Multimorbidity and Unobserved Heterogeneity in the Study of Clinical Mortality

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Abstract In most epidemiological data sets one cannot be certain that all risk factors are measured or observed. This paper studies the risk for mortality associated with diseases and deals with heterogeneity in mortality owing to unobserved covariates. We extracted medical records of 186 hospitalized patients from an urban health facility in Ghana. Patients with at least 2 diagnoses of chronic diseases were considered multimorbid. Using age of patients at death as survival time we executed our analysis with and without incorporating frailty effect to Cox proportional hazards (PH) model. The Cox PH model with Gaussian frailty fitted the data better when compared to the standard Cox PH model and Cox PH model with gamma frailty. On average patients were aged 62.3 ± 15.3 years, with 66.1% being multimorbid. Varying degrees of mortality risks were found for different diseases, with the highest associated with having pulmonary valve disorders (HR 7.99, 95% CI 1.45-44.0). Heterogeneity in mortality resulting from unmeasured factors was insignificant. This study demonstrates that patients share similar risk with respect to unobserved factors, but varying risk when conditioned on observables.

Keywords Cox PH model, proportional hazards, frailty, multimorbidity, hazard ratio, unobserved heterogeneity

1 Introduction

Multimorbidity or multiple chronic diseases is an increasingly common phenomenon in aging populations globally. Even with its worldwide recognition, it lacks sufficient attention in terms of research, staff training and clinical guide lines in the medical field in most developing parts of the world of which Ghana is of no exception. In the country, interests have been directed towards individual chronic diseases, meanwhile their joint occurrences have been found in medical records of patients. Presently, only two studies have analysed the joint existence of chronic diseases within the framework of chronic multimorbidity in Ghana [1,2].

However, in the industrialised countries multimorbidity is recognised as a new field of research and hence receiving a growing interest in most recent literature. Most studies are

largely configured to the prevalence of multimorbidity. In one study, the prevalence of multimorbidity was 60% among individuals aged 55-74 years [3]. This was much higher than that of asthma, hypertension and diabetes with respective prevalence of 6.5%, 29.6% and 8.7% [3]. Some studies on this line of research include the work of Britt, et al [4] in Australia, Marengoni, et al [5] in Sweden, and Fortin, et al [6] in Canada. A systematic review of various studies on the prevalence of multimorbidity in different countries published between 1980 and September 2010 revealed that the prevalence of multimorbidity varies from 3.5% to 98.5% in primary care and 13.1% to 71.8% in general population [7]. In Australia, the overall prevalence of multimorbidity was estimated as 37.1%, 29.0% of patients who attended a general practice and 25.5% of the general population [4]. Additionally, the overall prevalence of multimorbidity in the Dutch population was estimated as 13% and among those older than 55 years the prevalence was estimated as 37% [8].

Presently, there is no internationally accepted standard for assessing multimorbidity [9]. Consequently, different methods have been used in studies which aimed to identify disease combinations that are specific to multimorbidity. Some studies grouped diseases based on human body or specific organ domains, [10] analysed triadic combinations of diseases [11] and others employed multivariate statistical methods including cluster analysis, principal component analysis, and factor analysis [9,12-16]. These differences in study approach together with the incoherent operational definition of multimorbidity bring variations across studies. While some researchers defined multimorbidity as the concurrent presence of two or more chronic conditions in the same individual [9,17] to other research groups, only persons with at least three coexisting chronic conditions were considered multimorbid [11,15].

Multimorbidity is associated with negative outcomes, including reduced quality of life, mortality and functional decline [14,17-22]. Recently, Lynch, et al.[21] found medical and psychiatric multimorbidity as significant predictors of mortality among older adults with type 2 diabetes. In addition, the following disease pairs, dementia-hip fracture, dementia-cardiovascular diseases, and dementia-depression have been reported to be significantly associated with increased relative odds of disability in Swedish population [14]. Only few studies used survival analysis, specifically

Cox proportional hazards (PH) model in order to obtain the degree of mortality risk associated with multimorbidity [21,23]. An important issue in this field of work which has not been researched is subject specific heterogeneity or risk factors that are unobservable. Heterogeneity arises if some individuals are more prone than others to experience events, due to unknown or unmeasured factors, e.g. associated with genetic predisposition or lifestyle. To account for such unobserved heterogeneity Vaupel, et al. [26] introduced the univariate frailty models which are extensions of the Cox PH model. Additionally, the association between mortality and gender in multimorbidity has not been fully and sufficiently investigated.

Therefore, the purpose of this study was to elucidate how gender, single diseases and multiple diseases are associated with mortality. Furthermore, we wanted to appropriately account for unidentified patient specific heterogeneity using random effect or frailty variable. Data from Kwadaso Seventh Day Adventist (S.D.A) hospital in Kumasi, Ghana was used in this study.

2 Materials and Methods

2.1 Data

Data were gathered from patients medical records and mortality register of Kwadaso S.D.A. Hospital. The Hospital is a primary facility that provides general health care services in Kwadaso, a suburb of Kumasi, in Ghana. The time span of the data was 10 months, October, 2011 to July, 2012. Information on morbidity status, health outcome (i.e. mortality or discharge), gender and age of patients were retrieved for patients who were aged at least 30 years. Selection criterion of patients whose clinical information were utilized was based on diagnoses of chronic diseases with International Classification of Diseases (ICD-10) codes [24]. Moreover, only the disease with potential of severity that could affect mortality were extracted. Patients were considered as having multimorbid condition if they were recorded with at least two ICD-10 codes. A total of 186 patients were included in the study.

2.2 Statistical Methodology

To execute the statistical analysis in line with the objective we created a survival object from the clinical data by taking into consideration all censorships. Only right censored events were found. The event of interest in this case was death, consequently patients who were discharged from admission were considered right censored. In the coding scheme censored and uncensored events were given codes 0 and 1 to indicate whether death was unobserved or observed. Firstly, we assumed that our sample is homogeneous, consequently the Cox PH model [25] was employed. In this model, the hazard function for individual i was written as

$$\gamma_i(t) = \gamma_0(t) \exp(\beta^T X_i).$$

γ_0 is a baseline hazard function, left unspecified; X_i is the covariate vector of individual i , and t is the time to an event of interest. Practically, t was specified as the age of subjects at death. Two nominal covariates namely gender and disease were used. For each explanatory variable the first level was used as the base. The measure of effect was typically measured by hazard ratio (HR). This was defined as

$$HR = \exp(\beta)$$

Furthermore, we assumed that the hazards for mortality would be influenced by some unobserved risk factors and for that reason we incorporated random effect, so called frailty variable into the proportional hazards model [26]. The hazard function for the i th individual conditional on the frailty variable U was written as

$$\gamma(t) = U_i \gamma_0(t)$$

where U_i denotes the unobservable frailty variable for the i th individual. In this model the hazard of an individual depends additionally on an unobservable random variable U that acts multiplicatively on the baseline hazard function. We considered observed covariates, therefore the model was specified as

$$\gamma_i(t) = U_i \gamma_0(t) \exp(\beta^T X_i).$$

which is an extension of the Cox PH model, thus Cox PH with frailty variable. The frailty variables were assumed to follow the gamma and Gaussian distributions. The models were estimated using penalised likelihood based on Newton-Raphson algorithm in R [27]. Comparisons of models were based on estimates of log-likelihood (LL) ratios, Akaike Information Criterion (AIC) and concordance. Furthermore, model adequacy on the lines of PH assumption was checked numerically and graphically. A 5% level of statistical significance was used through-out the analysis.

3 Results

Characteristics of the 186 patients used in this study are presented in Table 1. Of these patients, 64.5% were male. Overall, the mean age was 62.3 ± 15.3 years (mean $\pm$ standard deviation) and the oldest patient was 97 years old. On average, female patients were 60.3 ± 16.4 years old. The mean age of male patients was 63.3 ± 14.5 . Additionally, 66.1% of the patients were multimorbid in the sense of having two or more chronic diseases, compared with 33.9% who were diagnosed with single diseases. Of the multimorbid individuals 54.8% and 11.3% were having two and three chronic diseases respectively. Entirely, mortality was observed in 39.2% of the patients, 39.4% and 39.2% in female and male patients respectively.

Table 1. Characteristics of patients stratified by survival and mortality status

Characteristics	Total	Survived	Died
Number of patients	186	113	73
%	100.0	60.8	39.2
Gender (% female)	35.5	60.6	39.4
% Male	64.5	60.8	39.2
Mean age all (SD)	62.3 (15.3)	64.0 (14.5)	59.6 (16.1)
Mean age female (SD)	60.3 (16.4)		
Mean age male (SD)	63.3 (14.5)		
Multimorbid patients (% pairs and triads)	66.1	39.2	26.9
(% triads)	11.3	5.9	5.4
(% pairs)	54.8	33.3	21.5
Non-multimorbid patients (% single disease)	33.9	21.5	12.4

Table 2. Percentage of Patients assigned to disease and disease combinations

Disease and disease combinations (ICD 10 Codes)	Total	Female	Male
Diabetes mellitus (E10)+Hypertension (I10)+hypertensive heart disease (I11)	2.2	1.1	1.1
Hypertension (I10)+Diabetes mellitus (E10)+peptic ulcer (K27)	3.2	2.7	0.5
Stroke (I64)+Diabetes mellitus (E10)+hypertension (I10)	5.9	1.6	4.3
Hypertension (I10)+Stroke (I64)	11.8	1.1	10.8
Hypertension (I10)+diabetes mellitus (E10)	32.8	9.1	23.7
Chronic Renal failure (N18)+Stroke (I64)	2.7	2.7	0.0
Hypertension (I10)+Myocardial infarction (I22)	7.5	0.0	7.5
Myocardial infarction (I22)	1.6	0.0	1.6
Stroke (I64)	7.5	3.8	3.8
Diabetes mellitus (E10)	7.5	4.3	3.2
Hypertension (I10)	11.8	5.9	5.9
Heart failure (I50)	2.7	2.1	0.5
Pulmonary valve disorders (I37)	1.6	0	1.6
Peptic ulcer disease (K27)	1.1	1.1	0.0

Furthermore, we found triadic combinations and pairs of specific diseases that pertain to multimorbidity as well as single chronic diseases in patients. Patients were assigned to their disease groups (Table 2). Three triadic combinations of chronic diseases in addition to four pairs were explored. The triadic combinations were diabetes mellitus+hypertension+hypertensive heart disease, hypertension+diabetes mellitus +peptic ulcer disease, and stroke+diabetes mellitus+hypertension. Similarly, hypertension+stroke, hypertension+diabetes mellitus, chronic renal failure+stroke and hypertension+myocardial infarction were the disease pairs found. The combination of hypertension and diabetes mellitus was by far the most frequent (32.8%), followed by hypertension alone (11.8%). Hypertension which emerged as the most common single disease appeared in all the three triads and three of the four pairs. Diabetes mellitus was also seen in all the triads and one of the pairs.

The overall survival pattern of patients is presented in Figure 1. From the figure there is evidence of censored events (i.e. the short vertical lines) occurring at ages prior to age 90 years. These depict the patients who recovered and were consequently discharged. Mortality was observed in all individuals who were aged 90 years and above.

Figure 1. Kaplan Meier curves for overall survival of patients

Fleming-Harrington survival curves presented in Figure 2, show the effect of gender and diseases (i.e. single and multiple) on probability of survival. Probability of survival decreased sufficiently towards zero in male patients. However, in female patients it was observed that the curve levels off at about 0.4, which suggests that a cured fraction may be present in the females. In general, the figure bears out the presence of variation in the probability of survival across the

Figure 2. Fleming-Harrington curves for survival by (a) gender and (b) chronic disease: diseases are identified by ICD 10 codes

Table 3. Fit Statistics of Standard Cox and Cox PH with Parametric Frailty

Model	LL	p-value	AIC	Concordance
Standard Cox PH	-302.7		633.4	0.660
Cox PH with Gamma frailty	-299.3	0.000	631.7	0.725
Cox PH with Gaussian frailty	-298.2	0.000	631.0	0.736

levels of gender and chronic diseases and their combinations. These therefore seems to suggest that gender and the identified chronic diseases are good candidates for explaining mortality in our data.

To assess the association of mortality with gender and diseases in terms of single diseases and multimorbidity (pairs and triads), Cox regression analyses with and without frailty were performed. Table 3 presents the fit statistics of the models. In comparison, the standard Cox model had the least log-likelihood (LL). However, incorporating gamma and Gaussian distributed frailties in the Cox framework significantly increased the log-likelihood, indicating improvements over the standard Cox model. Additionally, based on the Akaike Information Criterion (AIC) and concordance the Cox model with Gaussian distributed frailty out performed the rest of the models.

Numerical test for the assumption of proportionality for gender and the disease variable in the Cox PH with Gaussian frailty model are shown in Table 4. The only culprit is seemingly the combination chronic renal failure and stroke. However, the global chi-square statistic of 17.5 with corresponding p-value of 0.233 is statistically insignificant, implying that the assumption of proportionality has been met. In addition, summary of Schoenfeld residuals against time (age of patients) for a section covariates confirming the results of the numerical test are shown in Figure 3. These together suggests that the Cox model with Gaussian distribute frailty adequately represents our data.

Results of the Cox PH with Gaussian distributed frailty are shown in Table 5. From the table the hazard ratios (HR), corresponding 95% confidence interval (CI) and p-values for the association of mortality with gender and disease are presented. The hazard for mortality associated with male gender was 0.81 with 95% CI of 0.44 -1.48. Thus, holding the dis-

ease variable constant, the hazard of mortality was reduced by 19.0% for male gender compared to female. However, the corresponding p-value of 0.500 suggests that the mortality hazard for male gender does not differ significantly from that of female gender.

Moreover, the mortality hazards associated with having stroke, diabetes mellitus and hypertension concurrently as compared to having diabetes, hypertension and hypertensive heart disease was 0.15 (95% CI=0.03-0.63). This implies that holding gender constant, patients with the triads of stroke, diabetes mellitus and hypertension are substantially less likely to die than those with diabetes, hypertension and hypertensive heart disease (the baseline for disease). Similar patterns in mortality hazards were observed in patients with the co-existence of hypertension, diabetes mellitus and peptic ulcer compared to those with diabetes, hypertension and CVD (HR=0.09, 95% CI=0.01-0.51).

For those diseases found in pairs, having hypertension and stroke (HR=0.16, 95% CI=0.04-0.63), and the simultaneous presence of hypertension and diabetes mellitus (HR 0.19, 95% CI 0.06-0.60) were less fatal than having the baseline category for disease. Moreover, the coexistence of hypertension and myocardial infarction was associated with a hazard ratio of 0.16 (95% CI = 0.04-0.67). Mortality was about 8 times more likely in patients with pulmonary valve disorders compared with having diabetes, hypertension and hypertensive heart disease jointly. Also, having peptic ulcer alone showed increased risk for mortality than the baseline disease (HR = 3.09, 95% CI = 0.29-33.23), however, not significant. On the other hand, having stroke only, hypertension only and heart failure only compared with having diabetes, hypertension and hypertensive heart disease jointly were associated with respective hazard ratios of 0.05 (95% CI = 0.01-0.27), 0.20 (95% CI = 0.06-0.71) and 0.22 (95% CI = 0.02-2.02).

Figure 3. Plots of Schoenfeld residuals for a section of covariates in the Cox model with Gaussian frailty: variable factor(gen)2 for male gender and factor(diagn)2-factor(diagn)9 for disease variables: extreme departure from linearity depicts violation of proportional hazards assumption

The variance of frailty variable is 0.07 with corresponding p-value of 0.320. This indicates that heterogeneity in mortality due to unmeasured patient-specific factors is not significant, hence the patients share similar risk.

3.1 Discussion

While several studies on individual chronic diseases appear in medical literature, multimorbidity or multiple chronic diseases has been less considered. In Ghana, the work of Oduro and Tawiah, [1] and Nimako, et al. [2] are the only multimorbidity studies appearing in literature. The present study researched into multimorbidity and individual diseases using data from a Ghanaian health facility. The study showed a moderately high measure for multimorbidity as 66.1% of patients had at least two diseases. Among the diseases which occurred individually, hypertension (11.8%) was the most common, and also appeared in six out of seven of the diseases found in combination. Hypertension, being the most prevalent condition in our study fit well with existing evidence [9,12]. Additionally, hypertension and diabetes mellitus were the two diseases which occurred most commonly in combination. Specifically, three triadic combinations as well as four pairs of diseases were identified. The triads include diabetes mellitus+hypertension+hypertensive heart disease, hypertension+diabetes mellitus+peptic ulcer, and stroke+diabetes mellitus+hypertension. Similarly, the pairwise disease combinations found were hypertension+stroke, hypertension+diabetes mellitus, chronic renal failure+stroke, and hypertension+myocardial infarction. The most common

disease combination was hypertension and diabetes mellitus (36.6%), followed by the combination of hypertension and stroke (11.8%). Our results are in line with those of prior studies on multimorbidity. In particular, the combination of hypertension and diabetes mellitus in this study is consistent with a recent study done in Ghana [2] and also agrees with the work of Kirchberger, et al. [9] in Germany.

While several studies have found an association between multimorbidity and various health outcomes, there is limited evidence regarding the association between specific disease combinations and mortality. Generally, those studies assessing the impact of multimorbidity on health outcomes are largely based on functional decline and health related quality of life (HRQL) [14,17-20,22]. Furthermore, the relationship between gender and mortality in multimorbidity is not yet well-elucidated. We examined the possible independent association of mortality with gender and disease, in terms of single and disease combinations. We also considered modeling differences among patients as a random effect or frailty within the context of Cox PH regression analysis. Similar work has been done by Lynch, et al. [21] based on the standard Cox PH model. However, to the best of our knowledge, the present study is the first to explicitly examine patient specific unobserved heterogeneity in multimorbidity research.

Our analysis revealed a non-significant association between mortality and male gender, after controlling for the effect of the disease variable. Nonetheless, mortality was less riskier for male gender than female. Regarding the disease variable, we observed significant association for all the identified combinations, as well as the single diseases with the ex-

Table 4. Test for Assumption of Proportionality of Regression Coefficients

Variables	rho	chisq	p-value
Female			
Male	0.087	0.656	0.418
Diabetes+Hypertension+hypertensive heart disease			
Hypertension+Diabetes mellitus+peptic ulcer	0.015	0.016	0.899
Stroke+Diabetes mellitus+hypertension	-0.019	0.024	0.876
Hypertension+Stroke	-0.129	1.402	0.236
Hypertension+Diabetes Mellitus	-0.149	1.865	0.172
Chronic Renal failure+Stroke	-0.298	7.201	0.007
Hypertension+myocardial infarction	-0.005	0.002	0.963
Myocardial infarction	0.033	0.079	0.779
Stroke	-0.017	0.019	0.890
Diabetes Mellitus	-0.189	2.810	0.093
Hypertension	0.119	1.090	0.296
Heart failure	0.022	0.034	0.853
Pulmonary valve disorders	-0.113	0.826	0.363
Peptic ulcer disease	-0.016	0.017	0.896
Global		17.5	0.233

ception of peptic ulcer disease. Among the pairwise and triadic combinations, mortality risk was highest in those having diabetes, hypertension and hypertensive heart disease concurrently at baseline. Compared with patients having the triad of diabetes mellitus, hypertension and hypertensive heart failure, mortality hazard was 91.0% less likely in those who had hypertension, diabetes mellitus and peptic ulcer in combination. Similarly, having stroke, diabetes mellitus and hypertension (HR = 0.15) together as well as hypertension and stroke (HR = 0.16) simultaneously were less deadly than the baseline disease. The most risky condition was pulmonary valve disorders, with HR of 7.99 far higher than those diseases found in combination. These findings supplement evidence from prior studies [21,23]. Moreover, after accounting for the effect gender and disease variables we found that patients specific factors that impact mortality was insignificant. This study may well be the first to include unobserved heterogeneity in multimorbidity research.

A potential limitation of this study is that, we have assessed the effects of single and multiple diseases without taking into account severity of the diseases. Though the information on disease severity was not available in our clinical data, we limited the diagnoses included in our study to those diseases with potential of severity that could affect mortality. Moreover, the fact that data from a single clinic was used limits the extent to which our results can be generalized to the population of Ghana. However, this research paves the way for future studies such as multi-clinic and population based studies with bigger samples that could yield a paradigm of wider generalizability. Our findings would be very useful for the scientific community and clinicians due to limited evidence on this line of research, and in particular the fact that it is the first to assess the impact of specific disease combinations on mortality in Ghana.

Table 5. Hazard Ratio and 95% Confidence Interval Estimates for Each Disease Category

Variables	HR	95 % CI of HR	p-value
Female			
Male	0.81	0.44-1.48	0.500
Diabetes+Hypertension+ hypertensive heart disease			
Hypertension+Diabetes mellitus+peptic ulcer	0.09	0.01-0.51	0.007
Stroke+Diabetes mellitus+hypertension	0.15	0.03-0.63	0.010
Hypertension+Stroke	0.16	0.04-0.63	0.008
Hypertension+Diabetes Mellitus	0.19	0.06-0.60	0.005
Chronic Renal failure+Stroke	0.09	0.01-0.88	0.039
Hypertension+Myocardial infarction	0.16	0.04-0.67	0.012
Myocardial infarction	0.15	0.01-1.47	1.000
Stroke	0.05	0.01-0.27	0.000
Diabetes Mellitus	0.13	0.03-0.51	0.004
Hypertension	0.20	0.06-0.71	0.012
Heart failure	0.22	0.02-2.02	0.180
Pulmonary valve disorders	7.99	1.45-44.0	0.017
Peptic ulcer	3.09	0.29-33.2	0.350
Unobserved component			
Variance of Gaussian frailty variable	0.07		0.320

4 Conclusion

We have studied the mortality risks associated with chronic diseases in terms of multimorbidity and single diseases from a Ghanaian clinical data. Moreover, heterogeneity in mortality owing to unidentified risk factors has been researched. Our findings revealed that the risks for mortality associated with the coexistence of diabetes mellitus, hypertension and hypertensive heart disease is higher than the risk of their separate effects. These diseases in combination also showed increased risk for mortality when compared with other multiple chronic disorders with similar combinations. For instance, patients with the triads of stroke, diabetes mellitus and hypertension were substantially less likely to die than those with diabetes mellitus, hypertension and hypertensive heart disease. Pulmonary valve disorders was found to be the chronic condition with the highest risk. Mortality was about 8 times more likely in patients with pulmonary valve disorders compared with those having diabetes mellitus, hypertension and hypertensive heart disease concurrently. The risk for mortality appeared to be indistinguishable for male and female gender. Moreover, after accounting for effect of gender and diseases on mortality, patient-specific unobserved factors that increases their risk of mortality was insignificant. Knowledge presented in this study would afford the potential for systematic use of day to day medical records to identify groups of patients with high risk of mortality for needs assessment and targeted interventions in our research based health facility. Population based studies as well as multi-clinic studies are needed to aid the generalizability of findings to the Ghanaian community.

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