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Comorbidity among patients admitted to the Department of Surgery, Hammerfest Hospital

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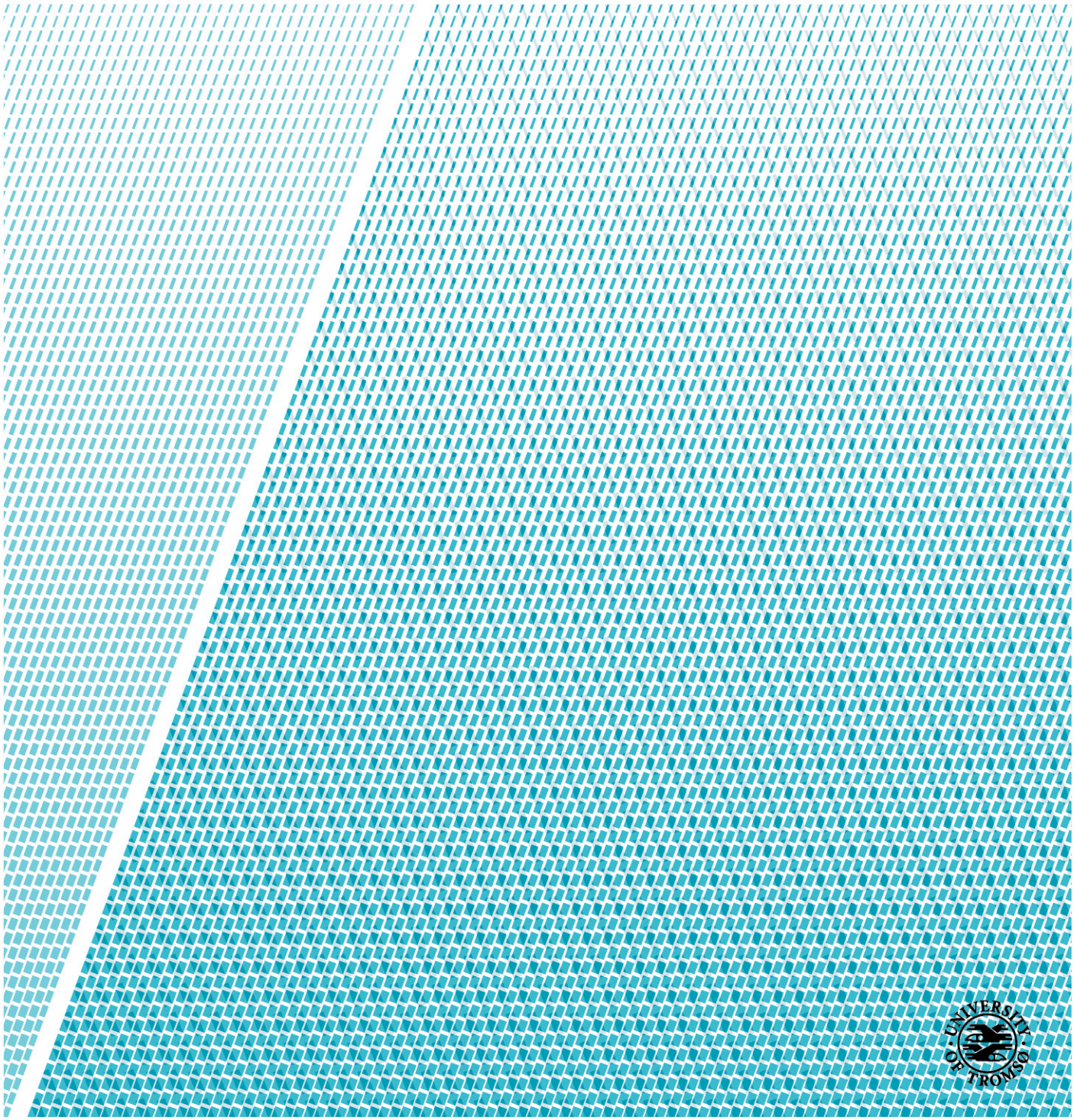
Master's thesis in MED-3950 submitted 4 June 2019



Foreword

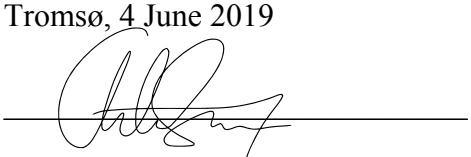
Comorbidity is an increasingly important term describing the health status in an aging population worldwide. Writing on comorbidity in a population living in the context of Finnmark with its geography, socioeconomic traits, history and culture, has been intriguing.

I have a firm belief in the importance of equal possibilities to healthy life choices. Through this work, the possibility of pointing out some areas of potential or concern has been a huge motivator. We have a national and public health care system in Norway, but Norwegian lives are highly local. Our efforts in structuring our health sector should be adjusted thereafter.

The following master thesis in MED-3950 was a project first formed by dr. Jan Norum. He was an oncologist situated both in the Hospital Trust of Finnmark, Hammerfest, and at the University Hospital in Tromsø.

Sadly, dr. Norum passed away in March 2019. It has been my goal to finish this project as planned. In April, I was pleased to have dr. Eyvind J. Paulssen, professor II at the Department of Clinical Medicine, UiT The Arctic University of Norway, agree to help me finish the project with academic guidance and statistical expertise. Also, Dr. Uwe Ugledahl, chief surgeon in the Hospital Trust of Finnmark, Hammerfest, agreed to supervise the final report.

Tromsø, 4 June 2019



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Abbreviations

BMI	Body Mass Index = kg/m^2
CCI	Charlson Comorbidiy Index
CKD	Chronic kidney disease
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
LEL	Low educational level
LOS	Length of stay
HEL	High educational level
MI	Myocardial infarction
MM	Multimorbidity
PRI	Patient registry index
PUD	Peptic ulcer disease
PVD	Peripheral vascular disease
QoL	Quality of Life
SES	Socioeconomic status

Abstract

Background: The citizens of Finnmark have higher mortality than Norway at large. Comorbidity can today be measured using methods like the Charlson Comorbidity Index (CCI). Comorbidity and the burden of smoking, measured in pack years, amongst patients admitted to Finnmark Hospital Trust have never been investigated. Knowledge of these variables can presumably lead to better patient treatment and follow up.

Objective: Measuring CCI, BMI and pack years in patients admitted to the Department of Surgery at Hammerfest Hospital in the Finnmark Hospital Trust. I wanted to investigate how these exposure variables impact on length of hospitalisation, measured by hospital stay >4 days.

Method: All patients admitted to the Department of Surgery between 18 November and 10 December 2018 were registered. Reading records one year prior to admission, I recorded all CCI-diagnoses and calculated individual comorbidity scores. Age, length of hospital stay, and smoking status was recorded. Pack years and BMI were calculated. Logistic regression analysis was used to evaluate the exposure impact on the outcome.

Result: Eighty patients were included in the analysis, of which 66.2% were men. Half of the patients were >70 years of age. Twenty-seven (32%) had >4 days of hospital stay. The mean CCI score was 5.20 (range 0- 13, SD 3.6). One unit increase in CCI score increased the risk of the outcome by 19% (OR 1.19, 95% CI 1.04-1.37). This effect disappeared in the multivariate logistic regression.

Conclusion: None of the examined variables displayed a significant effect on the length of the hospital admission in this study. The study is the first of its kind in Finnmark. Due to low internal validity the results should be interpreted with caution. Further research is needed to properly account for the burden of comorbidity in Finnmark Hospital Trust.

1 Introduction

There is a high prevalence of cardiovascular disease and diabetes in Finnmark (1-3). The prevalence of diabetes was highest amongst men and increasing with body mass index (BMI) (4). Compared to the rest of the country (hereafter: Norway) life expectancy in Finnmark County is low. For men, life expectancy has been reported to be 2-3 years shorter than in Norway. For men and women born 2011-2015, the life expectancy is 77.2 and 82.3 years, compared to 79.7 and 83.7 years in Norway (5, 6). According to the Norwegian Cause of Death Registry, more people die of cardiovascular disease, cancer, lung disease, and serious trauma in Finnmark than in Norway when applying standardized rates pr. 100 000 (Table 1).

There are both medical and economical arguments for awareness of multimorbidity (MM) within a population (7-9). In Denmark, the proportion of patients followed in multiple clinics simultaneously nearly doubled over a 10-year period (10). An increase in MM does not fit well with silo-based models of patient care with single-disease frameworks for patient follow-up, and poses a challenge to health care systems worldwide (11). Better understanding of the epidemiology of MM is necessary to develop adequate interventions to prevent it, reduce its burden and align health-care services closer to the patients' needs (12). Coaching given to the chronically ill elders and their caregivers to ensure that their needs are met during care transitions may reduce the rates of subsequent re-hospitalization (13). It is strongly suggested that low educational level (LEL) is associated with higher overall and premature mortality and that the association is affected by MM, lifestyle factors, and quality of life (QoL). This should be taken into account when treating people with MM in order to reduce the socioeconomic inequalities in mortality (14).

In Norway, an analysis of the geographical differences in mortality showed that level of education, income, and other sociodemographic factors could explain 70-80 percent of the geographical variation in mortality (15). This strongly suggests that MM-awareness and demographic variables in different regions of a country should be considered when structuring the health care facilities. The risk of medical errors during transition in care for patients with MM can be high (16), and furthers the argument of keeping track of patient comorbidity status in a health infrastructure so dependent on cooperation between primary and secondary health care as in Finnmark.

1.1 Definitions

1.1.1 Finnmark

Finnmark is the northernmost county in Norway. Finnmark Hospital Trust has two hospitals, situated in Hammerfest (west) and Kirkenes (east), two cities 492 km apart by road. Many patients live in rural areas. Finnmark has the longest transition time in Norway to inpatient clinic hospital care during the event of acute illness: 3 hours and 46 minutes on average for the 90 percentile (17). Patients, in general, do not live close to their hospital and are under the primary care of the local municipalities. There are 19 municipalities in Finnmark, of which 10 have Hammerfest Hospital as their local hospital in western Finnmark. In Finnmark, as in the rest of the country, fewer people smoke now than before. Still, people here smoke more than the average Norwegian (18). Also, the trend for using other tobacco products ("snus") is increasing. The people of Finnmark consume more medications than the rest of the country (19). Compared to the neighboring county of Troms and the country at large, Finnmark also has the lowest level of education (Table 2) and the highest degree of unemployment (Table 3).

1.1.2 Pack years

The prevalence of COPD and the incidence of lung cancer in Finnmark is the highest in Norway (20). Smoking is a known contributor to the burden of morbidity and death (21), and smoking cessation has proven useful to reduce mortality (22). Use of tobacco has potential adverse effects on surgery and perioperative complications and encouraged smoking cessation in a surgical setting is beneficial to the outcome (23-25). In non-cardiac surgical patients, smoking is associated with a 40 percent increase odds of 30-day mortality and a 30-100 percent increase odds of major morbidity, including surgical site infection, pneumonia, unplanned intubation, and septic shock (25). Making an effort to inform patients of the risks of smoking before being admitted to elective surgery improve perioperative results (26).

From the socioeconomic point of view, the trait of educational levels and its association with smoking habits is assumed to be one of the most important causes of social inequalities in life expectancy (27). It is shown in Norway that different smoking habits and subsequently differences in mortality due to smoke related diseases is an important cause of death, and further more that smoking is correlated with lower educational background (28).

We can note that in general: Smokers tend to have lower education levels than non-smokers; people with lower educational levels tend to be more multimorbid; and multimorbid patients

tend to have more risk factors for chronic diseases than others. In summary, smoking is strongly correlated to socioeconomic factors (29).

1.1.3 Comorbidity

Comorbidity is defined as having chronic conditions in addition to the main diagnosis of concern. I.e. the total and current disease burden in addition to “disease A”. Multimorbidity (MM) is defined as living with two or more chronic conditions at the same time (30). That is living with “disease A” and “disease B”, or more. The two terms are often intertwined, and the measurement of MM in a population is not yet standardized due to a great variety of methods and definitions (30-32). In this report, comorbidity is regarded as a measurable size describing concurrent disease when viewing a patient with a certain “disease A” presenting in the clinical setting. Comorbidity is measured using the Charlson comorbidity index (CCI) (33, 34). MM is viewed as a more descriptive variable, useful in population studies to evaluate the prevalence of multiple morbidities within the population.

Regarding MM, there is a relationship between smoking habits and the CCI score. In a study on acute coronary syndrome patients, the baseline characteristics differed significantly between the CCI=0 and the CCI≥3 group, particularly when considering risk factors such as hypertension, dyslipidemia and obesity (35). Additionally, the study found the proportion of current smokers was highest in the CCI0 group but steadily decreased the higher the weighted CCI.

2 Objectives

Rural populations have lower life expectancy, lower education levels, and a higher burden of smoking with all its adverse effects. As described above, the burden of comorbidity is higher in populations with these traits. Considering poorer public health status in Finnmark, it could be assumed that patients admitted to a surgical ward in Finnmark would have notable higher comorbidity at admittance.

Comorbidity at hospitalization in Finnmark hospital trust has never been measured. There are tools available for this (34, 36). CCI is one of the most used and validated tools to increase the representability of comorbidity in longitudinal studies (33-35), and the index is also validated for the Norwegian setting (34).

The main aim of this study was to investigate the comorbidity amongst patients admitted to the Department of Surgery at Hammerfest hospital using CCI. We wanted to compare it to the calculated Norwegian mean value of CCI (34). The secondary aim was to obtain information on the patients' burden of tobacco smoking and BMI, and impact on comorbidity and hospital length of stay (LOS). In this thesis, LOS is an outcome of interest, and we understand LOS as a proxy for health care consequences of MM.

As such, our research hypothesis (H_1) is that "length of hospital stay" is affected by "burden of comorbidity", and furthermore that "BMI" and "tobacco smoking" have an impact on this outcome. The null hypothesis to be statistically tested is that there is no correlation as suspected in H_1, described in Figure 1.

3 Material and methods

3.1 Material

3.1.1 Study population

We registered prospectively, between 18 November 2018 and 10 December 2018, continuously every person hospitalized at the Department of Surgery at Hammerfest hospital (n=105). Registered patients with lack of data (n=14), family or friends hospitalized together with the patient (n=5), and citizens outside Finnmark (n=2) were excluded from the study (total n=25). A total of N=80 patients were submitted to analysis in the study. The screening, exclusion, and inclusion of patients are shown in Figure 2.

3.1.2 Variables of interest

The following data were obtained from the electronic patient record (EPR, named DIPS®): Variables registered directly from DIPS: Age, sex, municipality, tentative diagnosis at hospitalization, state of emergency (elective or acute), final diagnosis. Calculated variables: BMI, CCI-score and hospital stay. We also registered the burden of tobacco smoking in terms of pack years, calculated using an online calculator (37).

3.1.3 Comorbidity index

The comorbidity score was calculated employing the CCI calculator provided by MDCalc online (38). We registered all comorbid conditions registered in the patient journal 12 months before the index date of admittance, as done by Nilssen et al. (34). Also, it was noted if patients died within four months following the index date. The CCI diseases of interest were recorded with weighted points in accordance with the online CCI calculator and original methods (33). The different score points of 1, 2, 3 and 6 were added used to calculate the CCI index score, making it an index reaching from min = 0 to max = 33 points. An overview of the points given to calculate the index is found in Table 4.

Also, age is weighed in with each decade >50 and up to >80 years of age adding 1 point on the CCI, min = 0 and max = 4 added points due to age.

3.2 Statistical analysis, approvals, and ethics

3.2.1 Ethics

The study was performed as a quality of care project. Consequently, no approval from the Regional Committee for Medical and Health Research Ethics (REK) was necessary. The project was approved by the Data protection officer at the Finnmark hospital trust.

Microsoft Excel was used for the database and some statistical calculations. Each patient was given a code number, and the key to the codes was kept separate in a locked draw. Descriptive statistics were performed employing SPSS version 24.

3.2.2 Descriptive statistics

Baseline characteristics for the study population are shown in Table 5. Additionally, hospital stay, CCI disease frequency, and geographical distribution of patient home municipalities is presented in three explanatory tables (Table 6-8).

3.2.3 Logistic regression analysis

For the logistical regression analysis performed in SPSS, the following considerations were made in plotting the different variables of interest. To avoid possible confounders on length of hospital stay, we dichotomized the variable and defined >4 days as “long hospital stay”. Choosing the mean length of stay has been the rationale in other studies investigating variables predicting hospital stay (39). The median length of stay in our population was 3 days, and the mode was 1 days (Table 6). We chose >4 days, as this represented 1/3rd of the study population, and to adjust for those with longer stay due to weekends other external factors (i.e. weather conditions, transportation, primary health care capacity).

We grouped the CCI into four groups: 0 = no comorbidities, 1-2 = low comorbidity burden, 3-4 = moderate comorbidity burden, and ≥5 as high burden of comorbidity, finding descriptive statistics / frequencies of the different groups. Charlson et al. (33) employ a similar grouping in a previous study. From CCI, we also calculated a variable that presented the comorbidity score, excluding the weighed effect of age, to be used in the logistic regression analysis, as age was entered as a separate parameter.

Smoking status was subdivided in 0=non-smoker, 1=smoker, 2=former smoker, 3=no information. For the statistical analysis, group 1 and 2 were regarded separately and as one,

considering the current burden of tobacco vs. life burden of tobacco. The variable of BMI was made binary, and as a simplification >25 was considered overweight.

Using univariate logistic regression analysis, we evaluated the impact from the covariates on the dependent variable, hospital stay >4 days. Binary exposure variables were sex (m=0, f=1), smoking status (current / not smoking), smoking status (ever / never), BMI >25 (yes, no). Continuous variables were pack years, CCI score, and CCI score minus age, and age. Age was also grouped in <50, 50-59, 60-69, 70-79, ≥ 80 years. CCI was grouped as explained above. The confidence interval was set to 95%. Using multivariate logistical regression analysis, we evaluated the combined implication on hospital stay of the exposure variables in the univariate logistic regression analysis that had a p-value <0.25, to allow for all exposure variables that possibly had an impact on the outcome.

4 Results

4.1 Patient characteristics

Patient characteristics are shown in the tables section (Table 5 and 6). Most patients were men (57.5%); most were in their 8th decade of life (32.5%); most had a previous or current history of smoking (72.2%); over 50% of the population was over 70 years of age at admittance. 1/4th of the population had only one day long hospital stay, and 56% had 1-3 days of hospital stay. Most of the patients stayed <4 days in hospital (66.2%).

4.2 Comorbidity burden

There was a total of 139 comorbid CCI-diseases registered, giving an average of 1.74 comorbidities per patient (Table 7). The top five CCI diseases in the study population were: Solid tumor (14%), chronic obstructive pulmonary disease (COPD) (12%), cerebrovascular disease (CVD) (11%), metastasis from cancer (9%) and MI (9%). Mean 10-year calculated survival rate in our study population was 0.40. In the four months following index date, a total of 11 patients passed away, making it 13.75% of the study population (n=80). Mean calculated CCI score was 5.20 (range 0-13, SD 3.6).

4.3 BMI, pack years and travel distance

The mean BMI in the study population was 25.8 (range 17-40, SD 4.7). The mean burden of pack years was 22.48 (range 0-212, SD 34.0).

Patients in the study sample came from 15 of the 19 municipalities in Finnmark County (Table 8). The five most prevalent patient municipalities were Alta (25%), Hammerfest (16%), Karasjok (14%), Porsanger (13%) and Måsøy (6%). 9% of the patients came from municipalities primarily bound to Kirkenes hospital in the eastern part of the Finnmark hospital trust. Calculating the average estimated travel distance per patient one way to Hammerfest hospital, the average distance was 156.55 km and required an estimated 2.6 hours of travelling time at 60 km/h average travel speed.

4.4 Univariate analysis

We found the exposure of age to increase the risk of hospital stay >4 days by 5% per year increase in age (95%CI 1.01-1.09), as shown in Table 9. Only age ≥80 had a significant

impact on the risk of hospital stay >4 days in the grouped age categories (OR 6.00, 95%CI 1.00-35.81). The increase in one unit CCI score increased the risk of the outcome by 19.4 % (95%CI 1.04-1.37). For the age-adjusted CCI score, the risk of outcome was 24.4% per increased score unit (1.04-1.50), with the score group ≥5 the significant of the grouped scores (OR 8.73 95% CI 1.62-46.94). For the age groups 50-59, 60-69, 70-79, smoking status, and BMI>25, there were no significant findings.

4.5 Multivariate analysis

None of the exposure variables that were significant in the univariate analysis had a significant impact on risk of hospital stay > 4 days when adjusted for each other, as shown in Table 10. CCI-score, age, sex, or smoker status had no significant impact on the risk of patients entering the outcome category of LOS >4 days.

5 Discussion

5.1 Discussion of findings

In the univariate logistic regression analysis an increase in age and CCI predicted increased risk of hospital stay > 4 days. When performing the multivariate analysis, this effect was eliminated. Neither CCI, nor age, sex, or smoker status, had a significant impact on the risk of prolonged hospital stay. Compared to findings in other studies (40-42), these results are unexpected.

5.1.1 Comorbidity in the study population

Nilssen et al. (34) created a patient register index (PRI) in Norway based on the CCI. Their calculated mean CCI was 0.43. In our study sample, the mean CCI and mean age-adjusted CCI was 5.20 and 2.95, respectively. The higher mean values in our analysis may be explained by the baseline differences in our sample populations. Their large sample constituted the entire Norwegian patient registry, and our much smaller sample was drawn from a selected group of patients admitted to the Department of Surgery in Hammerfest. Considering the study by Nilssen and co-workers more in detail, some baseline characteristics separated our study samples from theirs: First, their study sample was extracted from the Norwegian patient registry, with all age groups from zero up included – whereas over 50% of our patients were over 70 years of age. The majority (57%) in the PRI-study were female, we had the direct opposite distribution. 68% of the index visits were at hospitalization (in-patient), we had 100% of our patients registered at hospital admission to the Department of Surgery. Twenty-two % of the PRI-patients were registered with at least one CCI disease, compared to 77.7% in our population. However, one important similarity can be found: increasing age is related to increase in CCI.

Regarding the mean CCI in presumably more comparable populations prone to surgery, different studies report a mean CCI in their sample of 2.21 (40) and 2.90 (43) – more similar to our findings. However, these cannot put in direct comparison to our results due to our limited validity, as discussed in section 5.2.1 below.

In the PRI-study by Nilssen et al., the top five diseases were chronic pulmonary disease (4.9%), MI (4.0%), any malignancy (3.8%), CVD (3.8%) and CHF (2.9%). In the AMIS study (35) from Switzerland, top five were MI (18.0%), Diabetes without chronic

complications (14.7%), renal disease (7.1%), CVD (6.0%) and chronic lung disease (6.0%). Bear in mind that the AMIS study patients were admitted with acute coronary syndrome, and arguably the population could be expected to be more prone to cardiovascular disease and lifestyle disease burden. 4/5 and 3/5 of the equivalent CCI-diseases in our study sample (Table 7) were in the top five for the studies mentioned above.

In the literature, several studies point out the predictor impact of CCI on length of stay (LOS), though it is hard to find sample populations directly comparable to ours: In a study assessing LOS following robot-assisted prostatectomy, CCI was the only independent predictor (41). The CCI score has been associated with length of stay and hospital costs incurred following treatment for hip fracture (42). Among older adults hospitalized for acute stroke, higher global comorbidity (CCI $\geq$ 2) was associated with adverse clinical outcomes, and thereby LOS (40). Yet another study considered the utility of CCI as a predictor of LOS for lower extremity injury patients (44). In our report, it is hard to argue for any strong impact of CCI on LOS due to low internal validity. However, our findings do point in that direction, as concluded in the multivariate analysis.

5.1.2 The impact of smoking and BMI

The secondary aim of our study was to reveal the patients' burden of tobacco smoking and BMI and these two variables impact on comorbidity and hospital stay. In the univariate logistical regression analysis, we found no significant impact of increased BMI >25 on length of stay. This variable is inadequate in several ways. The mean BMI in our population was 25.8 (Table 5) and as discussed below the certainty of the measures at admittance are unclear. In retrospect, the cut-off value of BMI >25 could have been been increased. It might have given a different result in analysis if i.e. BMI >30 was the variable describing of overweight. Presumably, it should also be considered if high age and MM incurs a high BMI, or if this patient group has a lower BMI than average. It is beyond the scope of this report to further discuss these potential confounders.

Though our results did not show any significant effect of pack years on outcome, it should be noted that 72% of our patients have a history of smoking. For reasons discussed in the following sections, the lack of significant results in the analysis does not rule out that a history of smoking has an impact on length of hospital stay in Finnmark. As shown in the introduction, the literature is clear on the fact that efforts to encourage and facilitate smoke cessation prior to surgery is advisable.

5.2 Methodology

5.2.1 Internal validity

The present study employ a univariate and multivariate logistic regression to assess the impact of CCI and the other exposure variables on the binary outcome "hospital stay > 4 days" (yes/no). The multivariate logistic regression analysis allows us to control for different confounding effects. In the following discussion on validity, bias and reliability are considered (45, 46).

Selection bias

All admittances to the Department of Surgery at Hammerfest Hospital in the data collection period were registered. As delineated in the flow chart (Figure 2), certain patients were excluded to avoid the risk of selection bias (i.e., patients not from Finnmark or family of admitted patients). The data collection time is set in November and December, a tough and dark period in the arctic region. This has potential consequences for road traffic and the availability of flights to, from, and within in Finnmark. If this affects patients' willingness to travel the distance for elective surgery, or the possibility of going to Hammerfest (not Kirkenes or Tromsø) in an acute setting, it could be argued that this may give grounds for sampling error (45).

Information bias

Measurement errors or observational errors can lead to information bias. The risk of information bias is present regarding several of the variables included in the analysis. The outcome variable "hospital stay" was recorded by subtracting the time of admittance to the department from the time of exit. In the cases where patients were re-admitted (less than one week later for the same condition, or were readmitted less than one week later during an "open return") for the same condition, the total time of in-hospital stay was summarized. The same strategy was applied for the patients transferred between hospitals (Hammerfest/Kirkenes/Tromsø), or between departments within Hammerfest Hospital. Similar considerations were made for "same condition admittance" before the index date.

This strategy is prone to information bias due to an unclear definition of terms, and risk of measurement error in the process of recording the data. First, it can be asked if the transmissions and admittances were correctly dated and recorded. Second, if these pieces of information were correctly collected when going through the journals. Last, the limits of "one

week" was an arbitrary choice, and may itself be a measurement error. As explained above under methods and statistics, section 3.2.3, this kind of bias and the many possible confounding effects interplaying with the length of stay was attempted corrected for by dichotomizing the outcome variable, and performing a multivariate logistic regression analysis. In future studies, a different approach to investigating the dependent variable "length of hospital stay" could be interesting.

Regarding the exposure variables, i.e. the calculated variable of pack years, there are several steps of information from the "truth" to what is written in the patient records. In this study, there is also a risk of making mistakes when going through the records in hindsight, and when calculating the actual pack years. Similar risk of bias due to measurement error could be expected in the records of BMI and disease history, where there is a risk of information bias due to, i.e. patient recollection. In addition, factors such as smoking status and weight (unless measured) can be vulnerable to an interview effect, leading to measurement bias due to lack of desire to admit to socially disliked habits or traits.

During the review of journals in DIPS, it was notable that some central information was copied from previous journals, (i.e., information on disease history or the use of stimulants). This copy-paste solution is understandable; however, it begs the question if nuances or key information might get lost on the way. This could lead to information bias due to an implied "yes-effect" from the fact that it is assumed the patient has remained status quo since previous admittance.

Medical history records are vulnerable to information bias due to the limited patient recollection of personal medical history. The 17 different diagnoses were recorded in accordance with the limitations noted on the MDCalc website. During the recording of data from DIPS, a few uncertainties in diagnosis definition exist as a potential source of information bias. The following, MI, PUD and CKD, left some operational decisions that may be biased. Regarding any history of MI, it was noted in some journals both coronary bypass surgery and PCI treatment. Though presumably due to chronic occlusion, and not ACS, this leaves some uncertainty. These patients were not recorded as have history of MI, though it is unclear if that was the case. Regarding PUD, many patients received different proton pump inhibitor (PPI) medicaments, but only those who had a definite description of visually confirmed ulcerative disease in the upper GI was recorded. Though many patients had a note of "kidney failure" at different levels in their journals, the MDCalc has a limit for moderate

chronic kidney disease (CKD) only to be noted when creatinine >3 mg/dl (0.27 mmol/L). In DIPS' creatinine is measured in μmol/L, making the limit 270 μmol/L. None of our patients had creatinine levels this high at admittance, but due to history recording of severe renal disease, three patients were given this CCI diagnosis.

Bias in analysis

The risk of finding associations by chance is present in all research. To avoid the error of reporting a difference which is not real (a type 1 statistical error), we applied a level of significance of α=0.05, meaning that a p-value of <0.05 leads to a rejection of the null hypothesis (H_0). However, the risk is still that 1/20 samples from a population where the null hypothesis is true, the p-value will be <0.05. So, even though we have a significant finding in our study, there is still a 5% chance of type 1 error rejecting H_0. (46)

For a statistical test result; the larger the sample size, the narrower the CI, the larger the test statistics, and the smaller the p-value. In our case, the sample is >60, making it arguably large enough to calculate a CI regardless of the normal distribution in our sample. Yet N=80 leaves some limitations. For our significant results in the univariate analysis (Table 9), the confidence intervals were large. E.g.for the significant finding on age-adjusted CCI, OR was 1.244, and the 95% CI was 1.035-1.496. Interpreting this means that the true risk of entering the outcome category for one unit comorbidity index score increase would be somewhere between 3.5% and 49.6%. Our relatively small sample size also leaves us at risk of not giving value to what could have been important differences; that is, keeping the null hypothesis and rejecting that some of our exposure variables had a true impact on hospital stay >4 days. Furthermore, in our attempts to stratify the population into CCI categories and age groups, the risk of type 2 error is highly present, and our non-results should also be viewed with caution.

5.2.2 External validity

External validity is expected to be low, given the low internal validity. Already by choosing our study population from a Department of Surgery, the external validity of our potential findings is expected to be limited. It is not likely our findings can be generalized to all surgical patients admitted to Hammerfest Hospital, making it hard to argue for any external validity to comparable hospitals in other regions. This problem is exemplified above in section 5.1.1 when comparing the CCI in our study with the CCI found from the Norwegian patient registry study of Nilssen et al. (34). In summary, internal validity, and thereby also external validity, is not satisfactory in this study.

5.2.3 Other possible confounders

Age and CCI-score are known predictors to evaluate the risk of death from a comorbid disease. Populations more prone to having multiple morbidities have some common traits; as Lund Jensen et al. (14) have shown, MM is more prevalent among people of lower socioeconomic status (SES), and both MM and SES are associated with higher mortality rates. The study concluded that LEL is associated with a higher overall and premature mortality and that the association is affected by MM, lifestyle factors and QoL. As noted in the introduction, Finnmark at large pertains several of the risk factors having an impact on the increased burden of mortality and morbidity. This report does not further evaluate confounders related to the observed higher mortality and morbidity in Finnmark.

Alcohol consumption was noted, and 13 patients had a journal at admission describing the prior or current problem of exceedingly high alcohol consumption. Though this trait accounts for 16.5% of our study population, it is not a result our study design was planned to include, and the investigation is here regarded as interesting for a descriptive purpose. Mean 10-year calculated survival rate in our study population is 0.407, meaning an expected survival of only 4 out of 10 patients after ten years from admittance. This may not be so unexpected, considering >50% of the patients are older than 70 years at admittance. However, it is beyond the scope of this thesis to further investigate this variable. Also, 11 patients were recorded dead in DIPS within four months from the index date. Other and much larger studies doing similar validating of CCI, use one-year follow up or death within that time from index date as the end of follow up (34). Given the size of the sample, the limitation of follow up time, and the limited evaluation of the cause of death, this is not added to our analysis.

In Table 8 we show the estimated travel distance and “time in transit” for the patients in our sample. Though our estimate of 2,6 hours travel time is lower than the estimate presented in the introduction (17), it cannot be regarded as more than a mere curiosity due to differences in methods, a small sample size, and considerable approximations in our model. There are many other confounders to “time in transit” than “average travel speed” alone. However, the calculations on “time in transit” are included in Table 8 and presented here as a reminder on the fact of geography as a part of clinical decision making when working in Finnmark county.

5.3 Limitations, strengths and implications

As discussed in the section on material and methodology above, this study encounters many limitations. First, the study sample is very limited (n=80). Second, the data collection period is short and in a particular time of year– contributing to a small sample size, and to a seasonal risk of selection bias. Third, the data set is collected retrospectively from journal notes one year prior to the index date of admission, leaving room for the bias of information and human subjective error of interpretation in the clinical setting. Assumable, there can also be a difference of history depth priority depending on the acuteness of the clinical case in question, i.e., differences in accuracy of disease history, the actual weight or smoking status. Lastly, the lack of 1 year follow up limits the usability of the results, as we only have 4 months follow up time, and limited knowledge of cause of death other than the fact of death in DIPS.

As a preliminary attempt to record the comorbid status in the population undergoing surgery at Hammerfest hospital in Finnmark, to our knowledge this study is the first. We know that Finnmark has a higher mortality, a lower educational level, and a higher burden of tobacco than Norway at large. The lack of results in this study should encourage rather than discourage further research to investigate comorbidity in Finnmark Hospital Trust.

6 Conclusion

In this cross-sectional study of comorbidity, the mean Charlson Comorbidity Index (CCI) Score is 5.20 (range 0-13, SD 3.64). I found no effect of the CCI-score on length of hospital stay. Neither of the controls (age, sex, smoker status, or BMI) had a significant effect either. Due to the low internal validity, these results must be interpreted with caution. However, the study is the first of its kind in Finnmark Hospital Trust. Further research is needed to properly account for the burden of comorbidity in this region. A larger study sample and more elaborate investigation of length of hospital stay could strengthen the results in future studies.

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7 Figures and tables

Table 1: Cause of death in Finnmark County

Cause of death Finnmark county compared to Norway in total: Standardized rates[a] pr. 100.000 sorted by county sex and cause of death.[b]					
Cause of death		**County**	**Year**		
			1970	**1990**	**2017**
All		Total	1671	1428	893
		Finnmark	1937	1735	1116
Death from disease		Total	1588	1353	825
		Finnmark	1834	1635	1028
	Malignant tumors (cancer)	Total	270	290	239
		Finnmark	274	304	288
	Cardiovascular disease	Total	881	680	229
		Finnmark	1065	892	300
	Disease in respiratory organs	Total	188	157	103
		Finnmark	240	144	133
Injuries/intoxications		Total	83	75	51
		Finnmark	103	100	62

[a]Age adjusted rates, according to Eurostats and WHO standard populations.

[b](47)

Table 2: Level of education in Finnmark County

Highest level of education[a] – proportion (%), population >45 yoa, both sexes				
Geography	Level of education	Age	**Year**	
			2012	2016
Norway	>13 years of education[b]	+45	73	76
Troms County			68	73
Finnmark County			64	69

[a] Data collected from public statistics from Norwegian municipalities (48).

[b] Data >13 years of education / High school or higher education

Table 3: Level of unemployment in Finnmark County

Unemployment[a] – proportion (%), 15-74 years of age, both sexes		
Geography	**Year**	
	2012	2016
Norway	1,9	2,3
Troms County	1,7	1,6
Finnmark County	2,3	2,7

[a] Data collected from public statistics from Norwegian municipalities (48).

Table 4: Calculation of the Charlson Comorbidity Index (CCI)

The weighed points given to calculate the Charlson Comorbidity Index (CCI) score [a, b]	
Points	**Disease history**
1	History of myocardial infarction (MI); heart failure (CHF); peripheral vascular disease (PVD); cerebrovascular disease (CVD); dementia (DEM); chronic lung disease (here: COPD); connective tissue disease (CTD); peptic ulcer disease (PUD); mild liver disease (LD) and diabetes (DM).
2	Diabetes with target organ damage (DM+), hemiplegia (HP), moderate to severe renal disease (CRD), malignant neoplasm (solid tumour), leukaemia (LEUK), and lymphoma (LYMPH).
3	Moderate to severe liver disease (LD+).
6	Metastatic tumour (MET) and AIDS.

[a] *These were used to calculate the CCI index score, making it an index reaching from min = 0 to max = 33 points. In addition, age is weighed in with each decade >50 and up to >80 years of age adding 1 point on the CCI, min = 0 and max = 4 added points due to age.*
[b] (38)

Table 5: Baseline characteristics of the study population

Baseline characteristics of the study population			
		Descriptive statistics	
	N (%)	**Mean (range)**	**SD**
All patients	80 (100)		
Sex			
Female	34 (42.5)		
Male	46 (57.5)		
Age		65.57 (19 – 91.4)	17.52
<50	14(17.5)		
50-59	10 (12.5)		
60-69	14 (17.5)		
70-79	26 (32.5)		
≥80	16 (20.0)		
Hospital stay		7.93 (0 – 166) [a]	20.02
> 4 days	27 (33.8)		
Smoking	***79 (98.8)***		
Current smoker	26 (32.9)		
Ever smoked	57 (72.2)		
Pack years		22.48 (0 – 212)	33.99
BMI		25.80 (17 – 40)	4.70
Creatinine (μmol/L)		77.56 (26 – 241)	
10-year est survival rate		0.407[b]	
CCI score		5.20 (0 - 13)	3.64
Age-adjusted CCI		2.95 (0 - 9)	2.62

[a] When removing extreme result 166 and 55, mean = 5.33, when removing yet another extreme of 47, mean = 4.79.
[b] Calculated in excel from the sum of creatinine levels / N=80.
[c] Calculated in excel from the sum of each estimated 10-year survival rate as in the MDCalc (38), divided by N=80.

Table 6: Length of hospital stay at the Department of Surgery, Hammerfest hospital

Length of hospital stay in the study population [a]		
Observed	**Frequency**	**Relative F %**
0	3	4 %
1	**20**	**25 %**
2	**14**	**18 %**
3	**10**	**13 %**
4	6	8 %
5	6	8 %
6	4	5 %
7	1	1 %
8	2	3 %
10	1	1 %
12	1	1 %
15	1	1 %
16	1	1 %
17	3	4 %
18	1	1 %
20	1	1 %
21	1	1 %
27	1	1 %
47	1	1 %
52	1	1 %
166	1	1 %
	80	100 %

Median = 3, Mode = 1, IQ1=1, IQ3=6, IQR=5.

[a]Department of Surgery, Hammerfest Hospital, admitted patients in the period 18 November – 10 December 2018

Table 7: Comorbidity burden in the study population

Comorbidity burden in the study population: *Number and percentage of patients with CCI <1, 1-4, ≥5, and the frequency and proportion of the CCI diagnoses*		
CCI score [b]		
	Frequency	%
<1	8	10.0
1-4	29	36.3
≥5	43	53.8
		100%
CCI score minus age [a c]		
<1	18	22.5
1-4	39	48.8
≥5	23	28.8
		100%
Type of comorbidity	**Number of comorbidities**	**Proportion (%)**
Total n of comorbidities	*139*	
Average n of comorbidities per patient [d]	*1.74*	
Myocardial infarction	12	9
Congestive heart failure	6	4
Peripheral vascular disease	11	8
Cerebrovascular disease	15	11
Dementia	2	1
Chronic pulmonary disease	16	12
Connective tissue disease	10	7
Peptic ulcer disease	9	6
Mild liver disease	1	1
Moderate or severe liver disease	1	1
Diabetes without chronic complication	10	7
Diabetes with chronic complication	3	2
Hemiplegia or paraplegia	6	4
Renal disease	3	2
Solid tumor [e]	**20**	**14**
Metastasis	13	9
Leukemia	0	0
Lymphoma	1	1
AIDS	0	0

[a] *Distribution of Charlson comorbidity score without age weight, later used to for logistic regression analysis*
[b] *Q1=2, Q3=8, IQR=6*
[c] *Q1=1, Q3=5, IQR=4*
[d] *N=80*
[e] *Top five: Solid tumor, COPD, CVD, metastasis and MI.*

Table 8: Geographical distribution and estimated travel distance to hospital.

Geographical distribution *of home municipalities in the study population, and expected one way average travel distance* [a] *(km).*			
Municipality [b]	**N (%)**	**Distance travelled to Hammerfest**	
Total	80 (100)	Distance for one	Total distance
Alta	20 (25)	**141**	2820
Hammerfest	13 (16)	**2.4**	31,2
Sør-Varanger	2 (3)	482	964
Vadsø	2 (3)	464	928
Porsanger	10 (13)	**143**	1430
Nordkapp	3 (4)	**181**	543
Kautokeino	4 (5)	**268**	1072
Tana	0 (0)	353	0
Karasjok	11 (14)	**217**	2387
Båtsfjord	0 (0)	459	0
Vardø	1 (1)	494	494
Lebesby	1 (1)	261	261
Måsøy	5 (6)	**168**	840
Gamvik	1 (1)	368	368
Kvalsund	4 (5)	**32.7**	130.8
Hasvik [c]	2 (3)	**-**	-
Berlevåg	0 (0)	487	0
Nesseby	0 (0)	371	0
Loppa	1 (0)	**255**	255
Total distance km one way **(average distance per patient)**			12524 **(156.6)**
Hours to hospital one way average speed 70 km/h **(average time per patient)**			178.9 **(2.2)**
Hours to hospital one way average speed 60 km/h **(average time per patient)**			278.7 **(2.6)**

[a] *Shortest road distance from municipality center to Hammerfest Hospital. www.google.com/maps*

[b] *Municipalities corresponding to Western part of Finnmark Hospital Trust, marked in shadow*

[c] *Mainly boat traffic directly to Hammerfest*

Table 9: Univariate logistic regression analysis

Univariate logistic regression analysis: *Dependent variable = hospital stay > 4 days (yes/no)*				
Variable	**OR**	**95% CI**		**p-value**
		Lower	**Upper**	
Sex (female)	1.415	0.556	3.602	0.467
Age (years)	1.049	1.011	1.087	0.010
Age (group)				
<50	-	-	-	*Reference*
50-59	0.667	0.052	8.549	0.755
60-69	6.000	0.965	37.296	0.055
70-79	3.176	0.580	17.406	0.183
≥80	6.000	1.003	35.808	0.050
Smoking				
Current smoker	0.864	0.315	2.369	0.777
Smoker (current or previous)	1.983	0.639	6.159	0.236
BMI >25	0.677	0.256	1.793	0.433
CCI score	1.194	1.039	1.371	0.012
Age-adjusted CCI	1.244	1.035	1.496	0.020
Age-adjusted CCI (group)				
0	-	-	-	*Reference*
1-2	4.267	0.778	23.404	0.095
3-4	3.636	0.595	22.234	0.162
≥5	8.727	1.623	46.935	0.012

Table 10: Multivariate logistic regression analysis

Multivariate logistic regression analysis: *Dependent variable = hospital stay > 4 days (yes/no).*				
Variable	**OR**	**95% CI**		**p-value**
		Lower	**Upper**	
Sex (female)	1.991	0.681	5.825	0.209
Age (years)	1.044	0.998	1.092	0.062
Smoker (current or previous)	1.530	0.415	5.638	0.523
Age-adjusted CCI (grouped score)				
0	-	-	-	*Reference*
1-2	3.198	0.503	20.315	0.218
3-4	1.270	0.595	10.256	0.823
≥5	3.220	1.623	22.457	0.238

Figure 1: Model of research hypothesis H_1.

Our research hypothesis is that Charlson Comorbidity Index Score (CCI-score) can predict "hospital stay >4 days" at the Department of Surgery in Hammerfest.

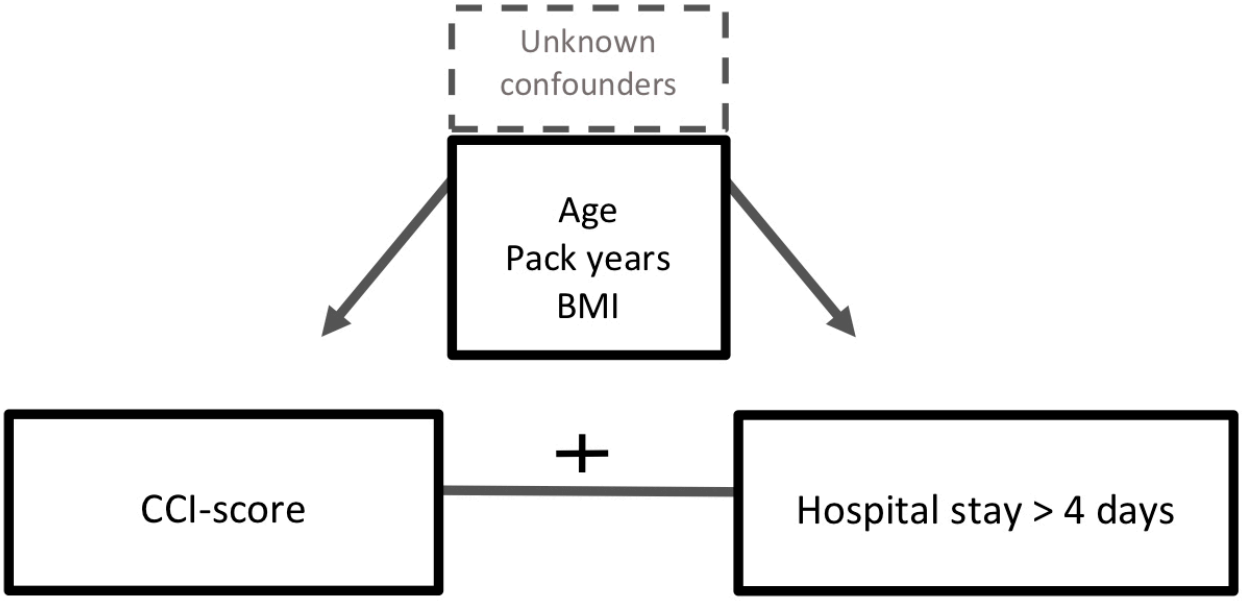
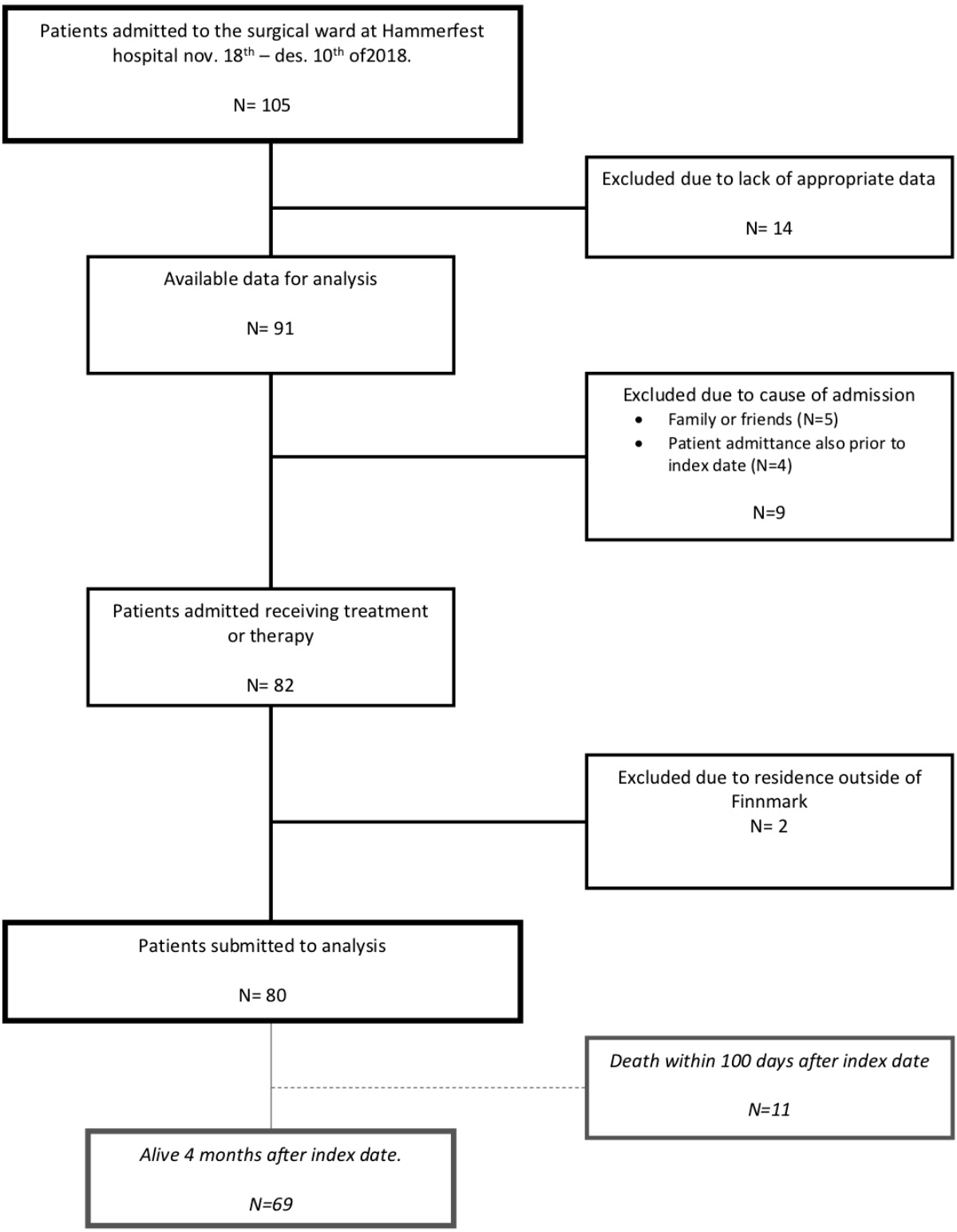


Figure 2: Flow chart.

This flow chart shows the exclusions and inclusions made to choose the patients submitted to analysis.



8 GRADE

The five GRADE schemes mandatory for MED-3950 are presented on the following pages.

GRADE 1: Referanse: Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.

Design: Kohortstudie	
Dokumentasjonsnivå	IIa
GRADE	B

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Objective of the study was to develop a prognostic taxonomy for comorbid conditions which singly or in combination might alter the risk of short term mortality for patients enrolled in longitudinal studies. **Konklusjon** The method of classifying comorbidity provides a simple, readily applicable and valid method of estimating risk of death from comorbid disease for use in longitudinal studies. Further work in larger populations is still required to refine the approach because the number of patients with any given condition in this study was relatively small. **Land** **USA** **År data innsamling** 1st jan 1962-31st dec 1969, follow up 5 and 10 years after, and 1984 follow up 1 year after	The index was built using the 1-year mortality from an inception cohort consisting of patients admitted to the medical service at New York Hospital-Cornell Medical center during one month in 1984. The index was then tested for its ability to predict risk of death from comorbid disease in a cohort of 685 patients who were treated for primary breast cancer at Yale New Haven hospital 1962-1969. The results were compared to the currently used method of classifying comorbid disease. Training population A: 607 admitted in one month 1984. 559 with complete 1-year follow up information. The patients who were not available for follow up tended to be younger and have fewer and less severe comorbid diseases. Testing population B: Cohort of 685 women with histologically proven breast cancer who received their first treatment at Yale New Haven Hospital 1.jan 1962-31st dec 1969. Complete follow up 5 and 10 years after admission for those eligible the closing date of the study. Classification of comorbidity: All comorbid diseases were recorded. Conditions that completely resolved (pneumonia, cholecystectomy) were not counted as comorbid diseases. Statistics: Outcome of interest: deaths attributable to comorbid conditions. Cancer deaths were handled by regarding the patient as withdrawn alive at the time of death. Chi-square testing and cox regression used for analysis. Unadjusted relative risks and adjusted relative risks were calculated. A scoring system was made that combined age and comorbidity. survival was 98.3%. If the combined score was 3, the calculation was $e^{0.9\ (\text{comorbidity} - \text{age score} = 3)} = e^{2.7} = 14.8,$ and the predicted survival was $0.983^{14.8} = 0.776$.	The 1-yr mortality rates for the different scores were: "0", 12% (181); "1-2", 26% (225); "3-4", 52% (71); and "greater than or equal to 5", 85% (82). The index was tested for its ability to predict risk of death from comorbid disease in the second cohort of 685 patients during a 10-yr follow-up. The percent of patients who died of comorbid disease for the different scores were: "0", 8% (588); "1", 25% (54); "2", 48% (25); "greater than or equal to 3", 59% (18). With each increased level of the comorbidity index, there were stepwise increases in the cumulative mortality attributable to comorbid disease (log rank chi 2 = 165; p less than 0.0001). In this longer follow-up, age was also a predictor of mortality (p less than 0.001). The index was first made for an overall burden by the number of comorbid disease. But secondly a weighted index was developed, taking into account both the seriousness and number of diseases. The study showed that only age and comorbidity (p<0,0001 for both) were significant predictors of risk of *comorbid* death. The RR for each increasing level of the comorbidity index was 2.3 (95% CI, 1.9-2.8) and for each decade of age 2.4 (95%CI, 2.0-2.9). *In essence* each decade of age and each rank of comorbidity added a similar risk. The risk of dying from a comorbid disease posed by an additional decade of age was equivalent to an increase of 1 in the comorbidity index. Table 3. Weighted index of comorbidity Assigned weights for diseases — Conditions 1 — Myocardial infarct; Congestive heart failure; Peripheral vascular disease; Cerebrovascular disease; Dementia; Chronic pulmonary disease; Connective tissue disease; Ulcer disease; Mild liver disease; Diabetes 2 — Hemiplegia; Moderate or severe renal disease; Diabetes with end organ damage; Any tumor; Leukemia; Lymphoma 3 — Moderate or severe liver disease 6 — Metastatic solid tumor; AIDS Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3).	**Sjekkliste:** **Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer?** Ja, dertil formålet var å måle belastningen av komorbiditet, og å finne om et slikt mål kunne brukes på to ulike grupper til sammenlignbart index-resultat. **Er gruppene rekruttert fra samme populasjon/befolkningsgruppe?** "Training group" were recruited in 1984, New york, and the testing population cohort was obtained from New Haven (just outside NY) two decades earlier, and consisted only of women with breast cancer. Likevel gir likheten i utfall etter komorbiditetsbyrde hos de to populasjonene nettopp styrken til studien. **Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?** **Var studien prospektiv?** Ja, både for trenings-kohorten og for test-kohorten. **Ble eksposisjon og utfall målt likt og pålitelig i de to gruppene?** **Ble mange nok personer i kohorten fulgt opp?** Forfatteren poengterer selv at dette er den første studien av sitt slag; og at senere validering på større populasjoner må gjøres. **Er det utført frafallsanalyser?** Ja **Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall?** Ja **Er det tatt hensyn til viktige konfunderende faktorer i design/gjennomføring?** Ja **Er den som vurderte resultatene (endepunktene) blindet gruppetilhørighet?** Ikke relevant her **Hva diskuterer forfatterne som.** **Styrke** Den første indeksen som på en enkel måte kan bidra til å ta høyde for komorbiditet i longitudinelle studier. **Svakhet** Dels ulik populasjon på test og trenings-kohort, ikke så store kohorter. **Viser forfatterne til annen litteratur som styrker/svekker resultatene?** Ja **Har resultatene plausible biologiske forklaringer? Ja**

GRADE 2: Referanse: Lund Jensen N, Pedersen HS, Vestergaard M, Mercer SW, Glumer C, Prior A. The impact of socioeconomic status and multimorbidity on mortality: a population-based cohort study. Clin Epidemiol. 2017;9:279-89.	**Design: Kohortstudie**	
	Dokumentasjonsnivå	IIb
	GRADE	B

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Multimorbidity (MM) is more prevalent among people of lower socioeconomic status (SES) and both MM and SES are associated with higher mortality rates. This study aims to investigate the association between educational level and mortality, and to what extent MM modifies this association. **Konklusjon** *LEL is associated with higher overall and premature mortality and that the association is affected by MM, lifestyle factors, and quality of life.* **Land** **Denmark** **År data innsamling** May 1, 2010 (baseline), march 29, 2014 (endpoint).	239,547 individuals were invited to participate in the Danish National Health Survey 2010. Mean follow up time was 3.8 years. Followed until death or emigration, or at the endpoint of the study. Inclusion criteria 25-89 years of age at baseline, residing in Denmark since January 1, 1995. MM was assessed by using information on drug prescriptions and diagnoses for 39 long-term conditions. Data on educational level was obtained from Statistics Denmark. Date of death was obtained from Civil Registration System, and information on lifestyle factors and quality of life (QoL) was collected from the survey. Main outcomes were overall and premature mortality (death before age of 75). **Kohorter**: study population cohort, and the two sub-cohorts termed survey responders and non-respondents. **Exposure**: MM status, educational level. **Main outcome**: Information on death (all-cause mortality). **Covariates**: self-reported obtained from the sub-cohort of responders to the Danish national health survey (physical activity, alcohol, smoking, BMI, ethnicity, quality of life. Other covariates: from Danish civil registration system (gender, dob, civil status. **Statistical analysis:** Demographic characteristics of both study and respondent cohort evaluated at baseline. HR for all-cause mortality CI95 calculated using cox proportional hazards model with age as the timescale. **Statistiske metoder**: Four different adjustment models were applied to consider the association between educational level and mortality, and how MM could modify this association. Multiple sensitivity analysis were performed. In one of them, all <35yoa were excluded, to test the hypothesis on a cohort who more certainly had completed their education.	**Hovedfunn:** Of a total of 12,480 deaths, 6,607 (9,5%) were of people with low educational level (LEL) and 1,272 (2,3%) were of people with high educational level (HEL). The mortality rate was higher among people with LEL compared with HEL in groups of people with 0-1 disease (HR 2.26, 95% CI (2-2.55)) and >=4 diseases (HR 1.14, 95% CI (1.04-1.24). Absolute number of death was six times higher among people with LEL than those with HEL in those with more than 4 diseases. Adjusting for potential mediating factors such as lifestyle and QoL eliminated the statistical association between educational level and mortality in people with MM. RR of overall and premature mortality for people with LEL compared with HEL decreased with increasing number of underlying conditions. The findings indicate that the relative effect on death decrease the more diseases you suffer from, because the diseases have a direct effect on mortality as seen from the absolute numbers. **Between exposes/unexposed:** The absolute number of long term conditions increased with decreasing educational level. Mortality increased with decreasing educational level and with increasing n of underlying diseases. In the **sub analysis** of premature deaths (<75yoa), the LEL group had 40% higher risk of premature death in the group with >4 conditions (HR 1,4: 95% CI 1.04-1.67). In the sub analysis of the survey respondents with QoL SF-12 survey, the association between educational level and mortality disappeared for people with MM when adjusted for lifestyle factors and SF-12.	Formålet klart formulert? Ja **Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? Sammenlignbare ved baseline?** Following a large and representative sample of the D population for up to 4 years, with low loss to follow-up. Even though the survey cohort and the non-responders diversed in baseline, the association between educational level, MM, and mortality was remarkably similar, speaking against any selection bias. Eksponerte individer var representative. **Ble eksposisjon og utfall målt likt og pålitelig?** Ja, i så stor grad mulig unngått klassifikasjonsbias, også testet ved subanalyser. **Var studien prospektiv**? Ja **Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias)** Ja **Er det utført frafallsanalyser?** Ja **Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall**? Ja **Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?** Ja **Tror du på resultatene?** Ja -**Bradford Hills criteria** (time sequence, dose-response gradient, biological plausibility, consistency….) Ja. **Kan resultatene overføres til den generelle befolkningen?** Ja – bidra til å stratifisere måten man vurderer den generelle bef **Annen litteratur som styrker/svekker resultatene?** Ja **Hva betyr resultatene for endring av praksis?** Bevissthet rundt utdanningsnivå og sykdomsbelastning når tiltak iverksettes for pas med MM. Hva diskuterer forfatterne som: **Styrke**: use of national registry; high accuracy on valid and complete data of interest. Large study sample, allowing enough participant with different educational background. **Svakhet:** Educational level affected by changes in the educational system over time. No standard measure for multimorbidity MM. Type of education not applied. No measure of human or social capital. Cannot rule out that some of the factors adjusted for (BMI, lifestyle factors) are intermediate factors: LEL may lead to them, and so to higher mortality. Thereby it could result in an underestimation of the true association between educational level and mortality.

GRADE 3: Referanse: Validity of Charlson Comorbidity Index in patients hospitalized with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012

Design: Kohortstudie	
Dokumentasjonsnivå	IIB
GRADE	B

Formål

This study aimed to assess the impact of individual comorbid conditions as well as the weight assignment, predictive properties and discriminating power of the Charlson Comorbidity Index (CCI) on outcome in patients with acute coronary syndrome (ACS).

Konklusjon

Comorbidities greatly influenced clinical presentation, therapies received and the outcome of patients admitted with ACS. Heart failure, diabetes, renal disease or metastatic tumors had a major impact on mortality. CCI seems to be an appropriate prognostic indicator for in-hospital and 1-year outcomes in ACS patients.

Land

Switzerland

År data innsamling

2002 - 2012

Materiale og metode

A prospective multi center observational study (AMIS Plus Registry) from 69 Swiss hospitals with 29 620 ACS patients enrolled from jan 2002 to sept 2012. ACS included acute MI, by characteristic symptoms and/or ECG changes and cardiac marker elevation (CKMB, Troponin I or T) and unstable angina. Categorical variables presented as percentages, continuous variables as mean +/-1SD. The main outcome measures were in-hospital and 1-year follow-up mortality.

Predictive properties of CCI were evaluated in three ways. 1) form a benchmark using logistic regression model with in-hospital mortality as a dependent variable, and CCI, age, gender as independent variables, 2) using a receiver operating characteristic (ROC) curve to assess discriminating ability of CCI alone or together with age in relation to the benchmark above, 3) CCI analyzed by comparing predicted and observed in-hospital and follow-up mortality in a logistic regression with CCI and age as predictors. To assess CCI as an independent predictor of in-hospital mortality, additional multivariate logistic regression analysis including more clinical and treatment variables was performed. SPSS V20 used for analysis.

Resultater

The frequency of the comorbidities in the study population is shown in table 1. The comorbidities remained unknown for 1091 (3,6%) of the patients. Of the eligible 29.620 patients, 27% were female (age 72.1 +/- 12.6 years) and 73% were male (64.2 +/- 12.9 years). 46.8% had comorbidities and they were less likely to receive guideline-recommended drug therapy and reperfusion.

Heart failure (adjusted OR 1.88; 95% CI 1.57 to 2.25), metastatic tumours (OR 2.25; 95% CI 1.60 to 3.19), renal diseases (OR 1.84; 95% CI 1.60 to 2.11) and diabetes (OR 1.35; 95% CI 1.19 to 1.54) were strong predictors of in-hospital mortality.

In this population, CCI weighted the history of prior myocardial infarction higher (1 instead of -0.4, 95% CI -1.2 to 0.3 points) but heart failure (1 instead of 3.7, 95% CI 2.6 to 4.7) and renal disease (2 instead of 3.5, 95% CI 2.7 to 4.4) lower than the benchmark, where all comorbidities, age and gender were used as predictors. However, the model with CCI and age has an identical discrimination to this benchmark (areas under the receiver operating characteristic curves were both 0.76).

CCI groups above zero were independent predictors of in-hospital mortality even after adjustment for the type of ACS and therapy received. In-hospital as well as 1-year follow-up mortality rose with increasing CCI scores.

Table 1 Frequency of the comorbidities in patients hospitalised with acute coronary syndrome between 2002 and 2012 (n=29 620)

Comorbidities	Number of patients	Percentage of population
Past history of myocardial infarction	5324	18.0
Heart failure	1075	3.6
Peripheral vascular disease	1591	5.4
Cerebrovascular disease	1776	6.0
Dementia	582	2.0
Chronic lung disease	1778	6.0
Connective tissue disease	361	1.2
Peptic ulcer disease	665	2.2
Mild liver disease	227	0.8
Diabetes	4359	14.7
Diabetes with target organ damage	1069	3.6
Hemiplegia	210	0.7
Moderate to severe renal disease	2101	7.1
Malignant neoplasm	1269	4.3
Leukaemia	92	0.3
Lymphoma	139	0.5
Moderate to severe liver disease	170	0.6
Metastatic solid tumour	268	0.9
AIDS (stage C)	47	0.2

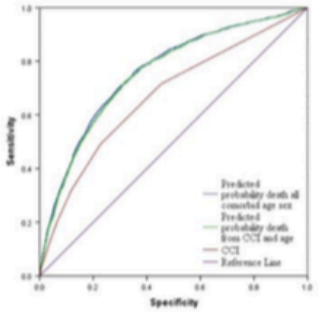


Figure 1 Receiver operating characteristic curve compared the discriminating ability of the Charlson Comorbidity Index (CCI) for predicting mortality if CCI was used alone (area=0.670; 95% CI 0.656 to 0.685), using CCI with age (area=0.756; 95% CI 0.743 to 0.768) and using all comorbidities, age and sex (area=0.761; 95% CI 0.748 to 0.773).

Diskusjon/kommentarer

Er formålet med studien klart formulert? ja

Ble utvalget fordelt til de ulike gruppene med randomiseringsprosedyre? Ikke relevant. Grupperingen er retrospektivt prospektiv, og vurderer utfall utfra CCI.

Ble alle deltakerne gjort rede for på slutten av studien? Ja

Ble deltakere/studiepersonell blindet mht gruppetilhørighet? Ja – oppgitt etter beste evne, som nevnt over var gruppering kun på CCI, og det sies i artikkelen at blinding ble forsøkt på alle sentre ved inkludering for å sikre materialets senere nytteverdi som forstadium til RCT-er.

Var gruppene like ved starten? Stor overvekt av menn, og totalt litt over halvparten hadde ikke komorbiditeter.

Ble gruppene behandlet likt? Studien viste at de med høyrer CCI fikk andre terapivalg

Hva er resultatene? Kan resultatene overføres til praksis. Ja, bekrefter at CCI kan brukes for å vurdere komorbiditet i AKS-populasjon, og bevissthet om å ikke ha bias i behandlingsvalg.

Ble alle utfallsmål vurdert? Ja **Er fordelene verdt ulemper/kostnader?** nei

Hva diskuterer forfatterne som.

Styrke: Ved utgivelse, den største multisenter studien som fokuserte på viktigheten av kronisk komorbiditet blant pasienter som legges inn med AKS. Ser ikke bare på 1-år mortalitet, men også CCI og behandlingskonsekvens. CCI nyttig både for in-hospital mortalitet, og 1-år mortalitet for ACS.

Svakhet: 1) frivillig deltakelse i AMIS Plus, så ikke alle sykehusene er med i hele perioden (selv om 70% faktisk er det). 2) ingen uavhengig vurdering av komorbiditetene, 3) andre akutte ikke-kroniske tilstander kan også komme samtidig med AKS og på virke resultatet (pneumoni, GI-blødning, slag, sepsis)

Viser forfatterne til annen litteratur som styrker/svekker resultatene? Ja

Har resultatene plausible biologiske forklaringer? Ja

GRADE 4: Reference: Nilssen Y, Strand T-E, Wiik R, Bakken IJ, Yu XQ, O'Connell DL, et al. Utilizing national patient-register data to control for comorbidity in prognostic studies. Clinical epidemiology. 2014;6:395-404.

Design: Kohortstudie	
Documentation level	IIb
GRADE	B

Objective

To construct an updated comorbidity index (Patient Register Index [PRI]) using national data collections from Norway and compare its predictive ability of 1-year mortality with the Charlson Comorbidity Index (CCI).

Conclusion

Adjustment for comorbidity is especially important for patients 50 years of age or older, and its effect on 1-year mortality is almost comparable to the age effect. The PRI is based on more recent data than the CCI, and is more representative of the general population due to its construction. Weighing CCI for a specific population slightly improves the performance of CCI.

Country

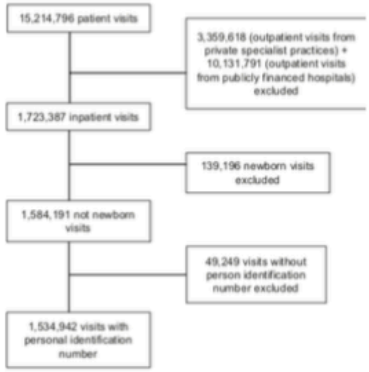
Norway

Year data collection

2010-2011

Material and methods

Data regarding over 1.11 million patients registered in the Norwegian Patient Register in 2010 and 2011 were used to construct the PRI. The PRI was evaluated by comparing its model fit and discrimination with the CCI. The NPR data consists of three main data sources for statistics: visits for medical treatment for in- and outpatients at publicly financed hospitals, and private hospitals and private specialist practices selling medical treatment services to the public hospitals. Does not include data on privately financed hospital treatments. To provide the total disease history of the patient, the personal identification number was used to link episodes of treatment registered at different hospitals, sectors and years. (See flow-chart.) Index visit was counted as the patients first visit; end of follow up date of death if dead within the first year of the index visit, or the date 1 year after the index visit. To register the diagnosis, Nilssen et al uses the ICD-10 coding applied by similar studies(1). To predict 1-y mortality, three logistic regression models were fitted, the base model, and two other models with CCI or PRI. The model fit was compared with several different measures. A sub analysis was performed on a test group of patients with and without each of the variables age, sex, and a comorbidity model.



igure 1 Flowchart shows the included and excluded patients in the stu opulation.

Results

Compared with the CCI, the PRI weights decreased for six, increased for four, and were unchanged for seven diseases. When the PRI was added to the model including age and sex, the age effects were reduced by up to 38% for patients older than 50 years. All measures of model fit improved for the PRI model.

The majority (57%) were female. For 68% the index visit was a hospitalization (in-patient). Twenty two percent of the patients were registered with at least one CCI disease. Below 50 years of age, the proportion was less than 3%. For age above 50, it increased with age, and more so for men. The five most common CCI diseases for men and women were MI, CVD, CPD, DM without chronic complications, malignancies. Overall proportion of deceased patients within 1 year: 4,8% (52,938 patients). Risk of death (1 year) was significantly higher for patients with at least one CCI disease compared to those with none (HR 4,5, CI 4.4-4.6). Table 1 sums up the proportions of comorbid diseases, and the calculations of CCI and PRI weights. The weights for four diseases was higher in PRI than in CCI (CHF, Dementia, LD mild and mod/severe). It was lower for six diseases (rheuma, DM +/- compl, Hemi/paraplegia, renal disease, AIDS/HIV). The PRI was marginally better than CCI in predicting one year mortality. Both were outstanding given C-statistics. Base model (sex age) had 0,869, while adding CCI and PRI respectively gave C-statistics 0,913 and 0,915. Max observed CCI and PRI values among patients were 12 and 15. Overall mean CCI was approximately equal to the mean PRI (0.43 vs 0.42).

Comorbidity	Number of patients	Proportion with comorbidity (%)	Number dead	Proportion dead (%)	HR	95% CI	CCI	PRI
No	861,553	77.4	12,296	1.4	1.0	–	0	0
Yes	251,788	22.6	40,642	16.1	4.46	4.36–4.55	>0	>0
Total	1,113,341	100.0	52,938	4.8				
Type of comorbidity								
No clvr dis	861,553	77.4	12,296	1.4	1.0	–	0	0
Myocardial infarction	44,034	4.0	7,741	17.6	1.25	1.22–1.28	1	1
Congestive heart failure	32,408	2.9	9,745	30.1	2.07	2.02–2.12	1	2
Peripheral vascular dis	18,459	1.7	3,253	17.6	1.36	1.31–1.41	1	1
Cerebrovascular dis	42,425	3.8	7,446	17.6	1.56	1.52–1.60	1	1
Dementia	15,225	1.4	5,391	35.4	2.34	2.27–2.41	1	2
Chronic pulmonary dis	54,410	4.9	7,769	14.3	1.65	1.60–1.69	1	1
Rheumatic dis	14,110	1.3	1,261	8.9	1.03	0.97–1.09	1	0
Peptic ulcer dis	5,408	0.5	931	17.2	1.45	1.36–1.55	1	1
Mild liver dis	6,007	0.5	496	8.3	2.72	2.49–2.98	1	2
Diabetes without clvr compl	38,237	3.4	4,654	12.2	1.20	1.17–1.24	1	0
Diabetes with clvr compl	8,558	0.8	1,421	16.6	1.44	1.36–1.51	2	1
Hemiplegia or paraplegia	3,265	0.3	224	6.9	1.60	1.40–1.83	2	1
Renal dis	3,905	0.4	536	13.7	1.67	1.54–1.81	2	1
Any malignancy	42,667	3.8	7,564	17.7	2.94	2.86–3.01	2	2
Mod or severe liver dis	1,184	0.1	390	32.9	7.47	6.67–8.27	3	5
Metastatic solid tumor	14,917	1.3	7,777	52.1	13.80	13.46–14.15	6	6
AIDS/HIV	536	0.05	31	5.8	3.61	2.53–5.14	6	3

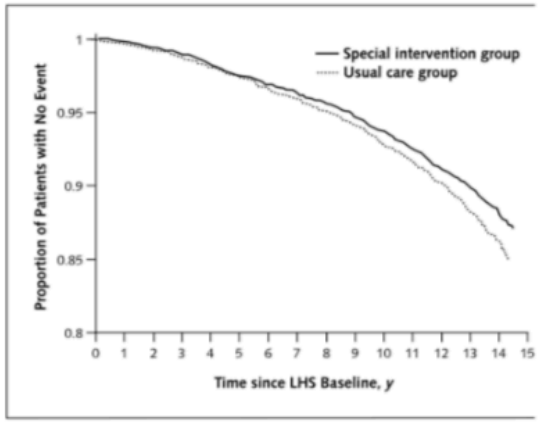
Notes: Hazard ratios (HRs) for 1-year mortality, and 95% confidence intervals (CIs), adjusted for age and sex, together with weights for both the CCI and Patient Register Index (PRI), are shown.
Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; dis, disease; clvr, chronic compl, complications; mod, moderate.

Discussion / comments

Studiens **formål** er klart formulert. Det er en registerstudie, og det ble tatt høyde for mulig **bias** mhp offentlig vs privat finansiering. Bias mtp spesialisthelsetjeneste vs pas som hovedsakelig er i primærhelsetjeneste ble også tatt høyde for.
Ble alle deltakerne gjort rede for på slutten av studien? Ja. Ble deltakere/studiepersonell **blindet** mht gruppetilhørighet? Ikke relevant.
Var guppene like ved starten? Majoriteten kvinner. Ellers inneholdt materialet alle relevante i NPR, og må så sies å være representativt.
Ble gruppene behandlet likt? Ikke relevant
Hva er resultatene? En nasjonalt tilpasset komorbiditetsindeks presterer marginalt bedre enn den generelle CCI. **Kan resultatene overføres til praksis**. Ja, bekrefter at CCI kan brukes for å vurdere komorbiditet, og at PRI kan gjøre dette enda bedre i norsk setting.
Ble alle utfallsmål vurdert? Ja **Er fordelene verdt ulemper/kostnader?** Ikke relevant
Hva diskuterer forfatterne som.
Styrke: 1-year follow up, mortalitet også utenfor sykehus, stort pasientgrunnlag fra NPR.
Svakhet: ikke validert vha eksterne data. Pasienter med kun poliklinisk visitt og medisinske prosedyrer/ingen prosedyrer ble ekskludert. Risiko for underrapport av enkelte diagnoser. **Viser forfatterne til annen litteratur som styrker/svekker resultatene?** Ja. **Har resultatene plausible biologiske forklaringer?** Ja

GRADE 5: Referanse: Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Annals of internal medicine. 2005;142(4):233-9.

Design: RCT	
Dokumentasjonsnivå	Ib
GRADE	A

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Assess the long-term effect on mortality of a randomly applied smoking cessation program. More particularly the report assesses the effects of the study intervention on mortality in the sample population 14.5 years after randomization. **Konklusjon** *Intensive smoking cessation program followed by 5 years of reinforcement leads to a substantial and significant reduction in all-cause mortality in people with mild to moderate airway obstruction.* **Land** **USA** **År data innsamling** 1993-31.12.2001	The Lung Health Study (LHS) was a randomized clinical trial of smoking cessation. Special intervention patients were compared to usual care patients. Special intervention patients were again divided into one group receiving bronchodilator, and another placebo inhaler. **In 10 clinical centers, 5887 participants were randomly assigned to the three groups.** Population was also subdivided into sustained quitters, continuing smokers, and intermittent quitters. The participants were all volunteers, smokers, who did not consider themselves ill but had evidence of airway obstruction and little evidence of other disease. Exclusion of patients with serious disease, hypertension, obesity, or excessive alcohol intake. At baseline the LHS participants were mostly middle aged, smoked heavily, had substantial smoking histories, and airway obstruction (FEV1/FVC-ratio <=0,7)and borderline low FEV1. The special intervention and usual care group did not differ significantly at baseline (except marital status). ***Intervention*** was strong physician message and 12 two hour group sessions, using behavior modification and nicotine gum. Quitters entered a maintenance program that stressed coping skills.	At 5 years, 21,7% of special intervention patients had stopped smoking since entry compared to 5,4% of usual care participants. After up to 14,5 years of follow up 731 patients died, 33% of lung cancer, 22% of cardiovascular disease, 7,8% of respiratory disease other than cancer, and 2,4% of unknown causes. All-cause mortality was significantly lower in the special intervention group. Compared to the usual care group: 8,8 per 1000 person-years vs 10,38 per 1000 person-years; p= 0,03**. Hazard radio for mortality in the usual care group compared to the special intervention group was 1,18 (95% CI, 1,02 to 1,37).** The all-cause mortality was significant comparing intervention vs usual care group for the youngest quartile of participants <45 years at baseline. Within the three subgroups of smokers-status there was no difference between intervention vs usual care groups – however there was a significant mortality difference between the usual care and special intervention group among participants smoking >40 cigarettes per day (HR 1.3, p=0.03). The significant results for the intervention group is attributed to the higher rates of smoker cessation. Smoking status established at 5 years changed relatively little in the next 6 years, especially amongst sustained quitters. *Figure 1.* **All-cause 14.5-year survival.**  461 of 3923 patients died in the special intervention group vs. 270 of 1964 patients in the usual care group ($P = 0.031$, log-rank test). LHS = Lung Health Study.	**Er formålet med studien klart formulert?** ja **Ble utvalget fordelt til de ulike gruppene med randomiseringsprosedyre?** Ja – beskrevet i egen artikkel **Ble alle deltakerne gjort rede for på slutten av studien?** Ja. **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** Ja – telefonoppfølging uten kjennskap til gruppetilhørighet. **Var guppene like ved starten?** Ja, med unntak av sivilstatus. Flere gift i intervensjonsgruppa p=0,04. **Ble gruppene behandlet likt?** Ja, med unntak av intervensjonen, fikk alle pas det grunnleggende tilbudet. **Hva er resultatene?** Main implication: Smoking cessation programs substantially reduce mortality even when only a minority of patients stop smoking. **Kan resultatene overføres til praksis**. ja **Ble alle utfallsmål vurdert?** ja **Er fordelene verdt ulemper/kostnader?** ja **Hva diskuterer forfatterne som.** **Styrke** Results comparable to similar studies, though no studies have (at this time) examined long term effects of randomly applied smoking cessation. **Svakhet:** Cannot contribute to why FEV1 independent of smoking habits can predict coronary artery disease and lung cancer. cannot argue that women are more sensitive to cigarette smoke than men. **Viser forfatterne til annen litteratur som styrker/svekker resultatene?** Ja **Har resultatene plausible biologiske forklaringer?** Ja