FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Intensive care at the end-of-life in patients dying of cancer and non-cancer chronic diseases: A nationwide study

Research year report

Thomas Lyngaa

Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Supervisors and collaborators

Søren Paaske Johnsen, MD, PhD, Clinical associate professor (main supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Christian Fynbo Christiansen, MD, PhD, Clinical associate professor (co-supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Henrik Nielsen, MSc (collaborator)
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Mette Asbjørn Neergaard, MD, PhD (collaborator)
The Palliative Team, Department of Oncology
Aarhus University Hospital, Denmark

Ander Bonde Jensen, MD, PhD, Professor (collaborator)
Department of Oncology
Aarhus University Hospital, Denmark

Kristina Grønborg Laut, MSc, PhD (collaborator)
Division of Epidemiology & Biostatistics
University of Leeds, United Kingdom

Preface

The present report is based on a study conducted during my research year at the Department of Clinical Epidemiology at Aarhus University Hospital, Denmark.

I am profoundly thankful to my main supervisor Søren Paaske Johnsen for allowing me the opportunity carry out this study and for introducing me to the world of clinical epidemiology.

To my supervisor, Christian Fynbo Christiansen, I am sincerely grateful for the many read-throughs, commenting and editing and for always keeping your door open, having time to explain, guide the process of the study along, and keeping the spirits high.

Thank you to Henrik Nielsen for untiringly answering statistical questions and providing revised data. Also thank you to the other members of the study group, for constructively commenting and revising the manuscript. Thank you to all the colleagues at DCE who have been helpful and smiling no matter the questions. And a special thank you to the flying spots for never failing to pick up a chat.

Finally I would like to thank my family, Happy and Vitus, for their endless support and reminder of what is truly important. I am looking forward to extending our family with another tiny member this summer.

Thomas Lyngaa, 2015

Funding

This study was supported by grants from:
The foundation of 17-12-1981
The Danish Heart Foundation
The Clinical Epidemiology Research Foundation

Abbreviations

aPR	Adjusted prevalence ratio
CCI	Charlson Comorbidity Index
CeVD	Cerebrovascular disease
CI	Confidence interval
CLF	Chronic liver failure
COPD	Chronic obstructive pulmonary disease
DID	Danish Intensive care Database
EOL	End-of-life
ICD-10	International Classification of Diseases, 10th. Revision
ICU	Intensive care unit
IHD	Ischemic heart disease
jPR	Justeret prævalens ratio
HF	Heart failure
NIV	Non-invasive mechanical ventilation
PR	Prevalence ratio
RRT	Renal replacement therapy
SI	Sikkerhedsinterval
US	United States of America

Contents

Abstract

Background: Patients with severe chronic diseases are often admitted to an intensive care unit (ICU) at the end-of-life (EOL). Many end their life lives in ICUs, although a clear majority of patients prefer to die at home. Palliative care has improved for cancer patients in recent years. This is largely a result of educating medical specialists and using multidisciplinary teams to create and implement individually structured care plans for terminally ill patients. It is not known to what extent the use of specialised palliative care, and focus on proactive planning of EOL care among cancer patients is also reflected by a lower use of intensive care. We aimed to examine the use of intensive care during ICU admission in patients dying of non-cancer diseases compared with patients dying of cancer.

Methods: A nationwide historical cross-sectional study was performed among 240,757 adults dying of either non-cancer chronic disease or cancer in Denmark between 2005-2011. Using the Danish Intensive Care Database, we identified all admissions and treatments in ICUs the last six months before death. We used adjusted prevalence ratios (aPR) estimated by binomial regression to compare six months prevalence of ICU admissions, treatment with invasive mechanical ventilation, non-invasive ventilation (NIV), renal replacement therapy (RRT), and inotropes/vasopressors. In addition, length of ICU stay and death during ICU admission was compared among non-cancer and cancer patients dying between 2009-2011.

Results: Overall 12.3% of non-cancer patients were admitted to an ICU within their last six months compared with 8.7% of the cancer patients. The overall aPR for ICU admission was 2.11 (95%CI: 1.98-2.24) for non-cancer compared with cancer patients and varied highly within the non-cancer patients; from an aPR of 0.19 (95%CI: 0.17-0.21) for patients with dementia to an aPR of 3.19 (95%CI: 2.97-3.41) for patients with COPD. Overall aPR for treatment among non-cancer patients compared to cancer patients was 1.40 (95% CI: 1.35-1.46) for mechanical ventilation, 1.62 (95% CI: 1.50-1.76) for NIV, 1.19 (95% CI: 1.07-1.31) for RRT, and 1.05 (95% CI: 0.87-1.28) for inotropes/vasopressors. The overall median admission length per admission was 29.5 hours for the non-cancer patients (interquartile range (IQR): 10.1-87.6) and 29.7 hours (IQR: 13.2-94.5) for cancer patients. Non-cancer patients had a borderline statistical significantly increased risk of dying in an ICU, i.e., aPR 1.23 (95%CI: 0.99-1.54), compared to cancer patients.

Conclusion: Patients dying of non-cancer diseases were twice as likely to be admitted to an ICU at EOL compared to patients dying of cancer. Further studies are studies are warranted in order to explore whether this difference in use of intensive care reflects an unmet need of specialised palliative care among terminal ill non-cancer patients.

Dansk resumé

Baggrund: Behandling på intensiv afdeling er ofte en del af den sidste tid før døden for patienter med alvorlige kroniske sygdomme. Mange dør på intensive afdeling trods et ønske om at dø i eget hjem. Den specialiserede palliative indsats er blevet udbygget i de seneste år, men primært for patienter med cancer. Der har særligt været fokus på uddannelse af sundhedsfagligt personale samt etablering af tværfaglige teams med henblik på at udarbejde og implementere individuelle planer for den palliative indsats i den sidste del af livet. Det er uvist i hvilket omfang den øgede fokus på det palliative behov hos patienter med cancer afspejler sig i et mindre behov for intensiv pleje og behandling. I det aktuelle studie blev brugen af intensiv behandling sammenlignet hos patienter der døde af henholdsvis non-cancer kronisk sygdom og patienter der døde af cancer.

Metode*:* Landsdækkende historisk tværsnitsstudie i Danmark af 250.757 voksne, der døde enten af non-cancer kronisk sygdom eller cancer i perioden 2005-2011. Gennem Dansk Intensiv Database identificerede vi alle indlæggelser samt behandling på intensiv afdelinger de sidste seks måneder før døden. Der blev brugt binomial regression til at beregne justerede prævalens ratioer (jPR) med henblik på at sammenligne periodeprævalensen af intensiv indlæggelse, respiratorbehandling, non-invasiv mekanisk ventilation (NIV), dialyse og inotropi-/vasopressor behandling. Endvidere blev indlæggelsestid og død under intensiv indlæggelse undersøgt blandt patienter, som døde i perioden 2009-2011.

Resultater: Blandt non-cancer patienterne blev 12,3% indlagt på en intensiv afdeling i deres sidste seks måneder, sammenlignet med 8,7% af cancer patienterne. jPR for intensiv indlæggelse var 2,11 (95%SI: 1,98-2,24) for non-cancer sammenlignet med cancer patienter. Der var stor variation i blandt non-cancer patienterne, idet den jPR var henholdsvis 0,19 (95% SI: 0,17-0,21) for patienter med demens og 3,19 (95%SI: 2,97-3,41) for patienter med kronisk obstruktiv lungesygdom. Den mest udtalte forskel på intensiv indlæggelse, for begge køn, fandtes i aldersgruppen 50-59 år (jPR kvinder = 3,77 95% SI: 3,36-4,22)(jPR mænd = 2,14 95% SI: 2,02-2,21). jPR for behandling blandt non-cancer patienter var 1,40 (95% SI: 1,35-1,46) for respirator; 1,62 (95% SI: 1,50-1,76) for NIV; 1,19 (95% SI: 1,07-1,31) for dialyse og 1,05 (95% SI: 0,87-1,28) for inotropi/vasopressorer. Den mediane indlæggelsestid på intensivafdeling per indlæggelse var 29,5 timer for non-cancer patienterne (interkvartilbredde (IKB): 10,1-87,6) og 29,7 timer (IKB: 13,2-94,5) for cancer patienter. Non-cancer patienterne døde oftere på intensiv afdeling sammenlignet med cancer patienter (jPR 1,23, 95%CI: 0,99-1,54).

Konklusion: Patienter der døde af non-cancer sygdomme havde dobbelt så stor risiko for at blive indlagt på en intensiv afdeling i den sidste del af livet, sammenlignet med patienter der døde af cancer.

Extract

Introduction

Chronic disease remains the dominant cause of death globally, with cancer being the leading,[1] followed by heart disease, cerebrovascular disease, and lung disease.[2] Patients with chronic disease require increased care, including intensive care, at the end-of-life (EOL),[3] defined as the last six months before death. Ageing populations are causing a higher prevalence of chronic diseases[4] and increased spending on EOL care in the coming years is therefore expected. More than a quarter of all health care funds are already being spent during the last year of the patients´ life.[5] In the US, the majority (>80%) of these are used for intensive care.[6]

Recent years have seen an increase in palliative treatment, particularly for cancer patients.[7] However, studies have found that patients with heart failure experience a similar burden of symptoms as patients suffering from advanced cancer,[8] and patients suffering from chronic disease obstructive pulmonary disease (COPD) receive less palliative care at the EOL, despite comparable symptoms, than patients with lung cancer,[9] and were more likely to die in a hospital setting compared to cancer patients.[10]

Intensive care may constitute a substantial emotional and physiological burden for both patient and relatives.[15] Deciding who should be admitted to an intensive care unit (ICU) remains a difficult task; however there is widely accepted consensus that there must be a considerable prospect of recovery.[16] Meanwhile, ensuring relevant, high quality care that meets patients' and relatives' expectations at all stages of illness, in a healthcare system with limited resources, is a major challenge.[5] Timely recognition of a non-curative disease stage and open discussions about prognosis and preferences could likely ease this task.[17,18] Existing research on the use of intensive care during EOL have focused on few diagnoses,[9] variation over time,[10] or not actually compared the differences they found;[3,6] leaving a requirement for more data on variation of use of intensive care to provide better understanding and support clinicians in rational use of intensive care in patients with cancer and other chronic diseases.

The differences in care patterns between non-cancer and cancer patients at the EOL are of particular interest, since increased level of care does not seem to be associated with a better survival, higher functional status, greater quality of life[19,20] or to be aligned with patients' preferences for treatment and place of death, leaving many without the care they wish for in their final months of life.[13,14]

The nationwide clinical databases and population-based medical registries in Denmark provide a unique opportunity to investigate the use of intensive care at the EOL in a setting with universal access to healthcare. Hence, we examined utilization of intensive care and death in ICU at the end-of-life comparing patients who died of non-cancer chronic diseases and cancer, respectively.

Materials and methods

Study design and setting

We conducted this nationwide historical cross-sectional registry study in Denmark, a country with a population of approximately 5.6 million inhabitants. The tax supported Danish health care system provides equal, universal access to hospital care, including intensive care, for all citizens. The study area is mixed urban-rural and encompasses 49 ICUs (2011). Unambiguous individual-level linkage between population-based registries was performed using the unique civil registration number assigned to each Danish citizen at birth and to residents on immigration.[21]

Study population

The Danish Registry of Causes of Death was used to identify the underlying cause of death for all decedents older than the age of 18 years, between January 1st 2005 and December 31st 2011. The Danish Registry of Causes of Death contains data on all decedents since 1970, and data entry is mandatory by law. Data include among others civil registration number, date of death, manner of death, and cause of death, both immediate and underlying, coded according to the Danish version of the International Classification of Diseases (currently 10th edition, ICD-10).[22] We grouped the underlying causes of death into two groups: cancer (cancer patients) or non-cancer patients (diabetes, dementia, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD) and chronic liver disease) (Appendix 1). These eight causes of death were the most common in Denmark in 2005-2011.[23] The remaining causes of death were grouped as "other" and comprised 144,010 individuals (37.4%) that were excluded from the analyses. Likewise, 48 patients (<0.1%) with missing information on residence were excluded.

Intensive care

Data on ICU admission within the last six months before death was identified through the Danish Intensive Care Database (DID). The DID is a clinical database established for nationwide quality monitoring and holds data from 2005 and onwards on patients admitted to any ICU in Denmark. Data

entry is mandatory by law. The positive predictive value of admission data in DID has been found to be between 87.2% and 98.7%.[24,25] Data include, among others, information on admission date, discharge status including death in an ICU, invasive mechanical ventilation (MV), non-invasive ventilation (NIV), inotrope/vasopressor therapy, and renal replacement therapy (RRT).[26]

Comorbidity

We obtained data on comorbid conditions using diagnoses from hospital admissions and outpatient clinical visits recorded in the Danish National Registry of Patients in up to ten years preceding death. We assessed comorbidity level by means of the Charlson Comorbidity Index (CCI).[27] This scoring system assigns between 1 and 6 points to 19 conditions. The standard CCI was calculated from the sum of weights for the 19 diseases (Appendix 2). We further modified the CCI by deducting points for the underlying cause of death and then calculated modified scores summing the weights for the other comorbid condition (Appendix 3). This was done to avoid including diseases into the analyses as both comorbid conditions and cause of death. Patients with a modified CCI score of ≥1 were categorised as "any comorbidity" while patients with a modified CCI of 0 were categorised as "no comorbidity".

Statistical analyses

Period prevalence of admission to ICU within six months before death for patients dying of non-cancer chronic diseases and for patients dying of cancer was calculated and compared by adjusted prevalence ratios (aPR) which were estimated using multivariable binomial regression adjusted for age, gender, comorbidity, and marital status. In all adjusted analyses we accounted for potential clustering by residential region. We repeated the analyses stratified by age groups and gender. Next, we calculated the prevalence proportions of patients treated with invasive mechanical ventilation, NIV, RRT, and inotropes/vasopressors among patients admitted to an ICU within the last six months before death. Analyses were stratified according to age and gender. Aggressiveness of treatment was defined as either "Full organ supportive treatment" (i.e. the patient had been treated with all of the aforementioned treatment modalities) or as "Partial organ supportive treatment" (i.e. the patient had been treated with three or less of the four assessed treatment modalities) (Appendix 4).
We calculated the median length of ICU stay along with the interquartile range. Due to availability of data in the DID, we restricted this analysis to the years 2009-2011.

Finally we calculated the proportion of deaths occurring in an ICU. This analysis was also restricted to the years 2009-2011 due to availability of these data from the DID. The proportion of deaths in ICUs

were compared for the non-cancer and the cancer patients using multivariable binomial regression adjusted for age, gender, any comorbidity, and marital status.

All statistical analyses were performed using Stata software (StataIC version 13.1: ©StataCorp LP, College Station, TX). The study was approved by the Danish Data Protection Agency (record no. 2009-41-3987 and 2014-41-3658).

Results

Descriptive data

We included a total of 240,757 adult decedents during the 7-year study period (Figure 1). Among these 134,298 (55.8%) died of the included non-cancer diseases and 106,459 (44.2%) died of cancer. The median age was 82 years for non-cancer patients and 74 years for cancer patients. Women comprised 52.6% of the non-cancer group compared to 48.7% of the cancer group (Table 1).

ICU admission

Within the last six months before death, 25,796 (10.7%) of all patients were admitted to an ICU (Table 1), including 12.3% of the non-cancer patients and 8.7% of the cancer patients. The overall aPR for admission to an ICU, during the last six months before death, was 2.11 (95% CI: 1.98-2.24) in patients dying of non-cancer disease compared to cancer. Compared to cancer patients, those dying of COPD were more likely to be admitted to an ICU during EOL (aPR 3.19 (95% CI: 2.97-3.41)), while patients dying of dementia were less likely to admitted to an ICU (aPR 0.19 (95% CI: 0.17-0.21)) (Table 2). Figure 2 shows the prevalence of ICU admission by age groups and gender. For both genders, the highest aPRs were found for the age group 50-59 years ((aPR women 3.77, (95% CI: 3.36-4.22), (aPR men 2.14, (95% CI: 2.02-2.27), when comparing non-cancer versus cancer patients). The difference between non-cancer and cancer patients progressively declined with age for both genders, with the 90+ years group presenting the lowest aPR estimates (aPR women 0.60 (95%CI: 0.50-0.73) and men 0.85 (95%CI: 0.65-1.11)) (Figure 2).

ICU treatment

Table 3 displays the use of ICU specific treatment modalities. Overall these were more often used in non-cancer patients compared with cancer patients. Of the non-cancer patients 55.6% received mechanical ventilation versus 42.2% of the cancer patients, corresponding to an aPR 1.40 (95% CI: 1.35-1.46). NIV treatment was given to 27.3% of the non-cancer patients and 16.4% of the cancer

patients resulting in an aPR of 1.62 (95% CI: 1.50-1.76) for NIV, ranging from 0.51 (95% CI: 0.45-0.58) for patients dying of dementia to 3.40 (95% CI: 3.00-3.85) for patients dying of COPD. Treatment with inotropes or vasopressors was used in 44.3% of the non-cancer patients and 38.9% of the cancer patients resulting in an overall aPR of 1.19 (95% CI: 1.07-1.31), whereas no difference in use of RRT was observed (aPR 1.05 (95% CI: 0.87-1.28)). No patients with dementia were treated with RRT, whereas the highest aPR was found among patients dying of diabetes (aPR 2.27, 95% CI: 1.91-2.69) (Table 3).

When looking at the combination of treatments (Appendix 4), we found that the proportion receiving full organ supportive treatment was 6.9% among the non-cancer patients and 7.5% among the cancer patients. No difference between non-cancer patients and cancer patients was observed after controlling for potential confounding (overall aPR = 1.02 (95% CI: 0.82-1.27). However, no patients dying of dementia received full organ supportive treatment and the highest aPR was found among patients dying of diabetes (aPR = 1.98 (95% CI: 1.60-2.44)) (Table 3).

Length of ICU stay

The overall median length of stay per ICU admission within the last six months before death was 29.5 hours for the non-cancer patients (interquartile range (IQR): 10.1-87.6). For cancer patients, the corresponding number was 29.7 hours (IQR: 13.2-94.5). (Table 4)

ICU death

The overall proportion of patients dying during ICU admission was 35.5% among non-cancer patients and 29.2% for cancer patients. We found an overall increased risk of dying during ICU admission for non-cancer in comparison with cancer patients (aPR 1.23, 95%CI: 0.99-1.54) (Data not shown).

Discussion

In this nationwide study, we found considerably higher utilization of ICU admission at the end-of-life among patients dying of non-cancer chronic diseases as compared to patients dying of cancer. In comparison with patients dying of cancer, patients with dementia as the underlying cause of death were unlikely to be admitted to the ICUs and received less treatment while the opposite was the case for patients dying of COPD and diabetes. While there was no overall difference in prevalence of full organ supportive treatment between non-cancer and cancer patients, patients dying of diabetes and heart diseases received full organ supportive treatment almost two times more often than cancer patients.

The finding of our study was supported by an American study[9] comparing the health care resource utilization of 1,490 patients from the Veteran Affairs medical centres with COPD to 459 patients with lung cancer. The authors found that COPD patients were twice as likely to be admitted to an ICU in the last six months before death compared to those with lung cancer. In our study we found that patients dying of COPD are three times more often admission to an ICU compared to all patients dying of cancer. While the study population in the American study was predominantly elderly white men, our study included both men and women. The difference in case-mix between the American study and our study could likely explain the higher admission rate found in our study, as our findings suggest that the admission rate among men were lower than it was among women.

No previous studies have to our knowledge directly compared the risk of death in ICU for non-cancer patients compared to cancer patients. One American study, however, measured terminal admissions associated with intensive care among non-federal hospitals in six states, as a measure of death during ICU admission.[6] In our study we were able to assess the prevalence of deaths occurring during ICU admission among all patients dying of non-cancer diseases and compare it to the prevalence of ICU deaths among all patients dying of cancer. When adjusting for other causes we found that patients dying of non-cancer diseases are 23% more likely to die in ICU compared to cancer patients. Bearing in mind that only about half of cancer patients have their wish fulfilled regarding place of death[14], this adds to the necessity for a better understanding of the large variation in care patterns between non-cancer patients and cancer patients at the EOL.

Consistent with the discussed studies, we find remarkable variation in health care at the EOL, indicating that triage might be diagnose-based and less likely to be driven by symptoms and prognosis, thus questioning whether treatment is aligned with patients' wishes.

A number of limitations should be taken into consideration when interpreting our results. We included all adult decedents that died of the eight specified chronic diseases during the study period. Cause of death was determined as underlying cause of death from the Danish registry of Causes of Death. The Danish Registry of Causes of Death is practically complete.[22] We based our analyses on the underlying cause of death of well-defined chronic diseases. However, determining the cause of death, both underlying and immediate, can be difficult. Validation of the registry of causes of death has only been validated for some diseases,[28] leaving some uncertainty about classification of the causes of death.

This could introduce misclassification of the non-differentiated type into the study, which would bias the results towards the null association.
In this study we aimed to control for the confounding by adjusting for a range of known potential confounders, however, unmeasured confounding cannot be ruled out. Of the variables we included in our study the ones affecting the estimates most were age, gender, and marital status.

In the large consensus statement, the ELDICUS project,[16] a wide array of intensive care experts generally agreed on a range of principles regarding the triage of intensive care patients. One of these was; that there must be a considerable prospect of recovery for the patient. If symptoms experienced by non-cancer patients are similar or worse than symptoms experienced by cancer patients,[8,9,29] then treatment should only display little variation. However, difficulties in predicting trajectories for non-cancer chronic diseases are offered as an explanation of the existence of differences in treatment.[11,17,18] This difficulty is also reflected in the reduced tendency to recognise these patients as terminal.[12] We can only speculate about the observed differences in use of intensive care during EOL, nonetheless, the difference in ICU utilization between non-cancer and cancer patients found in this study warrants consideration into whether the current allocation of ICU beds is optimal and how to better accommodate the demands of care for non-cancer patients at the EOL.

Conclusion

In our study we found that patients dying of non-cancer diseases are twice as likely to be admitted to an ICU at the EOL, in comparison to patients dying of cancer. This adds to the body of literature describing the large variation in health care at the EOL which emphasizes the need for further investigation into reasons behind this variation, to be able to provide the optimal care for patients at the EOL regardless of diagnosis.

Supplementary information

In this supplementary part of this report we discuss the methodological considerations relevant for this study, as well as a discussion of end-of-life care in a broader perspective including a presentation of problems related to triaging patients in the intensive care unit (ICU).
We furthermore present the results of an additional analysis, displaying the ICU admission rates at six months, one month, and one week, respectively, before death.

Background

Health care delivered at the end-of-life (EOL) covers a wide array of diseases, of which the majority are chronic.[30] Thus, the clinical needs of these patients differ according to their disease. The variability of care according to these diagnoses is sizable, leaving many patients neglected, without access to care in accordance with the individual patients' goals of care.[3]
Most people have specific wishes about where they want to die, if they want resuscitation, and if they want treatment or nutrition in their final time. In many cases, these desires are not articulated and for many of those who express their final will, these are not respected. This has been thoroughly investigated in the case of preferences of place of death.[14,31,32]
Furthermore, the tendency to choose aggressive, curative treatment become even more interesting as it is not reflected in a positive change in mortality outcome or quality of life for the patients.[30]

The on-going discussion of how ICU beds should be allocated is increasingly relevant as population grows simultaneously bigger and older, thus increasing demand of intensive care.[33] A key point in the debate is, whether the outcome of an ICU admission beneficial or not.[34] Triage of intensive care patients is very complex and cannot solely be based on rational scientific decisions. Organizational strategies, allocation of beds, patients' and relatives' wishes, eligibility, and professional considerations all partake in the definitive decision, making a uniform triaging system very difficult.[34]

Engaging patients and their relatives in a realistic discussion about prognosis and dialogue about preferences of the time before death, before the disease reaches a critical level, along with a more extensive offer of palliative care could lead the way to fulfil more patients' wishes and lower the use of futile treatment.[17,18]

Materials and methods

Methodological considerations and justification of methods applied

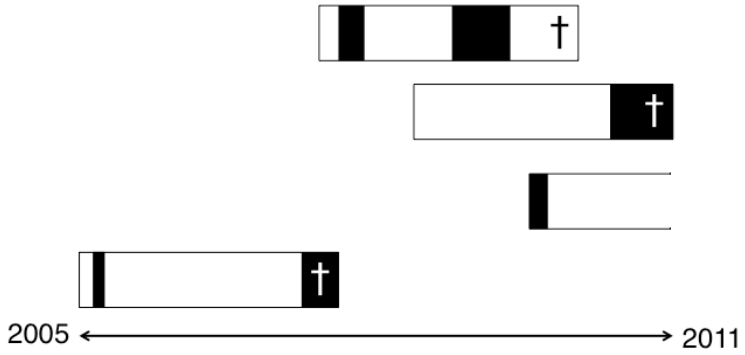
We designed a nationwide historical cross-sectional study, using data from national population-based registries. In our study we used data collected in the period 2005 to 2011; thus we used the designation historical. For each patient included in the study, the time-period analysed covered the last six months before death. We obtained data from all ICU in all of Denmark throughout the whole study period.

Figure S1 displays the structure of the design. We used the date of death as index date and collected all data for the six preceding months. The study population, setting and methods have been described at length in the extract. Cross-sectional studies are used to estimate prevalence at a given point or period, here over six months, making it possible to get an overview of the present state of the matter being examined. The cross-sectional design is not able to determine causation, as it cannot establish the direction of the effect. However, cross-sectional studies can be used to identify associations, which can serve as a basis for further examination of the causal pathways.[35] In many cases, large-scale surveys employ a cross-sectional design to report the occurrence of a given disease. These studies are purely descriptive. It is possible to employ relative measures in the design, thereby adding an analytic aspect to the cross-sectional study.

Our aim was to investigate the utilization of intensive care, at the end-of-life, among patients dying of non-cancer chronic diseases compared to patients dying of cancer. The study is based on the general hypothesis, that patients with non-cancer diseases, compared to cancer, are less likely to receive care that is aligned with their preferences. For this study, the specific hypothesis was that non-cancer patients are more prone to be admitted to an ICU in their final part of life than cancer patients.
For the purpose of our study aim, the cross-sectional design is a suitable, valid, and affordable method. This is especially due to the registries available, containing data collected from the universal tax supported health care in Denmark, which guarantees free and equal access to primary health care and hospitals, including intensive care.[36]

Supplemental figure S1

Example of inclusion of patients.



Each rectangle represents the last six months before death for a study participant. Death is indicated by the cross. The black part of the rectangle specifies ICU admission(s).

Data sources

With a vast array of databases compiled over many years, Denmark holds a special status when it comes to collected data on its population.[37] Systematic population-based registries began in the early 1900s, but church files dating back to 1645 registered all births and deaths within each parish.[38]

All Danish medical registries can be linked at individual level through the unique Danish civil registration number, assigned to all Danish citizens at birth or at immigration. [21] The registries used in this report are briefly mentioned here, as they have been described in detail in the extract

The Danish Registry of Causes of Death

Since 1983 the Danish Registry of Causes of Death has collected data on causes for all Danish residents, including Faroe Islands and Greenland. Data obtained in the registry contains, among other: one underlying cause of death and up to three immediate causes of death, manner and place of death, and whether and autopsy was performed. [38]

Danish Intensive Care Database

Data have been collected for the Danish Intensive Care Database (DID), a clinical database, since 2005. Data include: time of admission and discharge, discharge status including death in an ICU, and treatment given specifically in the ICU.[39]

Danish National Registry of Patients

The Danish National Registry of Patients contains data on all somatic hospital admissions since 1977. It includes contacts to emergency rooms and outpatient clinics from 1995. Data include, among others date of admission and discharge, data on hospital and ward, and diagnosis codes along with surgical procedures.

Effect measure

Throughout this report, we have used prevalence and prevalence ratio, adjusted for possible confounders, as effect measures.

For the supplemental analysis, we computed prevalence proportions of admission to ICU in the last six months, one month, and one week before death. Prevalence of non-cancer chronic diseases were compared to cancer by prevalence ratios estimated using multivariable binomial regression adjusted for age, gender, comorbidity and marital status. We included the region of residence into the analyses, as a cluster, to adjust for regional similarities in the process of admission to an ICU. This provides a more robust estimate.

Limitations

When conducting a study one must always be aware of possible limitations. As mentioned, when employing a cross-sectional design, it is only possible to determine whether an association is present. The direction of the association cannot be established, based on the data collected. This is due to cross-sectional quality of the data; risk factors and outcome are measured simultaneously. Another limitation is error. Generally error is divided into two categories: random error, which can be eliminated by increasing the study size, and systematic errors, which would remain even when increasing the study size infinitely.[35] Systematic errors are discussed in detail in the following.

Selection bias

This type of systematic error can occur if the groups compared differ in ways that can affect the study outcome, other than the factors being studied.[35] There are many ways selection bias can be introduced into a study. An often used example is voluntary health surveys, where persons volunteering often will be more health cautious, and thereby skew the results systematically, and introducing a bias in the selection process.

In the case of this study, selection bias could be introduced if systematic errors were introduced in the initial reporting of the data, to the registries. The Danish population-based databases used in this study, to a very large extent removes or minimizes the risk of selection bias as they cover the entire population and all hospital contacts

Information bias

Both exposure and outcome can be measured erroneously. Data for this study was obtained only from medical registries with prospectively collected data, largely eliminating the risk of recall bias, which is often a problem for survey data.[35]

Data in the DID is has an estimated 95% completeness. The accuracy has also been estimated in other studies, as a positive predictive value, to be between 87.2%-98.7%.[24,25]Meaning that it was unlikely that patients would be registered as admitted to an ICU if they were in fact not, and likewise unlikely to not be registered if they were actually admitted.

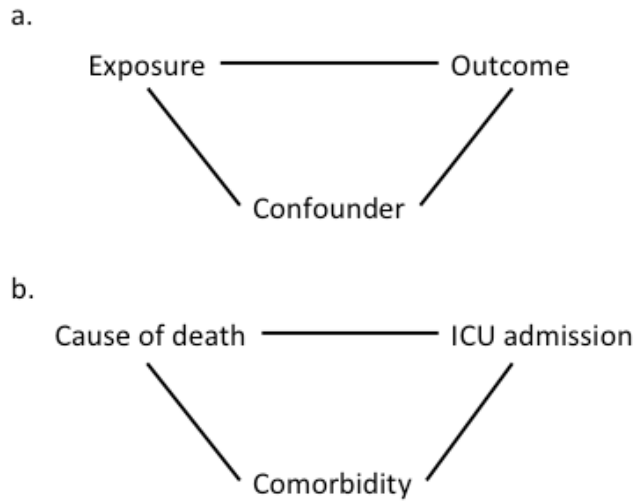
Registration to The Danish Registry of Causes of Death is virtually complete.[40] However, the registry is only validated with regards to some of the diagnoses.[22,28] Our analyses rely on the underlying cause of death rather than the immediate. Furthermore our population is restricted to only include patients who died of well-defined chronic diseases. However it is impossible to rule out bias on these grounds, as comprehensive knowledge on the validity of this registry is lacking.

Confounding

By confounding we refer to the mixing of effects. As shown in figure S2, a confounder must be associated both with the exposure and the outcome, however it must not be an effect of the exposure.[35] The regression model provides an advantageous way to adjust for confounding. We included relevant confounders in our analyses, such as age, gender, marital status, and comorbidity. These factors are known to influence use of hospital services. Naturally, the risk of unmeasured confounding remains.

Supplemental figure S2

Correlation between exposure, outcome and a confounder



a. General Correlation between exposure, outcome and a confounder.
b. Correlation between exposure, outcome and a confounder for this study.

Materials and methods used in supplemental analysis

In addition to both the analyses in the extract, we have conducted a supplementary analysis, estimating the admission to ICUs within six months, one month, and one week before death, respectively. This was in order to further asses the robustness of our main results.

Additional results

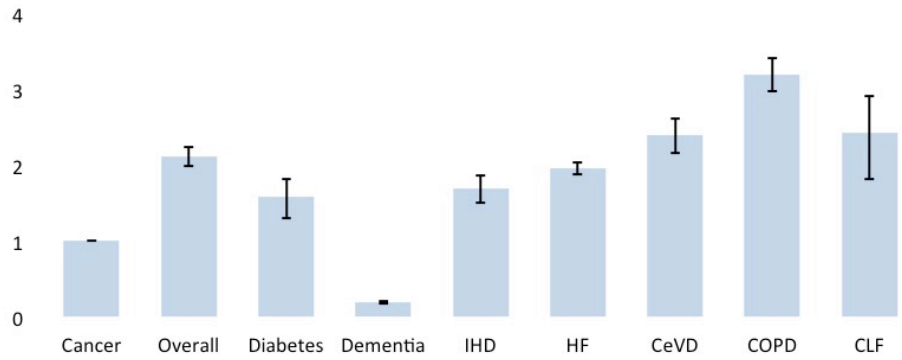
In this additional analysis of admission to ICU in the last six months, one month, and one week we found that the aPR for admission to ICU increased from 2.11 (95% CI: 1.98-2-24) for six months before death to 3.34 (95% CI: 3.11-3.59) for the last week before death, both overall non-cancer compared to cancer as cause of death.

The largest difference was observed among patients dying of cerebrovascular diseases with an increase in aPR from 2.39 (95% CI: 2.17-2.63) to 4.12 (95% CI: 3.85-4.42) from six months to one week, compared to cancer. For dementia aPR decreased slightly from an aPR of 0.19 (95% CI: 0.17-0.21) to 0.15 (95% CI 0.13-0.17), in the last six months and one week respectively, compared to cancer.

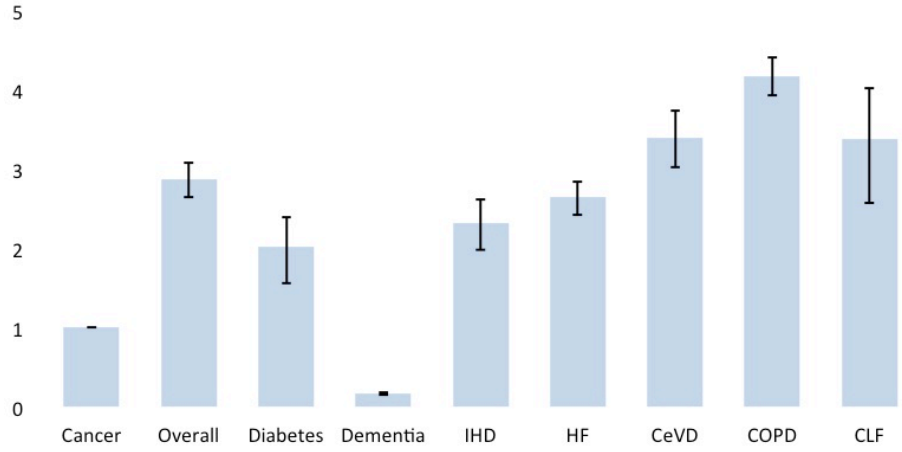
Supplemental figure S3 (Estimates shown in table S1)

Overall and stratified by cause of death, graphical presentation of adjusted prevalence ratios and 95% confidence intervals for admission to ICU in the last six months, one month, and one week, respectively, before death, in patients dying of chronic non-cancer disease compared to cancer.

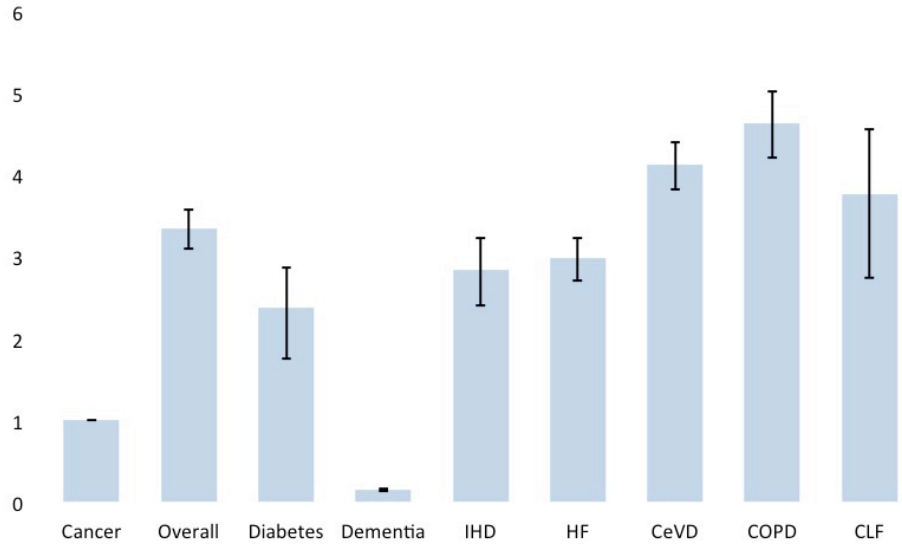
Six months



One month



One week



IHD=Ischemic heart disease, HF=Heart failure, CeVD=Cerebrovascular disease, COPD=Chronic obstructive pulmonary disease, CLF=Chronic liver failure

Additional perspectives

In the extract we demonstrated a clear overall association between non-cancer cause of death and admission to ICU in the last six months before death, compared to cancer as cause of death. In this supplemental section we display the use of ICU admission according to time to death. We found that the difference in prevalence of ICU admission between non-cancer patients and cancer patients increased risk as death became more imminent.

To our knowledge, no previous studies have examined how ICU admission rates changes during the last six months of life, comparing non-cancer with cancer patients. The change observed in our study from six months to one week, can be thought to reflect different mechanisms. As discussed in the extract, differences in disease trajectories along with a reduced tendency to discuss treatment goals in non-cancer patients are thought to cause different treatment patterns at the EOL. This could also explain the increase in ICU admissions observed in the last week. Some of the explanation for the increase in ICU admissions could also be due to differences in treatment requirements between non-cancer patients and cancer patients, closer to death.[41] However, to disclose the underlying causes for the documented differences is beyond the scope of this study.

All data used in this study originated from Danish national medical databases. Working with secondary data as these registries are provides considerable economic advantages in addition to the benefits of completeness and collection of data independent of a specific research hypothesis, making it less susceptible to bias. However it is important to consider the possible errors due to the manual data entering, such as missing data and large variation. [38]

With this study, we have added to the body of literature documenting large variation in both the admission to ICU and treatment during admission in the last six months before death. Choosing to use the Danish health registries to obtain data provided a reliable source of information.

References

1. WHO. WHO | cancer. WHO | Cancer Web site. http://www.who.int/mediacentre/factsheets/fs297/en/. Updated 2015. Accessed 2/5/2015, 2015.

2. WHO | the top 10 causes of death. WHO | The top 10 causes of death Web site. http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 1/22/2015, 2015.

3. Goodman D, Esty A, Fisher E, Chang C. Trends and variation in end-of-life care for medicare beneficiaries with severe chronic illness. . 2011:http://www.dartmouthatlas.org/downloads/reports/EOL_Trend_Report_0411.pdf. Accessed 8/17/2014.

4. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *The Lancet*. 2012;380(9836):37-43. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1016/S0140-6736(12)60240-2.

5. Curtis JR, Engelberg RA, Bensink ME, Ramsey SD. End-of-life care in the intensive care unit: Can we simultaneously increase quality and reduce costs? *Am J Respir Crit Care Med*. 2012;186(7):587-592. doi: 10.1164/rccm.201206-1020CP; 10.1164/rccm.201206-1020CP.

6. Angus DC, Barnato AE, Linde-Zwirble WT, et al. Use of intensive care at the end of life in the united states: An epidemiologic study. *Crit Care Med*. 2004;32(3):638-643.

7. Morrison RS, Meier DE. America's care of serious illness: A state-by-state report card on access to palliative care in our nation's hospitals. . 2011.

8. Bekelman DB, Rumsfeld JS, Havranek EP, et al. Symptom burden, depression, and spiritual well-being: A comparison of heart failure and advanced cancer patients. *J Gen Intern Med*. 2009;24(5):592-598. doi: 10.1007/s11606-009-0931-y [doi].

9. Au DH, Udris EM, Fihn SD, McDonell MB, Curtis JR. Differences in health care utilization at the end of life among patients with chronic obstructive pulmonary disease and patients with lung cancer. *Arch Intern Med*. 2006;166(3):326-331. doi: 166/3/326 [pii].

10. Teno JM, Gozalo PL, Bynum JP, et al. Change in end-of-life care for medicare beneficiaries: Site of death, place of care, and health care transitions in 2000, 2005, and 2009. *JAMA*. 2013;309(5):470-477. doi: 10.1001/jama.2012.207624; 10.1001/jama.2012.207624.

11. Lemiale V, Kentish-Barnes N, Chaize M, et al. Health-related quality of life in family members of intensive care unit patients. *J Palliat Med*. 2010;13(9):1131-1137. doi: 10.1089/jpm.2010.0109 [doi].

12. Sprung CL, Danis M, Iapichino G, et al. Triage of intensive care patients: Identifying agreement and controversy. *Intensive Care Med*. 2013;39(11):1916-1924. doi: 10.1007/s00134-013-3033-6 [doi].

13. De Korte-Verhoef MC, Pasman HR, Schweitzer BP, Francke AL, Onwuteaka-Philipsen BD, Deliens L. Reasons for hospitalisation at the end of life: Differences between cancer and non-cancer patients. *Support Care Cancer*. 2014;22(3):645-652. doi: 10.1007/s00520-013-2019-9 [doi].

14. Addicott R. Delivering better end-of-life care in england: Barriers to access for patients with a non-cancer diagnosis. *Health Econ Policy Law*. 2012;7(4):441-454. doi: 10.1017/S1744133112000230 [doi].

15. Wennberg JE, Fisher ES, Stukel TA, Skinner JS, Sharp SM, Bronner KK. Use of hospitals, physician visits, and hospice care during last six months of life among cohorts loyal to highly respected hospitals in the united states. *BMJ*. 2004;328(7440):607. doi: 10.1136/bmj.328.7440.607 [doi].

16. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in medicare spending. part 2: Health outcomes and satisfaction with care. *Ann Intern Med*. 2003;138(4):288-298. doi: 200302180-00007 [pii].

17. Zilberberg MD, Shorr AF. Economics at the end of life: Hospital and ICU perspectives. *Semin Respir Crit Care Med*. 2012;33(4):362-369. doi: 10.1055/s-0032-1322399 [doi].

18. Brogaard T, Neergaard MA, Sokolowski I, Olesen F, Jensen AB. Congruence between preferred and actual place of care and death among danish cancer patients. *Palliat Med*. 2013;27(2):155-164. doi: 10.1177/0269216312438468 [doi].

19. Schmidt M, Pedersen L, Sorensen HT. The danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi: 10.1007/s10654-014-9930-3 [doi].

20. Helweg-Larsen K. The danish register of causes of death. *Scand J Public Health*. 2011;39(7 Suppl):26-29. doi: 10.1177/1403494811399958 [doi].

21. The National Board of Health. The danish registry of causes of death. . 2012:http://www.ssi.dk/Sundhedsdataogit/Registre%20og%20kliniske%20databaser/De%20nationale%20sundhedsregistre/Dodsaarsager%20biologisk%20materiale/Dodsaarsagsregisteret.aspx. Accessed 8/19/2014.

22. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tonnesen E, Sorensen HT. The impact of pre-admission morbidity level on 3-year mortality after intensive care: A danish cohort study. *Acta Anaesthesiol Scand*. 2011;55(8):962-970. doi: 10.1111/j.1399-6576.2011.02480.x; 10.1111/j.1399-6576.2011.02480.x.

23. Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Norgaard M. Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the danish national patient registry: A short report. *Clin Epidemiol*. 2013;5:9-12. doi: 10.2147/CLEP.S37763 [doi].

24. The Danish Clinical Registries. Danish intensive database, annual report. . 2012:https://www.sundhed.dk/content/cms/12/4712_did-årsrapport-2012.pdf. Accessed 8/18/2014.

25. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess charlson comorbidity index conditions in the population-based danish national registry of patients. *BMC Med Res Methodol*. 2011;11:83-2288-11-83. doi: 10.1186/1471-2288-11-83; 10.1186/1471-2288-11-83.

26. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: A comparison of mortality and hospital discharge data with the danish MONICA registry. *J Clin Epidemiol*. 2003;56(2):124-130. doi: S0895435602005917 [pii].

27. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: Insights from SUPPORT. study to understand prognoses and preferences for outcomes and risks of treatments. *J Am Geriatr Soc*. 2000;48(5 Suppl):S146-53.

28. Murray SA, Sheikh A. Palliative care beyond cancer: Care for all at the end of life. *BMJ*. 2008;336(7650):958-959. doi: 10.1136/bmj.39535.491238.94 [doi].

29. Beernaert K, Cohen J, Deliens L, et al. Referral to palliative care in COPD and other chronic diseases: A population-based study. *Respir Med.* 2013;107(11):1731-1739. doi: 10.1016/j.rmed.2013.06.003 [doi].

30. Wennberg J, Fisher E, Goodman D, Skinner JS. Tracking the care of patients with severe chronic illness: The dartmouth atlas of health care 2008. . 2008.

31. Pritchard RS, Fisher ES, Teno JM, et al. Influence of patient preferences and local health system characteristics on the place of death. SUPPORT investigators. study to understand prognoses and preferences for risks and outcomes of treatment. *J Am Geriatr Soc.* 1998;46(10):1242-1250.

32. Neergaard MA, Jensen AB, Sondergaard J, Sokolowski I, Olesen F, Vedsted P. Preference for place-of-death among terminally ill cancer patients in denmark. *Scand J Caring Sci.* 2011;25(4):627-636. doi: 10.1111/j.1471-6712.2011.00870.x [doi].

33. Nielsson MS, Christiansen CF, Johansen MB, Rasmussen BS, Tonnesen E, Norgaard M. Mortality in elderly ICU patients: A cohort study. *Acta Anaesthesiol Scand.* 2014;58(1):19-26. doi: 10.1111/aas.12211 [doi].

34. Sprung CL, Baras M, Iapichino G, et al. The eldicus prospective, observational study of triage decision making in european intensive care units: Part I--european intensive care admission triage scores. *Crit Care Med.* 2012;40(1):125-131. doi: 10.1097/CCM.0b013e31822e5692 [doi].

35. Rothman K, Greenland S, Lash T. *Modern epidemiology.* 3rd. ed. Philidelphia: Lippincott, Williams & Wilkins; 2008.

36. Health care in denmark - sum.dk. http://www.sum.dk/Aktuelt/Publikationer/UK_Healthcare_in_DK.aspx. Accessed 2/5/2015, 2015.

37. Frank L. Epidemiology. when an entire country is a cohort. *Science.* 2000;287(5462):2398-2399.

38. Sørensen H, Christensen T, Schlosser H, Pedersen L, eds. *Use of medical databases in clinical epidemiology.* ; 2009.

39. Christiansen CF, Ronholm E. Danish intensive care database. *Ugeskr Laeger.* 2012;174(42):2544. doi: VP62182 [pii].

40. Tal og analyse: Dødsårsagsregisteret 2011. http://www.ssi.dk/Sundhedsdataogit/Registre/~/media/Indhold/DK%20-%20dansk/Sundhedsdata%20og%20it/NSF/Registre/Dodsaarsagsregisteret/D%C3%B8ds%C3%A5rsagsregisteret%202011.ashx. Accessed 4/7/2014, 2014.

41. Bronnum-Hansen H, Davidsen M, Thorvaldsen P, Danish MONICA Study Group. Long-term survival and causes of death after stroke. *Stroke*. 2001;32(9):2131-2136.

Tables

Table 1

Characteristics of decedents between 2005-2011 stratified by underlying cause of death as either cancer or chronic non-cancer disease (diabetes, dementia, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease or chronic liver failure)

	Chronic non-cancer disease, n (% of all non-cancer patients)		*Cancer, n (% of all cancer patients)*		*Total study population, n (% of all deceased)*	
Overall number	134,298	(100.0%)	106,459	(100.0%)	240,757	(100.0%)
Median age in years	82	[74-89][1]	74	[65-82][1]	79	[69-86]
Age group, stratified by gender						
18-49 years, women	922	(0.7%)	2,483	(2.3%)	3,405	(1.4%)
18-49 years, men	2,121	(1.6%)	1,973	(1.9%)	4,094	(1.7%)
50-59 years, women	2,232	(1.7%)	5,742	(5.4%)	7,974	(3.3%)
50-59 years, men	4,650	(3.5%)	5,809	(5.5%)	10,459	(4.3%)
60-69 years, women	5,309	(4.0%)	11,772	(11.1%)	17,081	(7.1%)
60-69 years, men	9,745	(7.3%)	14,043	(13.2%)	23,788	(9.9%)
70-79 years, women	13,789	(10.3%)	14,939	(14.0%)	28,728	(11.9%)
70-79 years, men	16,854	(12.5%)	17,650	(16.6%)	34,504	(14.3%)
80-89 years, women	29,629	(22.1%)	13,396	(12.6%)	43,025	(17.9%)
80-89 years, men	22,991	(17.1%)	13,042	(12.3%)	36,033	(15.0%)
90+ years, women	18,818	(14.0%)	3,469	(3.3%)	22,287	(9.3%)
90+ years, men	7,238	(5.4%)	2,141	(2.0%)	9,379	(3.9%)
Gender						
Female	70,699	(52.6%)	51,801	(48.7%)	122,500	(50.9%)
Male	63,599	(47.4%)	54,658	(51.3%)	118,257	(49.1%)
Marital Status						
Married	42,635	(31.7%)	53,771	(50.5%)	96,406	(40.0%)
Unmarried	17,158	(12.8%)	14,045	(13.2%)	31,203	(13.0%)
Divorced	12,512	(9.3%)	8,494	(8.0%)	21,006	(8.7%)
Widowed	61,993	(46.2%)	30,149	(28.3%)	92,142	(38.3%)
Geographical region of residence						
North Denmark Region	15,715	(11.7%)	11,931	(11.2%)	27,646	(11.5%)
Central Denmark Region	27,689	(20.6%)	22,428	(21.1%)	50,117	(20.8%)
Region of Southern Denmark	31,080	(23.1%)	23,669	(22.7%)	54,749	(22.7%)
Capital Region of Denmark	38,138	(28.4%)	30,680	(28.6%)	68,818	(28.6%)
Region Zealand	21,676	(16.1%)	17,751	(16.7%)	39,427	(13.4%)
Cause of death						
Cancer	-	-	106,456	(100.0%)	106,456	(44.2%)
Non-cancer chronic diseases	134,298	(100.0%)	-	-	134,298	(55.8%)
Diabetes	9,150	(6.8%)	-	-	9,150	(3.8%)
Dementia	18,298	(13.6%)	-	-	18,298	(7.6%)
Ischemic heart disease	39,466	(29.4%)	-	-	39,466	(16.4%)
Heart failure	10,779	(8.0%)	-	-	10,779	(4.5%)
Cerebrovascular disease	28,522	(21.2%)	-	-	28,522	(11.9%)
Chronic obstructive pulmonary disease	22,120	(16.5%)	-	-	22,120	(9.2%)
Chronic liver failure	5,963	(4.4%)	-	-	5,963	(2.3%)
ICU admission[2]						
No	117,796	(87.7%)	97,165	(91.3%)	214,961	(89.3%)
Yes	16,502	(12.3%)	9,294	(8.7%)	25,796	(10.7%)
Comorbidity[3]						
No	48,299	(36.0%)	32,876	(30.9%)	81,175	(33.7%)
Yes	85,999	(64.0%)	73,583	(69.1%)	159,582	(66.3%)

[1]Interquartile range

[2]Any admission to an ICU within the last 6 months before death

[3]Calculated as Charlson Comorbidity Index diseases excluding underlying cause of death

Table 2

Prevalence, adjusted prevalence ratio (aPR) and 95% confidence interval (CI) for admission to ICU in in the last six months before death, in patients dying of chronic non-cancer disease compared to cancer.

	ICU admission n=25,796 (100%)		
Causes of death	*%*	*aPR**	*95% CI*
Cancer	8.7%	1.00	[Reference]
Chronic non-cancer diseases	12.3%	2.11	[1.98 - 2.24]
Diabetes	11.4%	1.58	[1.34 - 1.86]
Dementia	0.7%	0.19	[0.17 - 0.21]
Ischemic heart disease	10.2%	1.69	[1.52 - 1.88]
Heart failure	9.8%	1.95	[1.86 - 2.03]
Cerebrovascular disease	13.2%	2.39	[2.17 - 2.63]
Chronic obstructive pulmonary disease	31.9%	3.19	[2.98 - 3.41]
Chronic liver failure	27.4%	2.42	[1.94 - 3.03]

*Adjusted for age, gender, marital status, any comorbidity and geographic region

Table 3

Prevalence, adjusted prevalence ratio (aPR) and 95% confidence interval (CI) of treatment during ICU admission, in the last six months before death, for mechanical ventilation, non-invasive mechanical ventilation (NIV), inotropic/vasopressor, dialysis treatment, and cumulated aggressiveness of treatment, reflected as full organ supportive treatment, in patients dying of chronic non-cancer disease compared to cancer, respectively.

	Mechanical ventilation n=13,101 (100%)			*NIV n=6,039 (100%)*			*Inotropes/vasopressor n=2,457 (100%)*			*Dialysis n=2,457 (100%)*			*Full organ supportive treatment n=1,836 (100%)*		
Causes of death	*%*	*aPR**	*95% CI*	*%*	*aPR**	*95% CI*	*%*	*aPR**	*95% CI*	*%*	*aPR**	*95% CI*	*%*	*aPR**	*95% CI*
Cancer	42.2	1.00	[Reference]	16.4	1.00	[Reference]	38.9	1.00	[Reference]	9.7	1.00	[Reference]	7.5	1.00	[Reference]
Chronic non-cancer diseases	55.6	1.40	[1.35-1.46]	27.3	1.62	[1.50-1.76]	44.3	1.19	[1.07-1.31]	9.4	1.05	[0.87-1.28]	6.9	1.02	[0.82-1.27]
Diabetes	49.7	1.27	[1.16-1.39]	17.3	1.03	[0.94-1.14]	48.2	1.31	[1.18-1.46]	22.2	2.27	[1.91-2.69]	14.3	1.98	[1.60-2.44]
Dementia	25.6	0.80	[0.68-0.94]	11.3	0.64	[0.46-0.88]	16.5	1.31	[1.18-1.46]	0	-	-	0	-	-
IHD	59.3	1.57	[1.53-1.61]	16.4	0.96	[0.90-1.03]	62.5	0.54	[0.39-0.73]	14.0	1.60	[1.20-2.14]	11.0	1.70	[1.31-2.20]
Heart failure	49.8	1.36	[1.22-1.51]	27.8	1.64	[1.53-1.75]	52.2	1.72	[1.60-1.86]	14.5	1.74	[1.33-2.28]	10.2	1.66	[1.16-2.39]
CeVD	69.6	1.66	[1.60-1.71]	8.2	0.51	[0.45-0.58]	33.3	1.49	[1.32-1.68]	3.6	0.40	[0.32-0.50]	2.64	0.37	[0.29-0.48]
COPD	43.3	1.11	[1.01-1.22]	58.5	3.40	[3.00-3.85]	33.3	0.86	[0.72-1.03]	5.3	0.62	[0.46-0.84]	3.8	0.59	[0.38-0.91]
CLF	61.1	1.30	[1.14-1.47]	13.4	0.90	[0.81-1.01]	52.2	0.90	[0.79-1.03]	12.6	1.19	[0.90-1.56]	9.4	1.12	[0.83-1.52]

*Adjusted for age, gender, marital status, any comorbidity and geographic region

IHD=Ischemic heart disease, CeVD=Cerebrovascular disease, COPD=Chronic obstructive pulmonary disease, CLF=Chronic liver failure

Table 4

Median and interquartile range (IQR) for length of ICU admission per admission, in hours

	Overall		*2009*		*2010*		*2011*	
	Non-cancer	*Cancer*	*Non-cancer*	*Cancer*	*Non-cancer*	*Cancer*	*Non-cancer*	*Cancer*
Median (IQR)	29.5 (10.1-87.6)	29.7 (13.2-94.5)	24.5 (8.5-78.7)	24.0 (8.8-90.4)	26.7 (10.1-90.6)	31.5 (13.8-104.1)	32.5 (11.4-89.1)	31.3 (14.8-93.6)
Number (% missing)	4,948 (32.4%)	2,844 (30.7%)	1,207 (51.4%)	597 (54.1%)	1,760 (27.9%)	1,019 (25.3%)	1,981 (17.3%)	1,228 (14.6%)

Supplemental table S1

Adjusted prevalence ratios (aPR) and 95% confidence intervals(CI) for admission to ICU in the last six months, one month, and one week, respectively, before death, in patients dying of chronic non-cancer disease compared to cancer.

	aPR, six months [95% CI] n=25,796		*aPR, one month [95% CI] n=19,430*		*aPR, one week [95% CI] n=13,78*	
Cancer	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
Overall	**2.11**	**[1.98 - 2.24]**	**2.86**	**[2.65 - 3.08]**	**3.34**	**[3.11 - 3.59]**
Diabetes	1.58	[1.34 - 1.86]	2.02	[1.65 - 2.48]	2.38	[1.89 - 3.01]
Dementia	0.19	[0.17 - 0.21]	0.17	[0.15 - 0.19]	0.15	[0.13 - 0.17]
IHD	1.69	[1.52 - 1.88]	2.31	[2.01 - 2.64]	2.84	[2.46 - 3.28]
HF	1.95	[1.86 - 2.03]	2.64	[2.44 - 2.86]	2.98	[2.73 - 3.26]
CeVD	2.39	[2.17 - 2.63]	3.39	[3.05 - 3.76]	4.12	[3.85 - 4.42]
COPD	3.19	[2.98 - 3.41]	4.17	[3.94 - 4.42]	4.63	[4.24 - 5.06]
CLF	2.42	[1.94 - 3.03]	3.37	[2.73 - 4.17]	3.76	[2.96 - 4.78]

IHD=Ischemic heart disease, HF=Heart failure, CeVD=cerebrovascular disease, COPD=chronic obstructive pulmonary disease, CLF=chronic liver failure

Figures

Figure 1

Flowchart for inclusion criteria of study population and grouping of patients into cancer and non-cancer patients. (%)

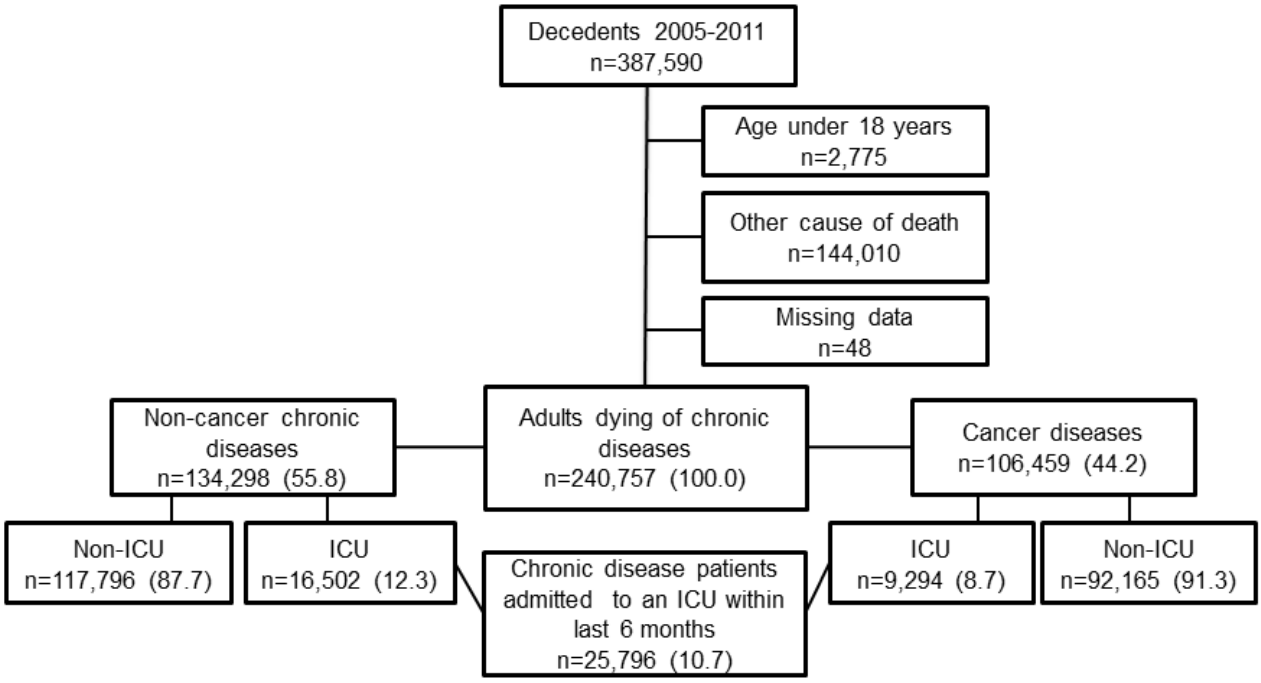
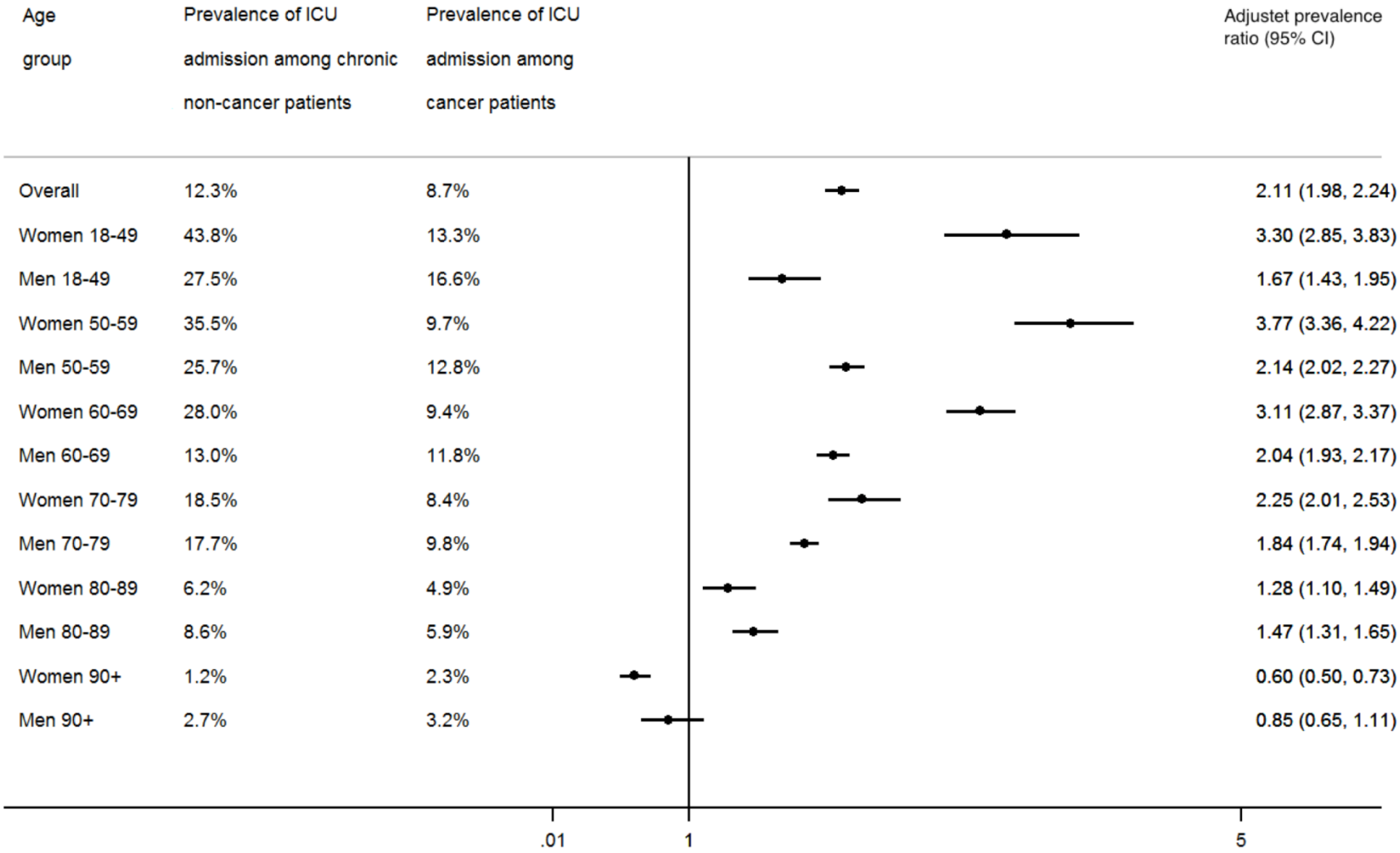


Figure 2

Prevalence of non-cancer and cancer patients, and Forest plot of the adjusted prevalence ratio for admission to an ICU within the last 6 months before death among patients dying of non-cancer chronic diseases compared to cancer.



Appendices

Appendix 1

List of ICD-10 diagnoses used to define chronic diseases as underlying cause of death

Cancer	C00-C97
Diabetes	E10□ E14
Dementia, incl. Alzheimer's	F00-F01, F03, G30
Ischemic heart disease	I20-25
Heart failure[†]	I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9
Cerebrovascular disease	I60-I69
Chronic obstructive pulmonary disease	J41-J44, J47
Chronic liver disease	K70, K73-74
"Other"	All other diagnoses

[†]Heart failure was defined according to the National Indicator Project – Heart Failure. Cancer, diabetes, dementia, ischemic heart disease, Cerebrovascular disease, chronic obstructive pulmonary disease and "other" were defined according to the Danish Registry of Causes of Death.

Appendix 2

Charlson Comorbidity Index diseases, corresponding ICD-10 diagnoses and weight used for index

	Charlson Comorbidity Index disease	*ICD-10 code*	*Weight*
1	Myocardial infarction	I21;I22;I23	1
2	Congestive heart failure	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	I60-I69; G45; G46	1
5	Dementia	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	K22.1; K25-K28	1
9	Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
10	Diabetes type 1	E10.0, E10.1; E10.9	1
	Diabetes type 2	E11.0; E11.1; E11.9	
11	Hemiplegia	G81; G82	2
12	Moderate-to-severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
13	Diabetes type 1 with end organ damage	E10.2-E10.8	2
	Diabetes type 2 with end organ damage	E11.2-E11.8	2
14	Any tumour	C00-C75	2
15	Leukaemia	C91-C95	2
16	Lymphoma	C81-C85; C88; C90; C96	2
17	Moderate-to-severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumour	C76-C80	6
19	AIDS	B21-B24	6

Appendix 3

Modification of Charlson Comorbidity Index by causes of death

	Cancer	*Diabetes*	*Dementia*	*IHD*	*HF*	*Cerebrovascular disease*	*COPD*	*Chronic liver failure*
Myocardial infarction*				■				
Congestive heart failure*					■			
Peripheral vascular disease†								
Cerebrovascular disease*						■		
Dementia*			■					
Chronic pulmonary disease*							■	
Connective tissue disease†								
Ulcer disease†								
Mild liver disease*								■
Diabetes type 1*		■						
Diabetes type 2*						■		
Hemiplegia†								
Moderate-to-severe renal disease*		■						
Diabetes type 1 with end organ damage*	■							
Diabetes type 2 with end organ damage*	■							
Any tumour*	■							
Leukaemia*								■
Lymphoma	■							
Moderate-to-severe liver disease†								
Metastatic solid tumour†								
AIDS†								

*If these diseases were present in patients as underlying cause of death, as indicated by the shaded boxes, 0 points were added to the CCI score. Example: A person with myocardial infarction and ulcer disease as comorbidity, who died of ischemic heart disease will have a CCI score of myocardial infarction (1) + ulcer disease (1)=total CCI score (2) – points for underlying cause of death, ischemic heart disease(1)=total modified CCI score (1)

†These diseases were not present as underlying cause of death

Appendix 4

Model for aggressiveness of treatment during admission to ICU

Points assigned	*Treatment modality*
1	Mechanical ventilation and/or non-mechanical ventilation treatment
1	Inotropic and/or vasopressor treatment
1	Dialysis treatment

Points assigned for each treatment modality. Example: Mechanical ventilation (1), non-mechanical ventilation (0), and dialysis (1) = total score (2)
Points grouped as 0-2 points: Partial organ support treatment and 3 points: Full organ support treatment.

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. *2006*.

20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published.*

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. *2009*.

46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. *2009*.

47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. *2009*.

51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. *2010*.

52. Henriette Thisted: Antidiabetic Treatments and ischemic cardiovascular disease in Denmark: Risk and outcome. *2010*.

53. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme. Region Midtjylland og Region Nordjylland 1997-2008. *2010*.

54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.

55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. *2010*.

56. Thomas Patrick Ahern: Estimating the impact of molecular profiles and prescription drugs on breast cancer outcomes. *2010*.

57. Annette Ingeman: Medical complications in patients with stroke: Data validity, processes of care, and clinical outcome. *2010*.

58. Knoglemetastaser og skeletrelaterede hændelser blandt patienter med prostatakræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

59. Morten Olsen: Prognosis for Danish patients with congenital heart defects - Mortality, psychiatric morbidity, and educational achievement. *2010*.

60. Knoglemetastaser og skeletrelaterede hændelser blandt kvinder med brystkræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

61. Kort- og langtidsoverlevelse efter hospitalsbehandlet kræft. Region Midtjylland og Region Nordjylland 1998-2009. *2010*.

62. Anna Lei Lamberg: The use of new and existing data sources in non-melanoma skin cancer research. *2011*.

63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. *2011*.

64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. *2011*.

65. Gitte Vrelits Sørensen: Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study. *2011*.

66. Anne-Mette Bay Bjørn: Use of corticosteroids in pregnancy. With special focus on the relation to congenital malformations in offspring and miscarriage. *2012*.

67. Marie Louise Overgaard Svendsen: Early stroke care: studies on structure, process, and outcome. *2012*.

68. Christian Fynbo Christiansen: Diabetes, preadmission morbidity, and intensive care: population-based Danish studies of prognosis. *2012*.

69. Jennie Maria Christin Strid: Hospitalization rate and 30-day mortality of patients with status asthmaticus in Denmark – A 16-year nationwide population-based cohort study. *2012*.

70. Alkoholisk leversygdom i Region Midtjylland og Region Nordjylland. 2007-2011. *2012*.

71. Lars Jakobsen: Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction. *2012*.

72. Anna Maria Platon: The impact of chronic obstructive pulmonary disease on intensive care unit admission and 30-day mortality in patients undergoing colorectal cancer surgery: a Danish population-based cohort study. *2012*.

73. Rune Erichsen: Prognosis after Colorectal Cancer - A review of the specific impact of comorbidity, interval cancer, and colonic stent treatment. *2013*.

74. Anna Byrjalsen: Use of Corticosteroids during Pregnancy and in the Postnatal Period and Risk of Asthma in Offspring - A Nationwide Danish Cohort Study. *2013*.

75. Kristina Laugesen: In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder (ADHD). *2013*.

76. Malene Kærslund Hansen: Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: A cohort study. *2013*.

77. Astrid Blicher Schelde: Impact of comorbidity on the prediction of first-time myocardial infarction, stroke, or death from single-photon emission computed tomography myocardial perfusion imaging: A Danish cohort study. *2013*.

78. Risiko for kræft blandt patienter med kronisk obstruktiv lungesygdom (KOL) i Danmark. (Online publication only). *2013*.

79. Kirurgisk fjernelse af milten og risikoen for efterfølgende infektioner, blodpropper og død. Danmark 1996-2005. (Online publication only). *2013*.

Jens Georg Hansen: Akut rhinosinuitis (ARS) – diagnostik og behandling af voksne i almen praksis. *2013*.

80. Henrik Gammelager: Prognosis after acute kidney injury among intensive care patients. *2014*.

81. Dennis Fristrup Simonsen: Patient-Related Risk Factors for Postoperative Pneumonia following Lung Cancer Surgery and Impact of Pneumonia on Survival. *2014*.

82. Anne Ording: Breast cancer and comorbidity: Risk and prognosis. *2014*.

83. Kristoffer Koch: Socioeconomic Status and Bacteremia: Risk, Prognosis, and Treatment. *2014*.

84. Anne Fia Grann: Melanoma: the impact of comorbidities and postdiagnostic treatments on prognosis. *2014*.

85. Michael Dalager-Pedersen: Prognosis of adults admitted to medical departments with community-acquired bacteremia. *2014*.

86. Henrik Solli: Venous thromboembolism: risk factors and risk of subsequent arterial thromboembolic events. *2014*.

87. Eva Bjerre Ostenfeld: Glucocorticoid use and colorectal cancer: risk and postoperative outcomes. *2014*.

88. Tobias Pilgaard Ottosen: Trends in intracerebral haemorrhage epidemiology in Denmark between 2004 and 2012: Incidence, risk-profile and case-fatality. *2014*.

89. Lene Rahr-Wagner: Validation and outcome studies from the Danish Knee Ligament Reconstruction Registry. A study in operatively treated anterior cruciate ligament injuries. *2014*.

90. Marie Dam Lauridsen: Impact of dialysis-requiring acute kidney injury on 5-year mortality after myocardial infarction-related cardiogenic shock - A population-based nationwide cohort study. *2014*.

91. Ane Birgitte Telén Andersen: Parental gastrointestinal diseases and risk of asthma in the offspring. A review of the specific impact of acid-suppressive drugs, inflammatory bowel disease, and celiac disease. *2014*.

    Mikkel S. Andersen: Danish Criteria-based Emergency Medical Dispatch – Ensuring 112 callers the right help in due time? *2014*.

92. Jonathan Montomoli: Short-term prognosis after colorectal surgery: The impact of liver disease and serum albumin. *2014*.

93. Morten Schmidt: Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use: Pharmacoepidemiological studies. *2014*.

94. Betina Vest Hansen: Acute admission to internal medicine departments in Denmark - studies on admission rate, diagnosis, and prognosis. *2015*.

95. Jacob Gamst: Atrial Fibrillation: Risk and Prognosis in Critical Illness. *2015*.

96. Søren Viborg: Lower gastrointestinal bleeding and risk of gastrointestinal cancer. *2015*.

97. Heidi Theresa Ørum Cueto: Folic acid supplement use in Danish pregnancy planners: The impact on the menstrual cycle and fecundability. *2015*.

98. Niwar Faisal Mohamad: Improving logistics for acute ischaemic stroke treatment: Reducing system delay before revascularisation therapy by reorganisation of the prehospital visitation and centralization of stroke care. *2015*.

99. Malene Schou Nielsson: Elderly patients, bacteremia, and intensive care: Risk and prognosis. *2015*.

100. Jens Tilma: Treatment Injuries in Danish Public Hospitals 2006-2012. *2015*.