *et al.* proposed an Elixhauser score adapted to the cancer type (breast, lung, prostate, and colorectal). The cancer-specific Elixhauser score appears to be a better prognostic score for two-year survival than the cancer-specific NCI (developed by Klabunde *et al.*) (20).

Although the CCI is the most widely used comorbidity score, it would be informative to assess which score is more predictive of mortality in cohorts with administrative data. Here, we compared the seven comorbidity scores available using administrative data coded using the ICD-10 in predicting four-month survival of our cohort of hospitalized lung-cancer patients.

Materials and methods

Data source and population

We included patients hospitalized in the Thoracic Oncology Unit of Grenoble Alpes University Hospital from 2011 to 2015 described in an earlier publication (24). Lung-cancer patients were included at their first hospitalization during the studied period.

The study was approved by our institutional review board and ethics approval was obtained on September 1, 2021 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

The database contains information on individuals including their age, gender, lung cancer' TNM staging, performance status at their first presentation case in multidisciplinary concertation meetings, and the histological type of the lung cancer.

Outcome and covariates

The outcome was median overall survival. Survival data were obtained from our district cancer registry, including the date of the last follow-up and the vital status at the last follow-up.

Age, gender, lung cancer TNM staging, histologic type, age at hospitalization, and age at diagnosis were included as covariates.

Comorbidity scores

Data concerning comorbidities were obtained by the Health Information Services Department and coded using the ICD-10. The diagnoses for comorbidities were recorded at the patients' discharge in our medical unit. Seven comorbidity scores were calculated: CCI, ACCI, CCI-lung, NCI, NCI-lung, Elixhauser, and Elixhauser-lung. We did not record metastatic solid tumors and lung cancer as comorbid conditions. The seven scores are summarized in Table 1.

Statistical analyses

For descriptive analysis, quantitative variables are expressed as medians [Interquartile ranges] and qualitative variables as n (%).

Comorbidity scores were calculated and survival estimated as the time between the day of hospitalization and the date of last follow-up (cut off at estimated median overall survival). The Kaplan Meier estimator was used to estimate the probability of survival. Log-rank tests were used to compare the probability of the event (death) between populations. The model was adjusted for each score. A Cox proportional hazards regression model was used to perform multivariable analyses of prognostic factors and calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for median survival for the seven comorbidity scores. A median cut-off was used for continuous variables in the multivariate analysis. Proportional hazards assumptions were verified using the Martingale method. Only covariables with a p-value < 0.2 were retained for multivariable analysis.

To compare comorbidity scores, a discrimination analysis using Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), the c-statistic, Harrell's c-statistic, sensitivity, specificity, and negative and positive predictive values was performed from a base model containing significant covariables from the multivariate analysis. The impact of the scores was compared using the base model (significant covariables in multivariable analysis) plus each index score alone by multivariable Cox regression. The model with the lowest AIC and BIC and the highest c statistic and Harrell's c statistic was considered to be the best predictive model.

A sensitivity analysis using a bootstrap method for each statistical indicator, with 1,000 samples from two thirds of the cohort (n = 380), was performed. Each indicator (AIC, BIC, c-statistic, and Harrell's c-statistic) was calculated for the 1,000 samples. Boxplots were generated for the four parameters. Then, the means of the 1,000 values of the c-statistics and Harrell's c-statistic were obtained and the mean compared between each to determine whether the differences were significantly relevant using Student's t test with Bonferroni's correction for multiple tests (a p-value < 0.002 was considered significant).

All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA). A p-value < 0.05 was considered significant, except for multiple comparisons in sensitivity analyses.

Results

Descriptive analyses and adjusted hazard ratios for four-month survival using the seven comorbidity scores

In total, 633 patients were enrolled in the study. The demographic characteristics of the population are presented in Table 2. The median age [Q25%;Q75%] at diagnosis was 65 [58-72] years and 540 (71%) of the patients were men. The median survival from hospital admission was 4 [1; 11] months. Among the cohort, 428 patients (74%) had metastatic lung cancer and 295 (47%) had adenocarcinoma. The diagnosis of cancer was made before hospitalization for most of the patients (518, 82%).

In multivariable analysis, only the presence of metastases, male gender, and histological type were prognostic factors of four-month survival.

We assessed the prevalence of each comorbidity that contributed to the the score for each comorbidity score (Table 3 for the Elixhauser score and Elixhauser-lung and Tables S2 and S3 in Supplementary Materials for CCI, CCI-lung, NCI, and NCI-lung). For the Elixhauser score, weight loss, fluid and electrolyte disorders, and chronic pulmonary disease were the three most common comorbidities, whereas weight loss, chronic pulmonary disease, and peripheral vascular disease were the most common

comorbidities for Elixhauser-lung. The common thread between the Elixhauser score, Elixhauser-lung, CCI, CCI-lung, NCI, and NCI-lung was the high prevalence of chronic pulmonary disease, which was among the three most common comorbidities in the cohort.

Among the seven scores, in terms of the p value and type 3 p value, an ACCI ≥ 5 , Elixhauser score > 11 , and Elixhauser-lung ≥ 4 were associated with lower survival. However, neither the CCI, CCI-lung, NCI, nor NCI-lung were associated with poorer survival (Table 4).

Discrimination analyses between the seven scores and the bootstrap method

We calculated the AIC, BIC, c-statistic, and Harrell's c-statistic (Table 5). Sensitivity, specificity, and the negative and positive predictive values were also calculated. The Elixhauser score had the lowest AIC and BIC and highest c-statistic and Harrell's c-statistic, indicating that this score is the best predictive model for estimating four-month survival in our cohort.

We confirmed this trend by generating boxplots from the sensitivity analyses of the AIC, BIC, c-statistics, and Harrell's c-statistic (Figure 1 in Supplementary Figures).

Student t tests for the c-statistic and Harrell's c-statistic between the means of the 1,000 values of the seven scores were performed (Table 6).

These tests confirm that the results for the comorbidity scores were significantly different from each other and that the Elixhauser score appears to be the best comorbidity score to evaluate the comorbidity burden for four-month survival in our cohort.

Discussion

The CCI has been shown to be associated with poorer survival for all TNM stage lung-cancer patients (12,25) and is the most widely used comorbidity score. Here, we performed the first study to compare seven comorbidity scores on a cohort of lung-cancer patients. Sarfati *et al.* suggested that the CCI, cancer-specific NCI, and Elixhauser score may be the preferred comorbidity scores when using administrative data (22). In this

study, we used the ICD-10 to identify comorbidity from administrative data and found the Elixhauser score to be the best score for predicting four-month mortality.

The Elixhauser score has already been compared to the CCI for patients with cancers other than lung cancer and found to be a better prognosis score for colorectal and oral cancer patients (26,27). Mehta et al. found that the lung cancer-specific Elixhauser performed better than the lung cancer-specific NCI and Elixhauser score (28). The outcome of the aforementioned study was two-year non-cancer mortality, which had a consequence on the statistical analyses because the authors had to consider competing risks. In addition, they studied comorbidities prior to the lung cancer diagnosis. More interestingly, they also compared these scores to the individual Charlson and Elixhauser comorbidity scores. The Elixhauser individual comorbidity scores performed better than the Charlson individual comorbidity scores. However, scores have been shown to be good substitutes for individual comorbidity variables in health services research (29). In a paper published by Yang et al., the ACCI predicted overall three-year survival better than the CCI or Elixhauser score (23). In contrast to Mehta *et al.*, they did not discriminate between death from cancer and other causes, but they did consider comorbidities prior to the diagnosis of lung cancer.

These scores differ not only in the way they were constructed (origin of the cohort and outcome chosen), but also in the weight assigned to each comorbidity; some use the beta coefficient obtained from the regression and others the hazard ratio. The beta coefficients and hazard ratios are related to each other by an exponential relationship, and although the use of beta coefficients is preferred when using a summary score (30), we calculated the comorbidity scores as they were described and published in the original papers.

There are several possible explanations concerning the better performance of the Elixhauser score. The Elixhauser score was developed using a short-term outcome: in-hospital mortality. The median overall survival in our cohort was four months, which is short relative to the other scores (i.e., the CCI), which were constructed using a long-term outcome, such as one- or two-year mortality. This result corroborates another publication concerning in-hospital mortality of non-cancer patients, in which the Elixhauser score

outperformed the CCI (31). Another possibility is the number of comorbidities taken into account in the Elixhauser score, which is more than for the other scores. Lung cancer patients have the most comorbidities at diagnosis relative to patients with other types of cancer, especially due to tobacco exposure (3,32). This could explain why the Elixhauser score best fit our cohort in predicting four-month mortality.

This study had several limitations. We assessed comorbidities that occurred both before and after lung cancer diagnosis and did not distinguish between death from lung cancer and that from other causes. There may have also been unknown confounders. Moreover, this was a retrospective monocentric study.

The use of ICD-10 codes to identify the comorbidities was a strength of our study, as they can be used to query easily available structured datasets and allow the comparison of comorbidity scores, as well as sensitivity analyses, which confirmed the superiority of the Elixhauser score for estimating four-month survival in our cohort.

Conclusions

Despite the extensive use of the CCI in the literature, other comorbidity scores are available, including scores based on administrative data coded using the ICD-10. In this original study, in which we compared seven comorbidity scores using administrative data, the Elixhauser score was the comorbidity score best suited to hospitalized lung-cancer patients for predicting four-month mortality. It could be informative to repeat these analyses with a longer follow-up of the patients.

Abbreviations

ACCI: Age-adapted Charlson Comorbidity Index

AIC: Akaike Information Criteria

BIC: Bayesian Information Criteria

CCI: Charlson Comorbidity Index

CCI-lung: Charlson Comorbidity Index adapted to lung cancer

CIRS: Cumulative Illness Rating Scale

CIRS-G: Cumulative Illness Rating Scale adapted for geriatric population

Elixhauser: Elixhauser score

Elixhauser-lung: Elixhauser score adapted to lung cancer

KFI: Kaplan Feinsein Index

NCI: National Cancer Institute combined index

NCI-lung: National Cancer Institute combined index adapted to lung cancer

SCI: Simplified Comorbidity Index

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891.

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Table 1. Summary of differences between the seven comorbidity scores used.

Score	Number of conditions	Scoring method	Score range
Updated CCI (14)	12 conditions	Based on 1-year-all-cause mortality Sum of weighted indices (derived based on hazards ratios) Updated by Quan <i>et al.</i> (14)	0 to 24
CCI-lung (15)	10 conditions	Based on the impact on 2-year non-cancer mortality Sum of weighted indices (derived based on hazards ratios)	0 to 15
ACCI (16)	12 conditions	Based on 1-year-all-cause mortality Age-adjusted CCI is equal to the CCI score but 1 point has to be added for each decade above 50 years	CCI + 1 point added for each decade above 50 years old
NCI (1)	14 conditions	Based on the impact on 2-yr non-cancer mortality Sum of weighted indices (derived from hazards ratios, available on the NCI website)	0 to 21.14
NCI-lung (15)	13 conditions	Based on the impact on 2-yr non-cancer mortality Sum of weighted indices (derived from beta coefficients)	-0.143 to 4.243
Updated Elixhauser (18)	21 conditions	Used initially as a count (30 conditions) but modified by Van Walraven <i>et al.</i> Based on in-hospital mortality as the sum of the weighted score (hazards ratios derived from beta coefficients divided by the coefficient in the model with the smallest absolute value) (18)	-19 to 89
Elixhauser-lung (19)	16 conditions	Based on the impact on 2-yr non-cancer mortality Sum of the weighted indices (derived from the beta coefficient x 10)	-2 to 28

Table 2. Baseline characteristics and adjusted hazard ratios of four-month survival in the cohort (n = 633)

Population (n = 633)	Univariate analysis			Multivariate analysis		
	Characteristics	HR [95% CI]	P value	HR [95% CI]	P value	Type 3 P Value
Overall survival, months	4 [1; 11]					
Length of stay in the hospital (days)	11 [6; 20]					
Performance status at the first case presentation in multidisciplinary concertation meetings*						
PS 0-1	212 (53.1)					
PS 2	126 (31.6)					
PS 3-4	61 (15.3)					
Men	540 (71.0)	1.3 [1.0; 1.6]	0.07	1.3 [1.0; 1.7]	0.03	
Metastasis	428 (74.2)	2.0 [1.5; 2.6]	< 0.01	1.9 [1.3; 2.9]	< 0.01	
Histological type						< 0.01
Adenocarcinoma	295 (46.6)	1		1		
Squamous-cell carcinoma	103 (16.3)	0.9 [0.6; 1.2]	0.40	1.0 [0.7; 1.4]	0.87	
Undifferentiated carcinoma	67 (10.6)	0.4 [1.2; 0.8]	0.40	1.2 [0.8; 1.7]	0.33	
Small-cell lung cancer	132 (20.9)	0.7 [0.5; 0.9]	< 0.01	0.7 [0.5; 0.9]	< 0.01	
Other types	36 (5.7)	1.9 [1.2; 2.8]	< 0.01	1.9 [1.3; 2.9]	< 0.01	
Age during hospitalization	66 [58;73]	1.1 [0.9; 1.3]	0.54			
Age at diagnostic	65 [58;72]	1.1 [0.9; 1.3]	0.60			
Time of cancer diagnosis						
Diagnosis before hospitalization	518 (81.8)	1				
Diagnosis during or after hospitalization	115 (18.2)	0.9 [0.7; 1.2]	0.47			

Quantitative variables are expressed as medians [Interquartile range], qualitative variables are expressed as n (%)

*Missing data: n = 234

Table 3. Description of comorbidity in the population according to the Elixhauser score and Elixhauser-lung.

Population (n = 633)	Elixhauser	Elixhauser-lung
Congestive Heart Failure	46 (7.3)	46 (7.3)
Cardiac arrhythmias	77 (12.2)	
Vascular disease	22 (3.5)	22 (3.5)
Pulmonary circulation disorders	40 (6.3)	40 (6.3)
Peripheral vascular disorders	48 (7.6)	48 (7.6)
Paralysis	46 (7.3)	46 (7.3)
Neurodegenerative disorders	42 (6.6)	42 (6.6)
Chronic pulmonary disease	91 (14.4)	91 (14.4)
Renal failure	26 (4.1)	26 (4.1)
Liver disease	19 (3.0)	
Lymphoma	4 (0.6)	
Cancer*	65 (10.3)	
Coagulopathy	27 (4.3)	27 (4.3)
Obesity	11 (1.7)	11 (1.7)
Weight loss	345 (54.5)	345 (54.5)
Fluid and electrolyte disorders	91 (14.4)	
Blood loss anemia	6 (1.0)	
Deficiency anemia	14 (2.2)	
Drug abuse	8 (1.3)	
Depression	29 (4.6)	29 (4.6)
Diabetes with complications		11 (1.7)
Hypothyroidism		17 (2.7)
Rheumatological disorders		4 (0.6)
Psychosis		9 (1.4)

Qualitative variables are expressed as n (%)

**excluding lung cancer and metastatic solid tumor*

Table 4. Adjusted hazard ratios for four-month survival among the population (n = 633)

Comorbidity score	Median [Interquartile range]	HR [95% CI]	P value	Type 3 P value
CCI	0.0 [0.0; 2.0]			0.1
0		1		
1 or 2		1.1 [0.8; 1.4]	0.63	
≥ 3		1.4 [1.0; 2.1]	0.04	
ACCI*	3.0 [2.0; 4.0]			< 0.05
≤ 2		1		
3		1.0 [0.8; 1.4]	0.88	
4		1.3 [0.9; 1.7]	0.13	
≥ 5		1.6 [1.1; 2.1]	< 0.01	
CCI-lung	0.0 [0.0; 1.0]			0.08
0		1		
1 ≤ CCI-lung ≤ 2		1.1 [0.9; 1.5]	0.31	
≥ 3		1.5 [1.0; 2.2]	0.03	
NCI*	0.0 [0.0; 1.7]			0.47
0 < NCI ≤ 1		1		
1 < NCI ≤ 2		1.2 [0.9; 1.5]	0.30	
2 < NCI < 3		1.1 [0.7; 1.7]	0.63	
NCI ≥ 3		1.3 [0.9; 1.8]	0.16	
NCI-lung	0.0 [0.0; 0.33]			0.22
< 0		1		
0 = NCI ≤ 0.2		1.3 [0.7; 2.3]	0.50	
0.2 < NCI ≤ 0.4		1.6 [0.8; 3.2]	0.14	
NCI > 0.4		1.4 [0.8; 2.7]	0.26	
Elixhauser	6.0 [2.0; 11.0]			< 0.01
Elixhauser ≤ 0 to Elixhauser ≤ 5		1		
6 ≤ Elixhauser ≤ 11		1.4 [1.0; 1.8]	0.02	
Elixhauser > 11		1.6 [1.2; 2.1]	< 0.01	
Elixhauser-lung*	3.0 [0.0; 5.0]			< 0.01
≤ 0		1		
1 ≤ Elixhauser-lung ≤ 3		1.2 [0.9; 1.7]	0.14	
4 ≤ Elixhauser-lung ≤ 5		2.1 [1.5; 3.0]	< 0.01	
Elixhauser-lung > 5		1.5 [1.1; 2.0]	0.02	

Adjusted for sex, presence of metastases, and histological type. Quantitative variables are expressed as medians [Interquartile range]; In bold: $p < 0.05$

*sex is no longer significantly different in multivariate analysis with this score

Table 5. Discrimination parameters between the seven comorbidity scores

	AIC	BIC	Harrell's c-statistic	C-statistic	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)
Base model*	4755.8721	4758.0284	0.6141	0.649	62.84	59.68	69.59	52.23
Base model+CCI	4753.5483	4755.7528	0.6189	0.657	61.34	61.88	62.07	61.15
Base model+ACCI	4745.7800	4747.9845	0.6249	0.663	63.23	61.99	66.46	58.60
Base model+CCI-lung	4752.0853	4754.2898	0.6209	0.658	61.27	61.95	61.76	61.46
Base model+NCI	4751.9881	4754.1925	0.6194	0.656	62.69	59.52	69.59	51.91
Base model+NCI-lung	4749.9826	4752.1871	0.6236	0.658	60.90	61.37	61.76	60.51
Base model+Elixhauser	4744.7953	4746.9998	0.6314	0.673	64.66	62.57	68.65	58.28
Base model+Elixhauser-lung	4749.5804	4751.7849	0.6251	0.669	63.84	61.05	69.28	55.10

**Adjusted for sex, metastasis, and histological type*

Table 6. Comparison of the mean 1,000 values for the c-statistic and Harrell's c-statistic between each score.

<u>C-statistic</u>						
	CCI	ACCI	CCI-lung	NCI	NCI-lung	Elixhauser
ACCI	<0.001					
CCI-lung	<0.001	<0.001				
NCI	<0.001	<0.001	<0.001			
NCI-lung	<0.001	<0.001	<0.001	<0.001		
Elixhauser	<0.001	<0.001	<0.001	<0.001	<0.001	
Elixhauser-lung	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<u>Harrell's c-statistic</u>						
	CCI	ACCI	CCI-lung	NCI	NCI-lung	Elixhauser
ACCI	<0.001					
CCI-lung	<0.001	<0.001				
NCI	0.004	<0.001	0.47			
NCI-lung	<0.001	<0.001	<0.001	<0.001		
Elixhauser	<0.001	<0.001	<0.001	<0.001	<0.001	
Elixhauser-lung	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table S1. Characteristics of comorbidity scores to assess their burden on survival used in the literature in lung cancer, adapted from (8)

Score	Year of publication	Initial data source	System or condition on which it is based and the number of items	Population	Scoring method	Examples of references in lung cancer after development of the score
Kaplan Feinstein Index (KFI) (22)	1974	Clinical notes	12 systems	188 patients with diabetes	Highest score of single item	(23,24)
Cumulative Illness Rating Scale (CIRS) (25) and CIRS adapted for geriatric population (CIRS-G)(26)	1968	Clinical notes	13 or 14 systems	Not available	Sum of systems concerned	(27–30)
Charlson Comorbidity Index score (CCI) (7)	1987	Clinical notes	17 conditions	604 patients in general medical units	Sum of weighted indices (weights being equivalent to the (rounded) adjusted relative risks for 1-year mortality for each condition Updated by Quan et al. (14) Age-adjusted CCI is equal to the CCI score but 1 point has to be added for each decade above 50 years (16)	(3–5,31–35)
Elixhauser (17)	1998	Administrative data	30 conditions	1,779,167 adults in acute care hospital	Used initially as a count but modified by Van Walraven et al. as a weighted score (18) for in-hospital death	(36)
Tammamagi (9,10)	2003	Administrative data	19 conditions for lung cancer and 77 conditions for breast cancer	1155 patients with lung cancer and 906 patients with breast cancer	Condition count	/
Simplified Comorbidity Index (SCI) (11)	2005	Clinical notes	7 comorbidity categories	735 patients with lung cancer	Impact on mortality (beta coefficients from multivariable models).	(37–40)

Table S2. Description of comorbidity in the population according to CCI and CCI-lung

Population (n=633)	CCI	CCI-lung
Congestive heart failure	46 (7.3)	46 (7.3)
Dementia	4 (0.6)	4 (0.6)
Chronic pulmonary disease	94 (14.9)	94 (14.9)
Rheumatological disease	4 (0.6)	4 (0.6)
Mild liver disease	12 (1.9)	
Moderate or severe liver disease	9 (1.4)	
Diabetes with complications	11 (1.7)	11 (1.7)
Hemiplegia or paraplegia	49 (7.7)	49 (7.7)
Renal disease	26 (4.1)	26 (4.1)
Acute myocardial infarction		4 (0.6)
History of myocardial infarction		23 (3.6)
Cerebrovascular disease		33 (5.2)
Cancer*	65 (10.3)	
AIDS	1 (0.2)	

Qualitative variables are expressed as n (%)

**excluding lung cancer and metastatic solid tumors*

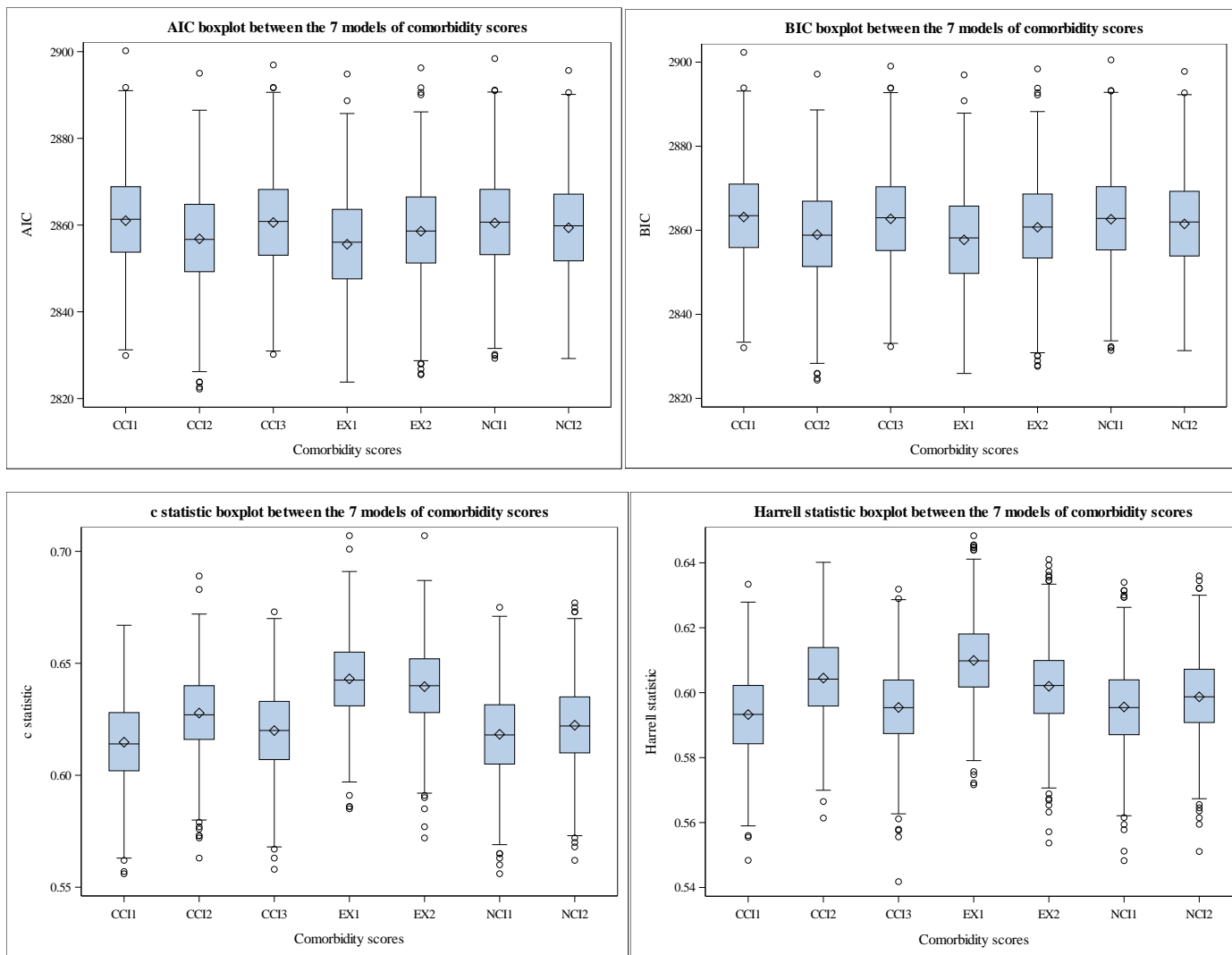
Table S3. Description of comorbidity in the population according to NCI and NCI-lung

Population (n=633)	NCI	NCI-lung
Acute myocardial infarction	4 (0.6)	4 (0.6)
History of myocardial infarction	23 (3.6)	23 (3.6)
Congestive Heart Failure	46 (7.3)	46 (7.3)
Peripheral Vascular disease	48 (7.6)	48 (7.6)
Cerebrovascular disease	33 (5.2)	33 (5.2)
Chronic Obstructive Pulmonary Disease	94 (14.9)	94 (14.9)
Dementia	4 (0.6)	4 (0.6)
Paralysis	49 (7.7)	49 (7.7)
Diabetes or diabetes with complications	65 (10.3)	70 (11.1)*
Renal disease	26 (4.1)	26 (4.1)
Mild liver disease or liver disease	15 (2.4)	
Peptic ulcer disease	6 (1)	6 (1)
Rheumatological disease	4 (0.6)	4 (0.6)
AIDS	1 (0.2)	

Qualitative variables are expressed as n (%)

**in the NCI-lung score, this comorbidity is divided for diabetes (59 (9.3)) and diabetes with complications (11 (11.7)). The difference is explained by the fact that five individuals were coded with both diabetes with no complications and diabetes with complications*

Figure 1. AIC, BIC, c-statistic, and Harrell's c-statistic boxplots for the 1,000 values of each score.



CCI1: CCI, CCI2: ACCI, CCI3: CCI-lung, EX1: Elixhauser, EX2: Elixhauser-lung, NCI1: NCI, NCI2: NCI-lung

5. Impact de la polymédication et des comorbidités sur la survie et sur l'administration du traitement systémique

Enfin, nous avons pu mener à bien l'étude nous permettant de répondre à la question posée.

- Concernant les comorbidités, le score d'Elixhauser a été utilisé comme décrit précédemment.
- Concernant les médicaments, nous avons récupéré la totalité des médicaments prescrits pour chacun des patients, au cours de toutes leurs hospitalisations, incluant les cures de traitement anticancéreux et les autres médicaments. Cette base de données sur les médicaments a été scindée en deux comme décrit dans le protocole. L'une comportait la première cure de traitement après la date de première hospitalisation. Une deuxième base contenait seulement les prescriptions médicamenteuses hors chimiothérapie.

Les listes de médicaments étaient fournies en ligne de médicaments, et donc pour un patient et pour une hospitalisation, plusieurs lignes de médicaments étaient présentes. Il a donc fallu sélectionner la première hospitalisation en oncologie thoracique, puis faire un data management afin d'avoir une ligne par patient, contenant les médicaments prescrits. Nous avons estimé qu'une seule administration de médicament suffisait pour être comptabilisée.

Nous avons exclu les traitements anticancéreux, les médicaments anti-émétiques et les substituts de perfusion de l'analyse, considérant que cela ne correspondait pas au traitement des comorbidités des patients.

Les résultats sont présentés dans la publication n°4.

Publication n°4

Impact of polypharmacy and comorbidities on survival and systemic treatment administration in a cohort of hospitalized lung cancer patients

Hélène Pluchart, Sébastien Bailly, Sébastien Chanoine, Denis Moro-Sibilot, Pierrick

Bedouch, Anne-Claire Toffart

Soumis

Impact of polypharmacy and comorbidity on survival and systemic treatment administration in a cohort of hospitalized lung-cancer patients

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Abstract

Introduction

Although polypharmacy has been described among cancer patients, very few studies have focused on those with lung cancer. We aimed to assess whether polypharmacy and comorbidity have an impact on systemic treatment administration and survival among lung-cancer patients.

Methods

In this retrospective monocenter cohort study, we included patients hospitalized in thoracic oncology for the first time between 2011 and 2015. The Elixhauser score was used to assess comorbidity and polypharmacy was estimated with a threshold of at least five prescribed medications. The Fine and Gray competitive risk model was used to estimate the impact of polypharmacy and comorbidity on systemic treatment administration within the first two months of hospitalization. The effect of comorbidity and polypharmacy on overall survival was evaluated by Cox proportional hazards analysis.

Results

In total, 633 patients were included (71% men), with a median age of 66 years. The median Elixhauser score was 6 and median overall survival was four months. Among the patients, 24.3% were considered to be receiving polypharmacy, with a median number of medications of 3, and 49.9% received systemic treatment within two months after hospitalization. Severe comorbidity (Elixhauser score > 11), but not polypharmacy, was independently associated with a lower rate of systemic treatment prescription (SdHR = 0.4 [0.3;0.6], $p < 0.01$) and polypharmacy, but not a high comorbidity score, was independently associated with poorer four-month survival (HR= 1.4 [1.1;1.9], $p < 0.01$)

Conclusions

This first study to evaluate the consequences of comorbidity and polypharmacy on the care of lung-cancer patients shows that a high comorbidity burden can delay systemic treatment administration, whereas polypharmacy has a negative impact on four-month survival.

Keywords

Lung cancer, comorbidity, polypharmacy, survival

Introduction

With a median age at diagnosis of 70 years (1), lung cancer mainly concerns the elderly. In addition to their being diagnosed at advanced stages (2,3), lung-cancer patients are mostly diagnosed with prior comorbidities due to smoking (4,5). Comorbidities negatively influence lung cancer survival and have consequences on treatment strategies (4,6,7).

In parallel, comorbidities are generally associated with polypharmacy because they require the prescription of medications. Moreover, anticancer treatment can lead to side effects and symptomatic treatment prescriptions, with frequent polypharmacy (8). The resulting consequences can be important. For example, polypharmacy for chronic comorbid conditions can induce drug-drug interactions with anticancer treatment (9) or lead to a higher risk of side effects (10).

Polypharmacy has been reported to be a potential risk factor for death (11). We aimed to determine whether comorbidity and polypharmacy have an impact on systemic treatment administration and survival, specifically for lung cancer patients.

Material and methods

Population

Patients hospitalized in the Thoracic Oncology Unit of Grenoble University Hospital from 2011 to 2015 were included. The design of this study has been described in an earlier publication (12). Lung-cancer patients were included at their first hospitalization during the study period. Ethics committee approval for the study was obtained on September 1, 2021 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Objectives

The primary objective was to assess the impact of polypharmacy and comorbidities on systemic treatment administration after the first hospitalization in thoracic oncology. The primary outcome was the time to systemic treatment administration after the date of hospitalization (within 2 months). Two months was chosen as the cut-off because it

corresponds to the postponement of systemic treatment administration due to toxicity and delays beyond this timepoint are considered to be due to reasons other than systemic treatment-related toxicity.

As a secondary objective, we assessed the impact of polypharmacy and comorbidity on overall survival, estimated as the time between the day of hospitalization and the date of last follow-up (cut off at median overall survival).

Data collection

The database contains information on individuals including age, gender, lung cancer tumor (T), node (N), and metastasis (M) (TNM) staging, histological type, performance status at the first case presentation in multidisciplinary concertation meetings, the Elixhauser score for comorbidities (13), and every medication administered throughout the hospitalization.

Polypharmacy was defined as > 5 administered medications. A medication was considered if the patient had at least one dose. Each medication was translated using its fourth, third, and second level in the Anatomical Therapeutic Chemical (ATC) Classification System. Anticancer treatment, anti-emetic drugs, blood substitutes, and perfusion solutions were not studied because they were not prescribed for chronic comorbidities.

Survival data were obtained from our district cancer registry, including the date of the last follow-up and vital status at the last follow-up.

Statistical analyses

For descriptive analyses, quantitative variables are expressed as medians [Interquartile range] and qualitative variables as n (%).

Median overall survival depending on comorbidity and polypharmacy was assessed by estimating the probability of survival using the Kaplan Meier estimator. Survival curves were compared using Log-rank tests. A Cox proportional hazards regression model was used to identify factors associated with survival. Univariable and multivariable analyses were performed. Proportional hazards assumptions were verified using the Martingale

method. Only covariables with $p < 0.2$ in univariable analysis were retained for multivariable analysis.

The impact of polypharmacy and comorbidities on systemic treatment administration was determined using the Fine and Gray competing risk regression model to account for the competitive risk of death (19). Sub-distributed hazard ratios (SdHRs) and their confidence intervals [CI95] were calculated.

Age, gender, metastasis, histological type, polypharmacy, the Elixhauser score, age at hospitalization, and age at diagnosis were included as covariates. A severe Elixhauser threshold score was defined as the third interquartile range of the median score. Performance status was not included because of missing data. For the secondary objective, TNM stage, time of diagnosis (after or before hospitalization), and time to systemic treatment prescription (used as a time-dependent variable) were also included.

All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA). A P-value < 0.05 was considered significant.

Results

Patient characteristics

In total, 633 patients were included, with a median age of 66 years (Table 1). They were mostly men (71%) and most patients had metastatic lung cancer (428 [74.2%]). According to the Elixhauser score, weight loss and chronic pulmonary disease were the two most common comorbidities in the population (345 [54.5%] and 91 [14.4%] patients, respectively).

The median number of medications was 3 [IQ25% 2- IQ75% 4] and the number of patients with polypharmacy was 154 (24.3%).

Medication description

Among the medications, the ten most prescribed ATC codes, according to the second level of the ATC classification system, are presented in Table 2. Approximately 4 of 10 patients received analgesics and corticosteroids for systemic use. A quarter of patients

also received mineral supplements, whereas drugs for constipation and antibacterial and antithrombotic agents were prescribed for 2 of 10 patients.

Factors associated with systemic treatment administration and survival

Median overall survival was four months and the median Elixhauser score was 6.0 [IQ25% 2.0; IQ75%11.0] (Table 1). By two months within hospitalization, 316 (49.9%) patients received systemic treatment, 175 (27.6%) died without receiving systemic treatment, and 142 (22.4%) were alive without receiving systemic treatment. systemic treatment was prescribed and administered after a median of 11 [IQ25% 4 ; IQ75% 22] days for patients receiving systemic treatment within two months.

Consideration of the SdHR with the competing event (death) for the outcome of systemic treatment administration showed that only severe comorbidity (Elixhauser score > 11) led to a lower rate of systemic treatment prescription (SdHR = 0.4 [0.3;0.6], $p < 0.01$) (Table 3).

Overall survival according to the Elixhauser score was 11.4 [IQ25% 2.0; IQ75% 17.0] months for an Elixhauser score between 0 and 5, 6.8 [1.0; 8.0] months for an Elixhauser score between 6 and 11, and 6.7 [IQ25% 1.0 ; IQ75% 8.0] months for an Elixhauser score > 11. Only polypharmacy (threshold of 5 medications) was a negative prognostic factor of survival in multivariate analysis (HR = 1.4 [1.1-1.9], $p < 0.01$) (Table 4).

Discussion

This study shows that severe comorbidity (assessed by the Elixhauser score) is associated with a lower rate of systemic treatment prescription within two months of hospitalization, whereas polypharmacy is an independent prognostic factor of death within four months of first hospitalization

We found polypharmacy to be present for 24.3% of patients, which is lower than that reported in previous studies concerning various cancer types. Previous studies found polypharmacy to range from 33 to 59.9% among lung-cancer patients (14,15). In these studies, the estimated number of drugs was based on the number of unique prescriptions

in the month prior to the diagnosis or as any therapeutic drug used to manage a comorbid condition outside of lung cancer between the last visit and day 1 of the oncology treatment. However, these studies did not indicate whether they counted, for example, anti-emetic drugs. In another recent study, the median number of prescribed medications during the six-month period before chemotherapy administration for lung cancer patients was 11 (16). Among elderly patients with any type of cancer, Nightingale et al. reported a mean number of medications of nine associated with a prevalence of polypharmacy of 41% (17). In this study, patient medications were assessed during a pharmacist-patient session to which they had to bring all medications (prescription, nonprescription, herbals, and supplements) they had at home. We did not have access to data on self-medications or herbal medications in our study. The lower rate of polypharmacy found in our cohort could be explained by the fact that complementary and alternative medicines are widely used by lung-cancer patients (reported to be from 30 to 50% of patients (18,19)). In addition, only prescribed medications were considered in our study, excluding anticancer treatment, anti-emetics, blood substitutes, and perfusion solutions. Within two months after hospitalization, 175 (27.6) patients died without receiving chemotherapy. Given the poor prognosis, certain medications were probably stopped in light of the benefit-risk balance for the patient.

Polypharmacy has been shown to be possibly related to greater chemotherapy toxicity (10). Here, we did not have information on the potential side effects after systemic treatment. Sud et al. reported the impact of polypharmacy on increased hospitalization rates, with toxicity rather than polypharmacy leading to the discontinuation of anticancer therapy among those aged 80 and over (20), whereas Lu-Yao et al. showed polypharmacy to be a predictive factor of inpatient hospitalization after chemotherapy administration (16). Another explanation may be due to the study design. We estimated polypharmacy by the number of medications received. Some may have been prescribed as symptomatic treatment due to an adverse event, increasing the number of medications received. It is possible that the burden of comorbidity itself influences the physician's decision whether or not to prescribe systemic treatment rather than the number of medications. Patients with severe comorbidity, defined by an Elixhauser score > 11, were significantly less likely to receive systemic treatment within two months after their first

hospitalization, with no impact of polypharmacy. One explanation may be that there is probably no treatment impact on systemic treatment prescription for comorbidities that are well managed by treatment. The impact of comorbidities on the prescription of treatment was expected, as concomitant comorbid conditions potentially lead to increased toxicity of systemic treatment (21). The 10 most prescribed drugs that we found, according to their second level ATC code, are consistent with those reported in the literature (4,22). The comorbidity burden has been reported to decrease the prescription of systemic treatment in colorectal, breast, and bladder cancer (23–25). Few studies in lung cancer are available but they also reported an association between a high comorbidity burden and systemic treatment administration (26–28).

In terms of the impact of polypharmacy and comorbidity on survival, our findings are consistent with those of Hakozaiki et al., who reported an association between polypharmacy and lower overall survival but not progression-free survival for lung cancer patients receiving immune oncology treatments (15). The impact of comorbidity on survival has also been reported to be less important for patients with a poor prognosis. Indeed, Piccirillo et al. showed that comorbidity was prognostically of less importance for diseases with a short-term prognosis, such as lung cancer (29).

A strength of our data is the large sample size, associated with a robust statistical analysis, provided by the use of several datasets with a deterministic linkage. Our study, however, also had several limitations. Because of the study design, we did not consider drug-drug interactions. In addition, no data on side effects after systemic treatment were available. Finally, we could not consider self-medication or complementary or alternative medicines due to the retrospective monocenter design of our study.

Conclusion

In this study, severe comorbidity had an impact on systemic treatment prescription, whereas polypharmacy was associated with poorer survival. Access to the National Health Insurance Cross-Scheme Information System could be useful to better describe

the link between polypharmacy, comorbidity, and their consequences on anticancer treatment and survival, and prospective studies should be performed.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891.

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Table 1. Description of the population

	Population (n = 633)
<i>Patients' characteristics and comorbidities</i>	
Age (years)	66 [58; 73]
Gender = Men	540 (71)
Elixhauser Score	6.0 [2.0; 11.0]
Two most common comorbidities according to the Elixhauser score	
Weight loss	345 (54.5)
Chronic pulmonary disease	91 (14.4)
Performance status at the first presentation in multidisciplinary concertation meetings*	
• PS 0-1	212 (53.1)
• PS 2	126 (31.6)
• PS 3-4	61 (15.3)
Metastasis	428 (74.2)
Histological type	
• Adenocarcinoma	295 (46.6)
• Squamous-cell carcinoma	103 (16.3)
• Undifferentiated	67 (10.6)
• SCLC	132 (20.9)
• Other	36 (5.7)
<i>Medication</i>	
Number of medications	3 [2-4]
Polypharmacy (excluding anticancer treatment, anti-emetic drugs, blood substitutes, and perfusion solutions)	154 (24.3)
<i>Outcomes/survival</i>	
Overall survival (months)	4 [1; 11]
Patients having systemic treatment within two months	316 (49.9)
Death within two months without receiving systemic treatment	175 (27.6)
Alive two months without systemic treatment	142 (22.4)
Time to systemic treatment administration (days)	13 [5-29]
Time to systemic treatment administration for patients receiving systemic treatment within two months (n = 316) (days)	11 [4-22]

Quantitative variables are expressed as medians [Interquartile range], qualitative variables are expressed as n (%)

**Missing data: n = 234*

Table 2. The ten most prescribed medications according to the second level of the ATC Classification System.

ATC Code (according to second level of ATC Classification System)*	Population (n = 633)
N02 (Analgesics)	265 (41.9)
H02 (Corticosteroids for systemic use)	258 (40.8)
A12 (Mineral supplements)	162 (25.6)
A06 (Drugs for constipation)	129 (20.4)
J01 (Antibacterials for systemic use)	118 (18.6)
B01 (Antithrombotic agents)	112 (17.7)
V03 (All other therapeutic products)	74 (11.7)
A10 (Drugs used in diabetes)	57 (9.0)
R03 (Drugs for obstructive airway diseases)	36 (5.7)
R06 (Antihistamines for systemic use)	40 (6.3)

Qualitative variables are expressed as n (%)

**Excluding anticancer treatment, antiemetics, and antiemetics, blood substitutes and perfusion solutions*

Table 3. SdHR for receiving systemic treatment considering death as a competing event among the population (n = 633)

	Univariable analysis			Multivariable analysis*		
	sdHR	CI95	P-value	sdHR	CI95	P-value
Elixhauser						
< 0 < x ≤ 5	1			1		
6 ≤ x ≤ 11	0.8	0.6-1.0	0.08	0.8	0.7-1.1	0.19
> 11	0.4	0.3-0.6	< 0.01	0.4	0.3-0.6	< 0.01
Polypharmacy	1.3	1.0-1.6	0.06	1.2	1.0-1.6	0.10

Quantitative variables are expressed as medians [Interquartile range]

**Adjusted for the presence of metastasis, male gender, and histological type*

Table 4. Adjusted hazard ratio of four-month survival among the population (n = 633)

	Overall survival	Univariable analysis			Multivariable analysis*		
		HR	CI95	P-value	HR	CI95	P-value
Elixhauser							
< 0 < x ≤ 5 (n = 234)	11.4 [2.0;17.0]	1			1		
6 ≤ x ≤ 11 (n = 245)	6.8 [1.0;8.0]	1.5	1.1-1.9	< 0.01	1.2	0.9-1.6	0.14
> 11 (n = 154)	6.7 [1.0;8.0]	1.8	1.3-2.4	< 0.01	1.1	0.8-1.5	0.64
Polypharmacy		1.2	1.0-1.6	0.09	1.4	1.1-1.9	< 0.01

*Adjusted for the presence of metastasis, TNM stage, male gender, histological type, time of diagnosis, and time to chemotherapy as a time-dependent variable

6. Discussion

Ce travail a permis de mettre en avant la complexité des relations qui existent entre le patient, son cancer, les comorbidités et la polymédication.

La revue narrative de la littérature propose une synthèse qui met en avant les liens entre ces entités. Toutefois, il y a peu de données spécifiques aux patients avec un cancer du poumon alors qu'il représente le cancer pour lequel il existe le plus de comorbidités au diagnostic [2,3]. Il y a donc un vrai intérêt à comprendre les impacts des uns sur les autres, afin de mieux anticiper, et prévenir leurs conséquences qui pourraient être délétères pour le patient et sa prise en charge.

6.1. Scores de comorbidités et survie

Grâce à cette étude, nous avons montré que c'est le score d'Elixhauser qui permet de mieux prédire la mortalité dans notre cohorte (survie censurée à 4 mois). Nous avons comparé 7 scores de comorbidités, choisis par leur facilité d'utilisation car utilisables avec la Classification CIM-10. D'autres scores existent et sont utilisables sans accès à la codification des comorbidités selon cette classification [18].

D'autres études ont comparé différents scores de comorbidités en cancérologie thoracique. L'étude de Mehta et al. s'est notamment intéressée aux score de Charlson, d'Elixhauser et du National Cancer Institute [58]. Ce travail propose un score d'Elixhauser adapté au cancer du poumon et c'est ce dernier qui prédit le mieux la mortalité à deux ans, non liée au cancer. Dans une autre étude s'intéressant à des patients ayant un cancer du poumon opéré, Yang et al. ont comparé le score de Charlson, le score de Charlson adapté à l'âge et le score d'Elixhauser sur la mortalité à trois ans (mortalité lié au cancer ou non). Dans cette étude c'est le score de Charlson adapté à l'âge qui est le meilleur score [59]. Plusieurs différences sont à noter entre ces études et celle que nous avons réalisé : Nous n'avons pas pu différencier les décès liés au cancer des décès liés à d'autres causes dans notre base de données, ce qui en fait une limite. De plus, nous avons étudié la survie à 4 mois, qui se rapproche de la mortalité hospitalière, mieux prédite avec le score d'Elixhauser. Cela est différent des autres scores qui étaient

associés à la survie à 1 an, voire 2 ans. Ainsi, il est important de choisir le score de comorbidité permettant le mieux de prédire la variable étudiée.

6.2. Polymédication et comorbidités

Enfin, grâce à l'évaluation de la polymédication et des comorbidités, nous avons pu voir leur impact sur la réalisation du traitement systémique à 2 mois après hospitalisation et sur la survie des patients avec une censure des données de survie à 4 mois (médiane de survie dans notre étude). Seuls 24.3% des patients avaient une polymédication, avec un nombre médian de médicaments de 3, en excluant les médicaments anti-émétiques, les anti-cancéreux et solutés de perfusion.

Dans la littérature, le nombre de médicament est plutôt de 5 à 11. Il est inférieur dans cette cohorte. Mais les méthodologies de décompte du nombre de médicament sont très différentes selon les études : certaines utilisent la consultation pharmaceutique en incluant les médecines alternatives et complémentaires ainsi que l'automédication [19], d'autres se basent sur les dossiers médicaux [26]. Dans le cancer du poumon, des études récentes ont montré des résultats différents des nôtres avec un nombre médian de 6 à 11 médicaments [27,28] (mais sans préciser la prise en compte des anti-émétiques pour l'étude de Hakozaki et al., et en utilisant les bases de données de Medicare qui est le système d'assurance-santé géré par le gouvernement fédéral des États-Unis pour l'étude de Lu-Yao et al.). Des résultats similaires à notre étude ont été cependant retrouvés [24,25]. Il apparaît donc que la méthode de comptabilisation du nombre de médicament dans les études n'est pas homogène et rend les comparaisons difficiles. Nous pouvons peut-être expliquer le faible nombre de médicaments par le fait que nous nous intéressons aux prescriptions en hospitalisation et que parfois, à l'admission les traitements peuvent être simplifiés du fait de l'état général du patient. Une autre explication est la forte proportion de décès à deux mois dans notre cohorte, de patients qui n'ont pas reçus de traitement systémique avec un taux de décès de 27.6%. Les traitements ont probablement été simplifiés pour ces patients au vu du rapport bénéfice-risque défavorable de ces traitements.

Cependant, il est intéressant de noter que parmi les classes de la classification Anatomique, Thérapeutique et Chimique (ATC) les plus prescrites figurent les classes des anti-thrombotiques, des médicaments anti-diabétiques et des médicaments des voies respiratoires, ce qui est en cohérence avec la littérature qui décrit qu'au diagnostic les patients ayant un cancer du poumon ont pour la plupart comme comorbidités au diagnostic : une bronchopneumopathie chronique obstructive, du diabète, une maladie rénale et des maladies vasculaires périphériques ou cérébrales [2,3].

Les comorbidités ont un impact sur l'administration du traitement systémique à deux mois après hospitalisation, ce qui est cohérent avec la littérature [2,6,7]. Cependant, celles-ci n'ont pas d'impact sur la survie dans l'analyse multivariée en prenant en compte la polymédication. Il a déjà été montré qu'il est difficile d'identifier l'impact des comorbidités sur des survies à court terme [60]. Enfin, la polymédication est bien un facteur indépendant de mauvais pronostic sur la survie à 4 mois des patients, ce qui a été également rapporté dans une autre étude récente [27], mais n'a pas d'impact sur l'administration du traitement systémique. Il a été plutôt décrit dans la littérature un impact sur la survenue d'effets indésirables après traitement systémique ou sur les hospitalisations après réalisation du traitement systémique [28,35,36].

6.3. Forces et faiblesses

L'appariement déterministe a permis de contrôler la qualité des données et l'absence de données manquantes sur les critères d'objectif principal et objectifs secondaires. Pour réaliser cet appariement déterministe il a fallu récupérer les données dans des bases existantes, et les reformater. L'étude montre que l'appariement déterministe de plusieurs bases de données est faisable à des fins d'étude pharmaco-épidémiologiques. Les données de comorbidités codées en utilisant la CIM-10 ont pu également mettre en avant l'importance d'évaluer le poids des comorbidités en comparant différents scores utilisant la CIM-10. Une telle comparaison de différents scores n'a pas été décrite dans la littérature. De même, l'impact de la polymédication et des comorbidités n'a pas été décrit dans le cancer du poumon dans la littérature. Les données sont déjà existantes et donc cela nécessite moins de temps pour récupérer la base de données complète qui recouvre plusieurs années. En effet, même si une étude prospective serait intéressante, elle serait

également difficile de par la grande quantité de données à récupérer, et pour le suivi qui en est nécessaire.

Parmi les faiblesses de ce travail, on peut noter la période de l'étude de 2011 à 2015 qui peut sembler ancienne compte tenu des évolutions thérapeutiques récentes. Tout d'abord, il s'intéresse à la période 2011 à 2015. En effet, les données du registre du cancer de l'Isère sont complètes à N-3. Ce travail est un travail rétrospectif et monocentrique, cela représente un faible nombre de patients car en réalisant l'appariement déterministe, toutes les données ne sont disponibles que pour 633 patients communs à toutes ces bases.

De plus, nous n'avons pas pu prendre en compte les nouvelles thérapies autorisées sur le marché depuis. En effet, les patients se fournissent en pharmacie de ville. Seule l'utilisation des données du SNIIRAM auraient pu nous le permettre. Les traitements des patients ont été estimés à partir de ceux administrés en hospitalisation et donc cela représente une estimation de l'exposition du patient au médicament, mais non des traitements pris au long cours par les patients. En effet, en hospitalisation il peut y avoir un arrêt de certains traitements chroniques. Au vu de la faible médiane du nombre de traitements (trois), la récupération des données via les données de prescription hospitalières n'est peut-être pas la plus pertinente pour mesurer l'exposition du patient aux médicaments. Cependant, quand on regarde les 10 classes ATC les plus prescrites cela est cohérent avec les comorbidités les plus souvent rencontrées chez ces patients. Les comorbidités ont été récupérées via le département d'information médicale, et seulement les comorbidités prises en charge durant l'hospitalisation ou en lien avec l'hospitalisation ont été prises en compte. Ainsi, certaines comorbidités n'ont probablement pas été identifiées.

7. Conclusion

En conclusion, ce travail a permis de montrer la complexité du lien entre le patient, ses comorbidités, la polymédication et leurs conséquences respectives des uns sur les autres. Il démontre également qu'il est possible de travailler sur des données massives en santé en regroupant les données de plusieurs bases de données, afin de répondre à des questions de pharmaco-épidémiologie. Le score de Charlson qui est majoritairement utilisé dans la littérature n'est pas forcément le score qui décrit au mieux l'impact des comorbidités sur la mortalité selon le type de cohorte que l'on utilise. Enfin, la polymédication estimée par l'exposition aux médicaments en hospitalisation est un facteur de mauvais pronostic sur la survie des patients.

8. Perspectives

La prochaine étape de ce travail est la validation de nos résultats pour la même cohorte de patients à partir des données de la Plateforme de Recueil et d'Exploitation de Données bloMEDicales (PREDIMED).

8.1. Données massives en santé et Plateforme de Recueil et d'Exploitation de Données bloMEDicales (PREDIMED)

Ce travail rentre également dans le champ de l'utilisation des données massives appliquées à la santé. Grâce à l'informatisation des données des patients et à l'élaboration d'algorithmes, l'utilisation de ces données dans le domaine de l'intelligence artificielle ouvre de très nombreuses possibilités dans le domaine de la santé qui ont déjà été décrites [61,62], comme l'utilisation de cette technologie pour faire un diagnostic, avec la même performance qu'une évaluation médicale [63]. En particulier, les entrepôts de données de santé permettent le stockage et l'utilisation de telles données. Au Centre Hospitalier Universitaire de Grenoble, la Plateforme de Recueil et d'Exploitation de Données bloMEDicales (PREDIMED) est un entrepôt de données de santé autorisé depuis le 10 octobre 2019 par la Commission nationale de l'informatique et des libertés et regroupe l'ensemble des données générées au cours de la prise en charge des patients au sein de l'institution, qu'elles soient relatives aux soins, administratives ou autres. Cet entrepôt de données a déjà pu démontrer autour de trois études de cas une preuve de concept. Le premier cas a été de sélectionner une population de patients en fonction de diagnostics (diabète), de données démographiques et de critères de traitement, le deuxième cas a étudié les mutations somatiques chez 60 patients en oncologie afin de déterminer la signature génétique des caractéristiques clinico-biologiques, et enfin 300 patients ayant un cancer du poumon ont été sélectionnés grâce aux mots-clés présents dans les dossiers informatiques, et en reliant toutes les données de ces patients dont leurs imageries [64]. Une autre perspective de ce travail serait donc de sélectionner les 633 patients de la cohorte et de récupérer les données nécessaires à ce travail via l'entrepôt de données PREDIMED et de comparer les résultats avec ceux obtenus précédemment. Ces entrepôts de données, qui ouvrent la porte à de nombreux

travaux, ont par exemple comme objectif de prédire la survenue d'une épidémie, détecter des événements indésirables liés aux médicaments. Toutes ces possibilités expliquent l'essor de l'intelligence artificielle dans le domaine de la santé. Ici, nous nous sommes intéressés à l'impact de la polymédication et des comorbidités sur l'administration du traitement systémique et donc de sa reprise. De nombreuses études s'intéressent à la création d'outils d'aide à la décision comme l'illustre l'étude DIAL proposée par l'Institut Francophone de Cancérologie Thoracique qui se penche sur la décision d'arrêt du traitement.

8.2. Système national d'information inter-régimes de l'Assurance maladie et information sur les thérapies par voie orale

Il serait intéressant de récupérer la dispensation de médicaments en pharmacie d'officine avec les données du SNIIRAM afin d'avoir une meilleure photographie de la prise de médicaments de ces patients. Le SNIIRAM constitue un des trois systèmes sources du système national des données de santé (SNDS). Il a été créé en 2017 dans le cadre de la loi de modernisation de notre système de santé, et est un dispositif résultant de la fusion des principales bases de données de santé publiques françaises dont le SNDS [65]. Le SNIIRAM contient des informations sur les prestations de soins (actes médicaux ou biologiques, délivrances de médicaments ou dispositifs médicaux...) remboursées par l'ensemble des régimes d'assurance maladie pour le secteur libéral, ainsi que des informations relatives aux bénéficiaires comme l'âge, le sexe, le lieu de résidence, le bénéfice de la couverture maladie universelle complémentaire, les affections de longue durée. Cet accès serait pertinent car les médicaments prescrits en hospitalisation ne sont parfois pas exactement ceux que prennent les patients à domicile.

De plus, au-delà de la prescription des médicaments pour traitement chronique, cet accès permettrait également d'avoir des données exhaustives sur la dispensation de thérapies par voie orale, thérapeutiques prescrites en cas de mutation du récepteur à l'épidermal growth factor ou de réarrangement de l'anaplastic lymphoma kinase.

Il serait donc pertinent de s'intéresser aux mêmes questions tout en utilisant les données de la SNIIRAM.

8.3. Vers une définition du médicament inapproprié chez le patient ayant un cancer du poumon ?

Chez la personne âgée, il existe la notion de médicament inapproprié défini en 2012 par les critères de Beers [66] ou par les critères dits STOPP pour Screening Tool of Older Person's Prescriptions [67]. Ce sont des médicaments pour lesquels le rapport bénéfice risque est défavorable dans cette population, avec un risque élevé d'effets indésirables ou d'interactions médicamenteuses. L'utilisation de médicaments inappropriés chez la personne âgée ont déjà été décrit dans un contexte de cancer [22,23,68]. De cette notion de médicament inapproprié chez la personne âgée, on peut se demander s'il n'existe pas également des médicaments appropriés, ou inappropriés chez le patient ayant un cancer du poumon.

En effet, Il a été décrit l'impact négatif de la classe des inhibiteurs de la pompe à protons lors de l'administration de thérapies par voie orale ciblant le récepteur de l'épidermal growth factor avec notamment un impact négatif sur la survie [33,69,70]. D'autres travaux se sont intéressés à la metformine qui aurait un effet suppresseur de tumeur associé à une meilleure survie globale et sans progression [29,71]. Les effets anticancéreux des statines restent des hypothèses et non constants [72–76].

En partant de ces hypothèses, en se focalisant sur ces classes médicamenteuses comme les statines ou la metformine il serait donc approprié de voir leur impact sur la survie dans notre cohorte.

8.4. Définition des comorbidités à partir du traitement médicamenteux

Nous sommes partis dans notre étude de la définition de comorbidité par le PMSI, en se focalisant sur les comorbidités prises en charge au décours de l'hospitalisation ou qui sont apparues au cours de cette hospitalisation.

Une piste serait de partir des traitements médicamenteux administrés en hospitalisation des patients pour définir les comorbidités présentes et confronter aux résultats que nous avons de comorbidités chez les patients.

Une publication récente de 2018 décrit les classes ATC (classification au 5ème niveau de chaque médicament) correspondant à 46 comorbidités appartenant au Rx-Risk Comorbidity Index [77]. Il serait judicieux de comparer les comorbidités obtenues par cet outil des comorbidités obtenues avec le PMSI.

En conclusion, ce travail montre la complexité du lien entre cancer du poumon, comorbidité, polymédication. Il montre également l'impact des comorbidités sur la prescription du traitement systémique et de la polymédication sur la survie des patients. Les prochaines étapes de ce travail seront de comparer ces données avec la plateforme PREDIMED et d'accéder aux données de pharmacie de ville avec la SNIIRAM.

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