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Assessing the lung cancer comorbidome: An analysis of German claims data

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ABSTRACT

Objectives: In presence of lung cancer, the additional impact of comorbidity on survival is often neglected, although comorbidities are likely to be prevalent. Our study examines the comorbidity profile and the impact of distinct conditions on survival in German lung cancer patients.

Material and methods: We investigated claims data from a large nationwide statutory health insurance fund of 16,202 patients initially diagnosed with lung cancer in 2009. We calculated the prevalence of comorbidities grouped according to an extension of the Elixhauser Comorbidity Index (EI). Effects of distinct comorbidities on 5-year survival were examined using multivariate Cox proportional hazards models, adjusted for sex, age and metastases at baseline. All analyses were stratified by initial lung cancer-related treatment regimen (Surgery, Chemotherapy/Radiotherapy, No treatment). Findings were visualized in the form of a comorbidome.

Results: Our study population was predominantly male (70.6%) with a mean age of 68.6 years, and a mean EI score of 3.94. Patients without treatment were older (74.4 years), and their comorbidity burden was higher (mean EI = 4.59). Median survival varied by subgroup (Surgery: 24.4 months, Chemotherapy/Radiotherapy: 8.8 months, No treatment: 2.0 months), and so did the comorbidity profile and the impact of distinct conditions on survival. Generally, the effect of comorbidities on survival was detrimental and the negative association was most pronounced for 'Weight Loss' and' Paralysis'. In contrast, 'Lipid Metabolism Disorders' and 'Obesity' were positively associated with survival. Noteworthily, highly prevalent conditions tended not to show any significant association.

Conclusion: We found specific comorbidity profiles within the distinct treatment regimens. Moreover, there were negative but also some positive associations with survival, and the strength of these effects varied by stratum. Particularly the positive effects of 'Obesity" and 'Lipid Metabolism Disorders' which were robust across strata need to be further investigated to elucidate potential biomedical explanations.

1. Introduction

According to the statistics from GLOBOCAN, about 1.8 million patients were newly diagnosed with lung cancer worldwide in 2012. With 12.9% of all incident cases, lung cancer was the most frequent cancer diagnosis. It was the most common cause of cancer-related death in men and the second common in women [1]. In Germany in 2010, around 35,000 men and 17,000 women were diagnosed with lung cancer [2]. It was the leading cause of cancer-related death in men (25%) and the third leading in women (14%). Despite advances in medical science, most patients still die within the first year of diagnosis, thus lung cancer is of high relevance for public health in Germany [2].

Because lung cancer is frequent in the elderly population, and smoking as its main risk factor is also related to other diseases, the additional occurrence of comorbidities is likely [3]. The comorbidity burden in lung cancer patients is higher than in the general population, especially for diseases related to the respiratory tract like COPD, but also for cardiovascular diseases [4]. Within a highly lethal disease like lung cancer, comorbid conditions themselves might be of lower importance for survival prognosis. But, when comorbidities have to be monitored closely by a physician, they might affect survival positively by leading to an earlier detection of the cancer resulting in better treatment options. In contrast, other diseases with similar symptoms may overshadow the lung cancer and thus lead to a later detection. As

Abbreviations: EI, Elixhauser Comorbidity Index; SU, surgery; CH/RA, chemotherapy/radiotherapy; NT, no treatment; COPD, chronic pulmonary disease

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comorbidities themselves, however, can also affect the choice of treatment or cause complications during therapy, they should not be neglected [5].

Several studies investigated the impact of comorbidities on survival in lung cancer patients, resulting in worse prognosis in patients with higher comorbidity burden [6], but, with in details conflicting associations. Since only few studies do not focus on subgroups with distinct cancer types, stages or treatment regimens [7–9], comprehensive knowledge about the associations between comorbidity and survival in lung cancer patients remains scarce. Moreover, there are differing data collection methods and concepts of comorbidity assessment [10], and comorbidity burden often is measured as an aggregated index which was constructed for a specific outcome [11]. Furthermore, patients with high comorbidity burden mostly are excluded from trials, especially in elderly patients [5].

Against this background, the primary aim of this study was to examine the prevalence of a comprehensive list of comorbidities within a broad population of lung cancer patients and their influence on survival. The second aim was to investigate potential differences of distinct conditions between different treatment regimens within lung cancer.

2. Material and methods

2.1. Sample selection and observation period

We analysed claims data from a large German Statutory Health Insurance (SHI) fund (AOK) covering ca. 30% of the resident population. Data were delivered by the Scientific Institute of the AOK (WIdO) and contained patient-level information on inpatient and outpatient diagnoses from 2007 to 2012. Diagnoses were given according to The International Statistical Classification Of Diseases And Related Health Problems, 10th revision, German Modification (ICD-10-GM). In addition the socio-demographic characteristics sex, age and district area at time of initial lung cancer diagnosis were provided as well as information on 5-year survival. The data was used with ethical consent (ethical vote no. 88–15) and the anonymity of identity was given in any phase of the analysis.

The details of the cohort have been described previously [12]. In brief, patients were included if they were newly diagnosed with lung cancer (ICD-10 code C34) in 2009, aged above 25 and continuously enrolled between 2007 and 2009 (n = 17,478).

As ICD diagnoses in our dataset were not provided with a precise diagnosis date, the earliest possible date of lung cancer diagnosis was set for each participant based on the first hospital admission date or the begin date of the first outpatient physician case, whichever came first. Records with an overlap of admission and discharge date to the adjacent quarters led to assignment of the lung cancer diagnosis to an earlier quarter. By this, concomitant diagnoses were not appropriately documented within the quarter of lung cancer diagnosis, which therefore led to a misclassification of comorbid conditions within our defined timespan. After exclusion of patients with an overlap, the overall sample size was 16,202 patients.

2.2. Assessment of comorbidities

As, within the German SHI system outpatient physician services are documented on a quarterly base we looked at comorbidities on a quarterly base. To measure the comorbidities present at baseline, we included ICD diagnoses from the quarter of the first lung cancer diagnosis and the two quarters prior to diagnosis. In order to be considered, ICDs had to be either inpatient (primary or secondary) diagnoses or outpatient diagnoses documented in two separate quarters. This algorithm corresponds to the morbidity-oriented risk structure compensation in the German health system [13]. Outpatient ICD diagnoses in Germany have to be categorized in: 'Z' = condition after, 'A' = exclusion diagnosis, 'V' = suspected diagnosis and 'G' = confirmed diagnosis. To identify relevant outpatient diagnoses we used ICDs marked as confirmed only.

Based on claims data and ICD codes, various comorbidity indices and concepts of classification, including adaptions or simplifications, have been established so far [5,14]. In order to analyse the effect of comorbidities on survival we used the 31 distinct comorbidities defined in the Elixhauser Comorbidity Index (EI), which provides a rather comprehensive set of comorbidity groups [15] and beyond this often showed to outperform other concepts [16,17]. All relevant diagnoses were summed up in comorbidity groups defined within the EI according to the coding algorithm of Quan et al. [18] implemented in a SAS-macro from the University of Manitoba [19]. Due to the nature of our study we excluded lung cancer from the category "Solid Tumor without Metastasis" and the whole comorbidity group 'Metastatic Carcinoma'. Patients diagnosed with both 'Uncomplicated' and 'Complicated Hypertension' or 'Uncomplicated' and 'Complicated Diabetes', were assigned to the more severe category. By this, we calculated the EI score itself for each patient by simply summing up the number of EI comorbidities, and created four EI score groups according to the empirical distribution within our cohort (group 1: EI-score 0–1, group 2: EI-score 2–3, group 3: 4–5 and group 4: EI-score > 6).

Since it was unclear whether the EI fully reflected the comorbidity burden of lung cancer patients, we additionally looked for high prevalence diagnoses with a high prevalence in the cohort using three-digit ICD-10 codes that are not included in the EI. In this context, we added 'Lipid Metabolism Disorders' (ICD-10 code E78) to the distinct comorbidities.

2.3. Outcome and covariates

We investigated the effect of comorbidities on all-cause mortality by analysing 5-year survival calculated as time from the date of lung cancer diagnosis to the date of death. Individuals were considered as alive (censored) if death was not reported or if patients lived beyond 1825 days (i.e. 5 years) post diagnosis.

As possible confounding variables we considered age and gender as established factors influencing survival. To best control for confounding, we investigated categorizations of age by comparing models with age in years, decades and quartiles. The lowest AIC value and thus the best fit was found for age in years. Metastases were classified as a confounding variable indicating cancer severity, and were defined as ICD-10 codes of C77–C80 following the inclusion criterion of 1 inpatient diagnosis or 2 assured outpatient diagnoses within the quarter of lung cancer diagnosis and the adjacent quarter [12].

Stratification

ICD-10 codes in our study did not include any information on tumour histology and TNM stage, which are established prognostic factors for survival. To best possibly address this issue, we performed stratified analyses according to initial lung cancer-related treatment regimen [12]. Thus, the population was divided into three strata that were supposed to discriminate between different TNM stages to a large extend: "Surgery" (SU) for individuals undergoing surgery alone or in combination with chemotherapy or radiotherapy, "Chemotherapy/Radiotherapy" (CH/RA) for those who underwent any of these therapies but no surgery, and "No treatment" (NT) if none of these three treatments was reported.

2.4. Statistical analysis

In a univariate analysis we compared overall length of survival using Kaplan-Meier plots and log rank tests ($p \leq 0.05$) for the different EI score groups.

To examine the association between comorbidities and overall survival, we derived multivariate Cox proportional hazards regression models by forward selection modelling: First, hazard ratios (HR) for the distinct comorbidities were calculated (adjusted by age, gender and

metastases at baseline); then, conditions showing a significant association with survival ($p \leq 0.05$) were considered further within the multivariate model. HRs and 95%-confidence intervals (CI) were reported.

Similar to previous studies, we visualized our findings in form of a comorbidome, combining the prevalence of distinct comorbid conditions with their multivariate impact on survival [20,21]. Within each treatment regimen, we present a graph of comorbidities with more than 10% prevalence and those with a significant multivariate association with overall survival ($p \leq 0.05$) despite of their prevalence.

To examine the robustness of our results, two sensitivity analyses were carried out. First, we restricted the identification of baseline comorbidities to the quarter in which the patient was diagnosed with lung cancer, including any inpatient diagnosis or confirmed outpatient diagnosis (SA1). We thereby considered that the results could be driven by timespan of assessment period and the restrictive requirement to outpatient diagnoses. Second, the Bonferroni correction was used to minimize the number of possible false positive results as a problem of multiple testing (SA2). To reduce the concurrent possibility of false rejection of comorbidities within steps of forward selection modelling, the critical limit for modelling was unchanged ($p \leq 0.05$), whereas it was corrected for the interpretation of the multivariate models ($p \leq 0.0016$ ($\alpha = 0.05 / 31$ comorbidity groups).

All analyses were performed using SAS version 9.4. The comorbidome was created in Microsoft Excel 2010.

3. Results

3.1. Baseline characteristics

Patient characteristics for the entire cohort and stratified for initial cancer-related treatment regimen are presented in Table 1. Around two-thirds of patients were male and lived in urban areas, overall and in all treatment subgroups. At time of first lung cancer diagnosis, the average age was 67.0 years in the subgroups SU and CH/RA and 74.4 years in NT. Similarly, the EI score was almost the same in SU and CH/RA, but higher in NT. Metastasis status at baseline revealed notable differences between the three strata, with 41.4% of SU but 70.1% of CH/RA and 41.4% of NT. Accordingly, survival was shortest in NT and longest in SU.

3.2. Prevalence of distinct comorbidities

Due to the prevalence < 5% and no significant association with survival ($p > 0.05$%) no results are presented for 'Peptic Ulcer Disease excluding bleeding', 'Psychoses', 'Lymphoma', 'Drug Abuse', 'Blood Loss Anemia' and 'AIDS/HIV'.

Contrasting prevalence between SU and CH/RA revealed similar proportions for most comorbidity groups, whereas some showed differences of more than 10%. We found higher proportions of 'Depression', 'Weight Loss', 'Other Neurological Disorders', and 'Paralysis' in CH/RA. In parallel, lower proportions were shown for 'COPD', 'Cardiac Arrhythmias', 'Solid Tumor without Metastasis', 'Obesity', and 'Complicated Hypertension'. Out of 22 comorbidity groups with more than 5% prevalence in the total cohort, 16 had the highest prevalence within NT. The difference to SU respectively CH/RA was most pronounced (> 30%) for 'Fluid and Electrolyte Disorders', 'Cardiac Arrhythmias', 'Congestive Heart Failure', 'Renal Failure', 'Complicated Diabetes', 'Weight Loss', 'Other Neurological Disorders', and 'Paralysis'. In contrast, we found that 'Obesity' had the lowest prevalence within NT. The data are presented in Table 2, 2nd, 5th and 8th column, respectively, and visualised as areas within the comorbidomes in Fig. 1.

SA1 showed comparable prevalences of comorbidities within the three strata, with slightly higher proportions within SU and CH/RA, and several slightly lower proportions within NT. Within all subgroups, there was only a slight increase of comorbidity prevalence (< 7%) in 'COPD', 'Solid Tumor without Metastasis', 'Depression' and 'Weight Loss' (+2.6%, +4.3%, and 4.9%, respectively) (see Appendix Table A.1, 2nd, 5th and 8th column, respectively).

3.3. Comorbidity and survival

Kaplan-Meier curves for grouped EI scores stratified by treatment regimen are shown in Fig. 2. We found significant differences ($p < 0.0001$) in survival between the EI score groups in the strata SU and CH/RA but not in the stratum NT ($p = 0.08$). Best prognosis was found in patients with SU and up to one comorbidity, and worst in patients with NT and more than five comorbidities.

HRs indicated stratum-specific associations of comorbidities and survival (see Table 2). In general, effects were small and tended to be larger in patients with cancer-related treatment, especially in those who underwent surgery. Looking at the distinct HR within the Cox models

Table 1
Baseline characteristics of the study sample: For entire sample and by initial cancer-related treatment regimen.

		Treatment group		
	Entire sample	Surgery	Chemo-/radiotherapy	No specific treatment
n	16,202	4,443 (27.4%)	8,364 (51.6%)	3,395 (21.0%)
Sex				
Male (%)	11,435 (70.6)	3,157 (71.1)	5,928 (70.9)	2,350 (69.2)
Mean age at diagnosis (SD)	68.6 (10.2)	67.0 (9.7)	67.0 (9.8)	74.4 (9.6)
Metastases at baseline[a] (%)	9,562 (59.0)	1,839 (41.4)	5,862 (70.1)	1,861 (54.8)
Elixhauser comorbidity Index[b]				
Mean (SD)	3.94 (2.41)	3.82 (2.34)	3.74 (2.39)	4.59 (2.46)
Number of EI conditions				
0–1 (%)	2,574 (15.9)	715 (16.1)	1,538 (18.4)	321 (9.5)
2–3 (%)	5,006 (30.9)	1,453 (32.7)	2,678 (32.0)	875 (25.8)
4–5 (%)	4,667 (28.8)	1,270 (28.6)	2,322 (27.8)	1,075 (31.7)
≥6 (%)	3,955 (24.4)	1,005 (22.6)	1,826 (21.8)	1,124 (33.1)
Survival				
Median survival in months	8.5	24.4	8.8	2.0
Alive after 1 year (%)	6,511 (40.2)	2,921 (65.7)	3,124 (37.4)	466 (13.7)
Alive after 5 years (%)	2,066 (12.8)	1,448 (32.6)	447 (5.3)	171 (5.0)

SD, standard deviation. EI, Elixhauser comorbidity Index.
[a] ICD-10 C77- C80.
[b] without lung cancer (ICD-10 C34) and metastases (ICD-10 C77- C80).

Table 2
Comorbidities and 5-year-survival by initial cancer-related treatment regimen: Prevalences (%) of comorbidities grouped according to an extended version of the EI, comorbidities with more than 5% prevalence within at least one subgroup. Univariate and multivariate Cox proportional hazards regression models with forward selection modelling (HR, 95%-CI), all regressions adjusted for age, sex and metastases at baseline.

	Surgery			Chemo-/radiotherapy			No treatment		
	Prev	univariate	multivariate	Prev	univariate	multivariate	Prev	univariate	multivariate
Comorbidity									
Hypertension Uncomplicated	54.6	0.94 (0.87–1.01)	–	54.0	1.01 (0.97–1.06)	–	56.8	0.93* (0.87–1.00)	0.94 (0.87–1.00)
Chronic Pulmonary Disease	53.4	0.99 (0.92–1.06)	–	46.8	0.96 (0.92–1.00)	–	47.8	0.88** (0.82–0.95)	0.86** (0.80–0.93)
Lipid Metabolism Disorders	41.0	0.92* (0.86–0.99)	0.90** (0.84–0.97)	39.4	0.92** (0.88–0.97)	0.90*** (0.86–0.95)	36.0	0.92* (0.86–0.99)	0.94 (0.87–1.01)
Fluid and Electrolyte Disorders	22.8	1.21*** (1.11–1.31)	1.08 (0.99–1.18)	24.0	1.46*** (1.38–1.53)	1.37*** (1.30–1.44)	36.4	1.32*** (1.23–1.42)	1.30*** (1.21–1.39)
Peripheral Vascular Disorders	24.0	1.11* (1.02–1.21)	1.07 (0.98–1.16)	26.0	1.05 (1.00–1.11)	–	26.6	1.01 (0.93–1.09)	–
Cardiac Arrhythmia	24.2	1.14** (1.05–1.24)	1.09 (1.00–1.18)	20.4	1.05 (0.99–1.11)	–	31.8	1.02 (0.95–1.10)	–
Congestive Heart Failure	19.0	1.16** (1.06–1.27)	1.08 (0.98–1.18)	18.8	1.12** (1.05–1.18)	1.07* (1.01–1.14)	33.4	1.10* (1.02–1.18)	1.10* (1.02–1.19)
Diabetes Uncomplicated	17.4	1.09 (0.99–1.20)	–	17.4	1.01 (0.95–1.07)	–	19.6	1.02 (0.94–1.12)	–
Renal Failure	13.6	1.18** (1.07–1.31)	1.10 (0.99–1.22)	14.4	1.16*** (1.09–1.24)	1.11** (1.04–1.18)	24.4	1.05 (0.97–1.14)	–
Solid Tumor without Metastasis	18.0	1.06 (0.97–1.16)	–	15.6	0.99 (0.93–1.05)	–	14.4	0.96 (0.87–1.06)	–
Depression	13.0	1.18** (1.06–1.32)	1.14* (1.03–1.28)	14.6	1.11** (1.04–1.18)	1.07 (1.00–1.14)	15.4	0.89* (0.81–0.98)	0.87** (0.79–0.96)
Liver Disease	14.8	1.03 (0.93–1.14)	–	13.4	1.08* (1.01–1.14)	1.05 (0.98–1.12)	13.2	1.05 (0.95–1.16)	–
Obesity	15.6	0.89* (0.81–0.99)	0.90* (0.81–0.99)	12.8	0.90** (0.84–0.96)	0.89** (0.83–0.96)	10.4	0.93 (0.83–1.04)	–
Diabetes Complicated	10.4	1.08 (0.96–1.20)	–	10.6	1.01 (0.94–1.08)	–	15.0	1.01 (0.92–1.11)	–
Hypertension Complicated	11.2	0.98 (0.88–1.09)	–	10.0	1.01 (0.94–1.08)	–	13.0	0.98 (0.88–1.08)	–
Hypothyroidism	9.8	0.91 (0.81–1.04)	–	9.8	0.95 (0.88–1.03)	–	8.4	0.91 (0.80–1.03)	–
Weight Loss	5.6	1.84*** (1.60–2.13)	1.75*** (1.51–2.02)	8.6	1.44*** (1.33–1.56)	1.34*** (1.24–1.45)	15.2	1.30*** (1.18–1.43)	1.27*** (1.16–1.40)
Alcohol Abuse	8.6	1.31*** (1.16–1.49)	1.20** (1.06–1.36)	8.6	1.18*** (1.09–1.28)	1.11* (1.02–1.20)	11.2	1.02 (0.91–1.15)	–
Valvular Disease	7.6	0.98 (0.86–1.12)	–	7.2	1.03 (0.95–1.12)	–	10.2	0.93 (0.83–1.04)	–
Other Neurological Disorders	5.6	1.42*** (1.23–1.64)	1.23** (1.06–1.42)	7.2	1.25*** (1.15–1.36)	1.14** (1.04–1.24)	11.6	1.07 (0.96–1.19)	–
Paralysis	3.6	1.82*** (1.53–2.16)	1.73*** (1.45–2.06)	6.4	1.37*** (1.26–1.50)	1.30*** (1.18–1.42)	9.2	1.16* (1.03–1.31)	1.16* (1.03–1.31)
Coagulopathy	6.0	1.50*** (1.30–1.73)	1.37*** (1.19–1.59)	6.2	1.24*** (1.14–1.36)	1.11* (1.01–1.22)	6.4	1.16* (1.01–1.33)	1.11 (0.97–1.28)
Pulmonary Circulation Disorders	3.6	1.47*** (1.25–1.72)	1.40*** (1.19–1.65)	3.8	1.06 (0.96–1.18)	–	6.2	1.15* (1.01–1.30)	1.14 (1.00–1.29)
Deficiency Anemia	4.6	0.96 (0.81–1.14)	–	3.4	1.00 (0.90–1.11)	–	6.0	0.97 (0.81–1.17)	–
Fixed covariates									
Female gender	28.9	included	0.77*** (0.71–0.84)	29.1	included	0.84*** (0.80–0.88)	30.8	included	0.88** (0.81–0.95)
Age (years, Mean)	67.0	included	1.03*** (1.02–1.03)	67.0	included	1.01*** (1.01–1.01)	74.4	included	1.01** (1.00–1.01)
Metastases at baseline	41.4	included	2.02*** (1.87–2.17)	70.1	included	1.51*** (1.44–1.59)	54.8	included	1.80*** (1.67–1.93)

Prev, prevalence; HR, hazard ratio; CI, confidence interval.
*** $p < 0.0001$.
** $p < 0.01$.
* $p < 0.05$.

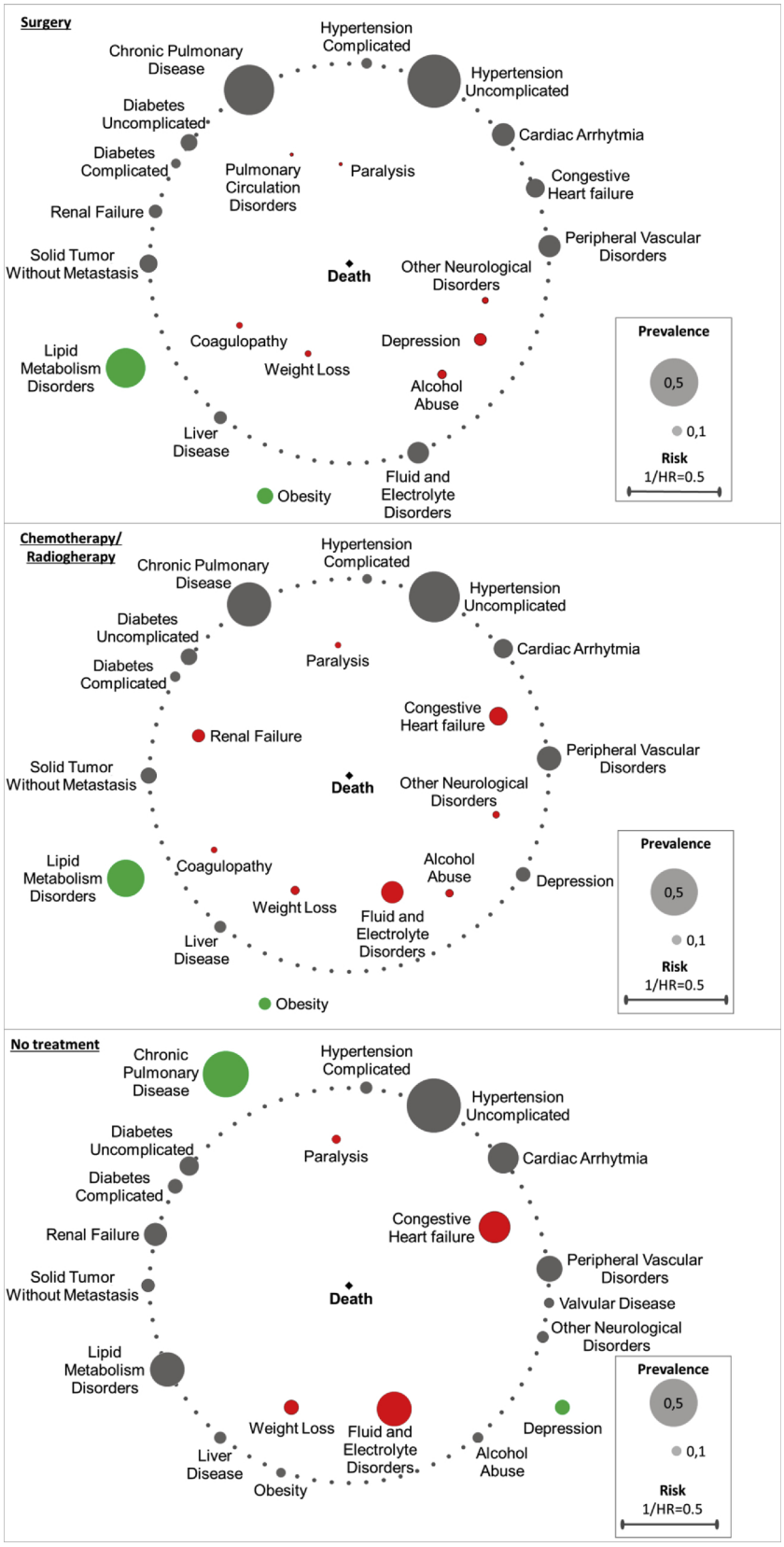

Fig. 1. Lung Cancer Comorbidome by initial cancer-related treatment regimen. Graphic expression of comorbidities with more than 10% prevalence in the subsample or comorbidities with the strongest association with survival [hazard ratio (HR) with $p \leq 0.05$] within stratified multivariate models (adjusting for age, sex and metastases at baseline). The area of the circle relates to the prevalence of the disease. Comorbidities with a statistically significant decrease in survival (HR > 1) are fully inside the dotted orbit, their proximity to the centre (death) expresses the strength of the association between the disease and risk of death (1/HR). Those comorbidities with a statistically significant increase (HR < 1) are fully outside. Comorbidities on the dotted line had no significant association with survival.

adjusted for fixed covariates, we found a higher number of significant negative associations within SU and CH/RA, compared to NT (number of HR > 1: 12, 10, and 6, respectively). Positive associations with survival were found for 2 (both SU and CH/RA) and 4 (NT) comorbidities. The profiles of relevant comorbidities were similar for SU and CH/RA, whereas that for NT was reduced and with an opposite direction for 'Depression' (from negative within SU and CH/RA to positive within NT). Beside this, only within NT the two most prevalent comorbidities 'Uncomplicated Hypertension' and 'COPD' showed a positive association with survival.

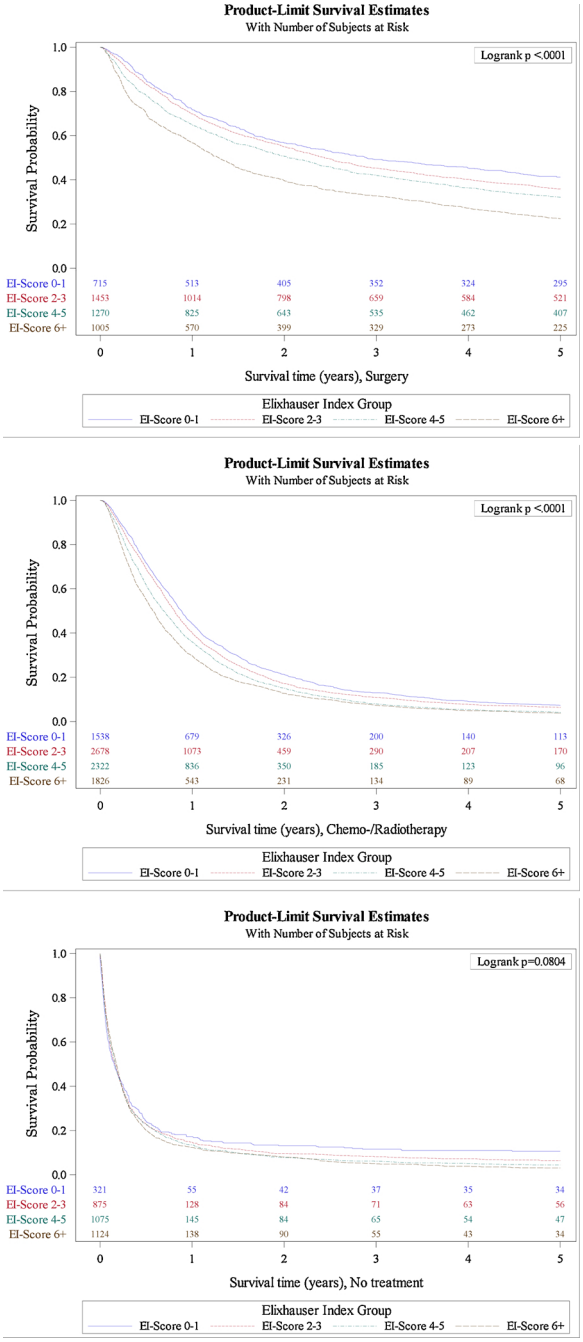

Fig. 2. Burden of comorbidity and survival by initial cancer-related treatment regimen: Kaplan-Meier-Plots representing overall survival probability within 5 years after diagnosis according to EI score groups.

Extending to the multivariate model, all effects pointed into the same direction as in the 'univariate' ones, but predictors for survival lost significance or showed reduced p-values, especially among SU patients. The pre-fixed covariates predominantly showed a strong statistical impact. The negative association for 'Metastases at baseline' was strong in all three subgroups. Female gender presented a reduced risk for mortality, which was also stronger within SU and CH/RA.

Contrasting the comorbidity impact between the distinct treatment regimen, only 'Weight Loss' and 'Paralysis' showed a significant detrimental association in all three strata. Within SU and CH/RA, 'Alcohol Abuse', 'Other Neurological Disorders' and 'Coagulopathy' remained as additional negative predictors and the positive impact of 'Lipid Metabolism Disorders' and 'Obesity' remained as well. A negative association for 'Depression' and 'Pulmonary Circulation Disorders' was found only within SU. Within CH/RA 'Fluid and Electrolyte Disorders', 'Congestive Heart Failure', 'Renal Failure' were additional significant predictors. Again, within NT the comorbidity profile was different and also showed less significant predictors. The most prevalent comorbidity 'Uncomplicated Hypertension' lost its protective effect. Only in patients within NT a positive association of COPD with survival was shown, and, in contrast to SU, 'Depression' was associated with a better prognosis. Further negative associations were found in patients with 'Fluid and Electrolyte Disorders' and 'Congestive Heart Failure', which were also shown within CH/RA.

Our results for prevalences and multivariate HRs of comorbidity groups are graphically presented in form of comorbidomes for subgroups of treatment regimen in Fig. 1. Here the specific patterns of negative and positive associations become obvious, particularly the similarity of SU and CH/RA.

3.4. Sensitivity analysis

Multivariate models within SA1 resulted in slightly different HRs within the treatment strata (see Appendix, Table A.1) but we found a changed pattern of relevant comorbidities: Within SU, 'Fluid and Electrolyte Disorders', 'Congestive Heart Failure' and 'Uncomplicated Diabetes' had an additional impact on prognosis. Within CH/RA, 'Coagulopathy' was no longer a negative predictor for survival. Within NT, we found an additional positive association with survival for 'Lipid Metabolism Disorders', 'Solid Tumor without Metastasis', and 'Valvular Disease', and a negative impact in patients with 'Coagulopathy', whereas 'Congestive Heart Failure' showed no longer a significant association.

After Bonferroni-Adjustment (SA2), 'Weight Loss' was the only covariate showing a significant association within all treatment strata. 'Paralysis' remained as another predictor only within SU and CH/RA. Survival of patients within SU was additionally associated with 'Pulmonary Circulation Disorders' and 'Coagulopathy'. 'Fluid and Electrolyte Disorders' maintained their negative impact on survival both within CH/RA and NT (see Appendix, Fig. A. 2).

4. Discussion

In this cross-sectional analysis of 16,202 incident lung cancer patients, comorbidities were of high prevalence and frequently showed a negative association with 5-year survival. As highlighted within the comorbidomes, comorbidities related to shorter survival tended to be of lower prevalence, whereas highly prevalent comorbidities mostly did not show any association with survival. Comorbidity burden differed by initial cancer-related treatment regimen and did not show a consistent shift in proportions: By trend, comorbidities were more frequent in patients without treatment, however some had the highest prevalence within the surgery-group. Within each treatment group, 'Weight Loss' and 'Paralysis' were the strongest negative predictors for survival. 'Lipid Metabolism Disorders' and 'Obesity' showed positive associations. As a general finding, the additional effect of comorbid conditions on survival was small and more pronounced among treated patients, whereas the additional impact of comorbidity burden remained low among patients without treatment.

A comparison of comorbidity burden across different studies is a sensitive issue, as comorbidity is measured differently and mostly preselected patients come from various settings. However, this can be done at least for established comorbidities within population-based studies with consideration of the different context. These show a high burden of comorbidity, especially for elder male patients [3,8,9]. The most frequent concomitant diseases are 'COPD', 'Cardiovascular Diseases', 'Peripheral Vascular Disease', 'Hypertension', 'Congestive Heart Failure', 'Diabetes' and 'Renal Disease', and 'Weight Loss' if investigated.

Findings in lung cancer patients in Nebraska showed a prevalence of 'Metastases' and 'COPD', that fitted very well with our results (both about 50%, respectively), but 'Congestive Heart Failure' was of higher prevalence within our study population (22%, and 13% in Nebraska) [9]. In comparison to Scottish lung cancer patients, we found a similar prevalence for 'COPD' (43%, and 49% in Scotland), but a much lower proportion of patients with 'Weight Loss' (9%, and 53% in Scotland) [8]. Contrasting our results with reports from the Dutch cancer registry, prevalences were much higher for 'COPD' (43%, and 22% in the Netherlands), 'Hypertension' (66%, and 12% in the Netherlands) and 'Diabetes' (29%, and 7% in the Netherlands). These differences could be explained by a different classification of comorbidities, especially the limitation to medically treated patients for 'Diabetes' in the Dutch study. Beside this, our prevalences showed different proportions as a result of different assessment of comorbidities, both from the timespan of our baseline and our inclusion criteria for diagnoses, considering both inpatient and outpatient diagnoses. Restricting identification of baseline comorbidities to the quarter of lung cancer diagnosis (SA1) resulted in higher prevalences for most comorbidities within SU and CH/RA, whereas within NT comorbidities tended to be of lower prevalence with the inclusion criteria of SA1. These shifts may be explained by additional outpatient diagnoses that could have occurred close to the lung cancer diagnosis, which were recorded only once within the initial quarter of lung cancer and therefore were missing within our main analysis. Patients within NT had a median survival of 2 months, which could have influenced the reporting rate for diagnoses [22]. Thus, our analysis could have underreported those comorbid conditions documented as a single inpatient diagnosis.

Among patients without lung cancer-related treatment in our study, the results for the prevalence of comorbidities met our expectations because this subgroup was older and thereby the general comorbidity burden was supposed to be higher. Unexpectedly, comorbidity burden was substantial as well among SU patients, even though surgery is mostly recommended for patients with higher performance status (i.e. those with less comorbid conditions). The higher proportions within surgery treated patients could also be the result of a different coding practice, i.e. because of a more precise documentation within certain circumstances [23].

The associations with survival within our study in general were small (HR: 0.86 up to 1.84), whereas other authors reported HRs beyond 2 or more [7,9]. This could be the result of inclusion criteria for the sample and the strong association of the adjusting fixed covariates 'Female gender' and 'Metastases at baseline', which were the strongest predictors for survival. We found similar HRs within SA1, but by trend more comorbidities showed associations within the multivariate models, noteworthy within NT. In contrast, within SA2 we found a remarkably reduced picture of categories, which could be useful impact for further investigations to improve the treatment of lung cancer patients.

Although they are not included within the EI we examined 'Lipid Metabolism Disorders' due to their high prevalence in our cohort. Here, we found an association with longer survival in patients with SU and CH/RA. Other studies found that patients with 'Lipid Metabolism Disorders' treated with statins had a better survival prognosis [24]. A first analysis that split patients with lipid metabolism disorders into treated and untreated ones (based on at least one statin prescription in the year of lung cancer diagnosis) revealed that the protective effect in our study was only present in treated lipid metabolism disorders. This indicates that the reduced HR in lipid metabolism disorders is most probably explained by statin therapy. However, this can only be seen as an indicator because comprehensive analysis of the effect of statin treatment requires a detailed look on adherence and dosage over time. This is beyond the scope of this paper which analyses the impact of baseline comorbidity- but not of comorbidity-treatment over time. Similar to other studies, we found that 'Obesity' was a predictor for improved survival [25], whereas 'Weight Loss' was associated with worse survival [26]. This effect is known as the "obesity paradox", which states that obese patients are at a higher risk of developing certain diseases, but increased body weight also leads to a better prognosis due to greater physiologic reserves. Further, we found that COPD has a protective effect within NT. This could be a result of lead-time bias by an earlier detection of lung cancer. However, in this context, it is surprising to see this effect in the NT group [9].

The role of some conditions in terms of concomitant disease vs. sequelae is ambiguous. 'Coagulopathy' could be an independent comorbid condition as well as a complication of chemotherapy [27].' Other Neurological Disorders' might be the result of metastases, while they also might exist as a comorbid condition per se [28]. In this context it needs to be considered, that some EI conditions are known to be a symptom of cancer cachexia. Extreme 'Weight Loss' is a result of metabolic changes during cancer and is highly related to 'Fluid and Electrolyte Disorders' and 'Lipid and Metabolism Disorders' [29]. Together with 'Depression' these categories could be considered as severity indicators rather than as concomitant comorbidities in lung cancer patients.

Beyond this, some comorbidity groups may act as competing risk factors or a risk modifier. 'Paralysis' is a symptom of stroke, which was found for about one third of patients with this comorbidity, but it may also be a side effect of chemotherapy or the result of metastases affecting the neurological system. We controlled both for chemotherapy and the presence of metastases, which are associated with the severity of cancer. Thus, it seems that complications resulting from immobility itself may lead to a worse survival prognosis, e.g. the development of emphysema that is known to be crucial for the survival prognosis.

Apart from the sensitive issue of interpreting comorbidity comprehensively, the following caveats exist: We did not have information on cancer stage or cancer histology in our data. Both stage and histology are known to be the strongest predictors for survival [30], and previous studies substantiated evidence that the effect of comorbidities on survival varies by stage [8,31]. However, we believe that by stratification on treatment regimen and adjustment for baseline metastases we addressed this issue in the best possible manner.

The treatment of a comorbidity itself probably influences survival, but, some comorbid conditions are likely mutually reinforcing. Given recent evidence on an enhanced mortality effect of combined ILD and lung cancer [32,33], it seems justified to assume corresponding interactions for other conditions as well. However, we did not include interaction-terms between comorbidities in order to keep the information obtained interpretable in a straightforward manner.

Despite these drawbacks, we assessed the first lung cancer comorbidome for Germany, by applying a rather exhaustive assessment of comorbid conditions. We accounted for inpatient and outpatient diagnoses and screened a period of six months before the initial lung cancer diagnosis for corresponding diagnoses. Therefore, our results for comorbidity burden are expected to be representative for a routine care setting and might be less prone to strategic coding decision during the immediate period around the lung cancer diagnosis. Moreover, we added highly prevalent conditions by amending the established EI with 'Lipid Metabolism Disorders'. Thus, we were able to show a very comprehensive picture of baseline comorbidity burden in lung cancer patients.

We had access to a large number of incident lung cancer patients within the German Statutory Health Insurance System. Baseline characteristics of our sample are comparable to results from the population-based lung cancer report for Germany [34]. Thus, we believe our results are representative. Our study has all advantages of health insurance data, having only minimal selection and no recall bias as well as minimal possible loss to follow-up. Further, our study is multicentered as it was based on information of health care providers within whole Germany, painting a reliable picture on comorbidity structures and treatment options within a representative population. We therefore believe that we gave maximal consideration of comorbidities among

incident lung cancer patients which are transferable beyond the German SHI context.

5. Conclusion

Investigating the impact of comorbidity on survival in lung cancer patients, we found specific comorbidity profiles among distinct treatment regimens. Despite by trend detrimental effects on survival some comorbid conditions showed a positive association. Our analysis thus not only supports the previously described 'Obesity paradox', but especially points out the crucial role of 'Lipid Metabolism Disorders', which is coming up as a hallmark within recent cancer research [24,29]. To further elucidate the mechanisms beyond the beneficial impact of 'Lipid Metabolism Disorders' a closer look on their treatment – particularly with statins – is highly recommended to optimize treatment decisions in lung cancer patients.

Conflict of interests

The authors declare that they have no competing financial or personal interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.030.

References

[1] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mahters, M. Rebelo, D.M. Parkin, D. Forma, F. Bray, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBAse No.11, International Agency for Research on Cancer, Lyon, France, 2013.
[2] Robert Koch Institute and the Association of Population-based Cancer Registries in Germany (editor), Cancer in Germany 2009/2010, 9th edition, Berlin (2013).
[3] C.M. Tammemagi, C. Neslund-Dudas, M. Simoff, P. Kvale, In lung cancer patients, age, race-ethnicity, gender and smoking predict adverse comorbidity, which in turn predicts treatment and survival, J. Clin. Epidemiol. 57 (2004) 597–609.
[4] M.L. Janssen-Heijnen, R.M. Schipper, P.P. Razenberg, M.A. Crommelin, J.W. Coebergh, Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study, Lung Cancer (Amsterdam, Netherlands) 21 (1998) 105–113.
[5] A. Gajra, Assessment of comorbidity in lung cancer: how, why, and in whom? J. Geriatr. Oncol. 7 (2016) 64–67.
[6] A.E. Dutkowska, A. Antczak, Comorbidities in lung cancer, Pneumonologia i alergologia polska 84 (2016) 186–192.
[7] C.M. Tammemagi, C. Neslund-Dudas, M. Simoff, P. Kvale, Impact of comorbidity on lung cancer survival, Int. J. Cancer 103 (2003) 792–802.
[8] D. Grose, D.S. Morrison, G. Devereux, R. Jones, D. Sharma, C. Selby, K. Docherty, D. McIntosh, G. Louden, M. Nicolson, D.C. McMillan, R. Milroy, Comorbidities in lung cancer: prevalence, severity and links with socioeconomic status and treatment, Postgrad. Med. J. 90 (2014) 305–310.
[9] K.M. Islam, X. Jiang, T. Anggondowati, G. Lin, A.K. Ganti, Comorbidity and survival in lung cancer patients, Cancer Epidemiol. Biomark. Prev. 24 (2015) 1079–1085.
[10] C.N. Klabunde, J.L. Warren, J.M. Legler, Assessing comorbidity using claims data: an overview, Med. Care 40 (2002) Iv-26–35.
[11] M. Extermann, Measurement and impact of comorbidity in older cancer patients, Crit. Rev. Oncol. Hematol. 35 (2000) 181–200.
[12] L. Schwarzkopf, M. Wacker, R. Holle, R. Leidl, C. Gunster, J.B. Adler, R.M. Huber, Cost-components of lung cancer care within the first three years after initial diagnosis in context of different treatment regimens, Lung Cancer (Amsterdam, Netherlands) 90 (2015) 274–280.
[13] German Federal Insurance Office, The New Risk Structure Equalisation, (2008).
[14] M. Yurkovich, J.A. Avina-Zubieta, J. Thomas, M. Gorenchtein, D. Lacaille, A systematic review identifies valid comorbidity indices derived from administrative health data, J. Clin. Epidemiol. 68 (2015) 3–14.
[15] A. Elixhauser, C. Steiner, D.R. Harris, R.M. Coffey, Comorbidity measures for use with administrative data, Med. Care 36 (1998) 8–27.
[16] M.T. Sharabiani, P. Aylin, A. Bottle, Systematic review of comorbidity indices for administrative data, Med. Care 50 (2012) 1109–1118.
[17] H.J. Chang, P.C. Chen, C.C. Yang, Y.C. Su, C.C. Lee, Comparison of Elixhauser and Charlson methods for predicting oral cancer survival, Medicine 95 (2016) e2861.
[18] H. Quan, V. Sundararajan, P. Halfon, A. Fong, B. Burnand, J.C. Luthi, L.D. Saunders, C.A. Beck, T.E. Feasby, W.A. Ghali, Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data, Med. Care 43 (2005) 1130–1139.
[19] K. Turner, C. Burchill, Elixhauser Comorbidity Index, SAS-Macro-Code, University of Manitoba, 2006, 2018.
[20] M. Divo, C. Cote, J.P. de Torres, C. Casanova, J.M. Marin, V. Pinto-Plata, J. Zulueta, C. Cabrera, J. Zagaceta, G. Hunninghake, B. Celli, Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 186 (2012) 155–161.
[21] M. Kreuter, S. Ehlers-Tenenbaum, K. Palmowski, J. Bruhwyler, U. Oltmanns, T. Muley, C.P. Heussel, A. Warth, M. Kolb, F.J. Herth, Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis, PLoS One 11 (2016) e0151425.
[22] J. Jaunzeme, S. Eberhard, S. Geyer, How "representative" are SHI (statutory health insurance) data? Demographic and social differences and similarities between an SHI-insured population, the population of Lower Saxony, and that of the Federal Republic of Germany using the example of the AOK in Lower Saxony, Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 56 (2013) 447–454.
[23] U. Nimptsch, Disease-specific trends of comorbidity coding and implications for risk adjustment in hospital administrative data, Health Serv. Res. 51 (2016) 981–1001.
[24] C.R. Cardwell, U. Mc Menamin, C.M. Hughes, L.J. Murray, Statin use and survival from lung cancer: a population-based cohort study, Cancer Epidemiol. Biomark. Prev. 24 (2015) 833–841.
[25] S. Li, Z. Wang, J. Huang, J. Fan, H. Du, L. Liu, G. Che, Systematic review of prognostic roles of body mass index for patients undergoing lung cancer surgery: does the' obesity paradox' really exist? Eur. J. Cardio-Thorac. Surg. 51 (2017) 817–828.
[26] R. Yang, M.C. Cheung, F.E. Pedroso, M.M. Byrne, L.G. Koniaris, T.A. Zimmers, Obesity and weight loss at presentation of lung cancer are associated with opposite effects on survival, J. Surg. Res. 170 (2011) e75–e83.
[27] M.A. Ruiz, I. Marugan, A. Estelles, I. Navarro, F. Espana, V. Alberola, L. San Juan, J. Aznar, J. Garcia-Conde, The influence of chemotherapy on plasma coagulation and fibrinolytic systems in lung cancer patients, Cancer 63 (1989) 643–648.
[28] J. Sørensen, H. Hansen, M. Hansen, P. Dombernowsky, Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis, J. Clin. Oncol. 6 (1988) 1474–1480.
[29] M. Merino Salvador, M. Gomez de Cedron, J. Merino Rubio, S. Falagan Martinez, R. Sanchez Martinez, E. Casado, A. Ramirez de Molina, M. Sereno, Lipid metabolism and lung cancer, Crit. Rev. Oncol. Hematol. 112 (2017) 31–40.
[30] M. Schmidt, G. Schubert-Fritsche, J. Engel, Epidemiology of lung cancer, Tumours of the Lungs and Mediastinum (2011) Tumorzentrum München.
[31] M.K. Gould, C.E. Munoz-Plaza, E.E. Hahn, J.S. Lee, C. Parry, E. Shen, Comorbidity profiles and their effect on treatment selection and survival among patients with lung cancer, Ann. Am. Thorac. Soc. 14 (Oct. (10)) (2017) 1571–1580.
[32] S. Tomassetti, C. Gurioli, J.H. Ryu, P.A. Decker, C. Ravaglia, P. Tantalocco, M. Buccioli, S. Piciucchi, N. Sverzellati, A. Dubini, G. Gavelli, M. Chilosi, V. Poletti, The impact of lung cancer on survival of idiopathic pulmonary fibrosis, Chest 147 (2015) 157–164.
[33] N. Girard, S. Marchand-Adam, J.M. Naccache, R. Borie, T. Urban, S. Jouneau, E. Marchand, A.C. Ravel, L. Kiakouama, B. Etienne-Mastroianni, J. Cadranel, V. Cottin, J.F. Cordier, Lung cancer in combined pulmonary fibrosis and emphysema: a series of 47 Western patients, J. Thorac. Oncol. 9 (2014) 1162–1170.
[34] P. Kaatsch, C. Spix, S. Hentschel, A. Katalinic, S. Luttmann, C. Stegmaier, S. Caspritz, J. Cernaj, A. Ernst, J. Folkerts, Krebs in Deutschland 2009/2010, (2013).