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RESEARCH ARTICLE

Reproducibility, reliability and validity of population-based administrative health data for the assessment of cancer non-related comorbidities

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Data Availability Statement: The data on which the comorbidity algorithm is run and tested is not our property. Nonetheless the algorithm is provided in appendix. The data are held by Public Health England and these data can be accessed under strict conditions detailed in <https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data>. The researchers will have beforehand obtained all the ethical and statutory approvals required for accessing such sensitive data.

Abstract

Background

Patients with comorbidities do not receive optimal treatment for their cancer, leading to lower cancer survival. Information on individual comorbidities is not straightforward to derive from population-based administrative health datasets. We described the development of a reproducible algorithm to extract the individual Charlson index comorbidities from such data. We illustrated the algorithm with 1,789 laryngeal cancer patients diagnosed in England in 2013. We aimed to clearly set out and advocate the time-related assumptions specified in the algorithm by providing empirical evidence for them.

Methods

Comorbidities were assessed from hospital records in the ten years preceding cancer diagnosis and internal reliability of the hospital records was checked. Data were right-truncated 6 or 12 months prior to cancer diagnosis to avoid inclusion of potentially cancer-related comorbidities. We tested for collider bias using Cox regression.

Results

Our administrative data showed weak to moderate internal reliability to identify comorbidities (ICC ranging between 0.1 and 0.6) but a notably high external validity (86.3%). We showed a reverse protective effect of non-cancer related Chronic Obstructive Pulmonary Disease (COPD) when the effect is split into cancer and non-cancer related COPD (Age-adjusted HR: 0.95, 95% CI:0.7–1.28 for non-cancer related comorbidities). Furthermore, we showed that a window of 6 years before diagnosis is an optimal period for the assessment of comorbidities.

Conclusion

To formulate a robust approach for assessing common comorbidities, it is important that assumptions made are explicitly stated and empirically proven. We provide a transparent

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and consistent approach useful to researchers looking to assess comorbidities for cancer patients using administrative health data.

Background

When modelling cancer survival in population-based research, it is relevant to account for potential confounders and effect modifiers, such as comorbid conditions, frequently linked to clinically relevant outcomes.[1, 2] Most studies found that cancer patients with comorbidity had poorer survival than those without comorbidity.[1] The presence of comorbidities may delay or favour a timely cancer diagnosis.[3–5] In addition, it has been hypothesised that patients with comorbidities do not receive standard cancer treatments such as surgery, chemotherapy, and radiation therapy as often as patients without comorbidities.[1] Thus, the use of individual comorbidities or comorbidity scores such as the Charlson index[6] will enrich our understanding of differences in cancer survival outcomes in observational population-based studies.

Comorbidities are defined as the coexistence of disorders, in addition to a primary disease of interest, which are causally unrelated to the primary disease (e.g. cancer).[7, 8] A myriad of comorbidity indices have been developed, some more specifically for cancer patients (simple condition, counts of simple conditions, weighted indices and organ-based system).[9]

The Charlson comorbidity index (CCI) is the most extensively studied and most widely used comorbidity index in the medical literature.[10] The widespread use of this index could be explained by the fact that it is not designed for patients with a particular disease and is recommended when overall mortality is the outcome of interest.[10] It does not require extensive information, which makes it appealing to researchers who access administrative data rather than individual clinical notes.[9] However, no gold standard approach to measure comorbidity in the context of cancer exists, and the source of data to ascertain comorbidities varies. [9] Two main sources of data are commonly used to ascertain comorbidities: clinical records and administrative data. In population-based research, administrative data has been suggested as the best available option to ascertain comorbidities and predict in-hospital mortality or 6-month mortality for the CCI.[9, 10]

A report regarding the administrative sources of data used for deriving comorbidities showed a lack of consistency, validity, and replicability of a broad majority of the studies deriving comorbidities.[9] Furthermore, the studies describing the comorbidity index did not offer a clear description of the underlying assumptions made to obtain the algorithm nor provide the code used, thereby limiting the opportunity to assess and replicate the work. Consequently, researchers can make differing assumptions in their evaluation of comorbidities, leading to conflicting findings.

We aimed to construct a robust algorithm that is both transparent and replicable to assess comorbidities using population-based hospital administrative data. First, we described and evaluated the assumptions underlying the development of an algorithm, using the hospital episode statistics (HES) in England for the period 2003–2013. We then evaluated the internal and external validity and quality of these data to extract and use comorbidity information.

Materials and methods

Study design, data and linkage strategy

We developed a retrospective longitudinal assessment of comorbidities for cancer patients diagnosed in England during 2013. Information on cancer patients with a malignant invasive primary tumour was obtained from cancer registrations in England. This contains patient and tumour variables including relevant dates (birth, diagnosis, last vital status), sex, age at diagnosis, deprivation, cancer site and morphology. We used population-based administrative hospital discharge data for the assessment of comorbid conditions. Namely, we analysed Hospital Episode Statistics (HES) data,[11] including accident and emergency (A&E), inpatient and outpatient data streams in England for the period 2003 to 2013. HES contains clinical, administrative, and demographic information about individual patients. The diagnostic information uses the International Classification of Diseases (10th revision) (ICD-10) [12] and operations are coded using the Office of Population Censuses and Surveys Surgical Operations and Procedures (4th edition) (OPCS-4).[13]

HES data had been linked to the cancer registrations from Public Health England using a deterministic linkage strategy based on an individual ID (NHS number), date of birth, sex and postcode.

Data management

Overall assumptions. Overall, we assumed that HES is a valid source of data for the assessment of comorbidities at a population-based level. However, the evaluation of comorbidities depends heavily on both age and probability of attending the hospital (outpatient/inpatient) in the years preceding the cancer diagnosis. Given the chronic aspect of comorbidities, we also assumed that once a comorbidity is recorded in HES, the patient suffers from that comorbidity up until the time of cancer diagnosis. To explain and evaluate our algorithm, we focussed on patients diagnosed with laryngeal cancer.

Algorithm. From HES, we selected all 14 diagnostic variables containing ICD-10 diagnosis codes[12] (version 4) for each episode registered. The time scale refers to time pre-cancer diagnosis, which we split into six-monthly intervals (Fig 1A). We compared the hospital episode start date to the cancer diagnosis date to confirm its inclusion in the different time

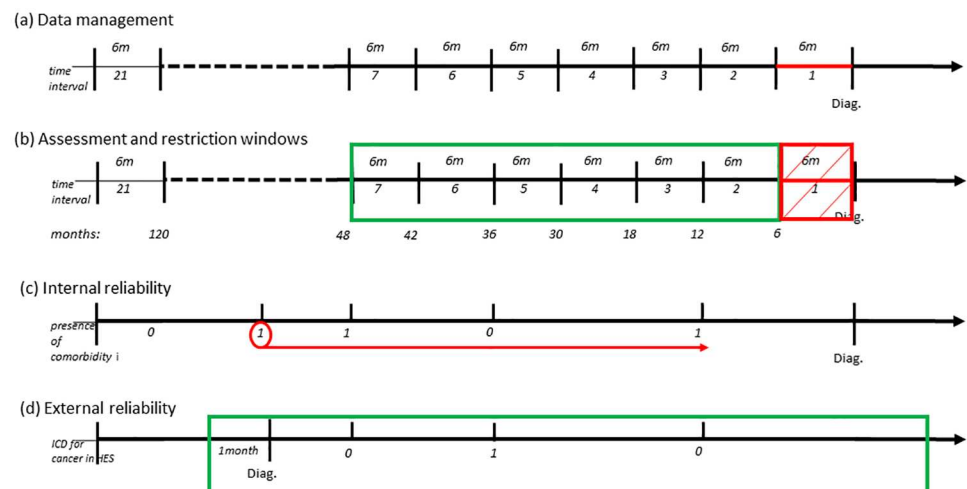


Fig 1. Graphical representation of data management and time-related assumptions.

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intervals. Each interval was examined independently. Each diagnosis field was scanned for the 17 co-morbid conditions that compose the CCI (listed in [S1 Table](#)) and morbid obesity.[\[14\]](#) If a comorbidity (i) was recorded in a given six-month interval (j), we updated the corresponding binary indicator variable ($x_{ij} = 1$). The assessment of comorbidities for periods longer than six months were simply the aggregation of the information contained in all binary variables derived for each six-monthly interval, assuming that once the comorbidity was identified it was just counted once. We also retained the episode date at which a comorbidity was first recorded. We consider the patient as the unit of analysis.

Time-related assumptions. Minimising the potential for selection bias when assessing comorbidities requires the development of an algorithm that will evaluate the same amount of person-time at risk for any given patient included in the assessment. It allows each patient to have the same probability of being diagnosed with comorbidities in relation to the time under assessment. [Table 1](#) shows the minimum number of years, for each cohort of patients, for which we can assess comorbidities. We used the 2013 cohort as a reference to which we compared the comorbidity information derived from shorter time windows. Given this data constraint, we had to consider carefully the optimal time window for the assessment of comorbidities based on the trade-off between long HES history and the number of cancer patient cohorts to evaluate.

Furthermore, considering the definition of comorbidity as the occurrence of disorders which are causally unrelated to cancer, we defined comorbidities identified shortly before diagnosis as cancer-related ([Fig 1B](#)). Thus there is a risk of a collider bias given that cancer-related comorbidities may be a common effect of exposure and outcome, and contradictory associations may arise between non-cancer related comorbidities and cancer survival. [\[15\]](#) To mitigate the possibility of selection bias we created restriction windows of 6, 12 or 24 months before the cancer diagnosis, during which comorbidities first registered were excluded. However, cancer-related comorbidities may be of interest in studies aiming to evaluate factors associated with the cancer treatment decision. In this particular case, the restriction mentioned above will not apply.

Validation and statistical analyses

First, to evaluate the optimal time window for the retrospective assessment of comorbidities, we compared the cumulative incidences of comorbidities for the 2013 cohort of laryngeal cancer patients using consecutive time restrictions, and showed the corresponding percentages of comorbidities lost.

Second, we used two semi-parametric Cox proportional hazard models to estimate the age-adjusted effect of non-cancer related comorbidities on cancer survival. The first model did not differentiate cancer- and non-cancer-related comorbidities. Then, the effect of comorbidities on cancer survival was compared with a second model where cancer and non-cancer related comorbidities were modelled as independent variables. For both models, we fitted three different versions relating to various lengths of the restriction window (6, 12 and 24 months).

Finally, to measure the reliability and consistency of HES to assess comorbidities we computed the intraclass correlation coefficient (ICC) [\[16\]](#) and calculated the percentage of agreement between two independent sources for cancer diagnosis information, namely HES and the cancer registrations.[\[17\]](#) We defined internal reliability as the extent to which two or more successive HES episodes for any given patient report identical or additional comorbidities ([Fig 1C](#)).[\[18, 19\]](#) We used non-linear generalised random effects models to derive the ICC for each of the 17 CCI conditions and their respective 95% CI. The external validity of HES was defined following the Centre for Disease Control (CDC) surveillance strategy for the assessment of

Table 1. Data structure of the cancer registrations linked to HES records for the evaluation of comorbidities.

		Cancer registrations																																					
1971...2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		2013																			
		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)		potential follow-up (years)																			
Restriction window:		6m	12m	6m	12m	6m	12m	6m	12m	6m	12m	6m	12m	6m	12m	6m	12m	6m	12m	6m	12m																		
Hospital Episodes Statistics																																							
2003		1	0.5	0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	7	6.5	6	8	7.5	7	9	8.5	8	10	7.5	9	2003							
2004		0			1	0.5	0	2	2.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	7	6.5	6	8	7.5	7	9	8.5	8	2004							
2005				0			0	1	0.5	0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	7	6.5	6	8	7.5	7	2005							
2006							0				0	1	0.5	0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	7	6.5	6	2006						
2007												1			0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	7	6.5	6	2007					
2008																1	0.5	0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	2008					
2009																		1	0.5	0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	2009			
2010																				1	0.5	0	2	1.5	1	3	2.5	2	4	3.5	3	5	4.5	4	6	5.5	5	2010	
2011																						0																2011	
2012																																							2012
2013																																							2013
2014																																							2014

Number in cell: minimum number of years available for assessment of comorbidities for patients diagnosed in the index year. Three scenarios are considered: no restriction window (no), 6 (6m) or 12 (12m) months restriction windows, during which comorbidities are not assessed.

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reliability between two different sources of data.[20, 21] Cancer registrations were considered as the gold standard for cancer diagnosis. The HES diagnostic fields were screened for a laryngeal cancer diagnostic code from 1 month before the cancer registry diagnosis date (Fig 1D). Then we estimated the percentage of agreement for cancer diagnosis between the two sources and derived 95%CI based on the exact test.[17]

All data management and statistical analyses were performed using STATA version 14.

Results

Fig 2 depicts time-varying proportions of comorbidity according to backward availability of HES data. The x-axis represents time from 10 years before the diagnosis of laryngeal cancer (2003) to the diagnosis time in 2013. We considered that, at 10 years of retrospective follow-up, we have reached the maximum number of comorbidities identifiable from HES, and prevalent in the patient population. From the time at diagnosis, the cumulative proportions of all possible comorbidities converged to 100%. Each comorbidity that composes the CCI is represented by a curve of the time-varying cumulative proportion. No restriction window was included in Fig 2A while Fig 2B and 2C illustrate the impact of a six-month and 12-month restriction window, respectively. The cumulative proportions of any comorbidities reach 80% and above soon after six years before the diagnosis: six years with no restriction window, six and a half years with a six-month restriction and seven years with a 12-month restriction: an overall window of six years already captures the vast majority of comorbidities there are to report in the ten years preceding the diagnosis.

The proportion of patients with COPD (Chronic Obstructive Pulmonary Disease) is high immediately before diagnosis and does not increase greatly with additional years, approximately 15%, reflecting that more than 85% of COPD is identified in the six months before the

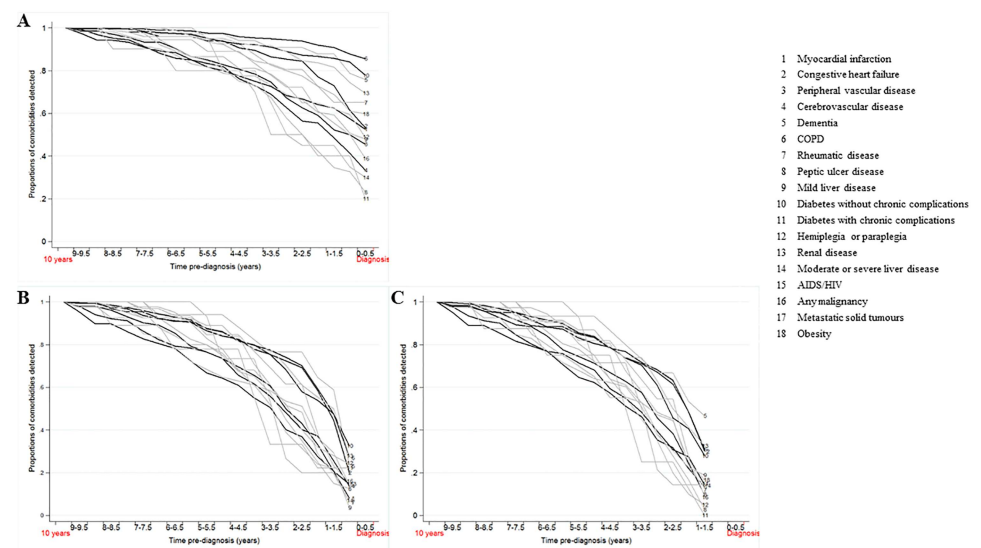


Fig 2. Proportions of individual comorbidities recorded for laryngeal cancer patients diagnosed in 2013 for increasing time periods pre-diagnosis, N = 1,789. 1: Myocardial infarction; 2: Congestive heart failure; 3: Peripheral vascular disease; 4: Cerebrovascular disease; 5: Dementia; 6: COPD; 7: Rheumatic disease; 8: Peptic ulcer disease; 9: Mild liver disease; 10: Diabetes without chronic complications; 11: Diabetes with chronic complications; 12: Hemiplegia or paraplegia; 13: Renal disease; 14: Moderate or severe liver disease; 15: AIDS/HIV; 16: Any malignancy; 17: Metastatic solid tumours; 18: Obesity.

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diagnosis. In Fig 2B and 2C, that proportion is restricted to around 30%. Furthermore, using a restriction window make all cumulative incidence curves follow the same pattern: between 0 and 40% of the final proportions of comorbidities are detected 6 or 12 months before diagnosis. The cumulative proportions of comorbidities increase at an approximate similar rate reaching 100% at ten years.

We provide absolute and relative measures of the impact of applying restriction windows on the assessment of comorbidities. Among the 1,789 laryngeal cancer patients diagnosed in 2013, 51% present with at least one comorbid condition. That proportion drops to 34% and 32% if a six- or 12-month restriction window is applied. It highlights that 17% of these comorbidities are first reported in the six months preceding the diagnosis (Table 2).

Overall, the reliability of the recording of comorbidities in HES is moderate for 7 comorbidities with an ICC ranging between 0.3 for rheumatic disease and 0.62 for dementia. All other comorbidities showed ICCs less than 0.3 for the 2013 laryngeal cancer cohort indicating weak internal reliability (Table 3). The ICC for the 2013 laryngeal cancer cohort and all the available data (cohorts from 2005 to 2013, N = 16,112) were similar, which indicated the absence of secular trends. Dementia, COPD, diabetes without chronic complication and renal disease showed a moderate ICC (≥ 0.5) while peptic ulcer and myocardial infarction consistently showed a lower ICC. In evaluating external reliability, we found that the proportion of agreement between ONS and HES was notably high (86.3%).

Table 4 shows the effect of cancer-related and non-cancer-related COPD on cancer mortality. COPD was defined as related to the cancer if first diagnosed within either 6, 12 or 24 months before the cancer diagnosis. For all three intervals, age-adjusted non-cancer related comorbidities were associated with higher odds of cancer mortality: hazard ratios were 1.26 (CI: 0.98–1.63), 1.26 (CI: 0.97–1.63) and 1.16 (CI: 0.86–1.56) for comorbidities assessed 6, 12 or 24 months away from the cancer diagnosis, respectively. Likewise, cancer-related comorbidities were consistently associated with a higher cancer mortality risk with all hazard ratios over 1.5. However, in multivariate adjusted Cox models where we included age, cancer- and non-cancer related comorbidities as independent predictors, the point estimate for the effect of non-cancer related comorbidities was reversed (HR: 0.98, CI: 0.72–1.32; 0.95, CI: 0.70–1.28; 0.86, CI: 0.62–1.19 for all three intervals assessed). Despite the lack of statistical significance

Table 2. Numbers and proportions of patients with comorbidities detected at selected time points through the ten years preceding laryngeal cancer diagnosis made in 2013, given three restriction windows, N = 1,789.

Time (years)	No restriction window		6-month restriction window		12-month restriction window	
	N.	prop.	N.	prop.	N.	prop.
1	755	0.42	145	0.08		
2	807	0.45	321	0.18	234	0.13
3	839	0.47	415	0.23	345	0.19
4	860	0.48	468	0.26	405	0.23
5	878	0.49	524	0.29	474	0.26
6	892	0.50	541	0.30	493	0.28
7	905	0.51	569	0.32	522	0.29
8	912	0.51	591	0.33	546	0.31
9	918	0.51	609	0.34	566	0.32
10*	918	0.51	614	0.34	572	0.32

*10 years is the maximum number of years we could screen for comorbidities

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Table 3. Reliability of HES data; Internal reliability: Intra-class correlation coefficient for each comorbidity; external reliability: Proportion of agreement for the diagnosis of the index cancer between the diagnostic fields of HES and the cancer registration data, by cancer and year of diagnosis.

	Larynx (2013)*			Larynx**		
	ICC	95% CI		ICC	95% CI	
Internal reliability						
Myocardial infarction	0.27	0.17	0.37	0.27	0.24	0.30
Congestive heart failure	0.33	0.21	0.44	0.39	0.35	0.44
Peripheral vascular disease	0.26	0.16	0.35	0.34	0.31	0.38
Cerebrovascular disease	0.29	0.20	0.38	0.33	0.30	0.36
Dementia	0.56	0.32	0.80	0.62	0.53	0.72
Chronic pulmonary disease	0.38	0.31	0.45	0.54	0.52	0.56
Rheumatic disease	0.30	0.11	0.50	0.50	0.42	0.57
Peptic ulcer disease	0.09	0.01	0.18	0.19	0.15	0.22
Mild liver disease	0.31	0.20	0.43	0.39	0.34	0.44
Diabetes without chronic complication	0.38	0.28	0.48	0.52	0.48	0.56
Diabetes with chronic complication	0.18	-0.06	0.41	0.42	0.31	0.53
Hemiplegia or paraplegia	0.29	0.12	0.46	0.34	0.27	0.42
Renal disease	0.19	0.07	0.31	0.49	0.44	0.54
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	0.29	0.01	0.58	0.35	0.27	0.43
Moderate or severe liver disease	0.31	0.10	0.53	0.28	0.20	0.36
Metastatic solid tumor	0.00	0.00	0.00	0.00	0.00	0.00
AIDS/HIV	0.25	-0.88	1.39	0.43	-0.10	0.96
Morbid obesity	0.18	0.06	0.31	0.30	0.24	0.36
External reliability						
Proportion agreement HES/ONS	86.31	84.62	87.87	86.26	85.72	86.79

*Larynx 2013-cohort, N = 1,789

** All cohorts, N = 16,112

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the change in the point estimates indicate a possible bias. [S1 Fig](#) illustrates the collider effect that cancer-related comorbidities (W2) might have on non-cancer related comorbidities (W1). Cancer related comorbidities (W2) acts as a collider that opens the backdoor path between unmeasured confounders associated with both non-cancer related comorbidities and the outcome (Y).

Discussion

This study highlights the importance of explicitly stating and empirically proving the assumptions made in the assessment of cancer comorbidities using administrative health data. We recommend considering time as an important confounder in the assessment of comorbidities by defining an optimal window and a restriction window. Furthermore, consistency of the optimal window ensures there is no selection bias associated with time, as all patients included in the incident cancer data have the same follow-up period to be assessed for comorbidities. We demonstrate that a 6-year window is an optimal period for identifying comorbidities in our setting. The purpose of the restriction window is to prevent paradoxical effects when assessing the impact of comorbidities on cancer survival. With empirical evidence we highlight the need for a restriction window of at least six months prior to laryngeal cancer diagnosis, when we consider the effect of COPD. Such exercise would need to be repeated for different

Table 4. Hazard Ratios (HR) for the effects of cancer-related* and non-cancer related* comorbidities on the overall hazard of death, laryngeal cancer patients diagnosed in England in 2013, N = 1,789.

Restriction window	COPD					
	Cancer-related			Non-cancer related		
	HR	95% CI		HR	95% CI	
6 months	0–6 months			>6 months		
M0				1.26	0.98	1.63
M1	1.50	1.21	1.86			
Full model	1.51	1.18	1.95	0.98	0.72	1.32
12 months	0–12 months			>12 months		
M0				1.26	0.97	1.63
M1	1.55	1.25	1.92			
Full model	1.59	1.24	2.03	0.95	0.70	1.28
24 months	0–24 months			>24 months		
M0				1.16	0.86	1.56
M1	1.56	1.26	1.92			
Full model	1.64	1.30	2.07	0.86	0.62	1.19

M0: model including non-cancer related comorbidities, adjusted for age. M1: model including cancer-related comorbidities, adjusted for age. Full model: model including both variables for comorbidities, adjusted for age.

* Cancer related comorbidities are those first recorded in the restrictions windows of 6, 12 or 24 months immediately preceding the cancer diagnosis; non-cancer related comorbidities are those recorded in the ten years preceding the cancer diagnosis, excluding the restriction window.

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combinations of cancer sites and comorbidities. Additionally, the code for the computing algorithm is available as proof of reproducible research ([S1 Code](#)).

The number of studies in cancer epidemiology using derived information of comorbidities from administrative or clinical data has grown in the last five years.[10, 22–26] There is a wealth of literature on comorbidity scores [23, 27, 28] and on adapting them to different data sets [29–31], varying numbers of comorbidities included for consideration, and varying subsets of the population [32–34] or diseases of interest.[35, 36] The literature mostly focusses on how administrative data compares to medical records [22] in terms of identifying relevant comorbidities, and if a particular score or modified score is a good predictor of mortality. [37, 38] However, there is no clear consensus on how to assess and estimate comorbidities using administrative or other type of health data. Furthermore, the majority of recent research analysing comorbidity data do not state major assumptions made to derive information on comorbidity; criteria such as validity and reliability are not routinely assessed.[20, 22–34] In epidemiological studies any assumption made during the data generation process and analysis must be stated. [39] Therefore, the first step to develop a uniform approach to assess and use comorbidities in future studies is to state the assumptions made to generate the data. We explicitly document and empirically prove the set of assumptions needed to derive comorbidity information from secondary care health administrative data.

Time is one of the most important confounders in epidemiology. Given patients with larger follow-up period might show higher probability of identifying comorbidities, we set an optimal window so that the assessment of comorbidities is independent of time (i.e., securing the same follow-up time for comorbidities for all cancer patients). Furthermore, the optimal window helps to maximise the equal number of years that all cancer patients included in the analysis were followed up.[40] Following the weak ICC for hospital administrative data presented

here for many of the comorbidities assessed, there is a rationale for using the longest possible assessment window in order to maximise the detection of existing comorbidities. An audit of HES codes showed 90.5% accuracy for identifying 8 major comorbidities, indicating that HES diagnostic fields can confidently predict the actual presence of the comorbidities. Improving the protocol for documenting comorbidities with clinicians and providing further training to administrative clerks could enhance the assessment of comorbidities using HES.[41]

We also compared the prevalence of comorbid conditions in our laryngeal cancer population with that of the general population: comorbidities sharing the same risk factors as laryngeal cancer were much more prevalent in our data, while all other comorbidities were comparable to published prevalence for the general population (data not shown). These results are in agreement with the HES clinical audit.[41]

Some studies have used a restriction window to assess the effect of comorbidities on cancer survival, although the assumptions made to set this window have not been explicitly justified or documented.[40, 42] To our knowledge, we are the first to empirically show the impact of neglecting this principle. A paradoxical association between cancer-related comorbidities and mortality, such as obtaining a protective effect from a risk factor (COPD) known to predict the outcome (mortality due to laryngeal cancer), occurs if a restriction window is not set. This paradoxical association occurs when the probability of the exposure is associated with the outcome being studied.[15] Likewise, a collider stratification bias may occur when we condition on a common effect of exposure and outcome, i.e. non-cancer related comorbidities conditioned on cancer-related comorbidities and cancer.[43] Therefore, when the interest of researchers is to explain the effect of comorbidities on cancer survival, we advise epidemiologists to think carefully about the particular effect of individual comorbidities on specific cancer sites to avoid reporting spurious or paradoxical protective effects of comorbidities.[44–46]

We show that there are fewer differences between a 6- and 12-month restriction window than between no window and a 6-month window, mostly related to cancer-related comorbidities recorded for the first time in the 6 or 12 months before the cancer diagnosis. This finding highlights the potential for earlier cancer diagnosis. In particular, the high proportion of COPD could reflect a mis-diagnosis of laryngeal cancer.

Despite documented differences between administrative data and medical records[47], both types of data produce comorbidity scores that have similar predictive power.[48, 49] We found over 86% agreement between the HES data and Cancer Registrations for the registration of laryngeal cancer. Other limitations include the necessary computing resources for handling big data, the availability of data for the assessment of comorbidities (2003 to 2015), the relatively small number of comorbidities we focused on, and the external validity of our findings limited to hospital records in England. However, our approach is general, and it could be valid in other settings. We recognise we are missing some lifestyle risk factors such as tobacco smoking, alcoholism, drug abuse and other conditions such as asthma, eating disorders and epilepsy, which would undoubtedly impact outcomes.

We encourage researchers to consider our recommendations for the assessment and use of comorbidities. We have clarified the set of assumptions used to identify cancer patients' comorbidities using hospital data. Moreover, we have demonstrated our assumptions through empirical analyses based on current epidemiologic knowledge. Our algorithm for the assessment of comorbidities could be considered as a state-of-the-art method for the evaluation of comorbidities using administrative health data in population-based cancer research epidemiology. Furthermore, we have shown that administrative hospital data is a valuable and consistent source of information allowing population-based cancer researchers to update comorbidities information for patients.

Supporting information

S1 Code. STATA code.

(DOCX)

S1 Fig. The direct acyclic graph for the collider stratification bias from non-cancer related comorbidities. W1: Non-cancer related comorbidities; W2: Cancer-related comorbidities;

W3: Age; Y: Death.

(XLSX)

S1 Table. Comorbidities and their ICD-10 codes, as defined for the Charlson comorbidity index, and obesity.

(XLSX)

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References

1. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. *Clinical epidemiology*. 2013; 5(Suppl 1):3–29. doi: [10.2147/CLEP.S47150](https://doi.org/10.2147/CLEP.S47150) PMID: [24227920](https://pubmed.ncbi.nlm.nih.gov/24227920/)
2. Glymour MM, Mayeda ER, Selby V. Selection bias in clinical epidemiology: causal thinking to guide patient-centered research. *Epidemiology*. 2016.
3. Corkum M, Urquhart R, Kendell C, Burge F, Porter G, Johnston G. Impact of comorbidity and healthcare utilization on colorectal cancer stage at diagnosis: literature review. *Cancer Causes & Control*. 2012; 23(2):213–20. doi: [10.1007/s10552-011-9875-8](https://doi.org/10.1007/s10552-011-9875-8) PMID: [22101505](https://pubmed.ncbi.nlm.nih.gov/22101505/)

4. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a Predictor of Stage of Illness for Patients With Breast Cancer. *Medical care*. 2005; 43(2):132–40. PMID: [15655426](#)
5. Terret C, Castel-Kremer E, Albrand G, Droz JP. Effects of comorbidity on screening and early diagnosis of cancer in elderly people. *The Lancet Oncology*. 2009; 10(1):80–7. doi: [10.1016/S1470-2045\(08\)70336-X](#) PMID: [19111248](#)
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases*. 1987; 40(5):373–83. PMID: [3558716](#)
7. Porta MS, Greenland S, Last JM, Oxford University Press., International Epidemiological Association. *A dictionary of epidemiology*. New York; Oxford: Oxford University Press.; 2008. <http://www.oxfordreference.com/view/10.1093/acref/9780195314496.001.0001/acref-9780195314496>.
8. Feinstein AR. The Pre-Therapeutic Classification of Co-Morbidity in Chronic Disease. *Journal of chronic diseases*. 1970; 23(7):455–68. PMID: [26309916](#)
9. Sarfati D. Review of methods used to measure comorbidity in cancer populations: no gold standard exists. *Journal of clinical epidemiology*. 2012; 65(9):924–33. doi: [10.1016/j.jclinepi.2012.02.017](#) PMID: [22739245](#)
10. Bannay A, Chaignot C, Blotiere PO, Basson M, Weill A, Ricordeau P, et al. The Best Use of the Charlson Comorbidity Index With Electronic Health Care Database to Predict Mortality. *Medical care*. 2016; 54(2):188–94. doi: [10.1097/MLR.0000000000000471](#) PMID: [26683778](#)
11. Health and Social Care Information Centre. Hospital Episode Statistics. 2016 [cited 2016 11/10/2016]. <http://content.digital.nhs.uk/hes>.
12. Organization WH. International Statistical Classification of Diseases and Related Health Problem, 10th revision. 2010.
13. Health and Social Care Information Centre. OPCS-4 Classification. 2016. <http://systems.digital.nhs.uk/data/clinicalcoding/codingstandards/opcs4>.
14. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of clinical epidemiology*. 2004; 57(12):1288–94. doi: [10.1016/j.jclinepi.2004.03.012](#) PMID: [15617955](#)
15. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004; 15(5):615–25. PMID: [15308962](#)
16. Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using Stata*. 3rd ed. College Station, Tex.: Stata Press Publication; 2012.
17. Weiss NS. *Clinical epidemiology: the study of the outcome of illness*. 3rd ed. Oxford; New York: Oxford University Press; 2006. ix, 178 p. p.
18. Bernardini J, Callen S, Fried L, Piraino B. Inter-rater reliability and annual rescoring of the Charlson comorbidity index. *Advances in Peritoneal Dialysis*. 2004; 20:125–7. PMID: [15384811](#)
19. Imamura K, McKinnon M, Middleton R, Black N. Reliability of a comorbidity measure: the Index of Co-Existent Disease (ICED). *Journal of clinical epidemiology*. 1997; 50(9):1011–6. PMID: [9363035](#)
20. German RR, Lee LM, Horan JM, Milstein RL, Pertowski CA, Waller MN, et al. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. *MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control*. 2001; 50(RR-13):1–35; quiz CE1-7.
21. Centers for Disease Control and Prevention. Guidelines for evaluating surveillance systems. *MMWR supplements*. 1988; 37(5):1–18. PMID: [3131659](#)
22. Kehl KL, Lamont EB, McNeil BJ, Bozeman SR, Kelley MJ, Keating NL. Comparing a medical records-based and a claims-based index for measuring comorbidity in patients with lung or colon cancer. *Journal of geriatric oncology*. 2015; 6(3):202–10. doi: [10.1016/j.jgo.2015.01.005](#) PMID: [25662785](#)
23. Sarfati D, Gurney J, Stanley J, Salmond C, Crampton P, Dennett E, et al. Cancer-specific administrative data-based comorbidity indices provided valid alternative to Charlson and National Cancer Institute Indices. *Journal of clinical epidemiology*. 2014; 67(5):586–95. doi: [10.1016/j.jclinepi.2013.11.012](#) PMID: [24582212](#)
24. Sarfati D, Gurney J, Lim BT, Bagheri N, Simpson A, Koea J, et al. Identifying important comorbidity among cancer populations using administrative data: Prevalence and impact on survival. *Asia-Pacific journal of clinical oncology*. 2013.
25. Brewer N, Borman B, Sarfati D, Jeffreys M, Fleming ST, Cheng S, et al. Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study. *BMC cancer*. 2011; 11:132. doi: [10.1186/1471-2407-11-132](#) PMID: [21486460](#)

26. Li H, Hodgson E, Watson L, Shukla A, Nelson JJ. Comorbidities and Concomitant Medication Use in Men with Prostate Cancer or High Levels of PSA Compared to Matched Controls: A GPRD Analysis. *Journal of cancer epidemiology*. 2012; 2012:291704. doi: [10.1155/2012/291704](https://doi.org/10.1155/2012/291704) PMID: [22570655](https://pubmed.ncbi.nlm.nih.gov/22570655/)
27. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *Journal of clinical epidemiology*. 1994; 47(11):1245–51. PMID: [7722560](https://pubmed.ncbi.nlm.nih.gov/7722560/)
28. Daskivich TJ, Kwan L, Dash A, Saigal C, Litwin MS. An Age Adjusted Comorbidity Index to Predict Long-Term, Other Cause Mortality in Men with Prostate Cancer. *The Journal of urology*. 2015; 194(1):73–8. doi: [10.1016/j.juro.2015.01.081](https://doi.org/10.1016/j.juro.2015.01.081) PMID: [25623745](https://pubmed.ncbi.nlm.nih.gov/25623745/)
29. Sarfati D, Hill S, Purdie G, Dennett E, Blakely T. How well does routine hospitalisation data capture information on comorbidity in New Zealand? *New Zealand Medical Journal*. 2010; 123(1310):50–61. PMID: [20360779](https://pubmed.ncbi.nlm.nih.gov/20360779/)
30. Crooks CJ, West J, Card TR. A comparison of the recording of comorbidity in primary and secondary care by using the Charlson Index to predict short-term and long-term survival in a routine linked data cohort. *BMJ open*. 2015; 5(6):e007974. doi: [10.1136/bmjopen-2015-007974](https://doi.org/10.1136/bmjopen-2015-007974) PMID: [26048212](https://pubmed.ncbi.nlm.nih.gov/26048212/)
31. Li B, Evans D, Faris P, Dean S, Quan H. Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *Bmc Health Serv Res*. 2008; 8.
32. Ahern TP, Lash TL, Thwin SS, Silliman RA. Impact of acquired comorbidities on all-cause mortality rates among older breast cancer survivors. *Medical care*. 2009; 47(1):73–9. doi: [10.1097/MLR.0b013e318180913c](https://doi.org/10.1097/MLR.0b013e318180913c) PMID: [19106734](https://pubmed.ncbi.nlm.nih.gov/19106734/)
33. Ahn DH, Mehta N, Yorio JT, Xie Y, Yan J, Gerber DE. Influence of medical comorbidities on the presentation and outcomes of stage I-III non-small-cell lung cancer. *Clinical lung cancer*. 2013; 14(6):644–50. doi: [10.1016/j.clcc.2013.06.009](https://doi.org/10.1016/j.clcc.2013.06.009) PMID: [23886797](https://pubmed.ncbi.nlm.nih.gov/23886797/)
34. Akushevich I, Kravchenko J, Akushevich L, Ukraintseva S, Arbeeve K, Yashin A. Cancer Risk and Behavioral Factors, Comorbidities, and Functional Status in the US Elderly Population. *ISRN oncology*. 2011; 2011:415790. doi: [10.5402/2011/415790](https://doi.org/10.5402/2011/415790) PMID: [22084731](https://pubmed.ncbi.nlm.nih.gov/22084731/)
35. Bang UC, Benfield T, Hyldstrup L, Bendtsen F, Beck Jensen JE. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. *Gastroenterology*. 2014; 146(4):989–94. doi: [10.1053/j.gastro.2013.12.033](https://doi.org/10.1053/j.gastro.2013.12.033) PMID: [24389306](https://pubmed.ncbi.nlm.nih.gov/24389306/)
36. Hemmelgarn BR, Manns BJ, Quan H, Ghali WA. Adapting the Charlson Comorbidity index for use in patients with ESRD. *Am J Kidney Dis*. 2003; 42(1):125–32. PMID: [12830464](https://pubmed.ncbi.nlm.nih.gov/12830464/)
37. Lund L, Jacobsen J, Norgaard M, McLaughlin JK, Blot WJ, Borre M, et al. The prognostic impact of comorbidities on renal cancer, 1995 to 2006: a Danish population based study. *The Journal of urology*. 2009; 182(1):35–40. doi: [10.1016/j.juro.2009.02.136](https://doi.org/10.1016/j.juro.2009.02.136) PMID: [19450859](https://pubmed.ncbi.nlm.nih.gov/19450859/)
38. Patterson RE, Flatt SW, Saquib N, Rock CL, Caan BJ, Parker BA, et al. Medical comorbidities predict mortality in women with a history of early stage breast cancer. *Breast cancer research and treatment*. 2010; 122(3):859–65. doi: [10.1007/s10549-010-0732-3](https://doi.org/10.1007/s10549-010-0732-3) PMID: [20077000](https://pubmed.ncbi.nlm.nih.gov/20077000/)
39. von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bulletin of the World Health Organisation*. 2007; 85(11):867–72.
40. Shack LG, Rachtel B, Williams EM, Northover JM, Coleman MP. Does the timing of comorbidity affect colorectal cancer survival? A population based study. *Postgraduate medical journal*. 2010; 86(1012):73–8. doi: [10.1136/pgmj.2009.084566](https://doi.org/10.1136/pgmj.2009.084566) PMID: [20145054](https://pubmed.ncbi.nlm.nih.gov/20145054/)
41. Navid A, Hajibandeh S, Mohan J, Hajibandeh S. Improving the accuracy of HES comorbidity codes by better documentation in surgical admission proforma. *British Journal of Hospital Medicine*. 2015; 76(12):707–12. doi: [10.12968/hmed.2015.76.12.707](https://doi.org/10.12968/hmed.2015.76.12.707) PMID: [26646333](https://pubmed.ncbi.nlm.nih.gov/26646333/)
42. Howlader N, Mariotto AB, Woloshin S, Schwartz LM. Providing clinicians and patients with actual prognosis: cancer in the context of competing causes of death. *Journal of the National Cancer Institute Monographs*. 2014; 2014(49):255–64. doi: [10.1093/jncimonographs/igu022](https://doi.org/10.1093/jncimonographs/igu022) PMID: [25417239](https://pubmed.ncbi.nlm.nih.gov/25417239/)
43. Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, et al. Illustrating bias due to conditioning on a collider. *International journal of epidemiology*. 2010; 39(2):417–20. doi: [10.1093/ije/dyp334](https://doi.org/10.1093/ije/dyp334) PMID: [19926667](https://pubmed.ncbi.nlm.nih.gov/19926667/)
44. Hatlen P, Grønberg BH, Langhammer A, Carlsen SM, Amundsen T. Prolonged Survival in Patients with Lung Cancer with Diabetes Mellitus. *Journal of Thoracic Oncology*. 2011; 6(11):1810–7. doi: [10.1097/JTO.0b013e31822a75be](https://doi.org/10.1097/JTO.0b013e31822a75be) PMID: [21964531](https://pubmed.ncbi.nlm.nih.gov/21964531/)
45. Braithwaite D, Moore DH, Satariano WA, Kwan ML, Hiatt RA, Kroenke C, et al. Prognostic Impact of Comorbidity among Long-Term Breast Cancer Survivors: Results from the LACE Study. *Cancer Epidemiology Biomarkers and Prevention*. 2012; 21(7):1115–25.

46. Sarfati D, Hill S, Blakely T, Robson B, Purdie G, Dennett E, et al. The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. *BMC cancer*. 2009; 9:116. doi: [10.1186/1471-2407-9-116](https://doi.org/10.1186/1471-2407-9-116) PMID: [19379520](https://pubmed.ncbi.nlm.nih.gov/19379520/)
47. van Doorn C, Bogardus ST, Williams CS, Concato J, Towle VR, Inouye SK. Risk adjustment for older hospitalized persons: a comparison of two methods of data collection for the Charlson index. *Journal of clinical epidemiology*. 2001; 54(7):694–701. PMID: [11438410](https://pubmed.ncbi.nlm.nih.gov/11438410/)
48. Malenka DJ, McLerran D, Roos N, Fisher ES, Wennberg JE. Using administrative data to describe casemix: a comparison with the medical record. *Journal of clinical epidemiology*. 1994; 47(9):1027–32. PMID: [7730905](https://pubmed.ncbi.nlm.nih.gov/7730905/)
49. Newschaffer CJ, Bush TL, Penberthy LT. Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. *Journal of clinical epidemiology*. 1997; 50(6):725–33. PMID: [9250271](https://pubmed.ncbi.nlm.nih.gov/9250271/)