Clinical and Experimental Health Sciences

A New Perspective on the Evaluation of Comorbidity Indices on Survival in Non-Small Cell Lung Cancer

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ABSTRACT

Objective: Mortality studies are interpreted by considering comorbid diseases related to the main disease. Existence, number, and type of comorbid diseases can have an important effect on prognosis. There are various comorbidity indices to include the effects of comorbid diseases in the model. With a new perspective, we aimed to emphasize the importance of evaluating the combination of comorbid diseases in cancer survival.

Methods: Retrospective cohort, data were collected from cases with Non-Small Cell Lung Cancer treated in Department of Chest Diseases. Initially, the effects of their comorbid diseases on the duration of survival were calculated with univariate analysis, then examined according to number of comorbidities, lastly their specific combinations' Hazar Ratio were calculated with Cox multivariate analysis. The most used comorbid indices in the literature were also included.

Results: Out of 247 non-small cell lung cancer (NSCLC) cases analysis, 220 (89%) were men. Median duration of follow-up was 277 days, at the end of the follow-up 197 cases had died. HR of two comorbid diseases in cases was 1.80, but 59.52 for the combination of "diabetes and interstitial lung disease" and 3.76 for "diabetes and previously cancer". Existing comorbid indices had no significant effect on survival time (p:0.684; 0.101; 0.273; 0.567, respectively).

Conclusion: We have offered a new perspective which takes into comorbid diseases related to main disease and specially their combinations when the risk is estimated in survival research. Accurate assessments of the list of comorbid diseases related to main disease hold significant importance in advancing this field.

Keywords: Comorbidity index, comorbid disease, survival analysis, non-small cell lung cancer

1. INTRODUCTION

Many types of research consider comorbid diseases significant, for instance survival not only dependent on pathologic stage, prognosis, age, and sex, but also on other factors such as comorbid diseases (1,2). Additionally, comorbid diseases can affect the diagnosis, treatment, prognosis, and outcome (3). In the literature, the effects of comorbid diseases are listed in various forms, such as scoring, severity of the comorbid diseases etc. (3). Alvan Feinstein noted that "the failure to classify and analyze comorbid diseases has led to many difficulties in medical statistics" in the 1970s (4). Previous comorbid indices approached more general to comorbid disease types, followed by age-adjusted or specific-disease comorbid indices (2,3,5). Comorbid indices have been used frequently in studies on cancer, although there is no specific type of measurement or gold standard for cancer patients and comorbidity can wield an important role in various types of research, and in some oncology studies it has a greater impact than age (6).

The ''Cumulative Illness Rating Scale (CIRS-1968)'', the ''Kaplan-Feinstein Classification (KFC-1974)'', the ''Charlson Comorbidity Index (CCI-1987)'' and the ''Index of Co-Existent Disease (ICED-1987)'' are valid and reliable and commonly used approaches to measure comorbidity that can be used in clinical research (4). Also, the most used is the CCI, the most detailed is the CIRS with scoring sheet, and the most complicated is ICED with scoring and also physical condition, The KFC is a useful and realistic comorbidity index for clinical diabetes research because of specifically designed for diabetes (6,7,8). In addition to these, more current and specific indices such as Modified Charlson Comorbidity Index, Elixhauser Comorbidity Measures, Ovarian Cancer Comorbidity Index (OCCI) are also available (6,9,10,11). These kinds of comorbid indices have been used regardless

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of the main disease however effect of comorbid diseases is changeable depending on the type of the main disease (10). Comorbidity indices are used in the studies or is tried to select the most suitable index for the study by comparing them, but the interaction of comorbid diseases was unobserved.

The purpose of our study is to comorbid diseases' effects on the survival time according to the specific combinations of their, by regarding the most used comorbid indices in existing literature. The most suitable dataset that motivated our study was the survival parameters of non-small cell lung cancer cases along with their comorbid diseases. Through this approach, we aim to underscore that different evaluation methods can yield different outcomes, impacting both result interpretation and the ability to predict prognosis within the area of comorbid studies.

2. METHODS

This study has been approved by the Ethics Committee of Istanbul University, Cerrahpasa Medical Faculty.

A retrospective cohort study was performed patient records from the Department of Chest Diseases 1998 to 2012. A homogeneous group was created from 455 cases by selecting 247 cases with non-small cell lung cancer (NSCLC) with no surgical operation and just taken chemotherapy, curative radiotherapy, chemotherapy-radiotherapy, and chemotherapy-palliative radiotherapy. Data collected by file review included type of treatment, survival status, survival time, comorbid diseases, age, diseases stages, smoking status, and gender. Comorbid diseases that were projected by senior consultant when selected are chronic obstructive pulmonary disease (COPD), diabetes, coronary heart disease, renal failure, asthma, interstitial lung disease, previously cancer. Sample size being insufficient by nature for reliable multivariate analysis, data was folded by four for more clearly statistical results when multivariate analysis.

Summary statistics of continuous data were presented as mean, standard deviation (SD), and median to describe the cases' characteristics. Categorical data were presented as frequencies and proportions. The normality of data distribution was assessed through the Shapiro-Wilk Test. The examination of inter-group differences in the context of two independent samples relied on either the Mann-Whitney U Test or the Independent Student t Test, depending on normal distribution of data. Survival Analysis was conducted utilizing the Kaplan-Meier method and evaluating survival difference between groups was tested using the Log-Rank Test. (12, 13). Risk factors on survival were determined by univariate and multivariate Cox proportional hazard analysis (14,15,16). All data analysis was conducted utilizing the Statistical Package for the Social Sciences (SPSS) v.28. Reported outcomes were accompanied by 95% confidence intervals, and statistical significance was considered at $p<0.05$.

3. RESULTS

Of 247 non-small cell lung cancer (NSCLC) cases analysis, 89% (n:220) were men and 11% (n:27) were women. The mean age at time of diagnosis was 62.15±9.95 years (median:62), ranged from 34 to 87 years. Median duration of follow-up was 277 days, at the end of the follow-up 197 cases had died, 50 cases have still lived. Some cases have some comorbid diseases like diabetes, COPD, coronary heart disease, renal failure, asthma, interstitial lung disease, previously cancer. The highest rate of these comorbid diseases was coronary heart disease with 13% (n:32) and the least rate was renal failure with 1% (n:2). 172 cases did not have any comorbid disease therefore 25.5% of cases had just 1 comorbid disease, 3% of cases had 2 comorbid diseases and 2% of cases had 3 or more comorbid diseases. The most frequent diseases stage was 3b (43.7%) and 7.6% of cases never smoked, 34.2% of cases quit smoking, and 58.2 of cases still smoke.

No statistical difference was found in ages between male-female or died-alive (p:0.096; t=-1.704, and p:0.070; Z=-1.813, respectively). The difference between female and male for survival time was not statistically significant (514.04±637.59 median 247, and 461.20±554.47 median 287.50, respectively. p:0.809; Z=-0.241). The median survival time for NSCLC survival was 332 days (95% Confidence Interval (CI) 305.931-358.069) with Kaplan-Meier Analysis (Figure 1). Log-Rank Analysis didn't indicate a statistically significant difference in two genders' survival (p:0.529; x^2=0.396). When evaluating risk factors for survival time with Cox proportional hazard analysis confirmed a statistically significant effect for age, diseases stages, and smoking status but didn't confirm for gender (p:0.002, <0.001, <0.001, 0.209, respectively).

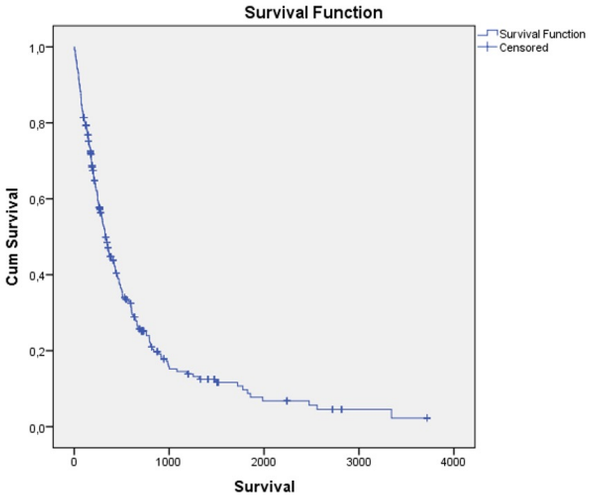

Figure 1. *Kaplan-Meier survival graph for NSCLC*

In univariate analysis, diabetes, COPD, renal failure and asthma comorbid diseases were not a statistically significant effect (p:0.255; 0.317; 0.404; 0.337, respectively) but the following three comorbid diseases significantly affected

survival time of cases: coronary heart disease (HR: 1.27; 95% CI:1.038-1.564) interstitial lung disease (HR: 12.29; 95% CI:7.308-20.652), previously cancer (HR: 1.62; 95% CI:1.131-2.306) (Table 1). In multivariate analysis, same comorbid diseases were still significantly effect on survival time and also they become more significant than univariate analysis, coronary heart disease (HR: 1.32; 95% CI:1.067-1.632), interstitial lung disease (HR: 13.17; 95% CI:7.816-22.187), previously cancer (HR: 1.68; 95% CI:1.174-2.402) (Table 2).

Table 1. *Univariate analysis results of comorbid diseases*

					95% CI for HR	
	β	S.E.	p	HR	Lower	Upper
Diabetes	0,141	0,124	0,255	1,151	0,903	1,468
COPD	0,144	0,144	0,317	1,155	0,871	1,531
Coronary Heart Disease	0,242	0,105	0,020*	1,274	1,038	1,564
Renal Failure	-0,297	0,356	0,404	0,743	0,370	1,492
Asthma	-0,243	0,253	0,337	0,784	0,477	1,288
Interstitial Lung Disease	2,508	0,265	<0,001*	12,285	7,308	20,652
Previously Cancer	0,480	0,182	0,008*	1,615	1,131	2,306

** p<0.05 significant, S.E.: Standard Error, HR: Hazard Ratio; CI: Confidence Interval*

Table 2. *Multivariate analysis results of comorbid diseases*

					95% CI for HR	
	β	S.E.	p	HR	Lower	Upper
Diabetes	0.117	0.128	0.362	1.124	0.875	1.444
COPD	0.099	0.145	0.494	1.105	0.831	1.468
Coronary Heart Disease	0.277	0.108	0.010*	1.320	1.067	1.632
Renal Failure	-0.229	0.357	0.522	0.796	0.396	1.601
Asthma	-0.333	0.260	0.201	0.717	0.430	1.194
Interstitial Lung Disease	2.578	0.266	<0.001*	13.168	7.816	22.187
Previously Cancer	0.518	0.183	0.005*	1.679	1.174	2.402

** p<0.05 significant, S.E.: Standard Error, HR: Hazard Ratio; CI: Confidence Interval*

Table 3 shows that analysis of total combinations in numbers; when cases who have two comorbid diseases whatever they are, compared with cases who haven't any comorbid disease (reference category), two comorbid diseases were significantly effect on survival time (HR: 1.80; 95% CI:1.225-2.640) and also founded same thing for cases who have four comorbid diseases whatever they are (HR: 9.94; 95% CI: 3.653-27.032).

If two comorbid diseases at random instead of content of combinations that have two diseases such as "diabetes+interstitial lung disease" or "diabetes+previously cancer", it might be inconvenient to show for comorbid diseases' effect on survival time; HR of 2 comorbid diseases in cases was 1.80 but the HR of "diabetes+interstitial lung disease" combination comorbid disease was 59.52 as the HR of "diabetes+previously cancer" combination was 3.76 (Table 4). Although there was not a statistically significant difference for cases who have three comorbid diseases (Table 3), the HR of "diabetes+COPD+coronary heart disease" was 2.31 HR. Cox regression survival graph for comorbid disease and their combinations at Figure 2. When evaluating age, diseases stages, and smoking status (were significantly in univariate analysis) as risk factors for NCSLC survival time in all combined comorbid diseases, and combinations that were significant already are still significant and also some combinations' HR were increase.

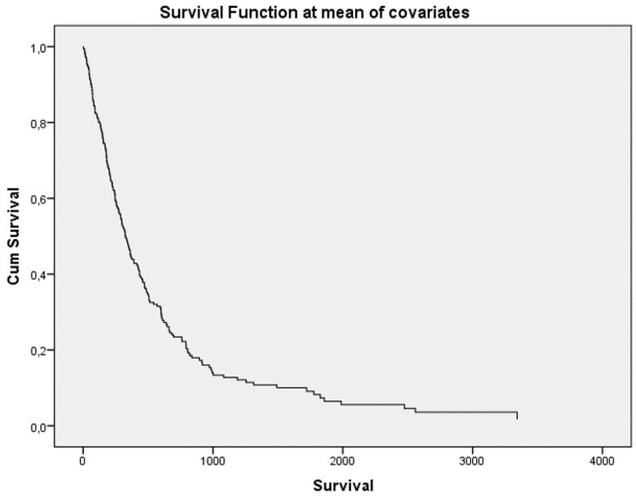

Figure 2. *Cox regression survival graph for comorbid diseases* combinations.

''Charlson Comorbidity Index'', ''Kaplan-Feinstein Classification'', ''Index of Co-Existent Disease'' and ''Cumulative Illness Rating Scale for Geriatrics'', had no significant effect for NSCLC on survival time (p: 0.684; 0.101; 0.273; 0.567, respectively).

Table 3. *Number of total comorbid diseases*

						95% CI for HR	
	n	β	S.E.	p	HR	Lower	Upper
0 Comorbid Disease	688			<0.001*			
1 Comorbid Disease	252	0.142	0.084	0.091	1.152	0.978	1.357
2 Comorbid Diseases	32	0.587	0.196	0.003*	1.798	1.225	2.640
3 Comorbid Diseases	12	0.122	0.292	0.675	1.130	0.637	2.005
4 Comorbid Diseases	4	2.296	0.511	<0.001*	9.937	3.653	27.032

** p<0.05 significant, S.E.: Standard Error, HR: Hazard Ratio; CI: Confidence Interval*

Table 4. *Multivariate analysis results of comorbid diseases with their combinations*

	β	S.E.	p	HR	95% CI for HR	
					Lower	Upper
Comorbid Combination			<0.001			
Diabetes	-0.012	0.164	0.942	0.988	0.716	1.363
COPD	-0.125	0.194	0.519	0.882	0.603	1.291
Coronary Heart Disease	0.264	0.123	0.033*	1.302	1.022	1.658
Renal Failure	-0.252	0.357	0.480	0.777	0.386	1.564
Asthma	-0.009	0.292	0.976	0.991	0.559	1.758
Interstitial Lung Disease	2.380	0.303	<0.001*	10.803	5.970	19.546
Previously Cancer	0.241	0.229	0.292	1.273	0.813	1.994
Diabetes+Coronary Heart Dis.	0.138	0.357	0.698	1.149	0.570	2.314
COPD+ Coronary Heart Dis.	0.377	0.357	0.291	1.458	0.724	2.938
Diabetes+Interstitial Lung Dis.	4.086	0.550	<0.001*	59.517	20.262	174.823
Diabetes+ Previously Cancer	1.323	0.505	0.009*	3.755	1.396	10.103
COPD+ Previously Cancer	0.843	0.504	0.094	2.323	0.866	6.233
Diabetes + COPD + Coronary Heart Dis.	0.838	0.357	0.019*	2.312	1.148	4.658
Diabetes + Coronary Heart Dis. + Asthma	-0.594	0.503	0.237	0.552	0.206	1.479
Diabetes + COPD + Coronary Heart Dis. + Interstitial Lung Dis.	2.412	0.512	<0.001*	11.158	4.093	30.420

** p<0.05 significant, S.E.: Standard Error, HR: Hazard Ratio; CI: Confidence Interval*

4. DISCUSSION

Comorbid diseases, which were significant in the univariate analysis, were still significantly effect on survival time in the multivariate analysis and also they become more significant than univariate analysis. When we regard all types of comorbid combinations in analysis as it is expected much more significant results and HR increase much more. Researchers require appropriate methods to adjusted results for underlying differences in cases' survival time (3,4,17). It is crucial to understand the impact of comorbidity on cases' survival to develop the accurate estimate of survival (8,18). Comorbid diseases in NSCLC have been examined with different approaches such as singular, total number of comorbid diseases, Charlson Comorbidity Index (1,19,20,21). Hovewer, as it is understood in our study, it is necessary to particularize real effects of comorbid diseases by doing together univariate analysis and multivariate analysis. Also, comorbid diseases should be taken together into consideration with their combinations not just single. Comorbidities that existing shouldn't be taken with number of total comorbid combination because different combination of comorbid diseases that have same number of diseases can have different power and significance. Interstitial lung disease was found to be the most influential comorbid disease, both in univariate, multivariate analyses and in combination with other comorbid disease. The combinations of diabetes and previous cancer, as well as COPD and previous cancer, were found to be effective.

In our study, an interesting point, none of most used comorbid indices had significant effect for NSCLC on survival time. In the light of these findings, it can be said that some comorbid diseases' power was hide or increased by other diseases, although there are some valid and reliable indices to measure effect of comorbidity that can be used in the literature (22,23,24). There aren't any indices that involve a comorbid disease list that is enough for all main diseases, different indices are necessary due to the presence of diverse comorbid diseases that can potentially impact the prognosis of various main diseases. Some comorbid indices may not include some comorbid diseases that have important effect for a main disease therefore using such indices isn't capable of an appropriate and confidential prediction, untrustworthy and can't specify required details as a result of this estimations will be fallacious. Indices that assumed same power for every disease can be misleading.

Our study is a pioneering work in providing a statistical perspective to the clinic, emphasizing the importance of extensive data collection, and paving the way for prospective research.

5. CONCLUSION

In conclusion, the inclusion of comorbid diseases is an essential aspect of survival research; however, accurate assessment is crucial for generating trustworthy results. Considering the importance of this aspect, research led by clinicians to compile comprehensive lists of comorbid diseases related to main disease, while also considering the severity of these comorbidities for indexing purposes, holds significant importance in advancing this field.

Limitations

The number of samples is small for the validity of the model in our study. Studies with larger data are needed. There are some potential limitations such as unrecorded severity of comorbid diseases in retrospective data.

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Research idea: ABK, BM
Design of the study: ABK, BM
Acquisition of data for the study: ABK, BM
Analysis of data for the study: ABK, BM
Interpretation of data for the study: ABK, BM
Drafting the manuscript: ABK, BM
Revising it critically for important intellectual content:
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