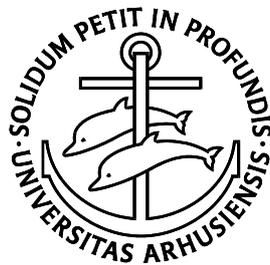


THE RELATIONSHIP BETWEEN CHRONIC OBSTRUCTIVE PULMONARY DISEASE,
COMORBIDITY AND MORTALITY FOLLOWING HIP FRACTURE

Dissertation by
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PREFACE

This dissertation was prepared as part of my requirements for the Doctor of Philosophy in Public Health, with a concentration in Epidemiology, jointly granted by the School of Public Health, University of Medicine and Dentistry of New Jersey (UMDNJ), and Rutgers, the State University of New Jersey. Dissertation committee members included dissertation director, Michael Brimacombe, PhD, and Kitaw Demissie, MD, PhD, Bart Holland, PhD, all of the School of Public Health, and Henrik Sørensen, DrMedSci, PhD, as my external committee member. This work was made possible due to a cooperative agreement between UMDNJ, School of Public Health and the Department of Clinical Epidemiology, Aarhus University Hospital. The health care databases at the Department of Clinical Epidemiology at Aarhus University Hospital are supported by the Western Danish Research Forum for Health Sciences.

This research focuses on a closed cohort of persons ≥ 40 years of age in Western Denmark who were hospitalized with a first time diagnosis of hip fracture between 1/1/1998-1/1/2003. I believe this work will make an important contribution to hip fracture research and improve our understanding of the predictors associated with high mortality following this event.

Cynthia de Luise

April 20, 2007

ABSTRACT OF THE DISSERTATION
THE RELATIONSHIP BETWEEN CHRONIC OBSTRUCTIVE PULMONARY DISEASE,
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By CYNTHIA DE LUISE

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Michael Brimacombe, PhD

Background: Hip fracture is associated with high mortality which has remained relatively unchanged for the last 20 years. Identifying predictors for survival is crucial in order to reduce mortality.

Objective: Using a large population based prospective cohort design, the association between chronic obstructive pulmonary disease (COPD), comorbidity and mortality following hip fracture was examined.

Methods: Among a population-based cohort in Western Denmark (1.4 million inhabitants), all persons ≥ 40 years of age with first-time hospitalization for hip fracture between 1/1/1998 and 1/31/2003 were identified. Prior hospitalization for COPD, other comorbid conditions, and prescription data were ascertained from the healthcare registries. Five controls from the source population without hip fracture were matched to hip fracture patients on age and gender. Kaplan Meier time-to-event estimation was used to produce survival curves, and life table technique to estimate 30-day, 90-day, 1-

year and overall mortality among hip fracture patients with and without COPD and other comorbidities. Cox regression analysis produced crude and adjusted relative risks (RR) and 95 % confidence intervals (CI) for 30-day, 90-day, 1-year and overall mortality following hip fracture associated with COPD and other comorbid conditions. Adjusted RRs for mortality comparing hip fracture patients to population controls without fracture were also computed.

Results: The study population (n=11,985) was followed for an average of 22 months, 71.4% was female, and the mean age was 80 years (range 40-109). The adjusted 30-day, 90-day, 1-year and cumulative mortality following hip fracture was 60-70% greater among patients with a history of COPD. Additional comorbidities that conferred from 1.5 to 3-fold higher risk of mortality at 1 year include congestive heart failure, dementia, tumor, leukemia, lymphoma and metastasis. When compared to age and gender matched controls without hip fracture, hip fracture increased 1-year mortality over 2-fold.

Conclusions: These results demonstrate both the importance of comorbidities, including COPD on subsequent mortality following hip fracture, as well as the strong independent risk of mortality conferred by hip fracture alone. Prevention of hip fracture and appropriate treatment of concurrent medical conditions should all be priorities in an attempt to improve survival in this population.

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INTRODUCTION

Hip fracture is a growing, worldwide epidemic among the elderly.[1, 2] The number of hip fractures worldwide is expected to double from 1.26 million in 1990 to 2.6 million by 2025 and to 4.5 million by 2050.[3] A hip fracture is associated with serious functional disability, illness and premature death, and entails significant expenditures in healthcare resources.[4-13] The incidence of hip fracture increases with age and is higher in women than in men.[14, 15] Osteoporosis is a major contributing factor for most hip fractures in the elderly.

Studies that focus on long term trends in hip fracture mortality demonstrate that there has been no appreciable decline in the hip fracture case fatality rate in the past 20 years.[16] Improving treatments for osteoporosis, fall prevention and identifying predictors for mortality after hip fracture are important ways to reduce the health burden associated with this event. However, until osteoporosis and falls can be prevented, more emphasis must be placed on improving the medical management of hip fracture and identifying and treating those factors that place a person at highest risk for mortality.

Male gender and older age are established predictors for increased mortality following hip fracture.[5-12] However, inconsistencies exist regarding the contribution of comorbid conditions to post-fracture mortality and the duration of increased risk of death following hip fracture.[5-10, 12, 13] Chronic obstructive pulmonary disease (COPD) is a common condition that increases in prevalence with increasing age and is strongly associated

with mortality, either from respiratory or other causes.[17] Attempts to clarify the impact of COPD on mortality after hip fracture are confined to only a small number of studies and hampered by relatively small sample size, few covariates and short follow-up.[9, 13]

Comorbidity is defined as a concurrent health condition in a person with an index disease (i.e. hip fracture).[18] Although there is evidence to support the importance of comorbidity on health status, it has rarely been studied as a single entity. Further, while comorbidity is related to mortality, quality of life and health care, its contribution to post-fracture mortality has been inconsistently demonstrated.[5, 6, 8, 9, 11-13, 19] This discrepancy may be due to differences in study populations, sample size and length of follow up. Two small population-based studies of community dwelling elderly patients demonstrated that in the absence of significant comorbid conditions, there was no difference in mortality among those who had sustained a hip fracture than among matched controls without hip fracture.[6, 12] In one of the studies, with increasing levels of comorbidity, mortality increased for both hip fracture patients and controls, with survival being worse at each level of comorbidity in the hip fracture group.[6] The comorbidities that significantly impacted survival in patients with hip fracture included pulmonary diseases (hazard ratio (HR) = 1.6, 95% confidence interval (CI) 1.1-2.3), dementia, cerebrovascular disease, congestive heart failure, and myocardial infarction. Two larger and more recent studies with longer follow-up, however, demonstrate that even after controlling for comorbidity, hip fracture confers a significantly increased risk of death which remains elevated for several years post-fracture.[8, 11] A prospective cohort of 7,512 ambulatory women aged 75 years or more without hip fracture was

followed for four years to assess the incidence of hip fracture.[8] After controlling for age and baseline health status, those who developed hip fracture were twice as likely to die during the follow up period than those who did not develop hip fracture (RR=2.1, 95% CI 1.6-2.8). While the greatest increase in mortality was in the first six months post-fracture, an increased risk of death persisted for up to three years. Similar results were observed in a population based cohort study of 2,235 incident hip fractures among women aged 50-81 identified from the Swedish National Inpatient Register.[11] After adjusting for age and prior hospitalization for serious disease, those with hip fracture had greater than twice the risk of death (RR=2.3, 95% CI 2.0-2.5) over an average of 5 years of follow up. Mortality was higher within the first 6 months post-fracture, and remained elevated for up to six years. In this same study, the causes of death with a higher rate in the hip fracture group included circulatory disease, respiratory disease, digestive diseases, psychosis and injury and poisoning.

Older age is known to increase the number of chronic conditions.[20, 21] Since hip fracture is associated with older age, patients who develop hip fracture would be expected to present with a high frequency of comorbidities. Diseases that affect the maintenance of normal physiology, such as the cardiopulmonary and renal system are strongly related to mortality.[19] Some disease combinations (i.e. index disease and comorbidity) may have a synergistic effect on outcome.[22-26] For instance, stroke with hip fracture, diabetes or osteoporosis led to a higher rate of disability than what would be expected from each of those conditions independently.[22] Prior research using NHANES I Epidemiologic Follow-up Study of 4,059 persons between 45-74 years of age

demonstrated that clinical and self-reported evidence of knee osteoarthritis and certain concurrent chronic diseases acted synergistically on subsequent disability.[23] Among the chronic conditions studied, pulmonary disease and knee osteoarthritis together conferred higher odds of subsequent disability than the individual odds of disability from these conditions. In another study, lung disease and cancer were synergistic in terms of the disability conferred by this combination of conditions.[25] A study that evaluated the impact of comorbidity on lung cancer survival found that both the comorbidity index, as well as 18 comorbidities were associated with lower survival both for early and late stage disease.[27] A systematic search of the causes and consequences of comorbidity concluded that persons with comorbidity have a higher risk of death, less functional status and quality of life, and use more health resources.[19] What is not completely clear is how quality of care may be partly responsible for these outcomes. Some therapies used for the index condition or comorbidities may have a deleterious effect on the patient's other conditions. These results have important implications for hip fracture patients, who may have one or more concurrent medical condition that may act synergistically on prognosis. This underscores the importance of emphasizing the adequate treatment of not just the index condition, but all the patients' concurrent diseases, as well.

Only a small number of studies have examined the association between COPD and hip fracture mortality.[9, 13] In a prospective four-year study of 2,806 persons admitted to hospital for hip fracture, Roche and colleagues found multiple comorbid conditions, and respiratory disease, in particular, to be an important preoperative predictor for 30-day

mortality following hip fracture (hazard ratio, HR = 1.8, 95% confidence interval CI, 1.3, 2.5).[9] Other important comorbid conditions contributing to 30-day mortality following hip fracture include malignancy, renal disease, and the use of enteral steroids. A multi-center, retrospective study of 290 Medicare beneficiaries with a discharge diagnosis of hip fracture during a two and a half year period identified a history of COPD to be an independent predictor of 30-day mortality after hip fracture (odds ratio, OR=11.1, 95% CI 2.0, 62.0).[13] In this study, a history of congestive heart failure and angina conferred even higher odds ratios as independent predictors of mortality.

This research consists of two population-based cohort studies that examine the effect of comorbidity, in general, and chronic obstructive pulmonary disease (COPD), in particular, on subsequent mortality in persons with a first-time hospital admission for hip fracture in three counties of Western Denmark. Hip fracture mortality is also compared to mortality of matched controls without hip fracture. The study setting represents a population of 1.4 million. Also included is an assessment of the Charlson comorbidity index in the hip fracture cohort and the development of a new index based on the importance of the individual comorbidities in the hip fracture cohort. The large, prospective, population-based nature of this study is expected to contribute important information to the existing literature by elucidating the association between comorbid conditions and COPD on subsequent hip fracture mortality over a long period of follow-up. Such data can help reduce the persistently high mortality that currently exists worldwide following hip fracture. The ability to achieve reductions in hip fracture mortality will have an important impact on the public health of elderly citizens, worldwide.

LITERATURE SEARCH STRATEGY

In order to assemble the published literature for this dissertation, I searched PubMed, MEDLINE and Google Scholar for primary research on hip fracture mortality. The search initiated in late 2004 when the dissertation was initially conceived and continued until early 2007 when the dissertation was being prepared. Boolean search terms used were hip fracture AND mortality, hip fracture AND survival, hip fracture AND chronic obstructive pulmonary disease, hip fracture AND comorbidity, and hip fracture AND prognosis. The publications of main interest were longitudinal studies that measured mortality after hip fracture. After collection of publications from the initial search, publications from the last decade were considered most relevant. Any additional primary research cited in these publications that were not identified on the initial search were also obtained and examined for their relevance. For the assembly of literature on the relationship between COPD and mortality, and comorbidity and mortality, additional searches were conducted using Boolean search terms, COPD AND mortality, and comorbidity AND mortality. Again, the literature search was focused on primary research conducted within the last 10 years.

This literature review represents the state of knowledge at the time the search was completed on the contribution of COPD and comorbidity to hip fracture mortality.

EXTENDED METHODS SECTION

Study population

Data for the studies were derived from the region around Aarhus University, Denmark covering North Jutland, Viborg, and Aarhus counties, Denmark. The total population of these counties is 1,400,000 persons, representing approximately 25% of the Danish population. In Denmark, the National Health Service provides tax-supported healthcare for all inhabitants, allowing free access to general practitioners and hospitals and also refunding a variable proportion of the costs of prescription drugs. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth or on immigration since 1968, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be performed.[28]

Hospital discharge, prescription, and mortality data have been linked into a research database administered by Aarhus University. Under the direction of Henrik Toft Sørensen, MD, PhD, the Department of Clinical Epidemiology, Aarhus University is one of three regional competence centers for clinical databases in Denmark that perform free and independent research at the international level. They are responsible for supervising and providing expertise on the conduct of clinical research using the research databases, ensuring the continuous development and data integrity of the databases, biostatistical support, and methods development. Numerous epidemiologic

studies have been conducted using the regional databases in Western Denmark over the past decade.[29]

The studies for this dissertation were approved by the Danish Data Protection Agency (Record No. 2004-41-3854) and the University of Medicine and Dentistry of New Jersey (UMDNJ) Institutional Review Board (Protocol No. 0120060003 and 0120060004), and conform to all regional scientific and ethical guidelines. This research was performed under a cooperative agreement between the Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark and UMDNJ School of Public Health, Newark, New Jersey. The health care databases at the Department of Clinical Epidemiology at Aarhus University Hospital are supported by the Western Danish Research Forum for Health Sciences.

Study Design

Using the same study population, this research consists of two population-based prospective cohort studies; one that focused on the association between a prior history of COPD and mortality following hip fracture (henceforth called the COPD Study), and another on the association between comorbid conditions and mortality following hip fracture (henceforth called the Comorbidity Study). A brief chapter on the assessment of the Charlson comorbidity index and a development of a revised index is included, as well.

Diagnosis of Hip Fracture

Using the hospital discharge registry data from the three counties (that have been merged into the research database), we identified all patients ≥ 40 years of age with ≥ 90 days of residence in Aarhus, Viborg or North Jutland counties who had a first time diagnosis of hip fracture between January 1, 1998 and January 31, 2003 (ICD-10 codes S.72.0 - fracture of neck of femur, and S.72.1 - pertrochanter fracture.[30] The discharge registries retain information at the individual level including civil registry number, date of admission, date of discharge, and up to 20 discharge diagnoses, assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. The 9th revision (ICD-9) was never implemented in Denmark.

COPD Study

Using the hospital discharge registries, we identified all persons in the hip fracture cohort who were hospitalized for COPD (primary discharge diagnosis) prior to the date of hospitalization for hip fracture (ICD-8 codes 491 - chronic bronchitis, 492 - emphysema, and ICD-10 codes J41 - simple and mucopurulent chronic bronchitis, J42 - unspecified chronic bronchitis, J43 – emphysema, and J44 - other chronic obstructive pulmonary disease.

Comorbidity Study

Using the hospital discharge registries, we identified history of hospitalization for or with 19 individual diagnoses in the Charlson comorbidity index.[31] This was performed by examining the patients' entire hospitalization history. The ICD-8 and ICD-10 codes for the 19 comorbidities are listed in Appendix. 1. These comorbidities include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer, mild liver disease, diabetes mellitus type 1 or 2, hemiplegia, moderate to severe renal disease, diabetes with end organ failure, any tumor, leukemia, lymphoma, moderate to severe liver disease, metastasis, and acquired immunodeficiency syndrome. The comorbidities selected for inclusion in the study were confined to those that make up the Charlson comorbidity index.

Source Population Control Group

Using the hospital discharge registries, five controls without history of hospitalization for hip fracture were matched on year of birth and gender from the Danish Civil Registration System. Controls were required to be residents of the counties at the time of the index subject's hospitalization. Controls may have been hospitalized for another condition on the index subject's hospitalization date, but were not required to be. Established in 1968, the Civil Registration System contains (for all Danish residents), the civil registry number, gender, date of birth, place of birth, residence, citizenship, emigration, continuously updated vital status data and civil registry numbers of parents and spouse.[32]

Covariates and prescription data

Using the Hospital Discharge registries, we recorded the five most common orthopedic surgical procedures performed following hip fracture for the entire study cohort (ICD-10 NFJ 81- internal fixation of fracture with other or combined methods, pertrochanteric, NFJ 70 – internal fixation of fracture, only with screws, femoral neck, NFB 12 – insertion of partial hip prosthesis, cemented, NFJ 80 – internal fixation of fracture with other or combined methods, femoral neck, and NFJ 61 – internal fixation of fracture with splints and plates including screws, pertrochanteric). In addition, other covariates included age in years, which was converted to three intervals (40-65, 66-85, 86+), gender and the Charlson comorbidity index as a measure of overall health status.[31] For the COPD Study, the index was modified to exclude COPD, which was controlled for separately. For the Comorbidity Study, comorbidity was examined in two ways: with the Charlson comorbidity index and by examining the component comorbid conditions that are included in the index. The Charlson index has been extensively used and validated for prediction of short-term mortality and has been adapted for use with hospital discharge data.[33, 34] In order to compute the index, ICD-8 and 10 codes for 19 hospital discharge diagnoses for the entirety of the patient's hospitalization history were identified for each patient from the hospital discharge registries. Prescription data were derived from the National Health Service in the three counties and merged into the research database, as well.[35] Prescription data were collected from 1989 in North Jutland county, in 1996 in Aarhus county, and in 1998 in Viborg county. As part of the tax-funded health care for all inhabitants in Denmark, the Danish National Health Service reimburses 50-75% of the cost for the purchase of most prescribed medicines.

Denmark is served by pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement for the Danish National Health Service in each county. These systems include information on the anatomical therapeutic chemical (ATC) classification system, the amount of drug prescribed, the personal identification number, and the date of drug dispensation.[36] For the Comorbidity Study, in order to further control for cardiovascular disease, we used ATC codes to identify prescriptions for beta blockers (C01A), nitrates (C01D), and statins (C10AA). For the COPD Study, we used ATC codes to identify prescriptions for oral steroids (ATC H02Axxx) and inhaled steroids (ATC R03BA01, R03BA02, R03BA05). Present baseline usage was defined as any usage up to 50 days prior to the date of hip fracture hospitalization for oral steroids, and up to 90 days prior to the date of hip fracture hospitalization for inhaled steroids, nitrates, beta blockers and statins. Any number of dispensings was classified as “exposed” and no dispensings was classified as “not exposed.”

Mortality

Thirty-day, 90-day, 1-year and overall mortality status was ascertained from the Civil Registration System, which maintains electronic records of vital status, such as emigration, death, date of death and residence.[32]

Statistical Analyses

Individuals were followed until the occurrence of study endpoints from the date of the hospital admission for hip fracture or index date for controls and continued until death, emigration or 12/31/2003, whichever came first. Those who did not experience an event

at the end of follow-up were right-censored. Demographic and clinical variables such as gender, age, (three categories: <65, 65-85, 86+), the Charlson comorbidity index, the frequency of individual comorbid conditions, including prior history of COPD, dispensings of medications, were presented as proportions or means, where appropriate. For both studies, the Kaplan Meier product-limit estimator was used to produce survival curves among persons with and without hip fracture, by COPD, age, and the Charlson comorbidity index. Kaplan Meier estimates the conditional probability of survival (the probability of surviving at the end of the interval on condition that the subject was a survivor at the beginning of the interval).[37] Survival curves were compared through the use of log rank tests. The log rank test is used to test the null hypothesis that there is no difference in the probability of death between the two groups at any point in time, or to test for trend among more than two survival curves. [37] Cox proportional hazards regression analysis was used to compute crude and adjusted relative risks associated with 30-day, 90-day, 1-year and overall mortality associated with a prior diagnosis of COPD (COPD study) and prior history of selected comorbidities (Comorbidity study). The main principle underlying the application of proportional hazards is that the ratio of two hazards, denoted as $h_1(t) / h_2(t)$ is constant, that is, independent of time.[37]

In order assess the clinical impact of COPD in the setting of hip fracture, attributable risks (AR) and 95% confidence intervals (CI) were computed as the difference in the mortality probabilities at each time period among persons with COPD and without COPD.

In order to compare the mortality estimates in hip fracture patients to the mortality experience in a comparable population without hip fracture, adjusted RRs were computed for mortality in persons with hip fracture and COPD compared to two control groups: those without hip fracture, but with COPD, and those without hip fracture and without COPD. For the Comorbidity study, hip fracture subjects were compared to subjects without hip fracture within the same strata of the Charlson comorbidity index. In the Comorbidity study, mortality after hip fracture was also examined within age categories and levels of the Charlson comorbidity index.

Validation Exercises

The final models were also analyzed using logistic and Poisson regression to determine the reliability of the effect estimates obtained in the Cox regression.[38, 39] The estimates derived from the three regression models revealed no important differences (results not shown), and therefore, the Cox regression estimates were retained. As an additional validation exercise, the entire hip fracture cohort was randomly divided into two equal groups (using a random number scheme computed in SAS) and relative risks were computed for one half of the cohort in order to compare effect estimates to those obtained for the entire cohort.[40] These exercises revealed no appreciable differences between the effect estimates produced using the entire cohort and those produced with half the cohort.

In addition to age, gender and the Charlson comorbidity index, covariates tested in the models included orthopaedic procedures, type of hip fracture (femoral neck versus pertrochanteric, as a proxy for fracture severity) and cardiovascular medications (for the Comorbidity Study). In the COPD study, medications tested in the models included oral and inhaled corticosteroids. Only those covariates that were significantly associated with mortality with a p value of < 0.05 were retained in the models. The proportional hazard assumption was examined. Precision of effect estimates were reported using 95% confidence intervals (CI). All analyses were conducted using SAS version 9.1.[40]

Assessment of the Charlson Comorbidity Index

The measurement of the component comorbidities in the Charlson index in relation to mortality provided an opportunity to evaluate the performance of the index in the hip fracture cohort. Adjusted relative risks for 1-year mortality derived for each component disease in the Charlson index were compared to the range of estimates derived in the original Charlson index, from which the weights were produced for each comorbidity. A new index was created, which consisted of the sum of the beta coefficients associated with the comorbidities that were associated with an adjusted 1 year mortality RR of at least 1.3, regardless of statistical significance (based upon the methods used to produce the original Charlson index). This has been suggested by some authors to be preferable method of weighting to the use the magnitude of the RRs as the weights.[41-43] The model for 1-year mortality containing only age and gender was compared to two models: 1) the model that included age, gender and original Charlson comorbidity index, and 2) the model that included age, gender and the revised index. In order to

compare the predictive accuracy of the various models in predicting mortality, three measures were examined: the likelihood ratio test (derived from the Cox regression model measuring time to 1-year mortality as the difference between the -2 Log L for the model without the comorbidity index and the model with the comorbidity index), the deviance and the c statistic, or the area under the receiver operator characteristics (ROC) curve, both of which were derived from the logistic regression model measuring 1-year mortality as a binary variable. The goal was to determine if the model could be improved by using a revised index that took into account the diseases of importance in the hip fracture cohort and used a weighting method that better reflects the multiplicative nature of the proportional hazards model.

Study Power Considerations

Approximately 12,000 incident hip fracture can be expected during the study period in the three counties, based on recent epidemiologic studies and after extrapolation to the size of the source population [44, 45] The prevalence of COPD in Denmark is at least 5% or more.[46] Applying this proportion to the hip fracture cohort, a sample of at least 600 persons who have a hospital discharge diagnosis of COPD is expected among the hip fracture cohort. The one-year mortality following hip fracture ranges from 6-37%, depending on the series.[1, 4, 5, 11] Applying these values in a standard power calculation, assuming an alpha level of 0.05, beta of 0.20, an exposed:non-exposed ratio of 20, a maximum number exposed (with COPD) of 600, the power to detect a difference in mortality between COPD and non COPD subjects as small as 1.5 is from 87-100%.[47] For the Comorbidity study, the power to detect a difference in mortality

will vary according to the prevalence of the comorbidity. For congestive heart failure (CHF), assuming an alpha level of 0.05, beta of 0.20, an exposed:non-exposed ratio of 33, and a maximum number exposed of 360 (prevalence of 3% in an elderly population), the power to detect a difference in mortality among those with a history of CHF compared to those without a history of CHF as small as 1.5 is from 72-100%.[48] The power estimates described will be lower for the fully adjusted models. In addition, these estimates are predicated on certain assumptions that may not hold in the hip fracture cohort. When making comparisons between the hip fracture cohort and the control group without hip fracture, a ratio of 5 controls without hip fracture per subject with hip fracture was chosen because this ratio typically will maximize the precision achieved.

MANUSCRIPT I

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND MORTALITY FOLLOWING
HIP FRACTURE: A POPULATION-BASED COHORT STUDY

ABSTRACT

Introduction: We assessed the impact of chronic obstructive pulmonary disease (COPD) on mortality among hip fracture patients, and compared mortality to persons without hip fracture in a population and register-based prospective cohort study.

Methods: The health care databases in Western Denmark (1.4 million inhabitants) were used to identify all persons ≥ 40 years of age with first-time hospitalization for hip fracture between 1/1/1998 and 1/31/2003. Prior hospitalization for COPD was assessed from hospital discharge registries. Five population controls without hip fracture were matched per hip fracture patient on age, gender and COPD status. Life table analysis and Cox regression analysis were used to compute overall risks, and crude and adjusted relative risks (RR) and 95% confidence intervals (CI) for 30-day, 90-day, 1-year and overall mortality among persons with and without a prior history of COPD. Mortality following hip fracture was also compared to that of matched population controls without hip fracture.

Results: A total of 11,985 persons were identified with a first-time hospitalization for hip fracture, of which 771 (6.4%) had a prior diagnosis of COPD. After controlling for covariates, the adjusted RR or mortality ratio for 30-day, 90-day, 1-year and overall mortality, and 95% CI following hip fracture in persons with and without COPD were RR=1.58 (95% CI=1.30-1.90), RR=1.52 (95% CI= 1.30-1.77), RR=1.58 (95% CI= 1.40-1.78), and RR= 1.71 (95% CI = 1.55-1.88), respectively. Compared to matched population controls without hip fracture, 1-year mortality in persons with hip fracture and COPD was from 2 to 3 times greater.

Conclusions: Persons with a history of COPD have a 60-70% higher risk of death following hip fracture than those without COPD. Hip fracture alone increased 1-year mortality 2 to 3-fold compared to persons without hip fracture.

INTRODUCTION

Hip fracture is a growing, worldwide epidemic among the elderly.[1, 2] Worldwide projections for 2025 and 2050 indicate that the number of hip fractures is expected to double from 1.26 million in 1990 to 2.6 million by 2025 and to 4.5 million by 2050.[3] A hip fracture is associated with serious functional disability, illness and premature death, and utilizes significant expenditures in healthcare resources.[4-13] Male gender and older age are established predictors for increased mortality following hip fracture.[5-11] However, inconsistencies exist regarding the contribution of comorbid conditions to mortality following hip fracture and the length of time the higher risk of death persists following fracture.[4-9, 11, 12] Chronic obstructive pulmonary disease is a common condition that increases in prevalence with increasing age and is strongly associated with mortality, either from respiratory or other causes.[17] Certain therapies used in COPD, such as oral and inhaled corticosteroids increase the risk of hip fracture.[44, 45, 49]

Attempts to clarify the impact of COPD on mortality after hip fracture are confined to only a small number of studies, and are hampered by relatively small sample size, few covariates and short follow-up.[9, 13] Such data are needed to potentially prevent death after hip fracture. Therefore, we aimed to examine the effect of COPD on mortality following hip fracture, and compare mortality to age and gender matched population controls without hip fracture in a large population-based cohort study.

MATERIALS AND METHODS

Study Population

We performed this study based on data derived from the population-based healthcare databases in the region around Aarhus University, Denmark covering North Jutland, Viborg, and Aarhus counties.[50] The total population of these counties is 1,400,000 persons, representing approximately 25% of the Danish population, and hospital discharge, prescription and mortality data have been linked into a research database maintained by Aarhus University. In Denmark, the National Health Service in each county provides tax-supported healthcare for all inhabitants, allowing free access to general practitioners and hospitals and also refunding a variable proportion of the costs of prescription drugs. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth or on immigration since 1968, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be performed.[28] This study was approved by the Danish Data Protection Agency (Record No. 2004-41-3854) and the University of Medicine and Dentistry of New Jersey (UMDNJ) Institutional Review Board (Protocol No. 0120060003), and conforms to all regional scientific and ethical guidelines.

Diagnosis of Hip Fracture and COPD

Using the hospital discharge registry data from the three counties (that were merged into the research database), we identified all patients ≥ 40 years of age with ≥ 90 days of residence in Aarhus, Viborg or North Jutland counties who had a first time diagnosis of hip fracture between January 1, 1998 and January 31, 2003 (ICD-10 codes S.72.0 - fracture of neck of femur, and S.72.1 - pertrochanter fracture).[30] The discharge registries retain information at the individual level including civil registry number, date of admission, date of discharge, and up to 20 discharge diagnoses and procedures assigned exclusively by the physician at discharge according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. The 9th revision (ICD-9) was never implemented in Denmark.

Using the hospital discharge registry files, we identified all persons in the hip fracture cohort who were hospitalized for COPD (primary discharge diagnosis) prior to the date of hospitalization for hip fracture (ICD-8 codes 491 - chronic bronchitis, 492 - emphysema, and ICD-10 codes J41 - simple and mucopurulent chronic bronchitis, J42 - unspecified chronic bronchitis, J43 – emphysema, and J44 - other chronic obstructive pulmonary disease).

General Population Control Group

For each hip fracture patient, we sampled five population controls without hip fracture matched on year of birth, gender, and COPD status from the Danish Civil Registration System.[32] Controls were required to be residents of the counties at the time of the index subject's hospitalization. Controls may have been hospitalized for another condition on the index subject's hospitalization date, but were not required to be.

Established in 1968, the Civil Registration System contains (for all Danish residents), the civil registry number, gender, date of birth, place of birth, residence, citizenship, emigration, continuously updated vital status data and civil registry numbers of parents and spouse.

Comorbidities, Covariates and Prescription Data

Using the hospital discharge registry files, we recorded the five most common orthopedic surgical procedures performed following hip fracture for the entire study cohort (ICD-10 NFJ 81- internal fixation of fracture with other or combined methods, pertrochanteric, NFJ 70 – internal fixation of fracture, only with screws, femoral neck, NFB 12 – insertion of partial hip prosthesis, cemented, NFJ 80 – internal fixation of fracture with other or combined methods, femoral neck, and NFJ 61 – internal fixation of fracture with splints and plates including screws, pertrochanteric). In addition, other covariates included age in years, which was converted to three intervals (40-64, 65-85, 86+), gender and the Charlson comorbidity index as a measure of overall health status, modified to exclude COPD, which was the main predictor in our study.[31] The Charlson index has been extensively used and validated for prediction of short-term

mortality [33] and has been adapted for use with hospital discharge data.[34] In order to compute the index, ICD-8 and 10 codes for 19 hospital discharge diagnoses (excluding COPD) were identified for each patient from the hospital discharge registries.

Prescription data were derived from the National Health Service in the three counties and merged into the research database, as well.[35] These systems include information on the anatomical therapeutic chemical (ATC) classification system, the amount of drug prescribed, the personal identification number, and the date of drug dispensation.[36]

We used ATC codes to identify baseline use of prescriptions for oral steroids (ATC H02Axxx) and inhaled steroids (ATC R03BA01, R03BA02, R03BA05). We defined present baseline use as any usage up to 50 days prior to the date of hip fracture hospitalization for oral corticosteroids, and up to 90 days prior to the date of hip fracture hospitalization for inhaled corticosteroids. Any number of dispensings was classified as “exposed” and no dispensings was classified as “not exposed.”

Mortality

Thirty-day, 90-day, 1-year and overall mortality status over the 6 year period was ascertained from the Civil Registration System, which was also used to select the controls for the study.[32]

Statistical Analyses

Individuals were followed until the occurrence of study endpoints from the date of the hospital admission for hip fracture or index date for controls and continued until death, emigration or 12/31/2003, whichever came first. Those who did not experience an event

at the end of follow-up were right-censored. Demographic and clinical variables such as gender, age, comorbidity index, the presence of comorbid conditions, including prior history of COPD were presented as proportions or means, where appropriate. Kaplan Meier time-to-event estimation was used to produce survival curves and life table technique to estimate 30-day, 90-day, 1-year and overall mortality among hip fracture patients with and without COPD. Survival curves were computed by hip fracture and COPD status. Survival curves were also stratified by age in three categories (<65, 65-85, and >85) and evaluated in the overall cohort and only among persons with COPD. Survival curves were compared using log rank tests. We also used Cox proportional hazards regression analysis to estimate crude and adjusted relative risks associated with 30-day, 90-day, 1-year, and overall mortality among hip fracture patients with and without COPD. In order to assess the clinical impact of COPD in the setting of hip fracture, attributable risks (AR) and 95% confidence intervals (CI) were computed as the difference in the mortality probabilities at each time period among persons with COPD and without COPD. In order to compare the mortality experience of hip fracture patients with COPD to the mortality experience in a comparable population without hip fracture, we sampled controls without hip fracture from the source population and matched 5 controls to each hip fracture patient on year of birth and gender. We then used Cox regression to compute adjusted RRs for mortality in persons with hip fracture and COPD compared to two source population control groups: those without hip fracture, but with COPD, and those without hip fracture and without COPD. In addition to age, gender and the Charlson comorbidity index (modified to exclude COPD), covariates analyzed in the models included orthopedic procedures, type of hip fracture (femoral neck versus

perthrochanteric, as a proxy for fracture severity), and oral and inhaled corticosteroids. Effect estimates were adjusted for those covariates that were significantly associated with mortality with a p value of <0.05 . Precision of effect estimates were reported using 95% confidence intervals (CI). All analyses were conducted using SAS version 9.1.[40]

RESULTS

Descriptive Data

We identified a total of 11,985 persons with a first time hospitalization for hip fracture between January 1, 1998 and 1/31/2003 (table 1). Average follow-up was 1 year and 10 months. Almost three-quarters (8,561) of the patients were female (71.4%). The mean age was 80 years (range 40-109). Ninety percent (10,794) of the cohort was over 65 and 30% (3,636) was over 85 years of age. Forty-seven percent (5,650) of the overall cohort had a Charlson comorbidity index of 0, 46% (5,450) had indices between 1 and 3, and the remainder had indices of 4 or greater. Among the comorbid conditions occurring with the highest frequency in the overall cohort were cerebrovascular disease (17.4%), any tumor (13.1%), congestive heart failure (9.7%), ulcer (8.4%), and myocardial infarction (7.1%). A total of 771 (6.4%) had a prior history of COPD.

Among persons with COPD, there were proportionally more males and fewer females (table 1). The COPD subgroup was slightly younger on average, than persons without COPD, and included proportionally more patients between the ages of 66-85, and fewer patients older than 85 years and younger than 65 years. There were proportionally more patients with COPD who had a Charlson index of at least 1. Comorbidities that were prevalent more often among the COPD subgroup were myocardial infarction, congestive heart failure, peripheral vascular disease, ulcer, renal disease, any tumor and metastasis. There was proportionately more oral and inhaled steroid use among persons with COPD compared to persons without COPD.

Mortality

Among persons with COPD, 30-day, 90-day and 1-year mortality was 16.9%, 25.8%, and 41.8%, respectively. Figure 1 displays survival curves by hip fracture and COPD status. Hip fracture, either in combination with COPD or alone, was associated with lower survival at each time period (log-rank test for trend - $p < 0.0001$). Figure 2 displays survival in hip fracture patients by age category, and Figure 3 displays survival in hip fracture patients with COPD by age category. Among all hip fracture patients, survival following hip fracture decreased with increasing age (log-rank test for trend- $p < 0.0001$). However, in patients with COPD, all patients 65 or over had disproportionately lower survival in the first year, which diverged according to age thereafter (log-rank test for trend $p < 0.001$). The survival curves approached proportionality as the curves did not intersect.

Attributable Risk

The attributable risk for mortality in hip fracture patients with COPD compared to hip fracture patients without COPD was measured by computing the absolute difference in the mortality probabilities between the two groups. For 30-day mortality, 90-day mortality, and 1-year mortality, the AR was 6.2%, 8.7%, and 14.4%, respectively. These proportions represent the percentage of deaths in 100 patients with hip fracture attributable to COPD.

Relative Mortality

Number of deaths, crude and adjusted relative risks and 95% confidence intervals for 30-day, 90-day, 1-year and overall mortality following hip fracture among persons with a prior history of COPD compared to persons without COPD are shown in table 2. At each time period examined and after adjustment for covariates, a prior history of COPD conferred approximately 60-70% higher risk of death after hip fracture.

Adjusted relative risks and 95% CI for 30-day, 90-day, 1-year and overall mortality comparing hip fracture patients with COPD to those without hip fracture are shown in table 3. When compared to persons without hip fracture, but with a history of COPD, the adjusted mortality risk for persons with hip fracture and COPD was from 2 to 3 times higher. When compared to persons with neither hip fracture, nor COPD, the adjusted mortality risk for persons with hip fracture and COPD was from 2 to over 3 times higher. While the risk of dying was highest in the first year following hip fracture (28.3% in all patients with hip fracture), it declined in each successive year following hip fracture. When compared to age-matched, non-hip fracture patients in whom annual mortality was relatively constant at about 7-8% per year, in hip fracture patients, annual mortality remained elevated for up to three years post-fracture (data not show). After three years following fracture, annual mortality was generally similar to non-hip fracture patients.

DISCUSSION

In a large population-based cohort of patients hospitalized for a first-time diagnosis of hip fracture over a 5-year period in Denmark, crude mortality for persons with concurrent COPD was 16.9% at 30 days, 25.8% at 90 days, and 41.8% at one year. This is in contrast to mortality in persons without COPD, which was 10.7% at 30 days, 17.1% at 90 days, and 27.4% at one year. The AR attributable to COPD was 14% for 1-year mortality. COPD increased the adjusted relative mortality by 60-70% in this cohort. In contrast to population controls without hip fracture, adjusted 1-year mortality RR estimates for persons with hip fracture and concurrent COPD were over 2 times higher.

Our population-based results are consistent with previous research related to hip fracture in general, with high mortality during the first year following hip fracture, and a higher risk of death for men and persons at the extremes of age (data for gender not shown).[4, 6-11] In addition, only two prior studies have examined the contribution of a prior history of respiratory disease or COPD on hip fracture prognosis.[9, 13] Among 2,448 prospectively followed hip fracture subjects in England, those with a history of respiratory disease had an age and sex adjusted hazard ratio for 30-day and one-year mortality of 1.6 and 1.4 (95% CI 1.1, 1.7), respectively.[9] In a multi-center, retrospective study of 390 Medicare beneficiaries with hip fracture, a history of COPD was an independent predictor of 30-day mortality (OR (odds ratio) = 11.0, 95% CI 2.0, 62.0).[13] Apart from these studies, there has been little additional research conducted on the impact of COPD on mortality after hip fracture.

Persons hospitalized with an acute exacerbation of COPD have very high in-hospital and post-hospital mortality rates.[51-54] Connors and colleagues reported that among a prospectively studied cohort of 1,016 adults hospitalized for an acute exacerbation of COPD (characterized by PaCO₂ of 50 Hg or more), in-hospital mortality was 11%, and the 60-day, 180-day, 1-year, and 2-year mortality was 20%, 33%, 43% and 49%, respectively.[51] Six months after, only 26% of the cohort was still alive. A prospective multi-center inception cohort study of 362 persons admitted to 42 intensive care units for an acute exacerbation of COPD found an in-hospital mortality of 24%, and for those at least 65 years of age, a mortality of 30% at discharge, 41% at 90 days, 47% at 180 days, and 59% at one year.[54]

In our observational study, we were unable to determine the exact mechanism for the association between COPD and mortality. However, this association is likely explained by one or more of the following factors 1) COPD severity and factors associated with COPD; 2) inappropriate pharmacotherapy or non-adherence; 3) adverse effects of pharmacotherapy; 4) comorbidities not captured in the Charlson comorbidity index. For example, side-effects of corticosteroid therapy may include immunosuppression, obesity, diabetes, all of which are independently associated with increasing surgical risk.[55, 56] While cause of death was not the main focus of this study, persons with COPD are at risk of dying from a number of causes other than obstructive lung disease.[57] COPD as the underlying cause of death is recorded in less than half of all COPD deaths, with over half of all deaths being non-respiratory in nature.[58] Rather

than the result of incomplete recording, there is evidence to suggest that COPD may increase the risk of death from other comorbid conditions and conversely, that certain comorbidities may increase the risk of COPD mortality.[59] Cardiovascular disease and ischemic heart disease, in particular, is a common comorbidity and cause of death in persons with COPD.[60] In a population-based cohort study of 5, 648 persons newly treated for COPD over a 7 year period, the proportion of deaths recorded with a primary cause as CVD was almost three times that of deaths recorded with a primary cause of COPD.[61] In the Lung Health Study, a large, multi-center clinical trial of smokers with mild to moderate lung function impairment, two thirds of all deaths were due to either lung cancer or cardiovascular disease, with coronary heart disease as the cause of most CVD deaths.[62] Finally, certain therapy for COPD (oral corticosteroids) has been associated with increased mortality in several studies.[63-65] While potentially a reflection of disease severity, in that oral corticosteroids may be prescribed more often to persons with more severe COPD who have a higher risk of death, oral steroids could also be related to increased mortality. Moreover, these medications have been associated with inducing reduction in bone mineral density and increasing the risk of hip fracture.[44, 45, 49]

Strengths of this study include Denmark's uniform national health care system permitting a population-based design. Complete or non-differential follow-up through population-based registries limits the potential for selection and surveillance bias. It is known that discharge diagnoses are not entirely accurate and the validity of these estimates depend on the accurate coding of COPD and hip fracture. However, the misclassification is

most likely low since 89.5 percent of patients in this region with a hospital discharge diagnosis of COPD also have filled a prescription for a COPD medication.[66] Hospital discharge diagnoses for hip fracture have been shown to be very accurate with a sensitivity of 96 percent and a positive predictive value of 94 percent.[67, 68] Any non-differential misclassification of COPD or hip fracture would tend to bias effect estimates toward the null indicating no association.[69]

While this study lacked clinical details, information on comorbidities was obtained using the Charlson index, which has been previously shown to have a high positive predictive value for short-term mortality.[31] An additional strength of this study is the use of the entire hospital discharge history to compute the Charlson comorbidity index, rather than a shorter period of time prior to the index date. The Charlson index allows for the adjustment of most underlying diseases, thereby minimizing their potential as confounding factors, but residual confounding cannot be excluded since the collection of potential confounding factors in this study relies solely on the availability of these data in the automated registry data. Another limitation of this study is the absence of cause of death, which would have provided insight into factors responsible for high mortality in this population. Causes of death in Denmark are recorded on death certificates, which were not available for this study. Because of this, it is not possible to make specific suggestions for the clinical care of COPD in patients who experience a hip fracture.

In conclusion, patients with incident hip fracture and a history of COPD had a 60-70% higher risk of death than those without COPD. Compared to population controls without

hip fracture, the combination of hip fracture and COPD raised the adjusted 1-year mortality risk from 2 to 3-fold. Identifying predictors of mortality following hip fracture, such as COPD, are necessary in order to better target preventive efforts and medical resources.

Table 1 Demographic Characteristics of Patients Hospitalized for Hip Fracture by COPD Status

	COPD Dx n=771 (%)	No COPD Dx n=11,214 (%)	Total n=11,985 (%)
Sex			
Male	297 (38.5)	3,127 (27.9)	3424 (28.6)
Female	474 (61.5)	8,087 (72.1)	8561 (71.4)
Age (mean in years)			
40-64 years	59 (7.7)	1,020 (9.1)	1,079 (9.0)
65-85 years	602 (78.1)	6,658 (59.4)	7,260 (60.6)
86-109 years	110 (14.2)	3,536 (31.5)	3,646 (30.4)
Charlson Index			
Mean (index)	1.5 (SE ± 0.08)	1.2 (SE ± 0.01)	1.16 (SE ±0.01)
0	271 (35.2)	5,379 (48.0)	5,650 (47.1)
1-3	428 (55.5)	5,022 (44.8)	5,450 (45.5)
4-12	72 (9.3)	813 (7.2)	885 (7.4)
Comorbid Conditions			
Myocardial infarction	77 (10.0)	774 (6.9)	851 (7.1)
Congestive heart failure	199 (25.8)	958 (8.5)	1,157 (9.7)
Peripheral vascular disease	71 (9.2)	696 (6.2)	767 (6.4)
Cerebrovascular disease	110 (14.3)	1,974 (17.6)	2,084 (17.4)
Dementia	30 (3.9)	532 (4.7)	562 (4.7)
COPD	771 (6.4)	0	771 (6.4)
Connective tissue disease	39 (5.1)	576 (5.1)	615 (5.1)
Ulcer	121 (15.7)	889 (7.9)	1,010 (8.4)
Diabetes mellitus 1 or 2	48 (6.2)	717 (6.4)	765 (6.4)
Moderate to severe renal disease	32 (4.2)	231 (2.1)	263 (2.2)
Diabetes mellitus w/end organ damage	20 (2.6)	332 (3.0)	352 (2.9)
Any tumor	111 (14.4)	1,453 (13.0)	1,564 (13.1)
Metastasis	16 (2.1)	184 (1.6)	200 1.7)
Oral Corticosteroids	208 (30.0)	514 (4.6)	722 (6.0)
Inhaled Corticosteroids	249 (32.3)	225 (2.0)	474 (4.0)

Abbreviations: N, number; Dx, diagnosis, SE, standard error

Figure 1 Survival by Hip Fracture and COPD Status

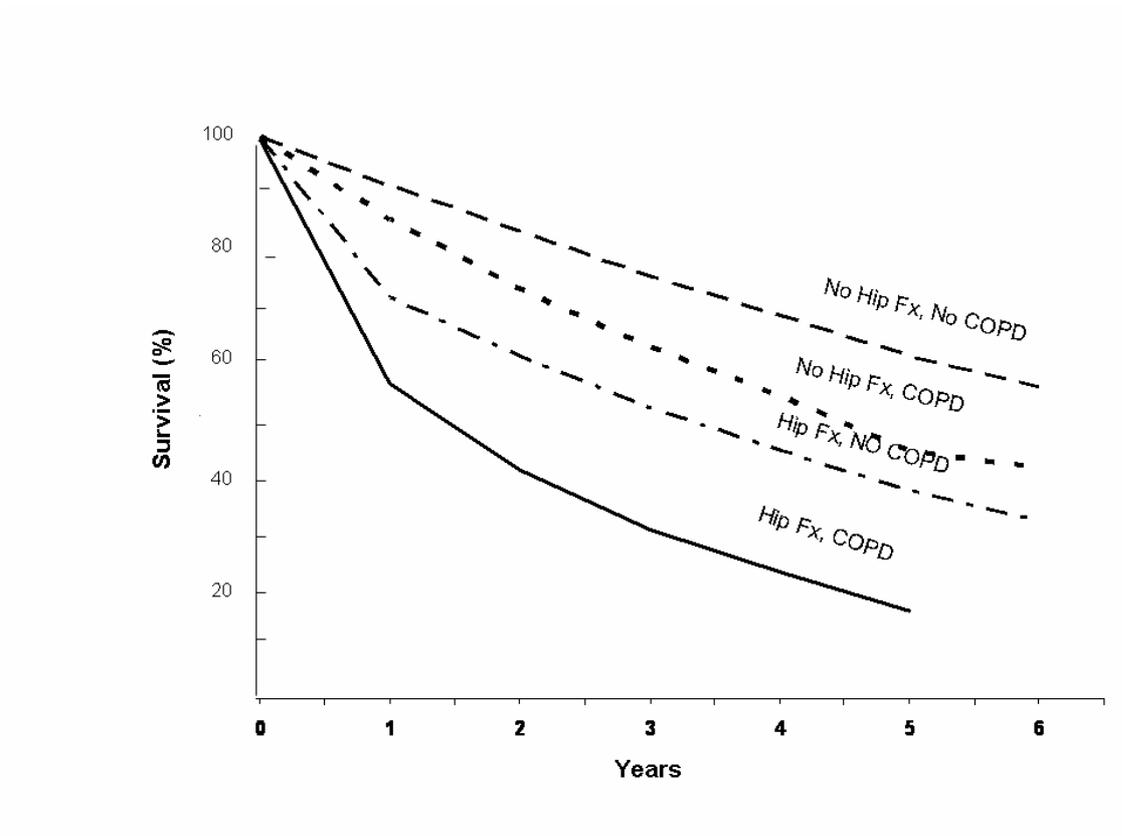


Figure 2 Survival in Hip Fracture Patients by Age

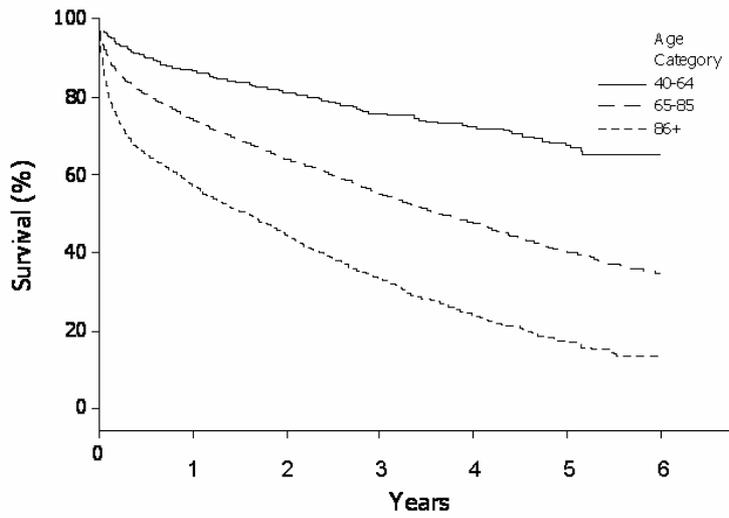


Figure 3 Survival in Hip Fracture Patients with COPD by Age

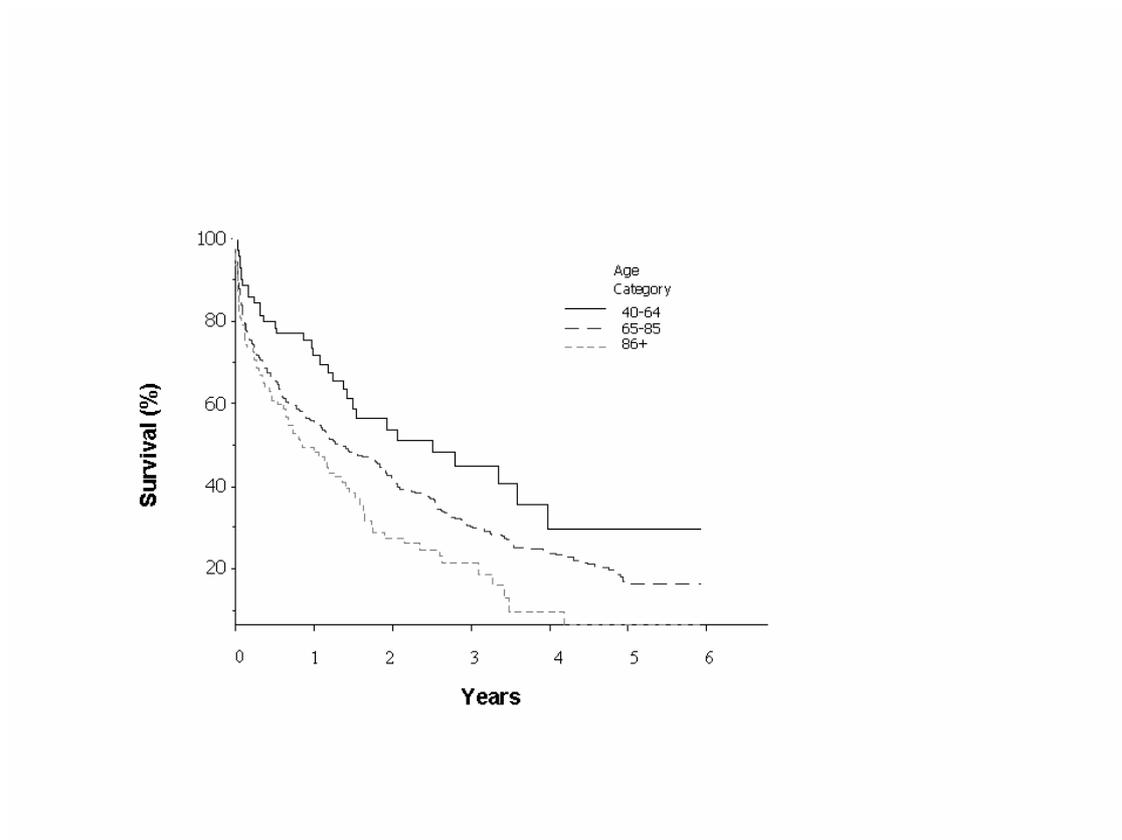


Table 2 Relative Risks for Mortality in Hip Fracture Patients with COPD

Endpoint	Number of deaths (%) (COPD)	Number of deaths (%) (without COPD)	Crude RR* (95% CI)	RR** (95% CI)
30-day	130 (16.9)	1194 (10.7)	1.75 (1.42, 2.15)	1.58 (1.30, 1.90)
90-day	199 (25.8)	1912 (17.1)	1.68 (1.42, 1.99)	1.52 (1.30, 1.77)
1-year	322 (41.8)	3073 (27.4)	1.79 (1.57, 2.04)	1.58 (1.40, 1.78)
Overall	488 (63.3)	5160 (46.0)	1.77 (1.61, 1.94)	1.71 (1.55, 1.88)

Abbreviations: RR, relative risk; CI, confidence interval

* Crude RR may differ from regression RR due to modeling assumptions

**adjusted for age, gender, oral corticosteroids and the Charlson comorbidity index

Table 3 Relative Risks for Mortality in Hip fracture Patients with COPD compared to Controls without Hip Fracture

Comparison Group	30-day	90-day	1-year	Overall
No Fracture No COPD				
Crude RR (95% CI)	3.97 (3.26, 4.85)	4.58 (3.94, 5.33)	3.74 (3.34, 4.19)	5.06 (4.62, 5.54)
Adjusted RR* (95%CI)	2.91 (2.35, 3.61)	3.37 (2.87, 3.95)	2.65 (2.36, 2.98)	2.87 (2.61, 3.14)
No Fracture With COPD				
Crude (RR (95% CI)	2.42 (1.74, 3.35)	3.10 (2.50, 3.84)	2.69 (2.34, 3.10)	2.93 (2.64, 3.25)
Adjusted RR* (95% CI)	2.37 (1.71, 3.30)	3.01 (2.43, 3.74)	2.66 (2.31, 3.06)	2.81 (2.53, 3.12)

Abbreviation: RR, relative risk; CI, confidence interval

* adjusted for Charlson comorbidity index

MANUSCRIPT II
COMORBIDITY AND MORTALITY FOLLOWING HIP FRACTURE: A POPULATION-
BASED COHORT STUDY

ABSTRACT

Introduction: We assessed the impact of different types of comorbidity on mortality following hip fracture, and compared mortality to persons without hip fracture in a population and register-based prospective cohort study.

Methods: The health care databases in Western Denmark (1.4 million inhabitants) were used to identify all persons ≥ 40 years of age with first-time hospitalization for hip fracture between 1/1/1998 and 1/31/2003. Prior hospitalization for selected comorbidities was assessed from hospital discharge registries. Five population controls without hip fracture were matched per hip fracture patient on age and gender. Life table analysis and Cox regression analysis were used to compute overall risks, and crude and adjusted relative risks and 95% confidence intervals for 30-day, 90-day, and 1-year mortality associated with prior hospital history of selected comorbidities. We also compared mortality following hip fracture with population controls without hip fracture.

Results: A total of 11, 985 persons were identified with a first-time hospitalization for hip fracture. Average follow-up was 1 year, 10 months. Females comprised 71% of the cohort. Ninety percent of the cohort was > 65 years of age. The 30-day, 90-day, 1-year mortality and overall mortality was 11.1%, 17.6%, 28.3% and 47.1%, respectively. In the cohort, overall, history of CHF, chronic obstructive pulmonary disease (COPD), dementia, tumor, and malignancy increased 1-year mortality from 50% to 3-fold. However, the youngest patients (<65 years) with COPD (RR=2.23, 95% CI 1.25, 3.98), peripheral vascular disease (RR= 2.64, 95% CI 1.45, 4.80), tumor (RR=7.28, 4.65, 11.40) and lymphoma (RR= 4.95, 1.54, 15.94) had a substantially higher relative risk of

mortality at one year than did older persons (>85 years) with the same comorbidities.

Stratified by Charlson comorbidity index, one-year mortality among hip fracture subjects compared to matched controls without hip fracture, was elevated from 2 to over 3- fold at 1-year (RR= 2.23, 1.97, 2.53 to RR = 3.49, 3.24, 3.77).

Conclusions: Comorbidities such as CHF, COPD, dementia, tumor and malignancy confer from 50% to 3-fold increased relative risk of mortality at 1 year following hip fracture compared to persons without these conditions. Even after stratifying by comorbidity index, hip fracture increased 1-year mortality more than 3-fold compared to persons without hip fracture.

INTRODUCTION

Hip fracture is a growing, worldwide epidemic among the elderly.[1, 2] Worldwide projections for 2025 and 2050 indicate that the number of hip fractures is expected to double from 1.26 million in 1990 to 2.6 million by 2025 and to 4.5 million by 2050.[3] A hip fracture is associated with serious functional disability, illness and premature death, and utilizes significant expenditures in healthcare resources.[4-13] Male gender and older age are established predictors for increased mortality following hip fracture.[5-7, 9-12] However, inconsistencies exist regarding the contribution and magnitude of comorbid conditions to mortality following hip fracture and the length of time the higher risk of death persists following fracture.[5-13]

While comorbidity is related to mortality, quality of life and health care expenditures, its contribution to post-fracture mortality has been inconsistently demonstrated.[1, 5-9, 11-13, 19] This discrepancy may be due to methodological differences among studies. Early studies suggested that in the absence of comorbidity, there was little additional risk of death after hip fracture.[6, 12] However, more recent and larger studies with longer follow-up demonstrate that even after controlling for comorbidity, hip fracture confers a significantly increased risk of death which remains elevated for several years post-fracture.[8, 11] Identifying those comorbidities that present the greatest risk of mortality in persons with hip fracture is critical in order to improve survival. Therefore, we aimed to examine the effect of comorbidity on mortality following hip fracture, and

compare mortality to population controls without hip fracture in a large population-based cohort study

MATERIALS AND METHODS

Study Population

We performed this study based on data derived from the population-based healthcare databases in the region around Aarhus University, Denmark covering North Jutland, Viborg, and Aarhus counties.[50] The total population of these counties is 1,400,000 persons, representing approximately 25% of the Danish population, and hospital discharge, prescription and mortality data have been linked into a research database maintained by Aarhus University. In Denmark, the National Health Service in each county provides tax-supported healthcare for all inhabitants, allowing free access to general practitioners and hospitals and also refunding a variable proportion of the costs of prescription drugs. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth or on immigration since 1968, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be performed.[28] This study was approved by the Danish Data Protection Agency (Record No. 2004-41-3854) and the University of Medicine and Dentistry of New Jersey (UMDNJ) Institutional Review Board (Protocol No. 0120060003), and conforms to all regional scientific and ethical guidelines.

Diagnosis of Hip Fracture and Comorbidities

Using the hospital discharge registry data from the three counties (that were merged into the research database), we identified all patients ≥ 40 years of age with ≥ 90 days of residence in Aarhus, Viborg or North Jutland counties who had a first time diagnosis of hip fracture between January 1, 1998 and January 31, 2003 (ICD-10 codes S.72.0 - fracture of neck of femur, and S.72.1 - pertrochanter fracture).[30] The discharge registries retain information at the individual level including civil registry number, date of admission, date of discharge, and up to 20 discharge diagnoses and procedures assigned exclusively by the physician at discharge according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. The 9th revision (ICD-9) was never implemented in Denmark.

Using the hospital discharge registries, we identified all persons in the hip fracture cohort who were hospitalized anytime in the past for or with 19 medical conditions that make up the Charlson comorbidity index.[31] These conditions include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer, mild liver disease, diabetes mellitus type 1 or 2, hemiplegia, moderate to severe renal disease, diabetes with end organ failure, any tumor, leukemia, lymphoma, moderate to severe liver disease, metastasis, and acquired immunodeficiency syndrome. See Appendix 1 for a list of ICD-8 and ICD-10 codes.

Population Control Group

For each hip fracture patient, we sampled five population controls without hip fracture matched on year of birth and gender from the Danish Civil Registration System.[32] Controls were required to be residents in one of the three counties at the time of the index subject's hospitalization for hip fracture. Controls may have been hospitalized for another condition on the index subject's hospitalization date, but were not required to be. Established in 1968, the Civil Registration System contains (for all Danish residents), the civil registry number, gender, date of birth, place of birth, residence, citizenship, emigration, continuously updated vital status data and civil registry numbers of parents and spouse.

Other Covariates and Prescription Data

Using the hospital discharge registries, we recorded the five most common orthopedic surgical procedures performed following hip fracture (ICD-10 NFJ 81- internal fixation of fracture with other or combined methods, pertrochanteric, NFJ 70 – internal fixation of fracture, only with screws, femoral neck, NFB 12 – insertion of partial hip prosthesis, cemented, NFJ 80 – internal fixation of fracture with other or combined methods, femoral neck, and NFJ 61 – internal fixation of fracture with splints and plates including screws, pertrochanteric). In addition, other covariates included age in years, which was converted to three intervals (40-64, 65-85, 86+) and gender. We also computed the Charlson comorbidity index as a measure of overall health status.[31] The Charlson index has been extensively used and validated for prediction of short-term mortality[33] and has been adapted for use with hospital discharge data.[34] Prescription data were

derived from the National Health Service in the three counties and merged into the research database, as well.[35] Prescription data were collected since 1989 in North Jutland county, since 1996 in Aarhus county, and since 1998 in Viborg county. As part of the tax-funded health care for all inhabitants in Denmark, the Danish National Health Service reimburses 50-75% of the cost for the purchase of most prescribed medicines. Denmark is served by pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement for the Danish National Health Service in each county. These systems include information on the anatomical therapeutic chemical (ATC) classification system, the amount of drug prescribed, the personal identification number, and the date of drug dispensation.[36] In order to further control for cardiovascular disease, we used ATC codes to identify prescriptions for beta blockers (C01A), nitrates (C01D), and statins (C10AA) among the entire cohort. Present baseline use was defined as any usage up to 90 days prior to the date of hip fracture hospitalization. Any number of dispensings was classified as “exposed” and no dispensings was classified as “not exposed.”

Mortality

Thirty-day, 90-day, 1-year and overall (6-year) mortality was ascertained from the Civil Registration System.[32]

Statistical Analyses

Individuals were followed until the occurrence of study endpoints from the date of the hospital admission for hip fracture or index date for controls and continued until death, emigration or 12/31/2003, whichever came first. Those who did not experience an event at the end of follow-up were right-censored. Demographic and clinical variables such as gender, age (three categories: <65, 65-85, 86+), the Charlson comorbidity index and the frequency of comorbid conditions were presented as proportions or means, where appropriate. Kaplan Meier time-to-event estimation and life table technique were used to produce survival curves by the Charlson comorbidity index and by the number of comorbidities. Survival curves were compared using log rank tests. Cox proportional hazards regression analysis was used to compute crude and adjusted relative risks associated with 30-day, 90-day, and 1-year, mortality among hip fracture patients with and without a history of selected comorbidities. Mortality was also examined within age categories and levels of the Charlson comorbidity index. We also assessed the risk of mortality due to hip fracture compared to no hip fracture within strata of the Charlson comorbidity index. Other covariates examined included orthopedic procedures, type of hip fracture (femoral neck versus pertrochanteric, as a proxy for fracture severity) and cardiovascular medications. Effect estimates were adjusted for those covariates that were significantly associated with mortality with a p value of <0.05. Precision of effect estimates were reported using 95% confidence intervals (CI). All analyses were conducted using SAS version 9.1.[40]

RESULTS

Descriptive Data

We identified a total of 11,985 persons with a first time hospitalization for hip fracture between January 1, 1998 and 1/31/2003 (table 4). Average follow-up was 1 year and 10 months. Almost three-quarters (8,561) of the patients were female (71.4%). The mean age was 80 years (range 40-109). Ninety-one percent (10,794) of the cohort was at least 65 and 30% (3,646) was over 85 years of age. A total of 5,650 (47.1%) of the cohort had a Charlson comorbidity index of 0, 4, 5650 (45.5%) had indices between 1 and 3, and the remainder had indices between 4 and 12. Among the comorbid conditions occurring with the highest frequency in the overall cohort were cerebrovascular disease (17.4%), any tumor (13.1%), congestive heart failure (9.7%), ulcer (8.4%), myocardial infarction (7.1%) and COPD (6.4%).

Mortality

In this cohort, 30-day, 90-day, 1-year mortality and overall mortality was 11.1%, 17.6%, 28.3% and 47.1%, respectively. Figure 4 displays survival curves by hip fracture status. Figures 5 and 6 display crude and age-adjusted survival curves among hip fracture patients by levels of the Charlson comorbidity index. Survival was worse after hip fracture by increasing levels of the Charlson comorbidity index (log-rank test - $p < 0.001$). Figure 7 displays survival in hip fracture patients by number of comorbidities. Similarly, survival following hip fracture decreased with increasing number of comorbidities (log-rank test- $p < 0.001$). Figure 8 displays survival in hip fracture patients by age. Survival

decreased with increasing age (log-rank test- $p < 0.001$). The survival curves in figures 4, 5, 6 and 8 approached proportionality as the curves did not intersect. In figure 7, survival curves in some strata intersected due to sparse data.

Relative Mortality

Adjusted relative risks and 95% CI for 30-day, 90-day, and 1-year mortality comparing hip fracture patients with and without selected comorbidities are shown in table 5.

Selected comorbidities conferring a 1.5 to 3-fold increased risk of death following hip fracture include congestive heart failure, dementia, COPD, tumor, leukemia, lymphoma, and metastasis.

Age-specific relative risks and 95% CI for 1-year mortality associated with selected comorbidities are shown in table 6. The 1-year mortality relative risk associated with a history of peripheral vascular disease, COPD, tumor, and lymphoma varied by age, with the youngest members (less than 65 years of age) having the highest relative risk for these conditions among the three age categories (<65 years, 65-85 years, ≥ 86 years). Persons in the highest age group (≥ 86 years) had much lower relative risks for 1-year mortality associated with these comorbidities. We hypothesized that older persons in the referent group may be more likely than younger persons to have other comorbidities that put them at risk for mortality, and this may serve to lower the relative risk between the groups. In order to further explore this, we examined the older age group with and without COPD, PVD, tumor and lymphoma and compared the frequency of other comorbidities in this group. We did not find a higher frequency of other comorbidities in

the group of older persons who did not have a history of COPD, PVD, tumor, and lymphoma. We then looked at the youngest age group (<65 years) and compared the frequency of comorbidities in persons with and without COPD, PVD, tumor and lymphoma. We found that in general, among younger persons (<65 years), there was a larger relative difference in the frequency of other comorbidities among persons with the condition than among persons without the condition as compared to older persons. It is unclear whether this may be wholly or partly responsible for the differences observed in the age-specific relative risks for mortality associated with these comorbidities.

Adjusted relative risks and 95% CI for 30-day, 90-day, 1-year and overall mortality by age categories and levels of the Charlson comorbidity index are shown in table 7. Relative to those aged less than 65 years, age greater than 85 was associated with a mortality risk 5 to 7 times greater. Compared those with no comorbidities, those with a Charlson comorbidity index from 4-12 had a 2-fold higher mortality risk. Table 8 shows adjusted relative risks and 95% confidence intervals for 30-day, 90-day, 1-year and overall mortality comparing hip fracture to no hip fracture within different strata of the Charlson comorbidity index. Within every stratum of the Charlson index, particularly in the stratum without comorbidity, hip fracture had a strong effect on both early and late mortality, after adjustment for age and gender (1-year mortality - RR=3.43, 95% CI 3.19, 3.68).

DISCUSSION

Number of comorbidities, a higher comorbidity index and older age substantially increased the risk of mortality after fracture. Specific comorbidities that increased the adjusted 1 year mortality by 1.5 to three-fold included congestive heart failure, dementia, COPD, tumor, leukemia, lymphoma, and metastasis. When stratified by age, persons in the youngest age group (< 65 years) with peripheral vascular disease, COPD, any tumor and lymphoma had greater relative risk of death at one year than older persons with the same comorbidities. We also observed that even in the absence of comorbidities, hip fracture increased 1-year mortality from 2 to over 3-fold compared to age and gender matched controls without hip fracture.

Our population-based results are consistent with previous research related to hip fracture in general, with high mortality during the first year following hip fracture, and a higher risk of death for men and persons at the extremes of age.[5, 7-12] Our results are also consistent with findings from some prior studies that demonstrate the importance of comorbidity as a predictor of mortality after hip fracture on the one hand,[6, 8, 9, 11, 13] and the independent effect of hip fracture on mortality, on the other hand.[8, 11] In a small population based cohort study of community dwelling elderly men who had sustained a hip fracture, with increasing levels of comorbidity, mortality increased for both hip fracture patients and controls, with survival being worse at each level of comorbidity in the hip fracture group.[6] The comorbidities that significantly impacted survival in patients with hip fracture included pulmonary diseases, dementia,

cerebrovascular disease, congestive heart failure, and myocardial infarction. Among 2,448 prospectively followed hip fracture subjects in England, persons with three or more comorbidities had an adjusted 30-day mortality of RR=2.5, (95% CI 1.6, 3.9). [9] In our study, we observed that COPD, cardiac failure, dementia, tumor and malignancy were important diseases relative to mortality after hip fracture. We also observed a higher 1- year mortality relative risk in persons less than 65 with COPD, PVD, tumor and lymphoma. This finding was unexpected. We postulated that in older persons, there may be competing comorbidities in the group of patients without the index condition which might serve to lower the RR for the index condition between the two groups. In order to further explore this, the frequency and relative difference in comorbidities were examined in the three age categories and stratified by persons with the index condition and persons without the index condition. Upon examination, it was not apparent that patients in the oldest age category had a higher frequency of other comorbidities relative to patients with the index condition in that age group. In fact, younger persons (<65 years) with the index condition had a higher frequency of other comorbidities than persons without the condition, and the relative differences were greater in younger patients than it was in older patients.

Our finding of the strong independent mortality risk conferred by hip fracture has been previously observed. A prospective cohort of 7,512 ambulatory women aged 75 years or more without hip fracture were followed for four years to assess the incidence of hip fracture.[8] After controlling for age and baseline health status, those who developed hip fracture were twice as likely to die during the follow up period than those who did not

develop hip fracture (RR=2.1, 95% CI 1.6-2.8). While the highest increase in mortality was in the first six months post-fracture, it persisted for up to three years. Similar results were observed in a population based cohort study of 2,235 incident hip fractures among women aged 50-81 identified from the Swedish National Inpatient Register.[11] After adjusting for age and prior hospitalization for serious disease, those with hip fracture had over twice the risk of death (RR=2.3, 95% CI 2.0-2.5) over an average of 5 years of follow up. While mortality was higher within the first 6 months post-fracture, it remained elevated for up to six years. In this same study, the causes of death with a higher rate in the hip fracture group included circulatory disease, respiratory disease, digestive diseases, psychosis and injury and poisoning.

The term multimorbidity is being increasingly used in place of comorbidity, particularly with respect to the geriatric population.[70] Multimorbidity represents a broader approach to disease management where concurrent diseases as a whole are viewed as relevant to the treatment of and survival of the patient. In addition, there is growing appreciation of the impact of treatments for one condition on another.[71] Much of the emphasis on multimorbidity has focused on cancer patients in whom there is evidence that multimorbidity impacts survival, but little understanding as to how and the degree to which certain diseases contribute to mortality risk. A similar lack of understanding exists for patients with hip fracture.

While comorbidity affects health outcomes, certain diseases have more impact on mortality than others. Diseases that affect the maintenance of normal physiology, such

as the cardiopulmonary and renal system are strongly related to mortality.[19] There is evidence to suggest that some disease combinations (i.e. index disease and comorbidity) may act synergistically.[22-26] For instance, stroke with hip fracture, diabetes or osteoporosis led to a higher rate of disability than what would be expected from each of those conditions independently.[22] The NHANES I Epidemiologic Follow-up Study of 4,059 persons between 45-74 years of age demonstrated that clinical and self-reported evidence of knee osteoarthritis and certain concurrent chronic diseases acted synergistically on subsequent disability.[23] Among the chronic conditions studied, pulmonary disease and knee osteoarthritis together conferred higher odds of subsequent disability than either the sum or the product of the individual odds of disability from these conditions. In another study, lung disease and cancer were synergistic in terms of the disability conferred by this combination of conditions.[26] These results have important implications for hip fracture patients, who may have one or more concurrent medical condition that may act synergistically on prognosis.

Strengths of this study include Denmark's uniform national health care system permitting a population-based design. Non-differential follow-up through population-based registries limits the potential for selection and surveillance bias. It is well known that discharge diagnoses are not entirely accurate and the validity of our estimates depend on the accurate coding of comorbidities and hip fracture.[28] Hospital discharge diagnoses for hip fracture have been shown to be very accurate with a sensitivity of 96 percent and a positive predictive value of 94 percent.[67, 68] In order to control for confounding and to measure the impact of each disease independently, we included the

individual diseases that make up the Charlson index in our models. Any non-differential misclassification of comorbidities or hip fracture would tend to bias effect estimates toward the null indicating no association.[69] An additional strength of this study is the use of the entire hospital discharge history rather than a shorter period of time to account for history of comorbid conditions. A limitation of this study may be the reliance on the diseases included in the Charlson comorbidity index as predictors of mortality. These diseases may not have represented the comorbidities of greatest importance in patients with hip fracture and in fact, effect estimates for mortality in the hip fracture cohort for these conditions rarely met or exceeded the range of relative risks obtained in the original index. On the other hand, diseases during the acute period following hip fracture include pneumonia, thromboembolic events and infection, which are not well-represented in the index. When the comorbidities were used as a summary index, residual confounding cannot be excluded since the collection of potential confounding factors in this study relies solely on the availability of these data in the computerized registry data. Another limitation of this study is the absence of cause of death, which would have provided insight into factors responsible for high mortality in this population. Causes of death in Denmark are recorded on death certificates, which were not available for this study.

In conclusion, we observed that comorbidity is important relative to hip fracture survival. Selected comorbid conditions increased the risk of both short and long term mortality following hip fracture, and some conferred a higher relative risk in younger persons. However, even in the absence of comorbidities, hip fracture was strongly associated

with increased mortality. Improved management of comorbidities may be necessary in order to improve survival in this population.

Table 4 Demographic Characteristics of Patients Hospitalized for Hip Fracture

	Total N=11,985 (%)
Sex	
Male	3,424 (28.6)
Female	8,561 (71.4)
Age (years) mean	80 (SE \pm 0.10)
40-64 years	1,191 (9.9)
65-85 years	7,148 (59.7)
86-109 years	3,646 (30.4)
Charlson comorbidity index (mean)	1.12(SE \pm 0.15)
0	5,650 (47.1)
1-3	5,450 (45.5)
4-12	885 (7.4)
Selected Comorbid Conditions	
Myocardial infarction	851 (7.1)
Congestive heart failure	1,157 (9.7)
Peripheral vascular disease	767 (6.4)
Cerebrovascular disease	2,084 (17.4)
Dementia	562 (4.7)
COPD	771 (6.4)
Connective tissue disease	615 (5.1)
Ulcer	1,010 (8.4)
Mild liver disease	149 (1.2)
Diabetes mellitus 1 or 2	765 (6.4)
Moderate to severe renal disease	263 (2.2)
Diabetes mellitus w/end organ damage	352 (2.9)
Any tumor	1,564 (13.1)
Leukemia	46 (0.4)
Lymphoma	71 (0.6)
Metastasis	200 (1.7)
Selected CV medications	
Nitrates	926 (7.7)
Statins	228 (1.9)
Beta blockers	1,211 (10.1)

Abbreviations: No., number; SE, standard error, CV, cardiovascular

Figure 4 Age-adjusted Survival by Hip Fracture Status

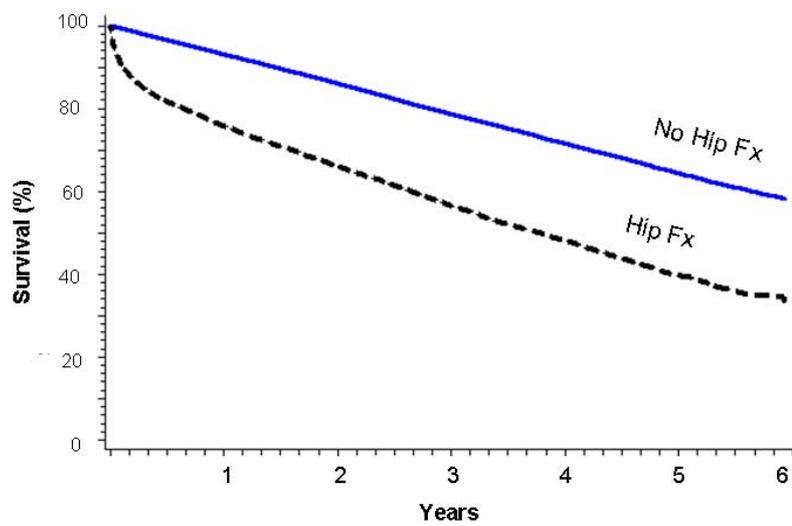


Figure 5 Survival in Hip Fracture Patients by Charlson Comorbidity Index

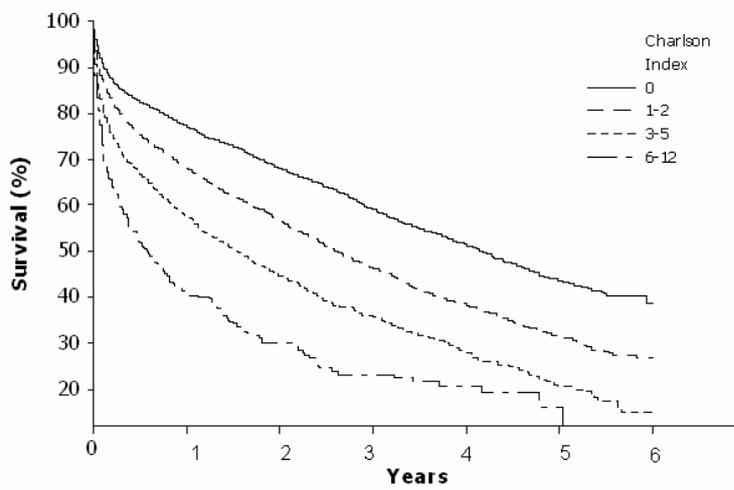


Figure 6 Age-adjusted Survival in Hip Fracture Patients by Charlson Index

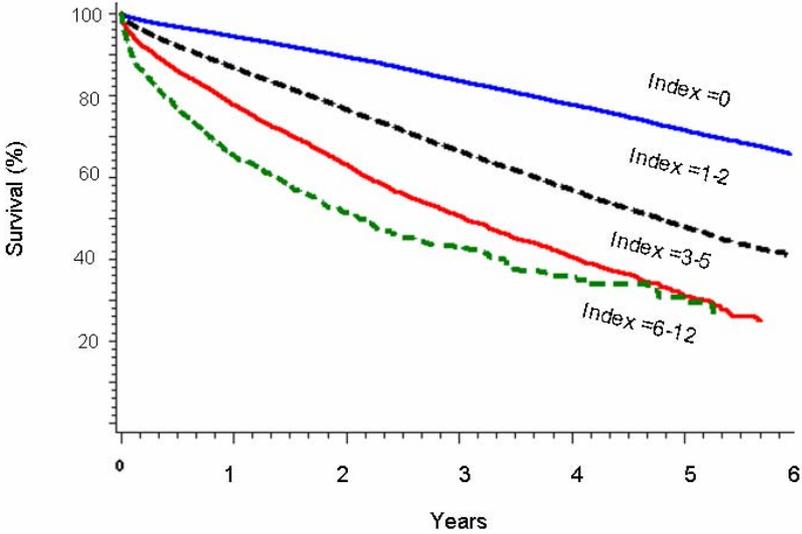


Figure 7 Survival in Hip Fracture Patients by Number of Comorbidities

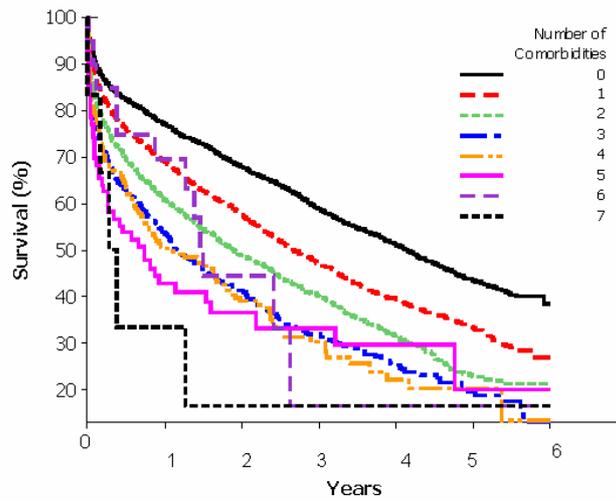


Figure 8 Survival in Hip Fracture Patients by Age

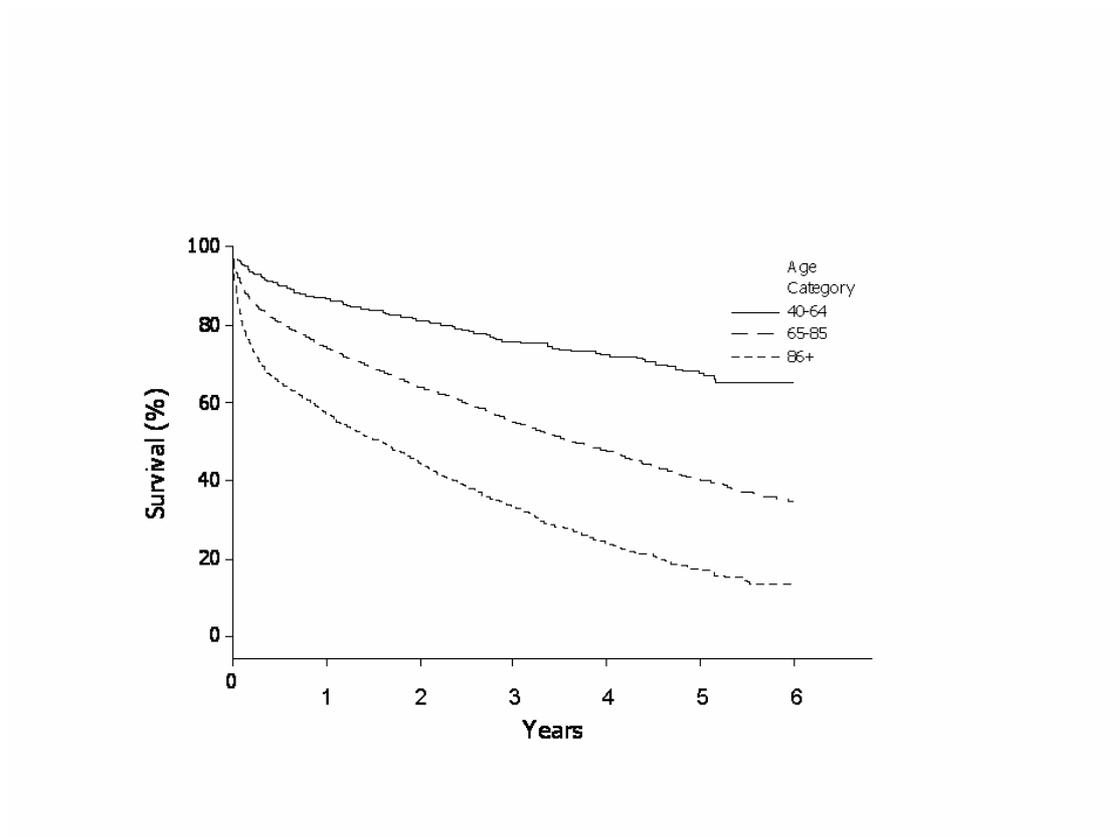


Table 5 Relative Risks for Mortality after Hip Fracture Associated with Selected Comorbidities

Disease	30-day Mortality RR* (95% CI)	90-day Mortality RR* (95% CI)	1-year Mortality RR* (95% CI)
Any tumor	1.32 (1.13, 1.53)	1.38 (1.23, 1.56)	1.45 (1.32, 1.59)
COPD	1.50 (1.25, 1.81)	1.52 (1.31, 1.76)	1.59 (1.41, 1.79)
CHF	1.73 (1.49, 2.01)	1.59 (1.41, 1.80)	1.59 (1.44, 1.76)
Dementia	1.35 (1.09, 1.68)	1.52 (1.29, 1.80)	1.58 (1.38, 1.80)
Leukemia	2.79 (1.57, 4.94)	2.59 (1.60, 4.20)	2.05 (1.33, 3.17)
Lymphoma	1.03 (0.51, 2.07)	1.40 (0.86, 2.27)	1.64 (1.34, 2.36)
Metastasis	2.54 (1.86, 3.45)	2.91 (2.30, 3.69)	2.99 (2.47, 3.62)
Myocardial infarction	1.07 (0.89, 1.29)	1.12 (0.97, 1.31)	1.13 (1.00, 1.28)
Peripheral vascular disease	1.18 (0.97, 1.44)	1.10 (0.93, 1.30)	1.15 (1.00, 1.310)

Abbreviations, RR, relative risk, CI, confidence interval, COPD, chronic obstructive pulmonary disease, CHF, congestive heart failure

*adjusted for age, gender, all other comorbidities in the Charlson comorbidity index, and nitrates

Table 6 Age-specific Relative Risks for Mortality after Hip Fracture Associated with Selected Comorbidities

Disease	Age <65 RR* (95% CI)	Age 65-85 RR* (95% CI)	Age 86+ RR* (95% CI)
CHF	0.60 (0.21, 1.70)	1.81 (1.59, 2.05)	1.36 (1.16, 1.59)
PVD	2.64 (1.45, 4.80)	1.17 (1.00, 1.36)	0.95 (0.73, 1.23)
Dementia	0.93 (0.20, 4.21)	1.81 (1.53, 2.13)	1.24 (0.97, 1.55)
COPD	2.23 (1.25, 3.98)	1.78 (1.56, 2.04)	0.90 (0.66, 1.24)
Tumor	7.28 (4.65, 11.40)	1.56 (1.38, 1.75)	1.10 (0.93, 1.30)
Leukemia	∞ (0. ∞)	1.88 (1.08, 3.26)	3.24 (1.60, 6.53)
Lymphoma	4.95 (1.54, 15.94)	1.33 (0.83, 2.13)	2.56 (1.33, 4.94)
Metastasis	2.16 (1.26, 3.70)	2.82 (2.24, 3.54)	1.86 (1.01, 3.44)

Abbreviations, RR, relative risk, CI, confidence interval, CHF, congestive heart failure, PVD, peripheral vascular disease, COPD, chronic obstructive pulmonary disease

*Adjusted for gender, nitrates, and all other comorbidities in Charlson comorbidity index

Table 7 Relative Risks for Mortality after Hip Fracture by Age and Charlson Comorbidity Index

	30-day Mortality RR* (95% CI)	90-day Mortality RR* (95% CI)	1-year Mortality RR* (95% CI)
Age 65-85**	3.02 (2.16, 4.22)	2.50 (1.96, 3.18)	2.26 (1.89, 2.69)
Age ≥ 86	7.15 (5.09, 10.04)	5.97 (4.67, 7.63)	4.93 (4.12, 5.90)
Charlson indices 1-3***	1.49 (1.32, 1.68)	1.43 (1.30, 1.57)	1.52 (1.41, 1.64)
Charlson indices 4-12***	2.74 (2.30, 3.26)	2.80 (2.45, 3.22)	2.95 (2.64, 3.29)

Abbreviations, RR, relative risk, CI, confidence interval

* Adjusted for gender, age, the Charlson comorbidity index and nitrates

** Referent group age <65

*** Referent group Charlson index 0

Table 8 Relative Risks for Mortality after Hip Fracture Compared to Controls without Hip Fracture Stratified by Charlson Comorbidity Index*

Charlson index	Mortality Endpoints			
	30-day RR (95% CI)	90-day RR (95% CI)	1-year RR (95% CI)	Overall RR (95% CI)
0	4.81 (3.97, 5.83)	4.70 (3.17, 5.30)	3.49 (3.24, 3.77)	2.77 (2.63, 2.91)
1-3	3.06 (2.64, 3.54)	2.97 (2.70, 3.26)	2.56 (2.41, 2.72)	2.06 (1.98, 2.15)
4-12	2.23 (1.68, 2.95)	2.48 (2.05, 3.02)	2.23 (1.97, 2.53)	1.83 (1.66, 2.02)

Abbreviations, RR, relative risk, CI, confidence interval,

* Referent group – age and gender–matched controls without hip fracture from source population

ASSESSMENT OF THE CHARLSON COMORBIDITY INDEX

According to de Groot and colleagues, the four major reasons for measuring comorbidity include the need to control for confounding, thereby improving the study's internal validity; to assess effect modification; to use comorbidity as a predictor of outcome; and finally as a way of developing a composite comorbidity measure in order to improve statistical efficiency.[33] The Charlson comorbidity index is one of the most widely used methods for assessing comorbidity in epidemiologic studies.[31, 41, 72, 73] It was developed based on 1-year mortality in 605 hospitalized patients admitted to a medical service during a one-month period. Comorbidities were identified through chart review and a weighted score was then assigned to each comorbidity based on the relative risk of 1-year mortality. The 19 comorbidities that became part of the Charlson index were those that had an adjusted relative risk of 1-year mortality of 1.3 or greater, whether or not they reached statistical significance of $p < 0.10$ or less. (The authors compared these results with those obtained by including only those comorbidities that reached a significance level of $p < 0.10$ and there were no appreciable differences). The sum of these weights is the index which is used as a summary measure of the burden of disease. It was validated in a cohort of 685 patients who were treated for primary breast cancer for its ability to predict 10-year mortality. Since that time, it has been modified for a number of different uses. To our knowledge there have been no studies which have assessed the performance of the Charlson comorbidity index in the setting of mostly elderly hip fracture patients. The examination of individual comorbid conditions in the

hip fracture cohort provided an opportunity to compare their relative strength of association with 1-year mortality to those obtained in the original Charlson index.

Table 9 displays the 19 comorbidities that make up the Charlson comorbidity index, the effect estimates derived for 1-year mortality in a fully adjusted Cox regression models associated with these conditions in the hip fracture cohort, the range of RR estimates associated with these 19 conditions obtained in the original Charlson index and its corresponding weight, and the beta coefficients from the fully adjusted Cox regression models associated for each condition in which the RR was at least 1.3.

As shown in table 9, ten comorbidities were associated with 1-year mortality in the hip fracture cohort with an RR of at least 1.3. These include congestive heart failure, dementia, COPD, mild liver disease, moderate to severe renal disease, tumor, leukemia, lymphoma, moderate to severe liver disease and metastasis. The 95% confidence intervals for eight of the ten comorbidities had lower bounds above 1. Effect estimates associated with these conditions in the hip fracture cohort for 1-year mortality range from 1.31 to 2.99. In many instances, the RR estimates for these conditions obtained in the hip fracture cohort failed to fall within the RR range obtained for the condition in the original Charlson index. The estimates were usually lower in the hip fracture cohort. Based on these results, it appears that several comorbidities which did not reach the RR of 1.3, such as myocardial infarction, peripheral vascular disease, cerebrovascular disease, connective tissue disease, ulcer, diabetes mellitus, and acquired

immunodeficiency syndrome were not as relevant to 1-year mortality in the hip fracture cohort as they were in the original Charlson index.

A revised comorbidity index was produced for the hip fracture cohort. The comorbidities included were the ten that achieved an RR of 1.3 for 1-year mortality in the fully adjusted model. The weight for each comorbidity was the beta coefficient derived in the Cox regression for 1-year mortality in the fully adjusted model. This has been suggested by some authors as a preferred method of weighting that conforms to the multiplicative nature of the proportional hazards model. [42, 43, 74] The raw index value was taken to be the sum of the weights. Cox regression was generated three times for the following models: 1) a model that contained only age and gender, both of which were significantly associated with 1-year mortality; 2) a model that contained age, gender and the original Charlson comorbidity index; and 3) a model that contained age, gender and the new comorbidity index consisting of the sum of the beta coefficients. Three measures were examined: 1) the likelihood ratio test, which consists of taking the difference between $-2 \times \text{Log likelihood}$ in the model containing age, gender, and the comorbidity index in a Cox regression and the model containing only age and gender in a Cox regression; 2) the deviance derived from the three logistic regression models measuring 1-year mortality, and 3) the c statistic (ROC curve), also generated from the logistic regression models. These measures were used to determine how much improvement was derived from the model containing either the Charlson index or the new index as compared to the model containing age and gender only (table 10).

Based on these measures, both the original Charlson comorbidity index and the revised index improved the model that contained only age and gender. The revised index performed slightly better on the basis of the likelihood ratio test. Also, the c-statistic (ROC or receiver operating characteristic curve) was slightly higher with the revised index than with the Comorbidity index. However, two notable issues are evident from these results. First, the model containing either of the two comorbidity indices only slightly improved the model that contains only age and gender. One would have expected a larger improvement than this. This may reflect the fact that comorbidities represented in the Charlson index are not as important in the hip fracture cohort as they were in the original population from which the index was developed. In fact, effect estimates for mortality in the hip fracture cohort for these conditions rarely met or exceeded the range of relative risks obtained in the original index. On the other hand, diseases during the acute period following hip fracture include pneumonia, thromboembolic events and infection, which are not well-represented in the Charlson index. The second observation is that the revised index only minimally improved the model over the Charlson index, suggesting that the original index is very robust, even when used in a dataset in which the comorbidities being measured have less importance toward 1-year mortality than they did in the original index.

Table 9 Comparison of Charlson Comorbidity Index and Relative Risks for 1-year Mortality after Hip Fracture Associated with Comorbid Conditions

Disease	RR* (95% CI)	RR range in CCI	CCI Weight	Revised Weight **
Myocardial infarction	1.13 (1.00, 1.28)	≥1.2 < 1.5	1	0.47
Congestive heart failure	1.59 (1.44, 1.76)	≥1.2 < 1.5		
Peripheral vascular disease	1.15 (1.00, 1.31)	≥1.2 < 1.5		
Cerebrovascular disease	1.08 (0.99, 1.18)	≥1.2 < 1.5		
Dementia	1.58 (1.38, 1.80)	≥1.2 < 1.5		
COPD	1.59 (1.41, 1.79)	≥1.2 < 1.5		
Connective tissue disease	1.04 (0.89, 1.22)	≥1.2 < 1.5		
Ulcer	1.08 (0.96, 1.21)	≥1.2 < 1.5		
Mild liver disease	1.31 (0.96, 1.79)	≥1.2 < 1.5		
Diabetes mellitus 1&2	1.15 (0.98, 1.34)	≥1.2 < 1.5		
Hemiplegia	0.53 (0.22, 1.27)	≥1.2 < 1.5		
Moderate/severe renal disease	1.36 (1.12, 1.64)	≥1.5 < 2.5	2	0.30
Diabetes mellitus with end organ damage	1.16 (0.93, 1.44)	≥1.5 < 2.5		
Tumor	1.45 (1.32, 1.59)	≥1.5 < 2.5	3	0.37
Leukemia	2.05 (1.33, 3.17)	≥1.5 < 2.5		
Lymphoma	1.64 (1.34, 2.36)	≥1.5 < 2.5		
Moderate/severe liver disease	1.67 (0.82, 3.42)	≥2.5 < 3.5	6	1.10
Metastasis	2.99 (2.47, 3.62)	>6.0		
AIDS	n/a	>6.0		

Abbreviations: RR, relative risk, CI, confidence interval, CCI, Charlson comorbidity index, COPD, chronic obstructive pulmonary disease, AIDS, acquired immunodeficiency syndrome

* Adjusted for age, gender, nitrates, and all other comorbidities in Charlson index

** Weights are the Cox regression beta coefficients associated with the comorbid condition in the adjusted model for 1-year mortality

Table 10 Comparison of Charlson Comorbidity Index and Revised Comorbidity Index in Predicting 1-year Mortality Following Hip Fracture

	Baseline model (age and gender)	Adding Charlson Index to baseline model	Adding Revised Index 1 to baseline model
Likelihood Ratio Test ¹	N/A	$\chi^2 = 445.83$ df=1 P<.0001	$\chi^2 = 499.07$ df=1 P<.0001
Deviance ²	10331.6	11969.6	11473.2
c statistic (ROC) ²	0.673	0.708	0.714

Abbreviations, ROC, receiver operating characteristic
 1: from Cox regression model for 1-year mortality
 2: from logistic regression model for 1-year mortality

CONCLUSIONS

In addition to older age and male gender, which are known risk factors for mortality after hip fracture, this research demonstrated that concurrent COPD, a high comorbidity index, and specific comorbid conditions increase 1-year mortality by 1.5 to 3-fold in a large population-based cohort of patients with hip fracture. The AR attributable to COPD was 14% for 1-year mortality in this cohort. In addition to COPD, specific comorbidities that increased the adjusted 1 year mortality included congestive heart failure, dementia, tumor, leukemia, lymphoma, and metastasis. When stratified by age, persons in the youngest age group (< 65 years) with peripheral vascular disease, COPD, any tumor and lymphoma had greater relative risk for death at one year than older persons with the same comorbidities. This research also demonstrated that even after stratifying for comorbidities, hip fracture in this cohort increased 1-year mortality from 2 to over 3-fold compared to age and gender matched controls without hip fracture.

The contribution of respiratory disease to mortality after hip fracture has not been extensively examined and yet, respiratory disease is a common condition in this age group.[75] Only two prior studies have examined the contribution of a prior history of respiratory disease or COPD on hip fracture prognosis.[9, 13] Among 2,448 prospectively followed hip fracture subjects in England, those with a history of respiratory disease had an age and sex adjusted hazard ratio for 30-day and one-year mortality of 1.6 and 1.4 (95% CI 1.1, 1.7), respectively.[9] In a multi-center, retrospective study of 390 Medicare beneficiaries with hip fracture, a history of COPD

was an independent predictor of 30-day mortality (OR (odds ratio) = 11.0, 95% CI 2.0, 62.0).[13] Apart from these studies, there has been little additional research conducted on the impact of COPD on mortality after hip fracture.

The results of this research are also consistent with prior studies that demonstrate the importance of comorbidity as a predictor of mortality after hip fracture on the one hand,[6, 8, 9, 11, 13] and the independent effect of hip fracture on mortality, on the other hand.[9, 11] In a small population based cohort study of community dwelling elderly men who had sustained a hip fracture, with increasing levels of comorbidity, mortality increased for both hip fracture patients and controls, with survival being worse at each level of comorbidity in the hip fracture group.[6] The comorbidities that significantly impacted survival in patients with hip fracture included pulmonary diseases, dementia, cerebrovascular disease, congestive heart failure, and myocardial infarction. Among 2,448 prospectively followed hip fracture subjects in England, persons with three or more comorbidities had an adjusted 30-day mortality of RR=2.5, (95% CI 1.6, 3.9).[9] COPD, cardiac failure, dementia, tumor and malignancy were important diseases relative to mortality after hip fracture in this study.

Our results demonstrated a higher 1- year mortality relative risk in persons less than 65 with COPD, peripheral vascular disease, tumor and lymphoma compared to older persons. This finding was unexpected. It was postulated that in older persons, there may be competing comorbidities in the referent group of patients without the index condition that may place them at risk of death, which would serve to lower the RR for the

index condition between the two groups. In order to further explore this, the frequency and relative difference in comorbidities were examined in the three age categories and stratified by persons with the index condition and persons without the index condition. Upon examination, it was not apparent that patients in the oldest age category had a higher frequency of other comorbidities relative to patients with the index condition in that age group. In fact, younger persons (<65 years) with the index condition had a higher frequency of other comorbidities than persons without the condition, and the relative differences for these conditions were greater in younger patients than they were in older patients. Whether this finding may partly explain the results we observed in the age-specific RRs is unclear.

Published research demonstrates that persons hospitalized with an acute exacerbation of COPD have very high in-hospital and post-hospital mortality rates.[51-54] In the largest published series among 1,016 adults hospitalized for COPD, in-hospital mortality was 11%, and the 60-day, 180-day, 1-year, and 2-year mortality was 20%, 33%, 43% and 49%, respectively.[51] Six months after, only 26% of the cohort was still alive. Persons admitted to the ICU for COPD have an even worse prognosis. Data from 42 intensive care units for 365 persons admitted for an acute exacerbation of COPD found a in-hospital mortality of 24%, and for those at least 65 years of age, a mortality of 30% at discharge, 41% at 90 days, 47% at 180 days, and 59% at one year.[54]

Based on these observational studies, it was not possible to determine the exact mechanism for the association between COPD and mortality. However, the association

is likely explained by one or more of the following factors 1) COPD severity and factors associated with COPD; 2) inappropriate pharmacotherapy or non-adherence; 3) adverse effects of pharmacotherapy; 4) comorbidities not captured in the Charlson comorbidity index. For example, side-effects of corticosteroid therapy may include immunosuppression, obesity, diabetes, all of which are independently associated with increasing surgical risk.[55, 56] While cause of death was not the main focus of these study, persons with COPD are at risk of dying from a number of causes other than obstructive lung disease.[57] COPD as the underlying cause of death is recorded in less than half of all COPD deaths, with over half of all deaths being non-respiratory in nature.[58] Rather than the result of incomplete recording, there is some evidence to suggest that COPD may increase the risk of death from other comorbid conditions and conversely, that certain comorbidities may increase the risk of COPD mortality.[59] Cardiovascular disease and ischemic heart disease, in particular, is a common comorbidity and cause of death in persons with COPD.[60] In a population based cohort study of 5, 648 persons newly treated for COPD over a 7 year period, the proportion of deaths recorded with a primary cause as CVD was almost three times that of deaths recorded with a primary cause of COPD.[61] In the Lung Health Study, a large, multi-center clinical trial of smokers with mild to moderate lung function impairment, two thirds of all deaths were due to either lung cancer or cardiovascular disease, with coronary heart disease as the cause of most CVD deaths.[62] Finally, certain therapy for COPD (oral corticosteroids) has been associated with increased mortality in several studies.[63-65] While potentially a reflection of disease severity, in that oral corticosteroids may be prescribed more often to persons with more severe COPD who

have a higher risk of death, oral steroids could also be related to increased mortality. Moreover, these medications have been associated with inducing reductions in bone mineral density and increasing the risk of hip fracture. [44, 45, 49]

A strong independent risk of mortality conferred by hip fracture alone has been previously observed. A prospective cohort of 7,512 ambulatory women aged 75 years or more without hip fracture were followed for four years to assess the incidence of hip fracture.[8] After controlling for age and baseline health status, those who developed hip fracture were twice as likely to die during the follow up period than those who did not develop hip fracture (RR=2.1, 95% CI 1.6-2.8). While the highest increase in mortality was in the first six months post-fracture, it persisted for up to three years. Similar results were observed in a population based cohort study of 2,235 incident hip fractures among women aged 50-81 identified from the Swedish National Inpatient Register.[11] After adjusting for age and prior hospitalization for serious disease, those with hip fracture had over twice the risk of death (RR=2.3, 95% CI 2.0-2.5) over an average of 5 years of follow up. While mortality was higher within the first 6 months post-fracture, it remained elevated for up to six years. In this same study, the causes of death with a higher rate in the hip fracture group included circulatory disease, respiratory disease, digestive diseases, psychosis and injury and poisoning.

The term multimorbidity is being increasingly used in place of comorbidity, particularly with respect to the geriatric population.[70] Multimorbidity represents a broader approach to disease management where concurrent diseases as a whole are viewed as

relevant to the treatment of and survival of the patient. In addition, there is growing appreciation of the impact of treatments for one condition on another.[71] Much of the emphasis on multimorbidity has focused on cancer patients in whom there is evidence that multimorbidity impacts survival, but little understanding as to how and the degree to which certain diseases contribute to mortality risk. A similar lack of understanding exists for patients with hip fracture.

While comorbidity affects health outcomes, certain diseases have more impact on mortality than others. Diseases that affect the maintenance of normal physiology, such as the cardiopulmonary and renal system are strongly related to mortality.[19] There is evidence to suggest that some disease combinations (i.e. index disease and comorbidity) may act synergistically.[22-26] For instance, stroke with hip fracture, diabetes or osteoporosis led to a higher rate of disability than what would be expected from each of those conditions independently.[22] The NHANES I Epidemiologic Follow-up Study of 4,059 persons between 45-74 years of age demonstrated that clinical and self-reported evidence of knee osteoarthritis and certain concurrent chronic diseases acted synergistically on subsequent disability.[23] Among the chronic conditions studied, pulmonary disease and knee osteoarthritis together conferred higher odds of subsequent disability than either the sum or the product of the individual odds of disability from these conditions. In another study, lung disease and cancer were synergistic in terms of the disability conferred by this combination of conditions.[26] These results have important implications for hip fracture patients, who may have one or more concurrent medical condition that may act synergistically on prognosis.

Strengths of this research include Denmark's uniform national health care system permitting a population-based design. Non-differential follow-up through population-based registries limits the potential for selection and surveillance bias. It is well known that discharge diagnoses are not entirely accurate and the validity of our estimates depend on the accurate coding of all comorbidities and hip fracture.[28] Hospital discharge diagnoses for hip fracture have been shown to be very accurate with a sensitivity of 96 percent and a positive predictive value of 94 percent.[67, 68] And, with respect to COPD, misclassification is most likely low since 89.5 percent of patients in our region with a hospital discharge diagnosis of COPD also have filled a prescription for a COPD medication.[66] In order to control for confounding and to measure the impact of each disease independently, individual diseases that make up the Charlson index were included in the regression models, and were also examined as an index. Any non-differential misclassification of comorbidities or hip fracture would tend to bias effect estimates toward the null indicating no association.[69] An additional strength of this research is the use of the entire hospital discharge history rather than a shorter period of time to identify history of comorbid conditions. The diseases included in the Charlson index allow for the adjustment of most underlying diseases, thereby minimizing their potential as confounding factors. However, residual confounding cannot be excluded since the collection of potential confounding factors in this study relies solely on the availability of these data in the computerized registry data. Another limitation of this study may be the reliance on the diseases included in the Charlson comorbidity index as predictors of mortality. These diseases may not have represented the comorbidities of

greatest importance in patients with hip fracture and in fact, effect estimates for mortality in the hip fracture cohort for these conditions rarely met or exceeded the range of relative risks obtained in the original index. On the other hand, diseases during the acute period following hip fracture include pneumonia, thromboembolic events and infection, which are not well-represented in the index. A new comorbidity index which accounts for the diseases specific to an elderly hip fracture population is needed. Another limitation of this research is the absence of cause of death, which would have provided insight into factors responsible for high mortality in this population. Causes of death in Denmark are recorded on death certificates, which were not available for this study. Because of this, we are unable to make specific suggestions for the clinical care of COPD in patients who experience a hip fracture.

In conclusion, comorbidity, and COPD, in particular, are important covariates relative to hip fracture survival. Selected comorbid conditions increased the risk of both short and long term mortality following hip fracture, and some conferred a higher relative risk in younger persons. However, even after stratifying by levels of comorbidity, hip fracture was strongly associated with increased mortality as compared to mortality among persons without hip fracture. Improved management of comorbidities may be necessary in order to improve survival in this population.

APPENDICES

APPENDIX I

International Classification of Diseases (ICD), Eighth and Tenth revisions

1. Myocardial infarction (ICD-8 410; ICD-10 I21, I22, I23)
2. Congestive heart failure (ICD-8 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10 I50, I11.0 I13.0, I13.2)
3. Peripheral vascular disease (ICD-8 440, 441, 442, 443, 444, 445; ICD-10 I70, I71, I72, I73, I74, I77)
4. Cerebrovascular disease (ICD-8 430-438; ICD-10 I60-I69, G45, G46)
5. Dementia (ICD-8 290.09-290.19, 293.09; ICD-10 F00-F03, F05.1, G30)
6. Chronic obstructive pulmonary disease (ICD-8 490-493, 515-518; ICD-10 J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3)
7. Connective tissue disease (712, 716, 734, 446, 135.99; ICD-10 M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86)
8. Ulcer disease (ICD-8 530.91, 530.98, 531-534; ICD-10 K22.1, K25-K28)
9. Mild Liver disease (ICD-8 571, 573.01, 573.04; ICD-10 B18, K70.0-K70.3, K70.0, K71.0, K73.0, K74.0, K76.0)
10. Diabetes mellitus type 1 and 2 (ICD-8 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10 E10.0, E10.1, E10.9, E11.0, E11.1, E11.9)
11. Hemiplegia (ICD-8 344; ICD-10 G81, G82)
12. Moderate to severe renal disease (ICD-8 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10 I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61)

13. Diabetes with end organ failure (ICD-8 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10 E10.2-E10.8, E11.2=E11.8)
14. Any tumor (ICD-8 140-194; ICD-10 C00-C75)
15. Leukemia (ICD-8 204-207; ICD-10 C91-C95)
16. Lymphoma (ICD-8 200-203, 275.59; ICD-10 C81-C85, C88, C90, C96)
17. Moderate to severe liver disease (ICD-8 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10 B15.-, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85)
18. Metastasis (ICD-8 I95-I98, I99; ICD-10 C76-C80)
19. Acquired immunodeficiency syndrome (ICD-8 079.83; ICD-10 B21-B24).

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