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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. Comorbidities will be assessed using Elixhauser score.

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 use 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 internal 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 study will serve as a “case study” for our institution in the context of a feasibility study to create a data warehouse (17,18).

Conflict of interest

HP, SC, JF, PD, PB have nothing to disclose related to the submitted work. ID received accommodations from BMS. ACT received personal fees and non-financial support from Astra Zeneca, BMS, MSD, Novartis, Boehringer Ingelheim, Roche, Pfizer.

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Figure legends

Figure 1. Dataset linkage method.

The highlighted data are the ones used for merging.

Figure 2. Statistical considerations for primary objective 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)	<ul style="list-style-type: none"> -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)	<ul style="list-style-type: none"> - 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)	<ul style="list-style-type: none"> - 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 1. Primary and secondary objectives, their endpoints, and statistical analyses.

	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

Table 2. Description of the four datasets.

Health information services department
Dataset A

District cancer registry
Dataset B

Multidisciplinary concertation meetings
Dataset C

Computerized prescriptions
Dataset D

First hospitalization in thoracic oncology between 2011 and 2015 with bronchopulmonary cancer (C34.0 to 9) in one of the diagnoses

Registered patient in the district cancer registry, with bronchopulmonary cancer, living in our department

Patient discussion at multidisciplinary concertation meetings

Computerized prescriptions of the 737 identifying numbers for all hospitalizations

n=1340

n=737

n=3353 case presentation for 1833 patients

n=635

Patient's identifying number

Dataset E

n=737

Name/First name

Date of birth

Dataset F

n=737

Patient's identifying number

Hospitalization start date

Dataset I

n=635

Chemotherapy base

Dataset G

n=635

Prescription base

Dataset H

n=635

→ Deterministic data linkage

Patient's identifying number

Hospitalization start date

Dataset J

n=635

-Patient's identifying number

-Hospitalization start date

-Principal and related diagnoses

-Vital status at last follow-up

-Date of last follow-up

-Performance status at the first

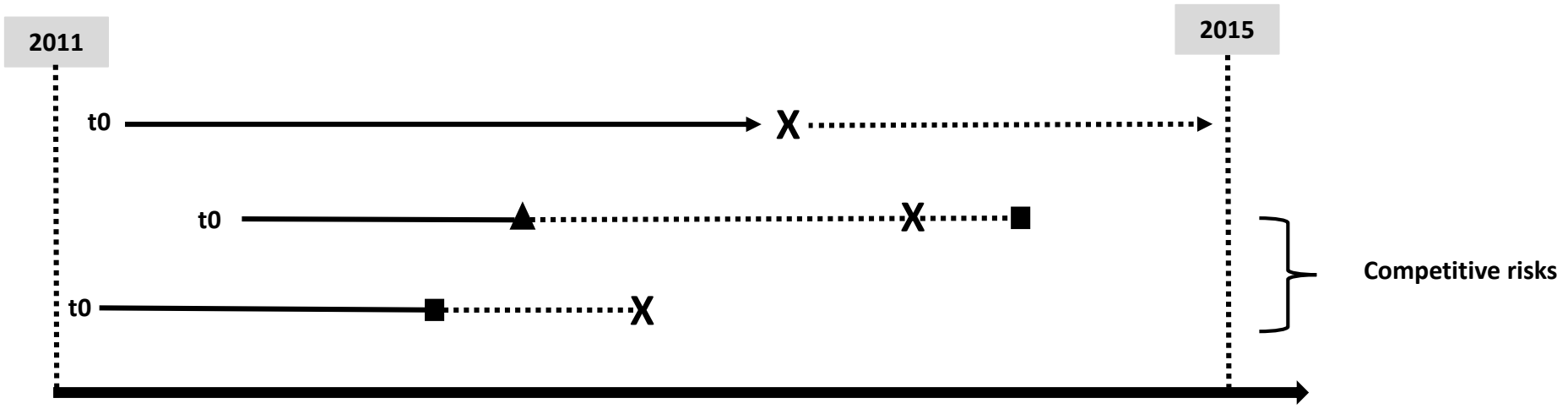
multidisciplinary concertation

meeting

-Start of chemotherapy treatment

-Prescribed drugs

Divided in two datasets



- Alive at two months without chemotherapy prescription
- Death
- ▲ Chemotherapy prescription
- t0 First day of first hospitalization in thoracic oncology unit between 2011 and 2015
- X Right censoring time : 2 months after first hospitalization (t0)