Elderly patients, bacteremia, and intensive care

risk and prognosis

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Elderly patients, bacteremia, and intensive care:

Risk and prognosis

PhD dissertation

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Preface

This dissertation is based on studies carried out during my employments at the Department of Clinical Epidemiology, Aarhus University Hospital, and the Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital, Denmark.

This work was made possible due to a number of persons. At first, I would like to express my sincerest gratitude to my three supervisors: Else Tønnesen, for her outstanding professional competence and valuable inputs, her never-failing encouragement, enthusiasm and positive attitude. Mette Nørgaard, for patiently teaching me clinical epidemiology and the art of scientific writing, and for her valuable engagement and support. Bodil Steen Rasmussen, for introducing me to research and for enthusiastically encouraging me to start this PhD, and for her valuable and constructive feedback and support.

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II. Nielsson MS, Christiansen CF, Johansen MB, Rasmussen BS, Tønnesen E, Nørgaard M. Mortality in elderly ICU patients: a cohort study. Acta Anaesthesiol Scand. 2014;58(1):19-26.

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List of abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II

CCI: Charlsons comorbidity index

CI: Confidence interval

CRP: C-reactive protein

DNPR: Danish National Patient Registry

ICU: Intensive care unit

IQR: Interquartile range

HR: Hazard ratio

MRR: Mortality rate ratio

POR: Prevalence odds ratio

PPR: Prevalence proportion ratio

SAPS: Simplified Acute Physiology Score

SIRS: Systemic Inflammatory Response Syndrome

SOFA: Sequential Organ Failure Assessment score

WBC: White blood cell

Content

1 Introduction

"..... I would especially commend
the physician who, in acute diseases,
by which the bulk of mankind are cutoff,
conducts the treatment better than others...."
— Hippocrates

1.1 Introduction to intensive care

In Denmark, the young specialty of intensive care medicine arose during the polio epidemic in Copenhagen in 1952.[1] The Danish anesthesiologist Bjørn Ibsen was called in as a consultant at the Epidemiological Hospital of Copenhagen as 27 of 31 patients with bulbar poliomyelitis had died despite treated in a respirator tank.[2] Ibsen treated the respiratory failure patients with tracheotomy and manual positive-pressure ventilation, which led to a substantial decrease in in-hospital mortality from 87% to 40%.[2] Furthermore, he organized a unit with 24-hour observation of the patients by mobilizing all available anesthesiologists and medical students. He described the use of fluid and vasopressors to the patients with cardiovascular failure, the monitoring of sufficient ventilation by the measurement of carbon dioxide, the feeding of the patients by placing a nasogastric tube, and daily multidisciplinary conferences in order to optimize the treatment for each patient.[3] These experiences led to the establishment of the first Danish intensive care unit (ICU) in 1953; under the leadership of Bjørn Ibsen.[1,4] During the years, the specialty of intensive care medicine has undergone massive expansion and includes life-sustaining, high-technology treatment of critically ill patients with threatening or failing vital functions. Contrary to Ibsen's requirements of the admitted patients being close to moribund otherwise not admitted, todays comprehension of patients eligible for ICU admission is the potential reversibility of one or more threatening vital functions.[5] Presenting with a variety of different pathologies, the heterogeneous population of ICU patients consists of acute/elective surgical or non-surgical patients or patients with pre-hospital critical

illness (e.g. major trauma, cardiac arrest etc.) with differences in preexisting morbidities and admission diagnoses. Thus, the definition of an ICU patient is not characterized by a single symptom or disease but rather by the presence at a specific location within the hospital; the ICU.[5]

1.2 The ageing world population and the impact on intensive care

The western population is ageing due to an increase in life expectancy with concurrent low levels of fertility sustained for decades.[6] In Europe, the proportion of people aged 65+ years is expected to rise from 17.4% in 2010 to 28.8% in 2050.[7] The fastest growing segment of the European population consists of those aged 80+ years with the proportion predicted to more than double by 2050 from 4.7% in 2010 to 11% in 2050.[7] The same pattern is seen in Denmark.[8] These demographic changes may challenge our health care services including our ICUs. At present, strain on ICU capacity is significant forcing physicians to perform triage decisions on ICU admission or not.[9] Disturbingly, studies have shown improved survival among patients admitted to an ICU compared with patients denied access and the survival benefit (admitted vs. rejected patients) is actually greater among the elderly compared with younger patients.[10] Yet, the elderly are more often rejected ICU admission than younger patients.[10] The high-technology ICU treatments are, however, expensive with an estimated cost per European ICU admission of approximately 3000 USD.[11] In Europe, only 5% of hospital beds are allocated beds in the ICU although consuming 20% of hospital costs.[9] Currently, patients aged 80+ years constitute approximately 10% of all admissions to an ICU[12–14] with the proportion tending to be rising. An Australian cohort study estimated an annual increase of 5.6% of patients aged 80+ admitted to the ICU during 2000-2005 with a predicted 72.4% rise in ICU and hospital bed-days by 2015.[14]

Given the limited amount of ICU beds, the high ICU treatment-associated expense, and the rising proportion of elderly people in the general population, data on the prognosis of elderly ICU patients is important in order to identify the patients of whom intensive care therapy will be of benefit, and the overall aim of this dissertation was to examine the effect of age on different outcomes within a cohort of ICU patients.

1.3 Definition of elderly

Human ageing is characterized by the gradual and progressive declines in structure and function (molecules, cells, tissues, and organs) commencing after the accomplishment of sexual maturity.[15] The degenerative changes start in the thirties progressing with advancing age.[16] Traditionally, chronological age is used to outline a population into elderly and younger age groups. Being closely related to retirement age, most developed countries accept the age of 60 or 65 years as distinction of an older or elderly person.[17] Even though no United Nation (UN) standard age criterion exists, there has been an UN agreement of the age of 60 years to specify the older population.[17] The older population can be categorized into *"the young-old"*, *"the old"*, and *"the oldest-old"*. However, no uniform age criterion exists in defining these categories. Some studies refer to *"the young-old"* as the age group of 60-70 years, some studies as the age group of 65-75 years, and yet other studies as the age group of 65-79 years. Similar differences exist in defining *"the oldest-old"* and the studies mentioned above referred to *"the oldest-old"* as the age group of ≥75 years, ≥80 years, or ≥85 years. For the purpose of this dissertation we thus categorized the patients into four age groups; 15-49, 50-64, 65-79, and 80+ years, and we defined elderly (*the oldest-old*) as patients aged 80+ years.

1.4 Critical illness in the elderly

During critical illness there is a need for compensation due to the increased physiological demands. Severe physiological degeneration of pulmonary, cardiovascular and renal function complicates compensation in the critically ill elderly.[16] The pulmonary changes include decreased chest wall compliance, increased energy expenditure during inspiratory work, decreased muscle strength and lung elasticity.[18–20] The cardiovascular changes are comprehensive including depressed myocardial contractility and decreased ventricular compliance, conduction abnormalities leading to increased rate of atrial arrhythmias, sick sinus syndrome and bundle branch block,[21] increased afterload, diastolic dysfunction, and decreased sensitivity to both endogenous or exogenous catecholamines. During periods of stress, e.g. critical illness, ejection fraction decreases in the elderly.[22] In addition, coronary artery disease is more common in the elderly, and during critical illness with an increase of myocardial activity this may lead to ischemia with concomitant pump failure.[23] Renal function declines with age leading to ineffective secretion and resorption,[24] decreased glomerular filtration rate (a reduction of 45% by age 80 years), and unchanged levels of serum creatinine despite a decrease in lean body mass leading to decreased creatinine production.[16] As a consequence of the decreased tubular function, elderly patients are in increased risk of dehydration and disturbances of

acid-base balance. Furthermore, preexisting morbidity may limit the elderly's ability to compensate to the increased physiological demands. The number of morbidities increases with increasing age, and ICU patients in general have higher levels of pre-existing morbidities than age- and sex-matched individuals from the general population.[25]

1.5 Bacteremia

Bacteremia is defined by the presence of viable bacteria in the bloodstream as evidenced by blood cultures in which contamination has been ruled out.[26,27] Contaminants include coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., and *Propionibacterium acnes* unless isolated from two or more separate blood culture sets. Candidaemia is, by convention, included in the term bacteremia. Thus, in the daily clinical setting bacteremia can be defined as the growth of bacteria or fungi in the bloodstream with associated clinical signs and/or symptoms of infection, determined by joint clinical and microbiological judgment.

There are numerous ways to classify bacteremia, e.g. classification according to the isolated microorganism(s), the presumed focus of infection, e.g. the lungs, or the place of acquisition. The Centers for Disease Control and Prevention (CDC) originally categorized bacteremias into either community-acquired or nosocomial (acquired in a hospital setting), referring to the place of acquisition[28]. In general, a cut-off point of 48 hours is used to distinguish nosocomial from community-acquired bacteremias as positive blood cultures drawn after more than 48 hours after hospital admission are considered nosocomial, and positive blood cultures drawn within the first 48 hours of hospital admission are considered community-acquired.[26,29,30] This distinction has been extended to a third category of health-care associated bacteremias referring to patients recently hospitalized or regularly present in a ambulatory hospital setting, e.g. patients in hemodialysis.[31] To distinguish community-acquired from health-care associated bacteremias patients are usually not allowed any hospital contact or stay within the prior 30 days of hospital admission.[32,33] In Denmark, the most commonly isolated microorganism is *E. coli*, irrespective of place of acquisition, followed by *S. pneumoniae* and *S. areus* among community-acquired bacteremias, and followed by *S. areus* and other enterobacteria among health-care associated and nosocomial bacteremias.[34] As previously stated, an ICU patient is usually characterized by the presence in the ICU. The patients may be transferred to the ICU once admitted to the hospital or they may be transferred days to weeks after hospital admission. Consequently, the ICU patient can present with bacteremia at ICU admission, which can be any of the three categories depending on the time spent in the hospital before being

transferred to the ICU, or the ICU patient can acquire bacteremia during ICU stay, which would be considered nosocomial. For the purpose of this dissertation, we categorized bacteremias as 1) bacteremia present at ICU admission or 2) bacteremia acquired after ICU admission. In addition, bacteremias can be grouped together based on similar characteristics of the isolated microorganisms; e.g. Gram-positive rods. A distinction is made between mono- and poly-microbial bacteremias; the latter defined by the presence of more than one viable microorganism. We thus categorized bacteremias into four groups; Gram-positive bacteremia, Gram-negative bacteremia, yeasts, and poly-microbial bacteremia, in the following referred to as type of bacteremia.

1.5.1 Interrelationship between bacteremia, sepsis and intensive care

Understanding the ICU population heterogeneity it is worth noting that infections in general are a common condition/complication in ICU patients. The international EPIC II study of prevalence and outcomes of infection in intensive care units revealed that 51% of all ICU patients had an infection on the study day.[35] The most common site of infection was the lungs (64%), the abdomen (20%), the bloodstream (15%), and the renal/urinary tract (14%) followed by the skin (7%), catheter-related (5%), the CNS (3%) and others (8%).[35] According to the present guidelines, sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection.[36] Systemic manifestations of infection include fever or hypothermia, tachypnea, tachycardia, hypotension, leukocytosis or leukopenia, altered mental status, hyperlactatemia, among several others.[36] None of the clinical signs or physiological or biochemical markers used to identify systemic manifestations of infection are specific to sepsis. Many disease states present with similar signs, e.g. pancreatitis, cardiogenic shock, burns, hemorrhages, major trauma, all of which are associated with critical illness and ICU admissions. Indeed, the SIRS (Systemic Inflammatory Response Syndrome) concept used to identify systemic manifestations of infections in the former 1991 definitions of sepsis[37] was so sensitive that nearly 90% of ICU patients fulfilled the SIRS criteria.[38] Thus, among ICU patients with signs of systemic manifestations of infection, the results of blood cultures play a crucial diagnostic role. Bacteremia is closely related to sepsis even though only approximately 50% of sepsis patients have bacteremia.[37] Sepsis can progress into severe sepsis (sepsis complicated by organ dysfunction) or septic shock (sepsis with associated acute circulatory failure). The occurrence of bacteremia increases with progressive septic state as 70% of patients with septic shock have positive blood cultures compared

with 25% of patients with severe sepsis and 15% of patients with sepsis.[39,40] Conversely, only 7-24% of bacteremic patients present with septic shock.[41–44]

1.5.2 The burden of bacteremia

Bacteremia remains of major clinical and public health concern with incidence rates in Western countries exceeding 100 episodes per 100,000 person-years. The incidence rate increases markedly with age[45] and during 1992 through 2006, Søgaard et al found an increasing age- and sex-standardized bacteremia incidence rate in Northern Denmark from 114 to 166 episodes per 100,000 person-years, corresponding to a 46% increase.[34] Despite an increase in bacteremia incidence rate with joined increase in total number of bacteremia-associated deaths, the authors found a slight decrease in 30-day mortality during 1992-2006. Yet, bacteremia-associated deaths are recently estimated to be among the top seven causes of death in many European countries and North America.[46]

The majority of bacteremia patients admitted to the hospital remain hospitalized at the ward, and only approximately 9% are transferred to the ICU.[34] Risk factors for acquiring bacteremia include older age, pre-existing morbidity, and a compromised immune system.[47] Furthermore, the use of intraluminal devices and invasive procedures are associated with an increased risk of bacteremia.[48] During recent years, great emphasis has been put on the prevention of catheter-related infections in the ICU, and the implementation of central-line bundles has proven to lower bacteremia risk during ICU admission.[49] However, with the ageing population with still more people surviving chronic diseases, bacteremia incidence may continue to increase which may imply increased strain on our ICUs due to increased admissions of bacteremic patients.

1.5.3 The bacteremic elderly patient

Elderly infected patients may more frequent than younger patients present with atypical manifestations of infection. They may solely present with confusion or delirium or with symptoms of weakness, malaise, anorexia, urinary incontinence or simply just by falling, and fever may more often be absent in the elderly compared with younger patients.[47,50–52] This may lead to a delay in the correct diagnosis. Blood cultures are usually drawn on suspicion of infection and physicians may refrain from ordering a blood culture in the bacteremic elderly patient – simply because of the

atypical presentation of infection. Hence, comparison of clinical manifestations between age groups is of major clinical relevance.

1.6 Prognosis of elderly ICU patients

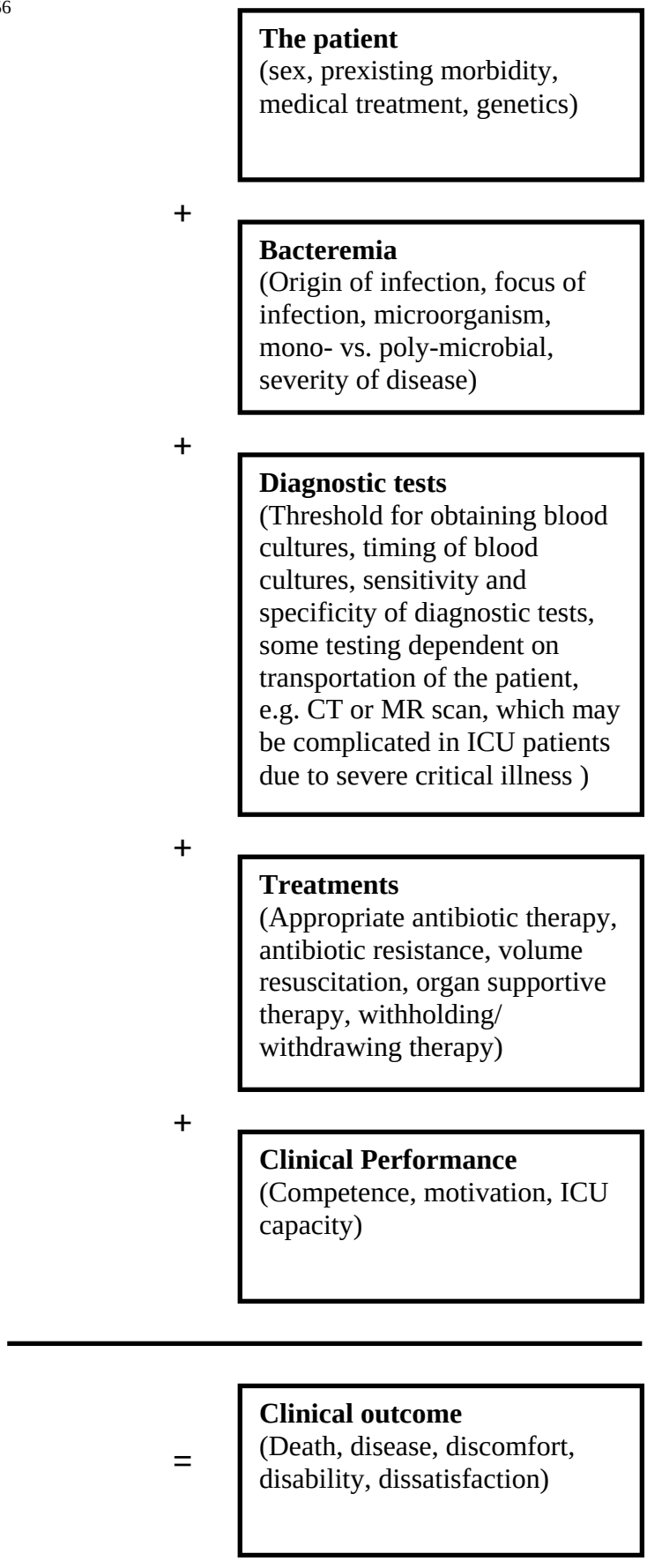
In medical terms, prognosis means the probability or risk of a particular outcome developed during a specific time.[53,54] The outcomes are distinct events such as death or development of disease, but also the measurements of symptoms (e.g. pain), functional status, and quality of life.[55] Several factors may influence any particular outcome, which is displayed in Figure 1.1.[56]

The prognosis of elderly ICU patients may be influenced by preexisting morbidity but also on treatments prior to ICU admission, the cause of admission and the severity of disease when entering the ICU, the timing of diagnostic tests performed, e.g. blood cultures in the elderly bacteremic patient, adequate antibiotic therapy and volume resuscitation, and decisions on withholding or the withdrawal of treatment.

Data on prognostic factors may improve our understanding of the clinical course in elderly ICU patients, which may help guide clinical decision-making. Prognostic studies can be divided in prediction studies and etiological studies.[53] While etiological studies have a hypothesis of a causal association between exposure and outcome, prediction studies are designed to predict an outcome based on many different variables. Hence, a predictive model may be able to predict the risk of a future outcome with high accuracy, but the model is not designed to reflect causality. Several prediction studies have identified age as an important predictor of mortality in ICU patients, and age is thus included in some severity of illness scores, e.g. the Simplified Acute Physiology Score (SAPS) or the Acute Physiology And Chronic Health Evaluation (APACHE) score, which were developed to predict in-hospital mortality.[57–59]

The studies throughout this dissertation are prognostic etiological studies examining causality of age on different outcomes. The effect of age may vary within the heterogeneous ICU population and we thus stratified our analyses by different subgroups to address potential effect-measure modification.[60]

Figure 1.1. Factors that may determine the outcome in elderly ICU patients (modified from *Sackett*)[56]



2 Background and existing literature

2.1 Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report.

Randomized clinical trials, the gold standard in clinical research, are considered superior to observational studies in examining an effect of an intervention.[61] Yet, not all research questions can be examined in a trial, e.g. when examining the effect of age on various outcomes - age cannot be randomized. In addition, clinical trials are often arduous and resource-intensive in the ICU setting as patients are often unconscious implying difficulties in obtaining informed consent. Danish health care registries constitute a cost-effective way of conducting observational ICU studies. Data are usually collected for administrative purposes, which reduces the risk for recall bias and non-response bias.[62] The data quality is very important when relying on the coding for any given exposure or outcome, or when using a specific coding to identify a study population, e.g. an ICU population. We used the Danish National Patient Registry (DNPR) to identify our ICU cohort by using the coding for ICU admission. In addition, we used the registered coding for mechanical ventilation and renal replacement therapy to evaluate the extent of ICU treatments.

We searched Medline using the following query (last search December 20, 2014):

((“Validity”[all fields] OR “positive predictive value”[all fields]) AND (“Danish National Patient Registry ”[all fields] OR “Danish National Registry of Patients”[all fields]))

This resulted in 91 hits. None of the studies examined validity of registered coding of mechanical ventilation and renal replacement therapy in the DNPR, and to the best of our knowledge, only 1 study examined validity of ICU admission in the DNPR. The study by Christiansen et al examined the coding for ICU admission and found a PPV of 98.7% (95% CI: 95.3-99.8) in a sample of 150 medical records from one hospital.[25]

2.2 Mortality in elderly ICU patients: a cohort study (study II)

As stated previously, prediction studies have identified age as an important predictor of both short- and long term-mortality in ICU patients.[63–65] The PREDICT study found age and comorbidity as the most important determinants of mortality in ICU patients for up to 15 years following ICU admission.[65] We aimed to examine the association of age on mortality and performed a Medline search using the following query (last search December 20, 2014):

((“Critical care”[MeSH] OR “Intensive Care Units”[MeSH]) AND (“Deaths”[MeSH] OR “Mortality”[MeSH]))

The search was limited to articles in English or Danish language, to human studies, and to ages (80 and over: 80+ years), which resulted in several studies (a total of 1256 hits). Most of the studies were predictive studies examining a wide range of prognostic factors. In addition, several studies investigated demographics, resource utilization, mortality trends over time etc. among patients aged 80+ years.[66–70] Even though these studies are very valuable in characterizing the critically ill elderly, they do not examine the effect of age on mortality. The study by de Rooij et al found severity of illness at admission as the most important factor determining ICU mortality in patients aged 80+ years.[70] This is supported by Roch et al, who investigated predictors of 2-year mortality in patients aged 80+ years following admission to a medical ICU.[67] Few studies had age as the primary exposure and most of them examined the association of age on in-hospital and short-term mortality. Table 2.1 displays the most important studies with study populations of more than 1,000 patients.[13,14,71–75]

In summary, in-hospital mortality increases with increasing age. Prediction studies have revealed age as important determinant of long-term survival. This is supported by Fuchs et al who investigated the impact of age on 28-day and 29-365-day mortality.[72] They included ICU patients above age 65 years, and only patients admitted because of non-surgical and acute surgical admissions. The 29-365-day mortality increased with increasing age and the HR was 1.85 (95% CI 1.57-2.17) in patients aged 85+ and 1.52 (95% CI 1.32-1.74) in patients aged 75-84 years compared with patients aged 65-74. The heterogenic ICU population consists of both non-surgical and acute/elective surgical patients, and the previous studies differed with respect to age categories, study population (the restriction to either acute/elective surgical or non-surgical ICU patients,

restriction to mechanically ventilated patients), and the adjustment for different covariates, which complicates comparison of existing studies. Thus, by including all ICU patients irrespective of admission type and age, this may improve generalization to the general ICU patient.

Table 2.1: Selected studies on short- and long-term mortality in ICU patients

First author/ Year	Design/setting	Study population	Age/age group	Outcome	Risk estimates	Adjusted relative risk estimates
Elia,[71] 2013	Cohort study, Germany	11,537 surgical ICU patients (18+ years) 2004-2009	18-50 51-65 66-75 76-85 85+	In-hospital mortality	OR	Each additional year of age increased the risk for death, OR 1.04 (1.03-1.04)
Fuchs,[72] 2012	Cohort study, USA	7,265 non-surgical and acute surgical ICU patients (65+ years), 2001-2008	65-74 75-84 85+	28-day mortality	OR	65-74: 1 (ref) 75-84: 1.52 (1.32-1.74) 85+: 1.85 (1.57–2.17)
				29-365-day mortality	HR	65-74: 1 (ref) 75-84: 1.52 (1.32-1.74) 85+: 1.85 (1.57–2.17)
Bagshaw,[14] 2009	Multicenter cohort study, Australia and New Zealand	120,123 ICU patients (18+ years), 2000-2005	18-40 40-64 65-79 80+	In-hospital mortality	OR	18-40: 1 (ref) 40-64: 1.77 (1.6-1.9) 65-79: 3.17 (2.9-3.4) 80+: 5.37 (4.9-5.9)
Reinikainen,[13] 2007	Multicenter cohort Study, Finland	79,361 ICU admissions (0+ years), 1998-2004	0-39 40-59 60-69 70-74 75-79 80+	In-hospital mortality	OR	0-39: 1 (ref) 40-59: 2.05 (1.84-2.29) 60-69: 3.17 (2.83-3.55) 70-74: 4.14 (3.68-4.66) 75-79: 5.41 (4.81-6.10) 80+: 7.08 (6.26-7.99)
Rosenthal,[73] 2002	Multicenter cohort study, USA	156,136 ICU patients (16+ years), 1991-1997	<35 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89 90+	In-hospital mortality	OR	<35: 1 (ref) 35-39: 1.15 (0.97-1.35) 40-44: 1.51 (1.30-1.75) 45-49: 1.70 (1.47-1.75) 50-54: 1.73 (1.50-1.98) 55-59: 2.01 (1.82-2.37) 60-64: 2.38 (2.10-2.70) 65-69: 2.52 (2.24-2.83) 70-74: 2.98 (2.66-3.35) 75-79: 3.26 (2.90-3.66) 80-84: 3.86 (3.42-4.34) 85-89: 4.09 (3.60-4.65) >90: 4.74 (4.09-5.49)
Hamel,[74] 1999	Multicenter cohort Study, USA	9,105 ICU patients (18+ years),	18	180-day mortality	HR	Each additional year of age increased the hazard of death by 1.0% (HR, 1.010 [1.007 to 1.013]) for patients aged 18-70 and by 2.0% (hazard ratio, 1.020 [1.013 to 1.026]) for patients >70
Cohen,[75] 1995	Cohort study, USA	14,848 mechanically ventilated ICU patients (18+ years), 1990	18	In-hospital mortality	Mortality (%)	85+: 70% 29+: 32%

2.3 Impact of age on the burden of bacteremia in intensive care unit patients (study III)

Bacteremia incidence rises with advancing age. A U.S. population-based cohort study examined bacteremia incidence in the general population according to age using a microbiological database to identify all positive blood cultures during a two-year period (2003-2005).[45] The incidence rate was nearly 10-fold higher among patients aged 80+ than in patients aged 40-59 years (1455.0 vs. 140.6 per 100.000 person, respectively). Following the ageing world population with a potential increase in ICU admissions of elderly patients, we hypothesized that the bacteremia burden was elevated in the elderly ICU patient compared with younger patients. The following query was used searching Medline (last search December 20, 2014):

((“Critical care”[MeSH] or “Intensive care units”[MeSH]) AND (“Bacteremia”[MeSH] or “Bloodstream infections”[all fields] or “Blood stream infections”[all fields]) AND (“Incidence”[MeSH] OR “Prevalence”[MeSH] OR “Epidemiology”[MeSH]))

The search was limited to articles in English or Danish language, to human studies, and to ages (80 and over: 80+ years), which resulted in 56 hits. After title and abstract review, only 4 were found to be of relevance and were selected for full article review.[76–79] Only two ICU studies examined the effect of age on bacteremia epidemiology.[76,77] The cross-sectional EPIC II study examined the effect of age on the prevalence of infections in the ICU. This study revealed a decrease in bacteremia prevalence with increasing age.[76] The study was a point-prevalence study with consequently no distinction between bacteremias present at ICU admission or acquired during ICU stay. The study by Blot et al investigated the effect of age on ICU-acquired bacteremia.[77] In accordance with the EPIC II findings, they found a decreasing bacteremia incidence with increasing age (8.4 /1000 patient days in patients aged 45-64 years, 5.5/1000 patient days in patient aged 65-74 years, and 4.6/1000 patient days in patient aged 75+). The remaining two studies by Laupland et al were prediction studies.[78,79] The first study examined risk factors associated with severe bacteremia requiring ICU admission.[78] The risk of severe bacteremia increased with increasing age (>65 years) with a relative risk of 7.0 (95% CI 5.6-8.7). The second study examined incidence, risk factors and associated mortality of ICU-acquired bacteremia.[79] The incidence of ICU-acquired bacteremia was 4.4%, and younger age (<65 years) was associated with increased risk of acquiring bacteremia.
We searched the reference list of the selected publication for other relevant articles and expanded the literature search to patients outside the ICU (510 hits). After reviewing title and abstract no

additional study examined age as primary exposure. In summary, when focusing on ICU-acquired infections, the incidence *decreases* with increasing age. On the other hand, the risk of severe bacteremia requiring ICU admission *increases* with increasing age. To the best of our knowledge, no prior study has examined bacteremia in ICU patients with discrimination of bacteremias present at ICU admission and acquired after ICU admission.

2.4 Mortality in elderly intensive care patients with early bacteremia: a Danish cohort study (study IV)

Mortality following bacteremia remains significant. A recent review estimated at least 158,000 deaths per year in Europe and at least 79,000 deaths per year in North America following bacteremia placing it among the top seven causes of death in many European countries and North America.[46] We aimed to examine mortality according to age in bacteremic ICU patients. The following query was used searching Medline (last search December 20, 2014):

((“Critical care”[MeSH] or “Intensive care units”[MeSH]) AND (“Bacteremia”[MeSH] or “Bloodstream infections”[all fields] or “Blood stream infections”[all fields]) AND (“Deaths”[MeSH] OR “Mortality”[MeSH]))

The search was limited to articles in English or Danish language, to human studies, and to ages (80 and over: 80+ years), which resulted in 33 hits. After title and abstract review, only one study was found to be of relevance. The study by Blot et al examined epidemiology of nosocomial bacteremia in the critically ill elderly including an estimation of in-hospital mortality.[77] The in-hospital mortality increased with age and was 56% in patients aged 75+ years, 49.1% in patients aged 65-75 years, and 42.9% in patients aged 45-64 years with corresponding adjusted HR 1.8 (95% CI: 1.4 - 2.4) and 1.2 (95% CI: 1.0 -1.5) respectively, compared with patients aged 45-64 years. We omitted the restriction to intensive care units in our literature search using the following query (last search December 20 2014):

((“Bacteremia”[MeSH] or “Bloodstream infections”[all fields] or “Blood stream infections”[all fields]) AND (“Prognosis”[MeSH] OR “Mortality”[MeSH]))

The search was limited to articles in English or Danish language, to human studies, and to ages (80 and over: 80+ years) and resulted in 747 hits. As for the literature search performed in study II, the

majority of studies were purely predictive studies examining many different prognostic factors leaving very few with age as primary exposure. Majority of studies investigated short-term mortality.[27,51,77,80–83] In addition, comparison of existing studies is complicated by smaller sample sizes and differences in study populations. The selected studies are displayed in Table 2.2. Data on long-term mortality remain sparse. Yet, prediction studies have found age as an important predictor of both 1-year[84] and 3-year mortality.[85]

Table 2.2: Selected studies on short-term mortality in bacteremic patients irrespective of type of admission

First author/year	Design/setting	Study population	Age/age group	Outcome	Risk estimates	Adjusted relative risks estimates
Blot,[77] 2009	Cohort study, 192-2006	984 ICU patients with nosocomial bacteremia	45-64 65-74 75+	In-hospital mortality	HR (95%CI)	45-64: 1(ref) 65-74: 1.2 (1.0-1.5) 75+: 1.8 (1.4-2.4)
Søgaard,[80] 2008	Cohort study, 1995-2004	2,851 medical patients with community-acquired bacteremia	15-64 65-79 80+	7-day mortality	HR (95 %CI)	15-64: 1 (ref) 65-79: 1.4 (1.0-2.0) 80+: 1.6 (1.1-2.2)
				30-day mortality		15-64: 1 (ref) 65-79: 1.5 (1.2-2.0) 80+: 1.8 (1.4-2.3)
Lee,[81] 2007	Cohort study, 2001-2002	890 ED patients with community-acquired bacteremia	18-64 65-84 85+	90-day mortality	HR (95 %CI)	Each additional year of age increased the risk for death by 1.01 (1.0-1.02)
Nørgaard,[82] 2005	Cohort study, 1992-2002	358 bacteremia patients with hematological malignancies	15-59 60-79 80+	7-day mortality	HR (95 %CI)	15-59: 1 (ref) 60-79: 1.6 (0.8-3.1) 80+: 1.8 (0.7-4.4)
				30-day mortality		15-59: 1 (ref) 60-79: 1.7 (1.1-2.7) 80+: 2.3 (1.2-4.3)
Pedersen,[27] 2003	Cohort study, 1992-1997	1844 patients with community-acquired bacteremia	15-64 65-74 75-84 85+	30-day mortality	OR (95 %CI)	15-64: 1 (ref) 65-74: 1.1 (0.8-1.6) 75-84: 1.5 (1.0-2.1) 85+: 1.9 (1.3-2.9)
Gavazzi,,[83] 2002	Surveillance study, Jan 1-Dec 31 1998	1740 hospitalized patients with bacteremia	65-74 75-84 85+	7-day mortality	OR (95% CI)	Estimates not given, but the authors conclude Overall no difference between age groups except for community-acquired bacteremia
Leibovich,[51] 1993	Cohort study, 1988-90	995 medical patients	60-79 80+	In-hospital mortality	OR (95% CI)	Each additional year of age increased the risk for death by1.1 (1.0-1.2) among patients aged 60-79 NS for patients aged 80+

3 Aims of this dissertation

- To examine validity of recorded coding of ICU admission, mechanical ventilation, and renal replacement therapy in the DNPR by estimating the PPV (study I).

- To examine recent changes in the proportion of elderly ICU patients in intensive care over time and to examine the association between age and mortality in ICU patients. In addition, to evaluate the impact of preexisting morbidity on the association between age and mortality in ICU patients (study II).

- To examine the impact of age on the burden of bacteremia during ICU admission and to describe the clinical manifestations at ICU admission associated with bacteremia in relation to age (study III).

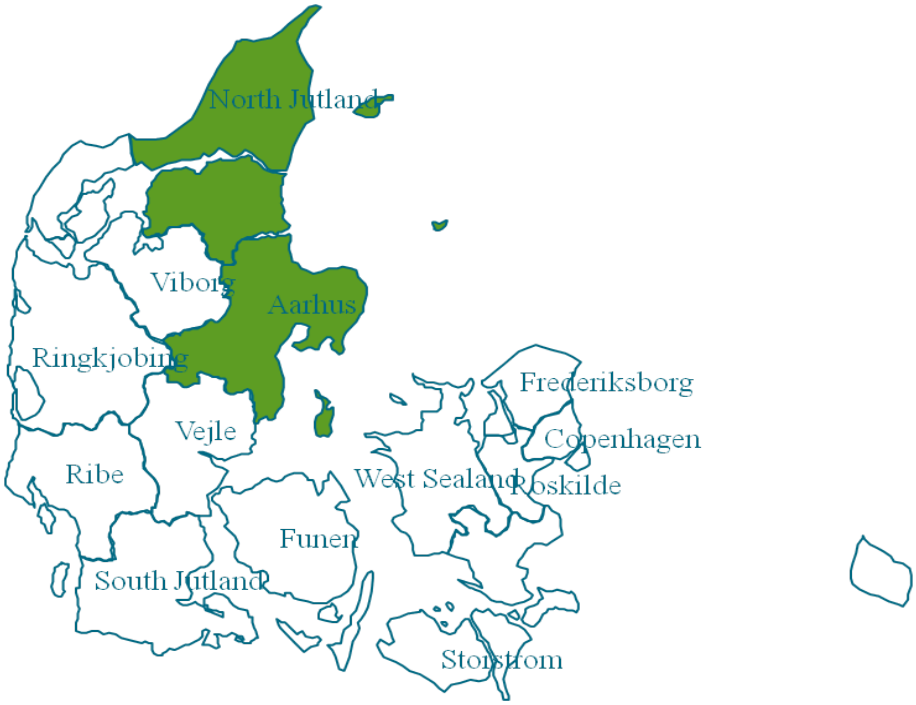
- To examine the impact of age on 7-day, 8-31-day, and 31-365-day mortality in a cohort of ICU patients with bacteremia. In addition, to examine the impact of age on mortality at different levels of preexisting morbidity (study IV).

4 Patients and methods

4.1 Setting

We conducted study I within the population of the former county of North Jutland (approximately 500,000 people). Studies II-IV were conducted within the population of Northern Denmark (the former counties of Aarhus and North Jutland), which counts approximately 20% of the Danish population (1.15 million people).

The Danish health care system provides universal tax-supported health care to all Danish citizens, which guarantees equal access to primary and hospital care, including access to all ICUs in Denmark. The study area is mixed urban-rural including 12 ICUs (1 neurosurgical ICU, 1 neurosurgical/multidisciplinary ICU, 2 cardiothoracic/multidisciplinary ICUs, 8 multidisciplinary ICUs).



4.2 Data sources

4.2.1 The Danish National Patient Registry (studies I-IV)

The Danish National Patient Registry (DNPR) includes information on all discharges from all non-psychiatric hospitals since 1977.[86,87] In 1995, information on all visits to emergency rooms and outpatient clinics were added. Data include the patient's civil registration number (CPR-number), dates of admission and discharge, procedure codes, one primary diagnosis and up to 19 secondary diagnoses coded by physicians. Diagnoses were classified according to the *International Classification of diseases* (ICD), 8th revision until 1993, and 10th revision thereafter. Information on ICU admission, including major treatments during ICU stay, has been recorded routinely since 2005.

4.2.2 The Civil Registration System (studies II-IV)

Established in 1968, the Civil Registration System (CRS) contains information on vital status, residency and exact date of death for all Danish residents.[88] Furthermore, this registry assigns the unique CPR-number to all Danish residents at birth or immigration, which allows the unambiguous linkage of all Danish medical and administrative registries.

4.2.3 The Laboratory Information System maintained at the Departments of Clinical Microbiology, Aalborg University Hospital and Aarhus University Hospital (studies III-IV)

The laboratory information system (ADBact, Autonik, Ramsta, Sköldinge, Sweden) is maintained at the Departments of Clinical Microbiology, Aalborg University hospital and Aarhus University Hospital. Data include the patient's CPR-number, date of blood culture drawn, species and results of antibiotic susceptibility testing. The blood culture system used during our study period was the BacT/Alert system (bioMérieux, Marcy l'Etoil, France). The nominal volume per blood culture was 28-32 ml (adult patients). In the former North Jutland County, a blood culture set comprised 3 bottles. In the former Aarhus County, a blood culture set comprised 2 bottles, and the drawing of two sets was recommended for adult patients.

4.2.4 The Clinical Laboratory Information System (LABKA) research database (studies III-IV)

The LABKA research database was established in the 1990's when the hospitals located in the former North Jutland and Aarhus County started transferring data to the database.[89] Data contains test results from every blood sample drawn at any public or private hospital or by any general practitioners and submitted to any clinical chemistry department located in the North and Central Denmark Regions, date of test, NPU-code and unit, and the patients CPR-number. Completeness of registration by geographical coverage was accomplished in 1997 and 2000 for the former North Jutland and Aarhus County, respectively.

4.2.5 The Aarhus University Prescription Database (studies III-IV)

The Aarhus University Prescription Database contains information on all reimbursed medications dispensed at all pharmacies of the North and Central Denmark Region.[90] Established in the 1990's, this registry includes the patients CPR-number, prescribed drug according to the Anatomical Therapeutic Chemical (ATC) classification, dosage, and date of sale. Completeness of registration for the study area was accomplished in 1998.

4.2.6 Medical records (study I)

We reviewed 147 medical records in study I. All notes for the entire hospital stay from date of ICU admission and onwards were reviewed to confirm ICU admission, treatment with mechanical ventilation, and renal replacement therapy as identified through the DNPR.

4.3 Study design

Study I was designed as a validation study; studies II-IV were designed as cohort studies.

4.4 Study population

The study population in all four studies was adult ICU patients (aged ≥ 15 years).

Study I: We used the DNPR to randomly select a total of 150 patients with a hospital admission during 1 January 2005 to 31 December 2010 from each of three categories: (1) 50 patients

registered with an ICU admission (2) 50 patients registered with both ICU admission and mechanical ventilation and (3) 50 patients registered with both ICU admission and renal replacement therapy.

Study II: We used the DNPR to identify all admissions to an ICU in Northern Denmark from 1 January 2005 to 31 December 2011. For patients with more than one ICU admission during our study period, each ICU admission was counted as a separate admission, if there was at least one year between the admissions (49,938 ICU admissions corresponding to 47,596 patients).

Study III: We used the DNPR to identify all first-time admissions to an ICU in Northern Denmark from 1 January 2005 to 31 December 2011. Residency in the study area one year prior to index hospitalization was required in order to ensure availability of data registered in regional registries (n=47,579).

Study IV: We linked data on bacteremia obtained from the Laboratory Information System maintained at the Departments of Clinical Microbiology in Aarhus and Aalborg, to the study cohort identified in study III in order to identify ICU patients with bacteremia, at date of ICU admission or within the first seven days of ICU stay. Thus, by linking these databases, we ended up with a total cohort of 1,348 bacteremia patients with a first-time ICU admission.

In ***studies II-IV***, information on the primary diagnosis of the current hospital stay was used to categorize the patients into major disease groups. In addition, we obtained information on surgical procedures registered in the DNPR, performed on the day of ICU admission or within seven days prior to ICU admission. Furthermore, patients registered with surgical procedures were categorized as elective or acute by using the coding for elective/acute hospital admission registered in the DNPR; hence, the patients were classified as non-surgical, elective or acute surgical ***(studies II-III).***

4.5 Exposures

4.5.1 The DNPR (study I)

The exposure in study I was the Danish procedure coding for ICU admission, mechanical ventilation, and renal replacement therapy registered in the DNPR (NABE/NABB [intensive care observation/intensive care therapy], BGDA0 [mechanical ventilation], BJFD00/BJFD02 [acute hemodialysis/continuous venovenous hemodiafiltration]).

4.5.2 Age at ICU admission (studies II-IV)

The exposure in studies II-IV was age at ICU admission categorized into the following age groups: 15-49; 50-64; 65-79; 80+.

4.6 Outcomes

4.6.1 Medical records (study I)

The outcome in study I was the actual admission to an ICU, treatment with mechanical ventilation, or treatment with renal replacement therapy as ascertained by reviewing each patients medical record. Thus, the gold standard in our validation study was the medical records.

4.6.2 Mortality (studies II and IV)

The outcome in studies II and IV was all-cause mortality after ICU admission (study II) or after date of drawn blood culture (study IV). Information on date of death was obtained from the Civil Registration System. We aimed to examine both short-term and long-term mortality and we divided our follow-up into a 0-30-day and 31-365-day period (study II), and a 0-7-day, 8-30-day, and 31-365-day period (study IV).

4.6.3 Bacteremia (study III)

The outcome in study III was bacteremia as defined by the first positive blood culture obtained from 2 days before to 7 days after ICU admission. This date was also regarded as first date of infection. Information on positive blood cultures was obtained from the laboratory information system, maintained at the Departments of Clinical Microbiology, Aalborg University Hospital and Aarhus University Hospital.

4.7 Covariates

Data on sex was obtained from the CRS.

4.7.1 Primary diagnosis of current hospital stay (study II)

Information on the primary diagnosis of the current hospital stay was obtained from the DNPR and used to categorize the patients into eight major disease groups (infectious diseases, cardiovascular

diseases, respiratory diseases, gastrointestinal/liver diseases, endocrine diseases, neoplasms, trauma/poisoning, and other diseases).[91]

4.7.2 Pre-existing morbidity (studies II-IV)

We obtained data on pre-existing morbidity from the DNPR to compute the Charlson Comorbidity Index (CCI).[92] The CCI was based on all hospital discharge codes registered within five years prior to the current hospitalization. Morbidity levels were divided into three groups: low (CCI score = 0), moderate (CCI score 1 and 2) and high (CCI score 3 or more).

4.7.3 Acute organ dysfunction (studies III-IV)

We used the LABKA research database to determine level of C-reactive protein (CRP) and white blood cell (WBC) count as a marker of inflammation. In addition, we obtained information on organ-specific dysfunction of kidney, liver, and coagulation system using laboratory cut-off values in the Sequential Organ Failure Assessment (SOFA) score.[93] If routine measurements on day of ICU admission were missing, we replaced it with a measurement on the day before or after admission.

4.7.4 Immune status (studies III-IV)

We used the Aarhus University Prescription Database to obtain information on patients with previous filled prescriptions for immunosuppressive therapy within 1 year prior to ICU admission (ATC: L01, L04, H02A, H02B) as a proxy for compromised immune system.

4.7.5 Type of bacteremia (study IV)

Based on the isolated microorganism, we categorized bacteremias into Gram-negative, Gram-positive, yeast or polymicrobial bacteremia.

4.8 Statistical analyses

In ***study II***, follow-up began at date of ICU admission and the patients were followed until death, emigration, for 365 days or to 1 January 2012, whichever came first.

In ***study III***, follow-up began on day 2 following ICU admission and the patients were followed until, death, emigration, for 6 days (days 2-7) or to 1 January 2012, whichever came first.
In ***study IV***, follow-up began at date of drawn blood culture and the patients were followed until death, emigration, for 365 days or to 1 January 2012, whichever came first.
All statistical analyses were performed using Stata software (version 11.2; StataCorp LP, College Station, TX). The study was approved by the Danish Data protection Agency (record no. 2009-41-3987).

4.8.1 Validity (study I)

In ***study I***, we examined the validity of the coding for ICU admission, mechanical ventilation, and renal replacement therapy and defined the positive predictive value (PPV) of each of the three procedure codes as the proportion of patients registered with the specific coding in the DNPR who also received this treatment according to their medical records. We estimated 95% CI's calculated with Jeffrey's CI's.

4.8.2 Prevalence (studies II-III)

In ***study II***, we estimated the prevalence proportion ratio (PPR) with 95% CI comparing the prevalence of elderly patients admitted to an ICU in 2005 with the prevalence in 2011. In addition, the PPR was estimated comparing the prevalence of elderly hospitalized patients in 2005 with the prevalence in 2011. In ***study III,*** we estimated the bacteremia prevalence at ICU admission (defined as a positive blood culture obtained within a time period from 2 days before to 1 day after ICU admission) by age group. We compared these by prevalence odds ratios (PORs) estimated using logistic regression adjusted for sex, CCI score and immunosuppressive therapy.

4.8.3 Cumulative incidence (studies II-IV)

In ***studies II and IV,*** we estimated the cumulative 1-year mortality using the Kaplan-Meier method (= 1 minus the survival probability with 95% CI). In ***study III***, we estimated the risk of developing bacteremia during days 2-7 after ICU admission. Follow-up began at day 2 after ICU admission, and if the patients died during our follow-up, death was a competing event to bacteremia. We therefore estimated the cumulative incidence of bacteremia accounting for death as competing risk.[94]

4.8.4 Cox proportional hazards regression (studies II-IV)

In ***studies II-IV,*** we used a Cox proportional hazards regression model to compute crude and adjusted hazard ratios (HRs) with 95% CI. In ***studies II and IV,*** the HRs represented mortality rate ratios (MRRs). The assumption of proportional hazards was checked by log (-log) plots and found acceptable.

Study II: We examined 0-30-day and 31-365-day mortality risk and compared MRRs between age groups using the age group of 50-64 as reference group. The analysis was adjusted for sex, primary diagnosis of current hospital stay, and CCI score. To control for worse prognosis among non-surgical and acute surgical patients than elective surgical patients, we stratified the analyses by admission type (non-surgical, acute/elective surgical).

Study III: We examined 2-7-day risk of bacteremia among patients without bacteremia at day 1 after ICU admission, and compared HRs between age groups using the age group of 15-49 as reference group. The analysis was adjusted for sex, CCI score, and immunosuppressive therapy. We expected bacteremia more often to occur among non-surgical and acute surgical patients than elective surgical patients. We therefore stratified the analysis by type of admission (non-surgical, acute/elective surgical).

Study IV: We examined 0-7-day, 8-30-day, and 31-365-day mortality risk and compared MRRs between age groups using the age group of 50-64 as reference group. The analysis was adjusted for sex, CCI score, type of bacteremia and immunosuppressive therapy.

4.8.5 Sensitivity analyses

Study III: Patients dying shortly after ICU admission are no longer at risk of bacteremia, and we therefore performed a sensitivity analysis of bacteremia PORs, with a redefinition of the time period to a positive blood culture obtained from 2 days before to the day of ICU admission.

5 Results

Below follows a summary of the main results obtained in the four studies.

5.1 Study I: Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report

We were able to locate 147 of the 150 medical records (98%). The three unavailable medical records were all patients identified though the DNPR with registered coding for intensive care admission only. These patients were excluded before analysis. Median age was 67.4 years (interquartile range (IQR) 56.7-75.4 years) and 64% were men. Of the 147 included patients, 141 (95.9% (95% CI: 91.8-98.3)) had been admitted to an ICU according to their medical records. Table 5.1 displays the PPV for the registered coding of ICU admission, mechanical ventilation, and replacement therapy in the DNPR.

Table 5.1: PPV and 95% CI for a registered coding for ICU admission, mechanical ventilation, and renal replacement therapy in the DNPR

Procedure coding	**n/N**	**PPV (95% CI)**
ICU admission	41/47	87.2% (75.6-94.5)
Mechanical ventilation	50/50	100% (95.1-100)
Renal replacement therapy	49/50	98% (91.0-99.8)

The 6 patients without a confirmed ICU admission were 3 young patients having surgery with uncomplicated post-surgery courses admitted to a district hospital. The remaining 3 miscoded patients were hospitalized with carotid artery surgery, stroke, and trauma, respectively, and were admitted to a university hospital.

One patient did not receive renal replacement therapy as registered in the DNPR. The misclassified patient, however, was admitted to an ICU.

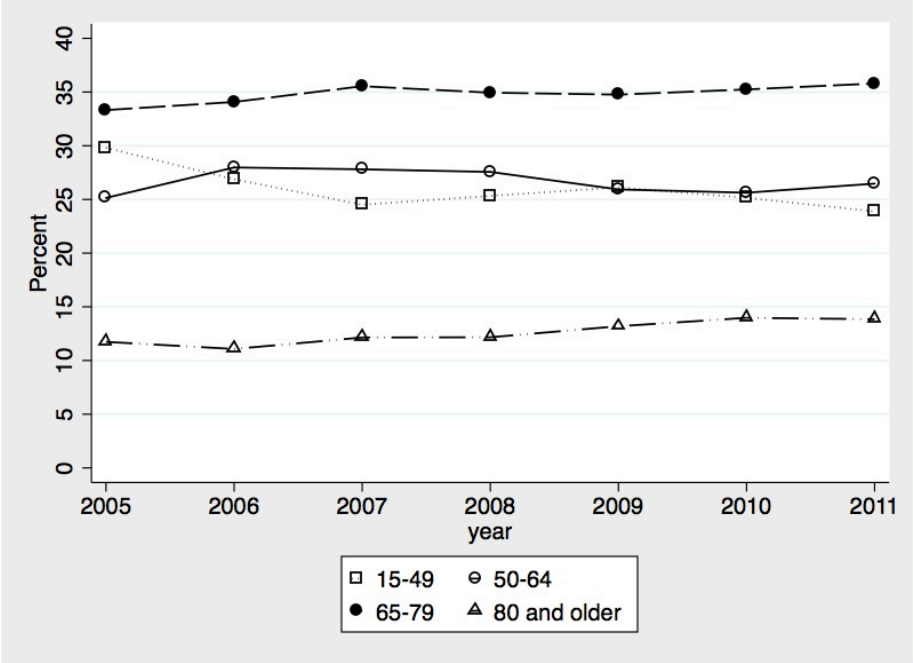
5.2 Study II: Mortality in elderly ICU patients: a cohort study

We identified 49,938 ICU admissions corresponding to 47,596 patients during the 7-year study period. Median age was 64 years (IQR 49-74 years), 57.5% were men, and 62.5% were surgical patients.

5.2.1 Prevalence of elderly patients admitted to an ICU by calendar year

Throughout the entire study period the prevalence of elderly ICU patients accounted for 12.6% of all admissions. The prevalence of elderly ICU patients increased slightly from 11.7% (898/7,653) in 2005 to 13.8% (845/6,104) in 2011 corresponding to a PPR of 1.18 (95% CI 1.08-1.29). By comparison, a smaller increase in hospital admissions of the elderly was seen from 13.4% in 2005 to 14.3% in 2011, which corresponded to a PPR of 1.06 (95% CI 1.05-1.08). During our study period there was no increase in the proportion of elderly people in the general population as people aged 80+ years accounted for 4.1% of the population in both 2005 and 2011.

Figure 5.1. Annual ICU admissions by age group

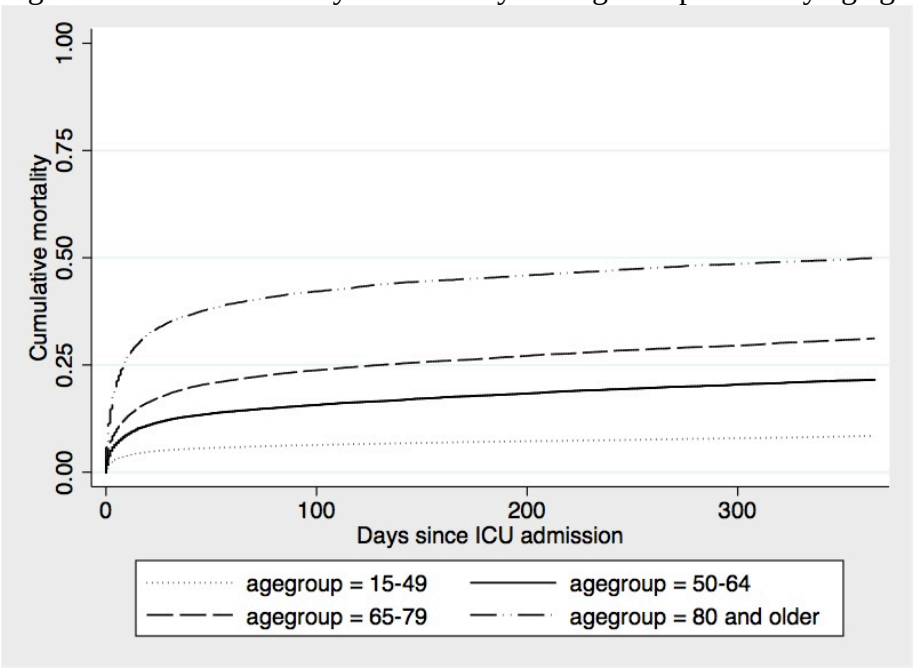


5.2.2 Mortality

49% of the elderly died within 1 year compared with only 11.7% (average mortality during the study period) of the elderly from the general population. By comparison, mortality was 31% in

patients aged 65-79 years, 21% in patients aged 50-64 years, and 8% in patients aged 15-49 years compared with 2.7%, 0.77%, and 0.10% among the same age groups in the general population.

Figure 5.2. Cumulative 1-year mortality among ICU patients by age groups



5.2.3 30-day and 31-365-day mortality stratified on type of admission

The 30-day and 31-365-day mortality are presented in Tables 5.2-4. Elderly patients had a higher mortality than younger patients irrespective of admission type. The absolute mortality was higher in non-surgical patients (Table 5.2) and acute surgical patients (Table 5.3) among all age groups than in elective surgical patients (Table 5.4). In elderly patients with elective surgical admissions, the 30-day adjusted MRR of 5.2 (95% CI 4.1-6.6) was higher than the adjusted MRR of 2.7 (95% CI 2.5-3.0) and 2.7 (95% CI 2.4-3.0) in non-surgical and acute surgical patients, respectively. By comparison, even though the absolute 31-365-day mortality was higher among non-surgical (Table 5.2) and acute surgical patients (Table 5.3) compared with elective surgical patients (Table 5.4) the relative risk of dying in the elderly was approximately the same. Standardization to the distribution of pre-existing morbidity in the age group of 50-64-year-old patients did neither change the 30-day nor the 31-365-day mortality substantially (Tables 5.2-4).

Table 5.2: Crude and adjusted risk of death and mortality rate ratio (MRR) within 30- or 31-365-day among intensive care unit patients admitted for medical (non-surgical) reasons by age

Age group, n	Dead, n / N	Mortality, %	Standardized mortality, % (95%CI)	Crude MRR (95%CI)	Adjusted* MRR (95%CI)	Adjusted** MRR (95%CI)
30-day						
≥80 years	1,019 / 2,332	43.7	43.2 (41.0-45.4)	3.0 (2.8-3.3)	2.8 (2.6-3.1)	2.7 (2.5-3.0)
65-79 years	1,529 / 5,523	27.7	26.0 (24.8-27.2)	1.7 (1.6-1.9)	1.6 (1.4-1.7)	1.5 (1.4-1.6)
50-64 years	789 / 4,655	17.0	17.0 (15.9-18.0)	1 (ref.)	1 (ref.)	1 (ref.)
15-49 years	318 / 6,223	5.1	7.3 (6.5-8.2)	0.3 (0.2-0.3)	0.4 (0.3-0.4)	0.4 (0.4-0.5)
31-365-day						
≥80 years	333 / 1,313	25.4	23.4 (21.0-25.8)	2.8 (2.5-3.3)	2.7 (2.3-3.1)	2.5 (2.1-2.9)
65-79 years	681 / 3,994	17.1	14.9 (13.8-16.0)	1.8 (1.6-2.1)	1.6 (1.5-1.9)	1.5 (1.3-1.7)
50-64 years	381 / 3,866	9.9	9.9 (8.9-10.8)	1 (ref.)	1 (ref.)	1 (ref.)
15-49 years	177 / 5,905	3.0	5.2 (4.4-6.0)	0.3 (0.2-0.4)	0.4 (0.3-0.4)	0.5 (0.4-0.5)

* Adjusted for sex and primary diagnosis of current hospital stay
** Adjusted for sex, primary diagnosis of current hospital stay, and Charlson comorbidity score

Table 5.3: Crude and adjusted risk of death and mortality rate ratio (MRR) within 30- or 31-365-day among intensive care unit patients admitted after acute surgery by age

Age group	Dead, n / N	Mortality, %	Standardized mortality, % (95%CI)	Crude MRR (95%CI)	Adjusted* MRR (95%CI)	Adjusted** MRR (95%CI)
30-day						
≥80 years	1,021 / 2,581	39.6	39.4 (37.3-41.5)	2.7 (2.5-3.0)	2.8 (2.6-3.1)	2.7 (2.4-3.0)
65-79 years	1,354 / 5,153	26.3	25.2 (24.0-26.4)	1.6 (1.5-1.8)	1.6 (1.5-1.8)	1.5 (1.4-1.7)
50-64 years	725 / 4,278	17.0	17.0 (15.8-18.1)	1 (ref.)	1 (ref.)	1 (ref.)
15-49 years	320 / 4,753	6.7	10.1 (8.9-11.3)	0.4 (0.3-0.4)	0.4 (0.4-0.5)	0.5 (0.4-0.5)
31-365-day						
≥80 years	419 / 1,560	26.9	26.8 (24.3-29.3)	2.4 (2.1-2.7)	2.4 (2.1-2.8)	2.2 (1.9-2.5)
65-79 years	764 / 3,799	20.1	18.5 (17.3-19.8)	1.7 (1.5-1.9)	1.7 (1.5-1.9)	1.6 (1.4-1.7)
50-64 years	447 / 3,553	12.6	12.6 (11.5-13.6)	1 (ref.)	1 (ref.)	1 (ref.)
15-49 years	145 / 4,433	3.3	6.7 (5.6-7.8)	0.2 (0.2-0.3)	0.3 (0.2-0.3)	0.3 (0.3-0.4)

* Adjusted for sex and primary diagnosis of current hospital stay
** Adjusted for sex, primary diagnosis of current hospital stay, and Charlson comorbidity score

Table 5.4: Crude and adjusted risk of death and mortality rate ratio (MRR) within 30- or 31-365-day among intensive care unit patients admitted after elective surgery by age

Age group	Dead, n / N	Mortality, % (95%CI)	Standardized mortality, % (95%CI)	Crude MRR (95%CI)	Adjusted* MRR (95%CI)	Adjusted** MRR (95%CI)
30-d						
≥80 years	157 / 1,353	11.6	11.5 (9.8-13.2)	4.5 (3.6-5.8)	5.2 (4.1-6.7)	5.2 (4.1-6.6)
65-79 years	308 / 6,690	4.6	4.5 (4.0-5.0)	1.7 (1.4-2.1)	2.0 (1.6-2.5)	1.9 (1.5-2.3)
50-64 years	117 / 4,372	2.7	2.7 (2.2-3.2)	1 (ref.)	1 (ref.)	1 (ref.)
15-49 years	33 / 2,025	1.6	2.2 (1.4-3.0)	0.6 (0.4-0.9)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
31-365-d						
≥80 years	142 / 1,196	11.9	11.7 (9.9-13.6)	1.5 (1.2-1.8)	1.9 (1.6-2.3)	1.9 (1.6-2.3)
65-79 years	684 / 6,382	10.7	10.3 (9.6-11.0)	1.3 (1.2-1.5)	1.6 (1.4-1.8)	1.5 (1.3-1.7)
50-64 years	354 / 4,255	8.3	8.3 (7.5-9.1)	1 (ref.)	1 (ref.)	1 (ref.)
15-49 years	85 / 1,992	4.3	6.3 (4.9-7.6)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.6 (0.4-0.7)

* Adjusted for sex and primary diagnosis of current hospital stay
** Adjusted for sex, primary diagnosis of current hospital stay, and Charlson comorbidity score

5.3 Study III: Impact of age on the burden of bacteremia in intensive care unit patients

We identified a study cohort of 47,579 adult ICU patients. From 2 days before to 7 days after ICU admission, a total of 15,304 patients (32.2%) had a blood culture drawn but only 1,872 (3.9% of all and 12.2% of those who were tested) had a positive blood culture. There was an age-related increase in bacteremia burden from 2.6% in patients aged 15-49 years to 4.1% in patients aged 50-64 years, 4.5% in patients aged 65-79 years, and 5.0% in patients aged ≥80 years.

5.3.1 Patients presenting with bacteremia at ICU admission

Table 5.5 presents the bacteremia prevalence at ICU admission. The prevalence increased from 1.9% in patients aged 15-49 years to 4.1% in the elderly corresponding to an adjusted POR of 1.8 (95% CI 1.5-2.2). The highest bacteremia prevalence was observed among non-surgical patients and among patients with high preexisting morbidity. The bacteremia prevalence was lower among surgical patients and was below 1% for elective surgical patients regardless of age. Stratification by preexisting morbidity revealed no substantial age-related differences in patients with moderate and high preexisting morbidity. Yet, among patients with low preexisting morbidity, the prevalence nearly tripled in elderly patients aged compared with the youngest age group from 1.4% to 3.9% corresponding to a POR of 2.8 (95% CI 2.2-3.5).

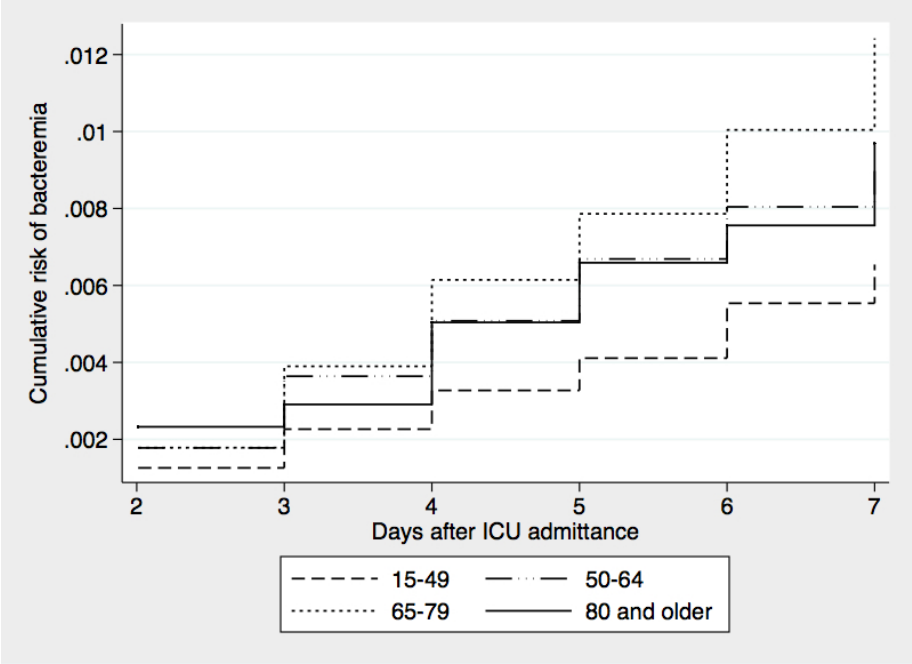
5.3.2 Bacteremia risk during days 2-7 after ICU admission

During day 2-7 after ICU admission, 4,859 (11.1%) of the 44,034 patients without bacteremia at admission, had a blood culture drawn of which 422 (1.0% of all and 8.7% of those tested) were positive. Bacteremia risk accounting for competing risk by death was approximately 1% in all age groups. Among patients with low preexisting morbidity and acute surgical patients, an age-related increased bacteremia risk was observed until age 79 whereafter a decrease was observed. Figure 5.3 displays the bacteremia risk treating death as competing risk by age.

Table 5.5: Bacteremia prevalence present at admission and prevalence odds ratios (PORs) during 2005-2011, n (%)

Age groups, (years)	**15-49 n=12,373**	**50-64 n=12,640**	**65-79 n=16,525**	**80+ n=6,041**
Overall				
Patients with a blood culture drawn	2,346 (19.0)	3,153 (24.9)	4,208 (25.5)	1,781 (29.5)
Bacteremia at admission	238 (1.9)	413 (3.3)	549 (3.3)	250 (4.1)
Prevalence odds ratios (95% CI)	1 (ref.)	1.5 (1.3-1.8)	1.5 (1.3-1.7)	1.8 (1.5-2.2)
Admission type				
Non-surgical patients				
Patients with a blood culture drawn	1,084(19.4)	1,421 (36.0)	2,075 (44.2)	946 (43.8)
Bacteremia at admission	132 (2.4)	224 (5.7)	291 (6.2)	139 (6.4)
Prevalence odds ratios (95% CI)	1 (ref.)	2.1 (1.7-2.6)	2.0 (1.6-2.6)	2.2 (1.7-2.8)
Acute surgical patients				
Patients with a blood culture drawn	1,083 (22.7)	1,378 (32.1)	1,656 (32.6)	729 (28.8)
Bacteremia at admission	96 (2.0)	158 (3.7)	221 (4.4)	103 (4.1)
Prevalence odds ratios (95% CI)	1 (ref.)	1.7 (1.3-2.2)	1.9 (1.5-2.4)	1.8 (1.3-2.4)
Elective surgical patients				
Patients with a blood culture drawn	179 (8.8)	354 (8.0)	477 (7.1)	106 (7.8)
Bacteremia at admission	10 (0.5)	31 (0.7)	37 (0.6)	8 (0.6)
Prevalence odds ratios (95% CI)	1 (ref.)	1.3 (0.6-2.8)	1.0 (0.5-2.1)	1.1 (0.4-2.8)
Pre-existing morbidity				
CCI* = low (0)				
Patients with a blood culture drawn	1,516 (15.8)	1,399 (22.9)	1,382 (22.5)	667 (28.0)
Bacteremia at admission	137 (1.4)	170 (2.8)	174 (2.8)	93 (3.9)
Prevalence odds ratios (95% CI)	1 (ref.)	2.0 (1.6-2.5)	2.0 (1.6-2.5)	2.8 (2.1-3.6)
CCI* = moderate (1-2)				
Patients with a blood culture drawn	597 (28.2)	1,133 (24.9)	1,762 (25.0)	732 (29.1)
Bacteremia at admission	68 (3.2)	138 (3.0)	210 (3.0)	108 (4.3)
Prevalence odds ratios (95% CI)	1 (ref.)	0.9 (0.7-1.3)	0.9 (0.7-1.2)	1.3 (1.0-1.8)
CCI* = high (>2)				
Patients with a blood culture drawn	233 (35.3)	621 (31.5)	1,064 (31.9)	382 (33.3)
Bacteremia at admission	33 (5.0)	105 (5.3)	165 (5.0)	49 (4.3)
Prevalence odds ratios (95% CI)	1 (ref.)	1.1 (0.7-1.6)	1.0 (0.7-1.4)	0.8 (0.5-1.3)

Figure 5.3: Cumulative 2-7- day risk of bacteremia acccounting for competing risk by death in relation to age, 2005-2011



5.4 Study IV: Mortality in elderly intensive care patients with early bacteremia: a Danish cohort study

We identified a cohort of 1,348 bacteremia patients with a first-time ICU admission. Median age was 67 years (IQR 55-76 years), 57.6% of the patients were men, and 53.7% were surgical patients. Approximately 34% of the patients had a primary diagnosis of infectious diseases.

5.4.1 Microorganisms and bacteremia-associated clinical manifestations and level of treatment by age group

The distribution of microorganisms in relation to age is displayed in Figure 5.4 and level of treatment and associated clinical manifestations are displayed in Table 5.6-7. The elderly presented with higher levels of CRP and WBC at ICU admission compared with younger patients. Despite increased levels of serum creatinine among the elderly, the elderly had lower platelet count and serum bilirubin at ICU admission than younger patients. The elderly were less frequent treated with mechanical ventilation, renal replacement therapy, and inotropes/vasopressors.

Figure 5.4: The distribution of microorganisms by age group (%), 2005-2011

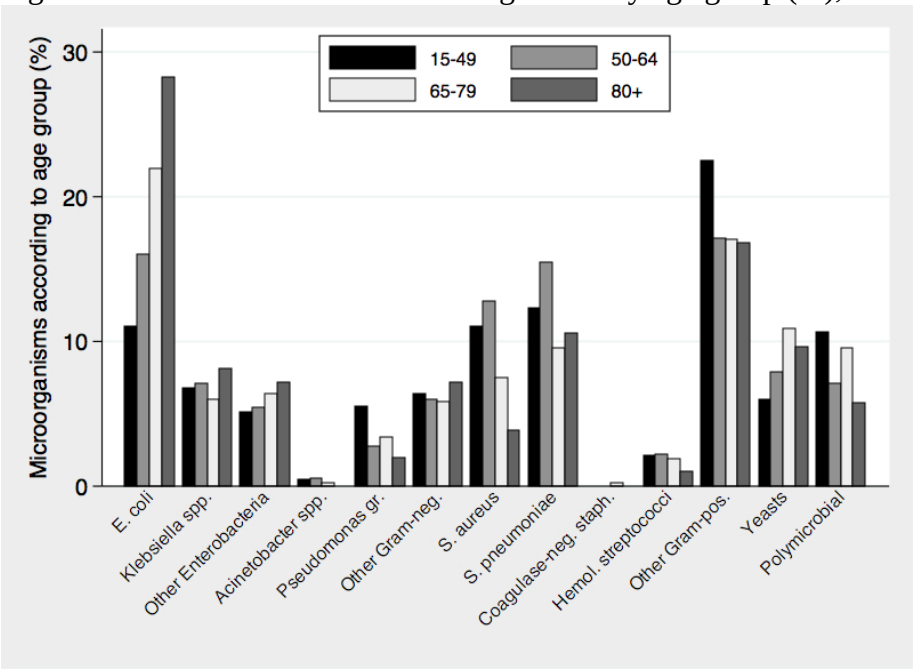


Table 5.6: Level of treatment by age group

Age groups, (years)	**15-49 n=236**	**50-64 n=369**	**65-79 n=534**	**80+ n=209**
ICU treatments				
Mechanical ventilation	131 (55.7)	230 (62.3)	328 (61.3)	89 (42.6)
Renal replacement treatment	43 (18.3)	82 (22.2)	119 (22.2)	27 (12.9)
Inotropes/vasopressors	116 (49.4)	226 (61.3)	334 (62.4)	117 (56.0)

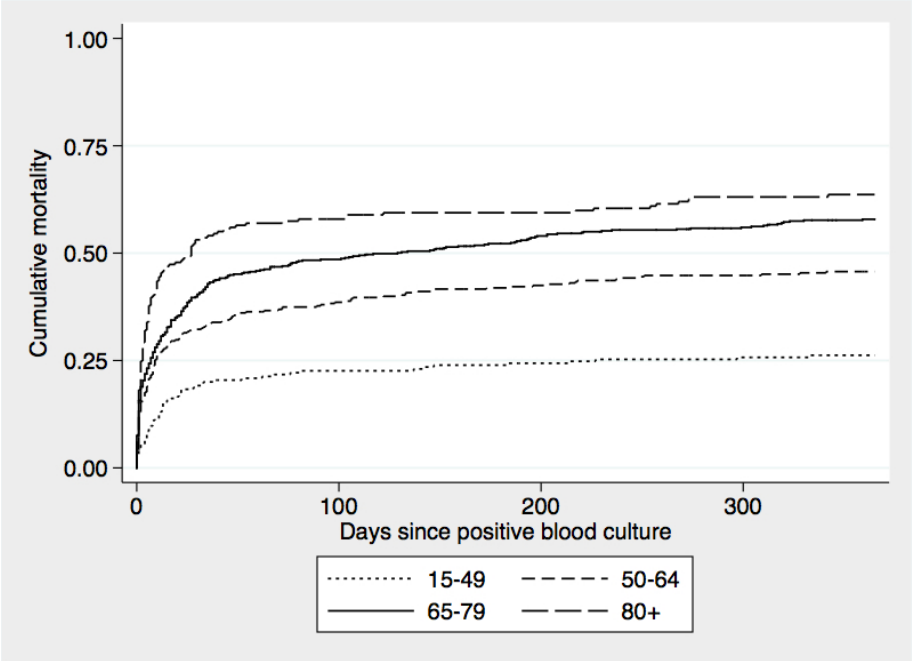
Table 5.7: Bacteremia-associated clinical manifestations at ICU admission by age group

Age groups, (years)	**15-49 n=236**	**50-64 n=369**	**65-79 n=534**	**80+ n=209**
C-reactive protein (CRP)				
CRP <10 mg/L	25 (10.6)	28 (7.6)	35 (6.5)	14 (6.7)
CRP 10-99 mg/L	69 (29.4)	111 (30.1)	146 (27.3)	50 (23.9)
CRP 100-249 mg/L	52 (22.1)	79 (21.4)	132 (24.7)	49 (23.4)
CRP > 250 mg/L	79 (33.6)	135 (36.6)	191 (35.7)	86 (41.2)
CRP missing	10 (4.3)	16 (4.3)	31 (5.8)	10 (4.8)
White blood cell (WBC)				
WBC < 3.5 x 10^9 L	28 (11.9)	48 (13.0)	63 (11.8)	12 (5.7)
WBC 3.5-10 x 10^9 L	48 (20.4)	97 (26.3)	135 (25.2)	49 (23.4)
WBC > 10 x 10^9 L	148 (63.0)	204 (55.3)	301 (56.3)	140 (67.0)
WBC missing	11 (4.7)	20 (5.4)	36 (6.7)	8 (3.8)
Laboratory cut-of values modified from SOFA-score				
Renal				
Creatinine < 110 μmol/L	124 (52.8)	185 (50.1)	243 (45.4)	70 (33.5)
Creatinine 110-299 μmol/L	80 (34.0)	123 (33.3)	218(40.8)	117 (56.0)
Creatinine >300 μmol/L	24 (10.2)	53 (14.4)	66 (12.3)	20 (9.6)
Creatinine missing	7 (3.0)	8 (2.2)	8 (1.5)	2 (1.0)
Liver				
Bilirubin < 20 μmol/L	115 (48.9)	176 (47.7)	261 (48.8)	107 (51.2)
Bilirubin 20-101 μmol/L	65 (27.7)	103 (27.9)	118 (22.1)	48 (23.0)
Bilirubin > 102 μmol/L	15 (6.4)	23 (6.2)	27 (5.1)	8 (3.8)
Bilirubin missing	40 (17.0)	67 (18.2)	129 (24.1)	46 (22.0)
Coagulation				
Platelets >150 x 10^9/L	122 (51.9)	191 (51.8)	303 (56.6)	132 (63.2)
Platelets 50-149 x 10^9/L	68 (28.9)	110 (29.8)	156 (29.2)	53 (25.4)
Platelets < 50 x 10^9/L	32 (13.6)	44 (11.9)	41 (7.7)	8 (3.8)
Platelets missing	13 (5.5)	24 (6.5)	35 (6.5)	16 (7.7)

5.4.2 Cumulative mortality according to age groups

A total of 49.4% of the patients died within 1 year. The 1-year risk of dying increased notably with increasing age with a mortality of 63.2% in the elderly compared with 57.2% in patients aged 65-79, 45.3% in patients aged 50-64, and 26.0% in patients aged 15-49 (Figure 5.5).

Figure 5.5: Cumulative 1-year mortality by age group, 2005-2011



5.4.3 7-day, 8-30-day, and 31-365-day mortality

Mortality was highest during the first 7 days after bacteremia diagnosis with a fourfold increase in the elderly (39.7%) compared with patients aged 15-49 (9.8%). The corresponding adjusted MRR was 4.2 (95% CI 2.6-6.7) in the elderly, 2.5 (95% CI 1.6-3.8) in patients aged 65-79 years, 2.1 (95% CI 1.3-3.4) in patients aged 50-64 years compared with patients aged 15-49 years. Among 7-day survivors, an age-related increase in 8-30-day mortality was seen, even though less pronounced than for 7-day mortality. In patients surviving 30 days, the 31-365-risk of dying increased with increasing age until age 80 whereafter a decrease was seen. Tables 5.8 display the 7-day, 8-30-day and 31-365-day mortality.

After stratification by preexisting morbidity, there was an age-related increase in 7-day and 8-30-day mortality within all three levels. Among 30-day survivors, only patients with moderate levels of pre-existing morbidity had an age-related increase in risk of death within 1 year. In patients with

low or high levels of pre-existing morbidity, risk of death within 1 year increased until age 80, whereafter a decrease was seen.

Table 5.8: 7-day, 8-30-day, and 31-365-day risk of death and crude and adjusted mortality rate ratios (MRR) among the 1,348 bacteremic patients admitted to an ICU by age

Age group	Dead, n / N	Mortality, %	Crude MRR (95%CI)	Adjusted* MRR (95%CI)
7-day				
15-49	23 / 235	9.8	1 (reference)	1 (reference)
50-64	80 / 369	21.7	2.4 (1.5-3.8)	2.1 (1.3-3.4)
65-79	137 /535	25.6	2.9 (1.9-4.5)	2.5 (1.6-3.8)
80+	83 /209	39.7	4.8 (3.0-7.6)	4.2 (2.6-6.7)
8-30-day				
15-49	22 / 212	10.4	1 (reference)	1 (reference)
50-64	39 / 289	13.5	1.3 (0.8-2.3)	1.2 (0.7-2.0)
65-79	79 / 398	19.9	2.0 (1.2-3.2)	1.6 (1.0-2.6)
80+	28 / 126	22.2	2.3 (1.3-3.9)	1.9 (1.1-3.3)
31-365-day				
15-49	16 / 190	8.4	1 (reference)	1 (reference)
50-64	48 / 250	19.2	2.4 (1.4-4.3)	2.1 (1.2-3.7)
65-79	90 / 319	28.2	3.8 (2.2-6.4)	3.1 (1.8-5.3)
80+	21 / 98	21.4	2.7 (1.4-5.3)	2.3 (1.2-4.5)

* Adjusted for sex, pre-existing morbidity level, type of bacteremia, and immunosuppressive therapy

6 Discussion

6.1 Methodological considerations

The overall aim of this dissertation was to examine the effect of age on different outcomes within a cohort of ICU patients. However, several limitations must be considered before inferring a causal relationship between age and the outcomes under study. As with all observational studies any given exposure could be associated with an outcome because of 1) *selection bias*, 2) *information bias*, 3) *confounding*, 4) *chance*, or 5) *cause*, which will be detailed addressed in the sections below (studies II-IV).

In addition, our studies were observational epidemiological studies with extracted data from large population-based administrative and medical databases. As with all registry-based research, data quality is of utmost importance. The optimal validation study includes evaluation of the PPV as well as the sensitivity, the specificity and the negative predictive value (NPV).[95] In study I, we were able to estimate the PPV of the registered coding in the DNPR. We did, however, not have data on completeness of registration or on patients not admitted to the ICU. Thus, we were not able to evaluate the sensitivity, the specificity, and the NPV. Yet, depending on the research question under study, an evaluation of whether any potential misclassification is random or differential may be more important than an evaluation of the degree of completeness.[95] We found high PPVs of the coding for ICU admission (87%), mechanical ventilation (100%), and renal replacement therapy (98%). This is important to the remaining studies in this dissertation as we used the coding for ICU admission to identify our cohort. The implication of any misclassification is reflected upon in section 6.1.2.

6.1.1 Selection bias

Selection bias is a systematic error, which arises when the association between exposure and outcome differs for participants and non-participants in a study.[60] It is related to procedures concerning the inclusion of participants into a study and to the potential loss of follow-up during a study period. In our studies, loss of follow-up is considered insignificant due to the high quality of the Civil Registration System. Selection bias may arise, however, if the threshold for ICU admission is associated with exposure. If elderly patients are denied admission to the ICU more

frequent than younger patients and as a consequence, only elderly patients in good pre-admission condition are admitted with concomitant reduced mortality, we may underestimate the effect of age on mortality. Consequently, our findings, including findings from other ICU studies, should not be generalized to critically ill patients outside the ICU.

6.1.2 Information bias

Information bias is a systematic error arising because of inaccurate measurement of data on either exposure or outcome.[60] Any measurement error will lead to the subject/variable under study being misclassified. Misclassification can be either differential or non-differential. If misclassification differs between comparison groups, the misclassification is differential. Non-differential misclassification refers to the misclassification being equally distributed between comparison groups. Non-differential misclassification tends to bias any association towards the null. This is, however, not the case with differential misclassification, which creates a more unpredictable bias of either the exaggeration or underestimation of an effect. Hence, a non-null result could be explained by differential misclassification.[60]

ICU patients

As stated above, we identified ICU patients in the DNPR by the coding for ICU admission. We found a PPV of 87.2% (95% CI: 75.6-94.5). A previous Danish study, however, examining the coding for ICU admission found a higher PPV of 98.7% (95% CI: 95.3-99.8).[25] This questions whether any potential misclassification in our studies is differential or non-differential. We do not expect the coding for ICU admission to be dependent on patient age, nor on mortality or bacteremia status. Thus, any misclassification would be non-differential and would bias our results towards the null.

Age

Our exposure in this dissertation was age categorized into four age groups. We calculated patients' age based on the unique CPR-number assigned to all Danish citizens at birth or immigration, and we expect misclassification to be absolutely minimal. If misclassification did occur, however, we do not expect it to depend on the outcomes under study and any potential misclassification would be non-differential.

All-cause mortality

In studies II and IV the outcome was time to death. We obtained information on date of death from the Civil Registration System. Updated on a regular daily basis, the Civil Registration System contains the exact date of death. Thus, any misclassification is very unlikely.

Bacteremia

We defined bacteremia by a positive blood culture. Blood cultures were obtained on suspicion of infection but bacteremia may have been present in patients not suspected of infection, leading to misclassification. The misclassification would be non-differential if the misclassified patients were equally distributed between age groups. Decisions on ordering blood cultures may differ by age due to the non-specific clinical manifestations in elderly bacteremic patients, e.g. absence of fever, anorexia, malaise, or urinary incontinence. Consequently, differential misclassification may arise if elderly patients have a blood culture drawn less frequent than younger patients. In our study cohort, however, patients aged 50+ years more often had a blood culture drawn than patients aged 15-49 years. In addition, the proportion of elderly patients with a blood culture drawn did not differ substantially from the proportion in patients aged 50-79 years. The proportion of blood cultures turning positive was marginally higher in patients aged 50+ years compared with the youngest age group, and we only suspect minor variation in the indication for drawing a blood culture.

6.1.3 Confounding

Confounding bias is also a systematic error. Confounding is considered as a mixing of effects, which refers to the mixture of the effect of an exposure with the effect of another risk factor.[60,96] A confounder is characterized by being associated with the outcome under study; it may be unequally distributed between exposed and unexposed, and it is not allowed to be a step in the causal pathway. Confounding can be controlled for in the study design by randomization, restriction or matching, or in the analysis by stratification, standardization or adjustment.

We were able to control for a number of pre-specified confounders. Still, our results could be affected by residual, unmeasured or unknown confounding. Residual confounding is due to misclassification of any potential confounding variable, e.g. pre-existing morbidity, or to improper categorization, e.g. type of bacteremia.

Information on preexisting morbidity was obtained from the DNPR to compute the CCI score. Being a hospital registry, the DNPR captures preexisting morbidities during hospitalization. The

coding, as registered in the DNPR, of each of the 19 diseases contained in the CCI has been validated with an overall PPV of 98.0% (95% CI: 96.9-98.8).[97] The PPVs ranged from 82.0% (95% CI; 68.6%, 91.4%) to 100% (one-sided 97.5% CI; 92.9%, 100%). Yet, some of the diseases contained in the CCI may be prone to lack of sensitivity as general practitioners in the primary care setting treat many diseases. Hence, we cannot entirely exclude residual confounding from misclassification having influenced our findings. Nevertheless, when stratifying on preexisting morbidity level the association between age and mortality was evident in patients with low level of preexisting morbidity (CCI=0) suggesting only minor impact on our findings from any residual confounding.

We lacked data on severity of illness, e.g. SAPS II score. As stated previously, age is part of SAPS II and APACHE II (greater points with increasing age).[57,58] The exposure in this dissertation is age. In order to use the score for adjustment we would have to extract the age point when computing the score. To the best of our knowledge, validation of the score without the age-point has not been performed. Thus, any conclusion based on the score without one of the variables in the score must be made with caution. In addition, any adjustment by severity of illness scores may be conflicting if some of the variables included in the score are part of the causal pathway thereby weakening any true effect.

In study II, the association between age and mortality could be confounded by sex, preexisting morbidity, and primary diagnosis of current hospital stay. We controlled for this confounding by standardization and by adjustment in a multivariate regression model. Furthermore, we stratified the analyses by surgical status to account for any different effect among non-surgical and surgical patients.

In study III and IV, we handled confounding by restriction to patients with more than one-year residency in the study area before ICU admission to ensure availability of prescription data. We used filled prescriptions for immunosuppressive therapy as proxy for a compromised immune system. If the patient with a filled prescription did not actually take the medication this would also be prone to misclassification. This would most likely bias our findings toward the null.

The multivariate regression model in study III were stratified by surgical status and adjusted for sex, preexisting morbidity, primary diagnosis of current hospital stay, and immunosuppressive therapy.

In study IV, we adjusted the multivariate regression model for sex, type of bacteremia, preexisting morbidity, and immunosuppressive therapy. Furthermore, we stratified analyses by preexisting morbidity, surgical status, type of bacteremia, and immunosuppressive therapy.

6.1.4 Chance

In all four studies, statistical precision was reflected by 95% CI. The precision was high in the main analyses in studies II and III. The bacteremia risk analysis in study III and especially the subgroup analyses in study IV were more prone to imprecision as reflected by wide confidence intervals.

6.2 Comparison with the existing literature

6.2.1 Study II: Mortality in elderly ICU patients: a cohort study

We found an approximately 18% ICU admission increase in the proportion of elderly patients from 11.7% in 2005 to 13.8% in 2011. In accordance to our findings, Ihra et al found an increase from 11.5% in 1998 to 15.3% in 2008 in the proportion of patients aged 80+ with an ICU admission.[66] This increase is lower than the 5.6% annual increase shown by Bagshaw et al and their prediction of a 72% rise in ICU and hospital bed-days of patients aged 80 or older by 2015 may be an overestimation, at least in Denmark.[14] Our findings of increasing 30-day mortality with age are supporting previous studies on short-term mortality. In accordance to our findings, Fuchs et al found age as risk factor of 28-day and 29-365-day mortality among ICU patients. They included 7,265 ICU patients above age 65 admitted following acute surgery or non-surgical reasons and found that patients aged 75-84 years and 84+ years had a higher 28-day mortality compared with patients aged 65-74 (OR 1.52 (95 % CI 1.32–1.74) and 1.85 (95% CI 1.57-2.17), respectively). In addition, a Cox regression analysis for 1-year mortality in 28-day survivors showed the same trend (HR 1.21 (95% CI 1.06-1.38) in patients aged 75-84 years and 1.59 (95% CI 1.37-1.85) in patients aged 84+ compared with patients aged 65-74 years). In our study, elderly ICU patients admitted due to non-surgical or acute surgical reasons had higher mortality than elderly patients admitted following elective surgery, which is supporting previous studies.[70] In a recent review by Nguyen et al, the authors suggested ICU admissions to be limited to elective surgical patients and only selected non-surgical or acute surgical elderly patients, due to the poor prognosis.[98] Yet, the survival benefit of admitted vs. rejected patients is greater among elderly patients compared with younger patients.[10] In addition, we found a markedly increased relative risk of dying within 30 days

among elderly patients admitted following elective surgery compared with the younger age groups with very low mortality. The reason for this might be that elderly patients are more vulnerable to any adverse effect of surgery, because of age-related decrease in physiological reserve. The association between age and mortality after ICU admission persisted even after the standardization of mortality to the distribution of preexisting morbidity in the age group of 50-64-year-old, thus substantiating the association between age and mortality.

6.2.2 Study III: Impact of age on the burden of bacteremia in intensive care unit patients

To the best of our knowledge, this is the first study to investigate the impact of age on bacteremia burden in an ICU cohort discriminating between bacteremia present at time of admission and acquired after admission. We found an overall bacteremia burden of 3.9%. Bacteremia prevalence at ICU admission was 2-3-fold higher in non-surgical and acute surgical patients aged 50+ years than in patients aged 15-49 years. Yet, above age 50 years we observed no further increase in the bacteremia prevalence. During days 2-7 after ICU admission an age-related increase in the bacteremia risk was seen until the seventies, thereafter a decrease was noted. The EPIC-II study found lower bacteremia prevalence among elderly ICU patients (≥75 years) compared with younger patients, but due to the cross-sectional design, they did not distinguish between bacteremias present at admission and acquired after ICU admission.[76] In accordance to our findings of lower bacteremia incidence in patients aged 80+ years compared with patients aged 65-79 years, the Belgian study by Blot et al on nosocomial bacteremia in elderly ICU patients found decreasing bacteremia incidence with age during 1992-2006.[77] In contrast to our finding of the highest risk of acquiring bacteremia in patients aged 65-79 years, the population-based cohort study by Laupland et al found younger age (<65 years) to be associated with an increased risk of developing ICU-acquired bacteremia with a relative risk of 1.77 (95% CI 1.01-3.11) compared with older patients. In summary, within the general population a markedly increased incidence of bacteremia with increasing age has been found.[45] However, the previous studies conducted within cohorts of ICU patients have shown both lower prevalence of bacteremia among the elderly[76] and a decreasing risk of acquiring bacteremia with increasing age after ICU admission.[77,79] In contrast, our findings suggest an age-related increase in bacteremia incidence until the seventies, and thereafter a decrease was seen. Our results are supported by a recent study investigating the impact of age on ventilator-associated pneumonia.[99] They found increasing prevalence with advancing age until age 75 years; 13.7 (n ventilator-associated pneumonia/1000 ventilation days) in patients aged 45-64, 16.6 in patients aged

65-74 years, and 13.0 in patients aged 75+ years.

Only approximately 9% of all hospitalized bacteremia patients are admitted to the ICU[34] and admittance to the ICU may differ according to age. A previous population-based Danish study of community-acquired bacteremia found that only 3% of patients aged 80+ years, who were admitted to hospital with community-acquired bacteremia, were transferred to the ICU compared with 8% of patients aged 15-64 years and 4% of patients aged 65-79 years.[80] Such age-related variation in admittance to the ICU can be caused by different mechanisms. Elderly patients may represent healthy ageing which may be less vulnerable to e.g. endotoxins[100,101] since age-related changes in both innate and adaptive immune responses seem to be related to ageing and survival to older age.[102] Also, strain on ICU capacity may have particularly strong influences on decisions to transfer elderly patients to treatment to the ICUs[10] which may result in admission to the ICU being most likely for elderly patients in a good pre-admission condition.[12] We did find a slightly lower level of preexisting morbidity among patients aged 80+ years compared with patients aged 65-79 years. This is, however, consistent with the comorbidity level found in the previous Danish study of community-acquired bacteremia in general, in which 35% of patients aged 80+ years had a CCI level of 0 compared with 31% of those aged 65-79 years.[80] This supports at least some healthy ageing effect. Interestingly, when stratifying by pre-existing morbidity we found that patients aged 80+ years had a lower risk of developing bacteremia after admittance to the ICU within each level of pre-existing morbidity than patients aged 65-79 years. ICU-studies on age-related differences in clinical manifestations associated with bacteremia have shown no major age-related differences in organ dysfunction in the ICU population.[10,77] Based only on serum creatinine measurements, we found increased levels of renal impairment among patients aged 80+. Since creatinine clearance decreases with increasing age and also depends on patient weight[103] our findings may even represent a conservative estimate of the differences. An increased risk of renal failure among elderly patients with bacteremia was also found in a study from Taiwan based on all patients who registered in the emergency department of a university medical center between June 2001 and June 2002 with a clinically significant, culture-positive, bloodstream infection.[81]

6.2.3 Study IV: Mortality in elderly intensive care patients with early bacteremia: a Danish cohort study

We found that half of the patients had died within 1 year. The mortality rate was highest in the first week after the first positive blood culture was obtained, and 7-day mortality was fourfold higher among the elderly compared with the youngest age group. Although less pronounced, the same age-

related pattern was seen for 8-30-day mortality. Our findings of increased 7-day and 8-30-day mortality in the elderly compared to younger patients are supporting previous studies.[27,51,77,80–83] In contrast, the elderly actually had a 25% lower 31-365-day mortality than patients aged 65-79 years. Previous prediction studies assessing 1-3-year mortality following bacteremia have revealed age as an important predictor.[84,85] Their study population, however, consisted of hospitalized patients irrespective of admissions to the ward or an ICU, whereas our study was restricted to critically ill ICU patients representing only approximately 9% of all hospitalized bacteremic patients.[34] Nevertheless, as mortality in the elderly was markedly increased within the first week/month of infection compared with younger patients, this may imply a discard of the frailest elderly. In addition, the elderly were less frequent treated with mechanical ventilation, renal replacement and inotropes/vasopressor, which may be a marker of withholding or the withdrawal of treatment. The higher 31-365-day mortality in patients aged 65-79 years compared with the elderly may be explained by the presence of higher levels of preexisting morbidity, and a primary diagnosis of current hospital stay of cancer as well as treatment with immunosuppressive therapy being more frequent in patients aged 65-79 compared with the elderly. Nevertheless, even among patients with low preexisting morbidity the 1-year mortality was decreased in the elderly compared with patients aged 65-79 years. The previous Danish study by Søgaard et al. investigated the effect of age at different levels of preexisting morbidity on 30-day mortality among patients with community-acquired bacteremia.[80] According to our findings, they found higher mortality with advancing age with HRs of 2.0 (95% CI 1.6-2.5) in patients aged ≥80 years compared with patients aged 15-64 years, and increased levels of preexisting morbidity among patients aged ≥80 years did not fully explain differences in mortality between age groups.

7 Main conclusions

Study I: Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report

The PPVs of the registered coding for ICU admission, mechanical ventilation and renal replacement therapy were high, and the DNPR remains a valuable source for observational ICU studies.

Study II: Mortality in elderly ICU patients: a cohort study

We found an 18% increase in the proportion of elderly patients admitted to the ICU during the 7-year period and advancing age was associated with increased mortality among ICU patients irrespective of admission type. In addition, mortality among elderly patients was increased compared with younger patients irrespective of adjustment for preexisting morbidity indicating that preexisting morbidity did not entirely explain the association.

Study III: Impact of age on the burden of bacteremia in intensive care unit patients

Bacteremia prevalence at ICU admission was increased in ICU patients aged 50+ years with no further increase with advancing age above 50 years. Except for elevated serum creatinine at admission, the elderly less frequently presented with organ dysfunction at ICU admission compared with younger patients. Once admitted to the ICU, the bacteremia risk was very low (~1%) with an age-related increase until the seventies, whereafter a decrease was seen.

Study IV: Mortality in elderly intensive care patients with early bacteremia: a Danish cohort study

We found an age-related increase in 7-day and 8-30-day mortality in bacteremic ICU patients, whereas the elderly had a lower 31-365-day mortality compared with patients aged 65-79 years. The effect of age on mortality was evident within all three levels of preexisting morbidity.

8 Perspectives

ICU admissions and treatments are associated with considerably burden and costs are high. The population is ageing which may affect our health care services including additional strain on our ICUs. This dissertation adds knowledge to the prognosis of elderly ICU patients. During our study period, we found an 18% increase of ICU admissions of elderly patients even though hospital admissions of the elderly only increased by 6%, and the proportion of elderly in the general population were the same. Thus, it seems as if the rising proportion of elderly patients in our ICUs may be associated with other aspects than the demographic changes. Not surprisingly, the elderly had a worsened prognosis than younger patients. Mortality was higher in the elderly and the age-related mortality-increase persisted irrespective of level of preexisting morbidity. Among bacteremic ICU patients, the 7-day mortality was fourfold higher in the elderly compared with the youngest age group. Conversely, the lower 31-365-day mortality in the bacteremic elderly compared to patients aged 65-79 years raises the following questions:

- Does the higher 7-day mortality in the elderly simply reflect an early discard of the frailest elderly?
- Does the lower prevalence of ICU treatments in the elderly reflect clinicians' decisions upon withholding or withdrawal of treatment leaving more elderly to die than the younger more aggressively treated patients?
- Does the lower 31-365-day mortality in the elderly compared to patients aged 65-79 years reflect a better long-term prognosis in bacteremic elderly due to the selected elderly population (patients aged 65-79 years had a higher prevalence of preexisting morbidity, were more often treated with immunosuppressive therapy, and had a higher prevalence of cancer)?
- Is current selection of patients into the ICU appropriate?
- What are the mechanisms behind the increased mortality in the elderly?

These questions remain unanswered in this dissertation. The Danish health care system provides an optimal setting for conducting large population-based ICU studies. Using the unique CPR-number, assigned to all Danish citizens at birth, linkage of several medical and administrative databases is possible creating large cohorts with detailed information on hospital stays, preexisting morbidity,

laboratory data, prescription data and virtually complete long-term follow-up data. Despite the highly valuable and valid data on hospital admission and stay obtained from the DNPR, more detailed clinical data are needed in order to address some of the questions posed above: an assessment of the severity of illness, e.g. by the SAPS II score, more detailed information on hemodynamic parameters, body temperature, volume resuscitation, treatment with antibiotics and other in-hospital medical treatments during ICU stay, and the assessment of the withholding or withdrawal of treatment. Currently, many clinical data are already included in the Danish electronic medical record. These data will be available in future studies and will add to the examination of risk and prognostic factors in elderly ICU patients.

9 Summary

The Western population is ageing with the proportion of people aged ≥80 years predicted to increase from 4.7% in 2010 to 11% in 2050. ICU admissions of elderly (aged ≥80) patients tend to be rising which may challenge our health care services. Bacteremia is a severe infection and the incidence increases with advancing age. Furthermore, ICU patients are at increased risk of acquiring bacteremia because of the use of intraluminal devices, compromised immune system etc. Hence, prognostic data of elderly ICU patients are crucial in order to guide clinical decision-making.

This dissertation includes a validation study (study I) and three population-based cohort studies (studies II-IV) among ICU patients admitted during 2005-2010 (study I) and 2005-2011 (studies II-IV). The studies were conducted in the former county of North Jutland (study I) and in Northern Denmark; former counties of Aarhus and North Jutland (studies II-IV) using Danish population-based medical and administrative registries.

The aims of this dissertation were to examine 1) validity of recorded coding of ICU admission, mechanical ventilation and renal replacement therapy in the Danish National Patient Registry (DNPR) by estimating the positive predictive value (PPV), 2) recent changes in the proportion of elderly patients in intensive care over time and the effect of age on mortality, 3) the effect of age on the burden of bacteremia among ICU patients, and 4) the effect of age on mortality among ICU patients with bacteremia.

In study I, we were able to locate 147 medical records of identified 150 patients registered with the coding of ICU admission in the DNPR. Of the 147 included patients, 141 (95.9% [95% CI: 91.8-98.3]) had been admitted to an ICU according to their medical records. The PPV for a registered coding of ICU admission was 87.2% [95% CI 75.6-94.5] (n=41/47), 100% [95% CI 95.1-100] (n=50/50) for a registered coding of mechanical ventilation, and 98% [95% CI 91.0-99.8] (n=49/50) for a registered coding of renal replacement therapy.

In study II, we included 49,938 ICU admissions corresponding to 47,596 patients. We observed a slight increase in the prevalence of elderly (aged ≥80 years) ICU patients from 11.7% (898/7,653) in 2005 to 13.8% (845/6,104) in 2011 with a corresponding prevalence proportion ratio (PPR) of 1.18 [95% CI 1.08-1.29]. A smaller increase in hospital admissions of the elderly was seen from 13.4% in 2005 to 14.3% in 2011 (PPR of 1.06 [95% CI 1.05-1.08]), and during the same period there was no increase in the proportion of elderly people in the general population as people aged ≥80 years accounted for 4.1% of the population in both 2005 and 2011. Mortality increased with

advancing age among ICU patients irrespective of admission type. Furthermore, mortality increased with advancing age irrespective of adjustment for preexisting morbidity.

In study III, we included 45,579 patients with a first-time ICU admission. From 2 days before to 7 days after ICU admission, a total of 15,304 patients (32.2%) had a blood culture drawn of which 1,872 (3.9% of all and 12.2% of those tested) were positive. Bacteremia prevalence at ICU admission (defined as a positive blood culture obtained from 2 days before to 1 day after ICU admission) was increased in patients aged ≥50 years, and no further increase in prevalence was observed with advancing age above 50 years. After ICU admission (during days 2-7 after admission), the risk of acquiring bacteremia was very low (~1%) with a minor age-related increase until age 79 years whereafter a decrease was observed.

In study IV, we included 1,348 ICU patients with bacteremia (defined as the first positive blood culture obtained at date of ICU admission or within the first seven days after ICU admission). The 1-year cumulative risk of dying increased markedly with increasing age (63.2% in the elderly compared with 57.2% in patients aged 65-79, 45.3% in patients aged 50-64, and 26.0% in patients aged 15-49). An age-related increase in 7-day mortality was observed with a fourfold higher mortality in the elderly compared with patients aged 15-49. The same pattern was observed in 8-30-day mortality, although less pronounced. Among 30-day survivors, an age-related increase in 31-365-day mortality was observed until age 79 years whereafter a decrease was seen.

In conclusion, we found that data obtained from the DNPR remains a valuable source for observational studies of intensive care. During our study period, admissions of elderly patients to the ICU slightly increased even though hospital admissions of elderly patients did not increase at similarly levels, and the proportion of elderly in the general population were the same. Prognosis after ICU admission is worse in the elderly compared with the younger age groups, and mortality is especially increased within the first seven days after ICU admission. Bacteremia prevalence is increased in patients ≥50 years and the bacteremia risk once admitted to the ICU is very low.

10 Dansk resume

I den vestlige verden forventes andelen af ældre mennesker ≥80 år at stige fra 4.7% i 2010 til 11% i 2050. Ligeledes synes andelen af ældre patienter ≥80 år, der indlægges på intensiv afdeling at stige, hvilket potentielt kan medføre en øget belastning af vores sundhedssystem. Bakteriæmi er en alvorlig tilstand og forekomsten øges med stigende alder. Endvidere er intensivpatienter i øget risiko for at udvikle bakteriæmi pga. øget anvendelse af invasive katetre og monitorering, øget forekomst af komorbiditet mm. Det er derfor vigtig at have kendskab til prognosen for ældre patienter efter intensiv indlæggelse i forhold til klinisk beslutningstagen.

Denne afhandling indeholder et valideringsstudie (studie I) samt tre kohortestudier (studie II-IV) blandt patienter indlagt på intensiv afdeling i perioden 2005-2010 i det gamle Nordjyllands Amt (studie I) samt i 2005-2011 i de gamle Aarhus og Nordjyllands Amter (studie II-IV). Data til studierne er indhentet fra flere forskellige danske registre.

Formålet med afhandlingen var 1) undersøge datakvaliteten i Landspatientregisteret af koderne for intensiv indlæggelse, respiratorbehandling samt dialysebehandling, 2) at belyse ændringer over tid i forekomsten af ældre patienterne på intensiv afdeling samt sammenhængen mellem alder og dødelighed, 3) at belyse sammenhængen mellem alder og forekomsten af bakteriæmi blandt intensivpatienter samt risikoen for at udvikle bakteriæmi efter intensiv indlæggelse i relation til alder, 4) at belyse sammenhængen mellem alder og dødelighed blandt intensivpatienter med bakteriæmi.

Studie I: Efter at have gennemgået 147 patientjournaler, registrerede i Landspatientregisteret med koder for intensiv terapi, fandt vi, at 141 (95.9% [95% CI: 91.8-98.3]) patienter havde været indlagt på en intensiv afdeling. Den positive prædiktive værdi for registreret kodning for intensiv indlæggelse var 87.2% [95% CI 75.6-94.5] (n=41/47), 100% [95% CI 95.1-100] (n=50/50) for registreret kodning for respiratorbehandling, og 98% [95% CI 91.0-99.8] (n=49/50) for registreret kodning for dialysebehandling.

Studie II: Vi inkluderede 49.938 intensiv indlæggelser svarende til 47.596 patienter. Vi fandt en lille øgning i forekomsten af ældre patienter indlagt på en intensiv afdeling over den 7-årige studie periode fra 11,7% (898/7.653) i 2005 til 13,8% (845/6.104) i 2011 svarende til en prævalens proportions ratio på 1,18 [95% CI 1,08-1,29]. Til sammenligning var der en mindre øgning i forekomsten af hospitalsindlæggelser blandt ældre patienter fra 13,4% i 2005 til 14.3% i 2011 (PPR 1,06 [95% CI 1,05-1,08]), og der var ingen øgning i andelen af ældre i baggrundsbefolkningen, idet

personer ≥80 år udgjorde 4,1% i både 2005 og 2011. Dødeligheden blandt intensiv patienter steg med stigende alder uafhængig af indlæggelsestype, og øget forekomst af komorbiditet kunne ikke forklare den øgede dødelighed blandt de ældre patienter.

Studie III: Vi inkluderede 47.579 patienter med en førstegangsindlæggelse på intensiv afdeling. I alt 15.304 (32.2%) patienter havde fået foretaget en bloddyrkning i perioden fra 2 dage før til 7 dage efter intensivindlæggelse, hvoraf 1.872 var positive (3,9% af alle og 12.2% af de, der havde fået foretaget bloddyrkning). Prævalensen af bakteriæmi ved ankomst til intensiv (defineret som den første positive bloddyrkning fra 2 dage før til 1 dag efter intensivindlæggelse) var øget blandt patienter ≥50 år, og der var ikke den store forskel i prævalens med stigende alder over 50 år. Risikoen for at erhverve bakteriæmi efter intensivindlæggelse (fra 2-7 dage efter intensivindlæggelse) var meget lav (~1%). Der var en mindre aldersrelateret stigning indtil en alder af 79, hvorefter der var et lille fald i risikoen for bakteriæmi.

Studie IV: Vi inkluderede 1.348 intensivpatienter med bakteriæmi. Den kumulerede 1-års dødelighed steg markant med stigende alder (63,2% af de ældre sammenlignet med 57,2% af de 65-79-årige, 45,3% af de 50-64-årige, and 26.0% af de 15-49-årige). 7-dages dødeligheden steg markant med stigende alder og de ældre havde en firedobbelt højere dødelighed end de 15-49-årige. Et lignende mønster gjorde sig gældende for 8-30-dages dødeligheden, om end mindre udtalt. Der var ligeledes en aldersrelatereret stigning i 31-365-dages dødeligheden indtil en alder af 79 år, hvorefter der var et lille fald i dødeligheden.

Sammenfattende viste vores studier en lille stigning i forekomsten af ældre patienter indlagt på intensiv afdeling selvom forekomsten af ældre med hospitalsindlæggelser ikke steg tilsvarende og andelen af ældre personer i baggrundsbefolkningen var den samme i 2005 og 2011. Prognosen efter intensivindlæggelse er værre for ældre patienter end for de yngre aldersgrupper, og dødeligheden er markant øget indenfor de første syv dage efter intensivindlæggelse. Prævalensen af bakteriæmi er øget blandt patienter ≥50 år og risikoen for erhvervelse af bakteriæmi efter intensivindlæggelse var meget lav.

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Study I

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ORIGINAL RESEARCH

Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report

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Background: Large health care databases provide a cost-effective data source for observational research in the intensive care unit (ICU) if the coding is valid. The aim of this study was to investigate the accuracy of the recorded coding of ICU admission, mechanical ventilation, and acute dialysis in the population-based Danish National Patient Registry (DNPR).

Methods: We conducted the study in the North Denmark Region, including seven ICUs. From the DNPR we selected a total of 150 patients with an ICU admission by the following criteria: (1) 50 patients randomly selected among all patients registered with an ICU admission code, (2) 50 patients with an ICU admission code and a concomitant code for mechanical ventilation, and (3) 50 patients with an ICU admission code and a concomitant code for acute dialysis. Using the medical records as gold standard we estimated the positive predictive value (PPV) for each of the three procedure codes.

Results: We located 147 (98%) of the 150 medical records. Of these 147 patients, 141 (95.9%; 95% confidence interval [CI]: 91.8–98.3) had a confirmed ICU admission according to their medical records. Among patients, who were selected only on the coding for ICU admission, the PPV for ICU admission was 87.2% (95% CI: 75.6–94.5). For the mechanical ventilation code, the PPV was 100% (95% CI: 95.1–100). Forty-nine of 50 patients with the coding for acute dialysis received this treatment, corresponding to a PPV of 98.0% (95% CI: 91.0–99.8).

Conclusion: We found a high PPV for the coding of ICU admission and even higher PPVs for mechanical ventilation, and acute dialysis in the DNPR. The DNPR is a valuable data source for observational studies of ICU patients.

Keywords: critical care, epidemiology, intensive care unit, positive predictive values, validity

Introduction

Health care databases constitute a cost-effective way of conducting studies on intensive care unit (ICU) patients. The data are usually collected for administrative purposes, thus reducing the risk of recall bias and nonresponse bias.[1] The researchers who conduct an observational study using existing data are not able to control the data collection and the quality of the data. Therefore it is important to examine the validity of these data.

Few studies have examined the quality of coding for ICU admission in medical databases. A Canadian study used different combinations of codes to identify ICU admissions and found positive predictive values (PPV) ranging from 34% to 91%.[2] However, another recent Canadian study evaluated the accuracy of administrative data for identifying admission to adult ICUs. They found even higher PPVs ranging from 98% to 99%.[3] Additionally, a French study evaluated ICU admissions among women

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with severe maternal morbidity.[4] They found a PPV of 98% (95% confidence interval [CI]: 95.8–100). Still, this study was restricted to women of reproductive age with at least one code related to pregnancy, delivery, or the postpartum period.

Several studies have measured the validity of different diseases and procedure codes registered in the Danish National Patient Registry (DNPR),[5–8] but only one study examined the validity of ICU admission coding and found a PPV of 98.7% in a sample of 150 records from one hospital.[9] Few, if any, data exist on the validity of specific ICU procedure codes for interventions such as mechanical ventilation and acute dialysis. We therefore estimated the PPV of recorded coding of ICU admission, mechanical ventilation, and acute dialysis in the DNPR.

Methods

We conducted this validation study in the North Denmark Region with a population of approximately 500,000 people (corresponding to 11% of the total Danish population). Through the DNPR, we randomly selected 50 patients from each of the following categories admitted during January 1, 2005–December 31, 2010: (1) patients registered with an ICU admission (the Danish procedure codes: intensive care observation (NABE)/intensive care therapy (NABB); (2) patients registered with an ICU admission who also had a mechanical ventilation code (procedure codes: NABE/NABB + BGDA0 [mechanical ventilation]); and (3) patients registered with an ICU admission who also had an acute dialysis code (procedure codes: NABE/NABB + BJFD00 [acute hemodialysis]/BJFD02 [continous venovenous hemodialfiltration]), altogether yielding a validation cohort of 150 patients.

Since 1977, the DNPR has recorded more than 99% of all discharges from Danish hospitals. Data include the civil registration (CPR) number, dates of admission and discharge, surgical and other procedures, and one primary and up to 19 secondary discharge diagnoses classified according to the International Classification of Diseases, 8th revision until 1993 and 10th revision thereafter.[10,11] Intensive care admissions, including major treatments, have been recorded routinely since 2005.

The procedure coding for intensive care is registered each time a patient is admitted to an intensive care unit during hospitalization. The procedure codes are assigned a date corresponding to the date of ICU admission. Procedure codes for any mechanical ventilation and acute dialysis are assigned at least once per ICU admission.

All medical records were reviewed by one of the authors (LBH). All notes for the entire hospital stay from date of ICU admission and onwards were reviewed to identify ICU admission, treatment with mechanical ventilation, and acute dialysis. Medical records with uncertain information about admission and treatments were also reviewed by another author (MSN), and agreement was reached by consensus. We estimated the PPV of each of the three procedure codes as the proportion of patients registered with the specific coding in the DNPR who also received this treatment according to their medical records. All estimates are presented with 95% CIs calculated with Jeffrey's CIs.[12] Furthermore, we stratified the PPV of the coding for ICU admission by admission to either a district or a university hospital.

The statistical analyses were performed using STATA® software (version 11.2; StataCorp, College Station, TX, USA).

Table 1 PPV and 95% CI for a registered coding of ICU admission, mechanical ventilation, and acute dialysis in the DNPR

Procedure coding	n/N	PPV (95% CI)
ICU admission	41/47	87.2% (75.6–94.5)
Mechanical ventilation	50/50	100% (95.1–100)
Acute dialysis	49/50	98% (91.0–99.8)

Abbreviations: CI, confidence interval; DNPR, Danish National Patient Registry; ICU, intensive care unit; PPV, positive predictive value.

Results

We were able to locate 147 of the 150 medical records (98%). The three unavailable medical records were all patients selected from the DNPR with the coding for intensive care admission only and the patients were excluded before the analyses. The median age at admission date was 67.4 years (interquartile range [IQR], 56.7–75.4 years) and 64% were men. Of the 147 patients, 141 (95.9%; 95% CI: 91.8–98.3) had been admitted to an ICU according to their medical records.

Of the 47 patients selected solely on the coding for ICU admission in the DNPR, 41 were admitted to an ICU according to their medical records corresponding to a PPV of 87.2% (95% CI: 75.6–94.5). The PPVs of registered procedure coding are shown in Table 1.

Thirty-two patients were admitted to a university hospital, of which 29 had a confirmed admission to an ICU, yielding a PPV of 90.6% (95% CI: 77.0–97.3). Of the remaining 15 patients admitted to a district hospital, 12 had a confirmed ICU admission corresponding to a PPV of 80.0% (95% CI: 55.6–94.0). The three patients from district hospitals without a confirmed ICU admission were young patients having surgery with uncomplicated postsurgery courses. The three miscoded patients from the university hospital were hospitalized with carotid artery

surgery, stroke, and trauma, respectively. Furthermore, of the 47 patients selected from the DNPR based on the coding for ICU admission, 27 had neither a code for mechanical ventilation nor acute dialysis. Among these 27 patients, six patients had not been admitted to an ICU according to their medical records.

All 50 ICU patients registered and identified by the coding for mechanical ventilation received this treatment according to their medical records corresponding to a PPV of 100% (95% CI: 95.1–100). In addition, this corresponded to a PPV of ICU admission of 100% (95% CI: 95.1–100) in this subgroup of ICU patients.

Of the 50 ICU patients identified by the coding for acute dialysis, one did not receive this treatment, corresponding to a PPV of the coding for acute dialysis of 98% (95% CI: 91.0–99.8). The misclassified patient, however, was admitted to an ICU, making the PPV of ICU admission in this subgroup of patients 100% (95% CI: 95.1–100).

Discussion

We found that the coding for ICU admission in the DNPR had a high PPV. The coding was almost perfect for mechanical ventilation and acute dialysis.

Our PPV, however, is lower than the PPV of 98.7% (95% CI: 95.3–99.8) found by Christiansen et al in a previous Danish study.[9] This is probably because the latter study included admissions to ICUs in a single university hospital and did not include any district hospitals.

The majority of the few miscoded patients in our study were hospitalized in relation to surgery and probably coded as admitted to an ICU because of admission to the postoperative recovery room. Furthermore, we found that patients with the coding of ICU admission only had a higher likelihood of being misclassified. These potential problems should be considered when using the DNPR to identify ICU admissions.

We were unable to evaluate the proportion of ICU patients not registered in the DNPR, thereby hindering the possibility of estimating the sensitivity, specificity, and negative predictive value required in the optimal validation study.[13] If the coding in future studies is used to define ICU admission or treatments as exposure or outcome, misclassification might lead to information bias. However, in most circumstances registration will probably not depend on the other exposure or outcome under study and any bias would be towards the null leading to an underestimation of the true effect of the exposure.

In conclusion, our finding of high PPVs indicates that the coding of intensive care admission and treatment in the DNPR in a vast majority of cases corresponds to actually receiving the ICU treatment. Thus, the DNPR remains a valuable source for observational studies of ICU patients.

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Disclosure

The authors report no conflict of interest in this work.

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Study II

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Mortality in elderly ICU patients: a cohort study

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Background: The population is aging. We examined changes in the proportion of elderly (≥ 80 years) intensive care unit (ICU) patients during 2005–2011 and the association between age and mortality controlling for preexisting morbidity.
Methods: Through the Danish National Patient Registry, we identified a cohort of 49,938 ICU admissions (47,596 patients) in Northern Denmark from 2005 to 2011. Patients were subdivided in age groups (15–49, 50–64, 65–79 and ≥ 80 years) and calendar year. We estimated 30-day and 31–365-day mortality and mortality rate ratios (MRRs), stratified by admission type (medical and elective/acute surgical patients). Mortality was compared between age groups adjusting for sex and preexisting morbidity using 50–64-year-olds as reference.
Results: The proportion of elderly patients increased from 11.7% of all ICU patients in 2005 to 13.8% in 2011. Among the elderly, the 30-day mortality was 43.7% in medical, 39.6% in acute surgical, and 11.6% in elective surgical ICU patients. The corresponding adjusted 30-day MRRs compared with the 50–64-year-olds were 2.7 [95% confidence interval (CI) 2.5–3.0] in medical, 2.7 (95% CI 2.4–3.0) in acute surgical, and 5.2 (95% CI 4.1–6.6) in elective surgical ICU patients. The 31–365-day mortality among elderly patients was 25.4% in medical, 26.9% in acute, and 11.9% in elective surgical ICU patients, corresponding to adjusted MRRs of 2.5 (95% CI 2.1–2.9), 2.2 (95% CI 1.9–2.5), and 1.9 (95% CI 1.6–2.3), respectively.
Conclusions: During 2005–2011, there was an 18% increase in the proportion of elderly ICU patients. Advancing age is associated with increased mortality even after controlling for preexisting morbidity.

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During the coming decades, the European demographic changes may challenge our health care services. The proportion of people aged 80 years or older is a fast-growing segment of the European population, and it is estimated to more than double by 2050 with an increase from 4.7% in 2010 to 11.0% in 2050.* Patients aged 80 years or older currently account for approximately 10% of all intensive care unit (ICU) admissions in Europe[1,2] and Australia.[3] An increase in ICU admissions of patients aged 75 years or older have been shown, with the proportion rising from 8.5% in 1987 to 11.1% in 2002 for conditions other than cardiac surgery and from 5.4% to 24.3% for patients admitted after cardiac surgery.[4] Furthermore, an annual increase of 5.6% of ICU admissions among patients aged 80 years or older during 2000–2005 has been estimated, and the authors predicted a 72.4% rise in ICU and hospital bed days in patients aged 80 years or older by 2015.[3] However, data documenting an increase to this extent remain sparse.[5]

In-hospital mortality after ICU admission increases with advancing age.[1,2,6–8] Still, many elderly survive their critical illness, and age alone should not be the sole criterion for excluding elderly from ICU treatment.[9] Instead, factors like severity of illness and functional status seem to determine the prognosis in elderly ICU patients.[9] Furthermore, preexisting morbidity, advancing with age, is associated with increased mortality among ICU patients.[10]

While most previous studies only included ICU or in-hospital mortality, a study from a large academic tertiary medical center in the United States included 7265 ICU patients above the age of 65 and found that patients aged 75–84 years had a higher 28-day mortality compared with patients aged 65–74 [odds ratio 1.52 (95% confidence interval [CI] 1.32–1.74)]. In addition, Cox regression analysis for 1-year mortality in 28-day survivors showed the same

*Eurostat: Demography report 2010- Older, more numerous and diverse Europeans. http://epp.eurostat.ec.europa.eu/portal/page/portal/product_details/publication?p_product_code=KE-ET-10-001 [Accessed 6 February 2013]

trend (hazard ratio1.21 95% CI 1.06–1.38).[11] This study only included patients admitted because of medical or acute surgical reasons.

To examine recent changes in the proportion of elderly ICU patients in intensive care over time and to examine the association between age and mortality among ICU patients, we therefore conducted a cohort study among all ICU patients aged 15 years or older. We also evaluated the impact of preexisting morbidity on the association between age and mortality among ICU patients.

Materials and methods

Study design and settings

We conducted this cohort study in Northern Denmark (the former counties of Aarhus and North Jutland), which counts approximately 20% of the Danish population (1.15 million people). The Danish health care system provides universal tax-supported care to all Danish citizens, guaranteeing equal access to primary and hospital care, including all ICUs in Denmark. The study area is mixed urban–rural and includes 12 ICUs that count eight university hospital units (two neurosurgical ICUs, two cardiothoracic/multidisciplinary ICU, and four multidisciplinary ICUs) and four multidisciplinary units at regional hospitals.

In Denmark, all citizens are assigned a unique civil registration number (CPR number) at birth, which allows linkage of population-based registries. We linked the Danish National Patient Registry (DNPR) and the Civil Registration System (CRS) using the CPR number.

ICU patients

Through the DNPR, we identified all admissions to an ICU in Northern Denmark from 1 January 2005 to 31 December 2011 for all patients aged 15 years or older. For patients with more than one ICU admission during this period, we counted each ICU admission as a separate admission if there was an interval of at least 1 year between the admissions.

Since 1977, the DNPR has been recording all admissions from nonpsychiatric hospitals, and since 1995, visits to emergency rooms and outpatient clinics have been included as well.[12,13] Data contain information on the patient's civil registration number, dates of admission and discharge, procedure codes, one primary diagnosis, and up to 19 secondary diagnoses coded by physicians. Diagnoses were classified according to the *International Classification of Diseases*, 8th revision until 1993 and 10th revision thereafter. Information on ICU admission, including major treatments during ICU stay, has been recorded routinely since 2005. The positive predictive values (PPVs) of ICU admission, mechanical ventilation, and acute dialysis were 87.2% (95% CI 75.6–94.5), 100% (95% CI 95.1–100), and 98.0% (95% CI 91.0–99.8), respectively.[14] In addition, ICU discharge date has been recorded since 2009, with a completeness of approximately 80–90% since 2010.†

ICU patients were identified through the DNPR by use of the Danish procedure coding for ICU admission as described in a previous study.[14] The date of first ICU admission was defined as the first day a procedure code was used. Length of stay (LOS) was estimated for ICU patients admitted during 2010–2011. We obtained information on surgical procedures performed on the day of ICU admission or within 7 days prior to ICU admission; hence, the patients were classified as either surgical or medical patients. The surgical patients were categorized as elective or acute by using the coding for elective/acute hospital admission registered in the DNPR. Finally, information on the primary diagnosis of the current hospital stay was used to categorize the patients into eight major disease groups (infectious diseases, cardiovascular diseases, respiratory diseases, gastrointestinal/liver diseases, endocrine diseases, neoplasms, trauma/poisoning, and other diseases).

Preexisting morbidity was defined as previous diagnoses of the 19 diseases included in the Charlson comorbidity index (CCI).[15] We computed the CCI based on all hospital discharge codes registered in the DNPR within 5 years before the current hospital admission. The CCI score has been validated as a predictor of mortality for use with administrative data for several categories of patients,[16] including ICU patients.[17] We divided morbidity levels into three groups: low (CCI score = 0), moderate (CCI score 1 and 2), and high (CCI score 3 or more).

Mortality

Information on vital status and date of death was obtained from the CRS.[18] Since 1968, the CRS has been updated on a daily basis. The CRS contains

†*Dansk Intensiv Database. Årsrapport 2011. https://www.sundhed.dk/content/cms/12/4712_aarsrapport-2011-did-290612.pdf [Accessed 13 February 2013]*

information for the entire Danish population on migration and changes in vital status, including the exact date of death.

Statistical analysis

Baseline characteristics of the ICU patients were described in contingency tables. The main variable under study was age at ICU admission, categorized into the following age groups: 15–49 years, 50–64 years, 65–79 years, and ≥ 80 years. We defined elderly as patients/people aged 80 years or older. The proportion of elderly patients admitted to the ICU during the entire study period was described. In addition, the prevalence proportion ratio (PPR) with 95% CI was estimated comparing the proportion of elderly in 2005 with the proportion in 2011. The annual proportions were illustrated graphically according to age group. For each year in the study period, we compared the proportion of elderly ICU patients with the proportion of elderly among all hospitalized patients. In a subset analysis, we estimated median LOS by age group for patients admitted during 2010–2011.

Follow-up began on the date of the first ICU admission, and the patients were followed until death, emigration, or for 365 days, whichever came first. The Kaplan–Meier method was used to estimate the 1-year mortality probability as 1 minus the survival probability with 95% CI. We plotted cumulative mortality for ICU patients according to age groups.

ICU patients form a heterogeneous group with worse prognosis among medical and acute surgical patients than among elective surgical patients.[19,20] Consequently, the analyses were stratified by type of admission (medical or elective/acute surgical). To compare the risk of death among the different age groups, we computed standardized 30-day and 31–365-day mortality using direct standardization to the distribution of preexisting morbidity in the age group of 50–64-year-old patients. Mortality rate ratios (MRR) were estimated using a Cox proportional hazards model. We compared the mortality rates among patients aged 15–49, 50–64, 65–79, and≥ 80 years of age, adjusting for sex, primary diagnosis of current hospital stay, and CCI score using the age group of 50–64-year-old as a reference group. The assumption of proportional hazards was checked graphically and found reasonable, except for the stratum containing elective surgical patients. We therefore split the 1-year follow-up into two time periods, 0–30 days and 31–365 days, and the assumption of proportional hazards was found to be reasonable for the two time periods.

To investigate the association between age and mortality, we performed a logistic regression of 30-day and 1-year mortality against a restricted cubic spline function of age in years. We then plotted the resulting curve against age to illustrate the association graphically.

To evaluate the impact of preexisting morbidity on the association between age and mortality, we repeated the Cox proportional hazards analysis omitting the preexisting morbidity variable.

All statistical analyses were performed using Stata software (version 11.2; StataCorp LP, College Station, TX, USA). The study was approved by the Danish Data protection Agency (record no. 2009-41-3987).

Results

Descriptive data

A total of 49,938 ICU admissions corresponding to 47,596 patients were identified during the 7-year study period. Median age was 64 years (interquartile range 49–74 years), 57.5% were men, and 62.5% were surgical patients. The prevalence of preexisting morbidity increased with advancing age until the age of 79 years; thereafter, a slight decrease in prevalence was seen among patients aged 80 and older (Table 1).

Cardiovascular disease was the most frequent primary diagnosis of current hospital stay among elderly patients followed by gastrointestinal/liver disease. By comparison, cardiovascular disease followed by neoplasms was the most frequent primary diagnosis of current hospital stay among patients aged 50–79, whereas it was trauma/poisoning and other diagnoses for patients aged 15–49 (Table 1).

The proportion of ICU admissions of elderly patients by calendar year

The proportion of elderly ICU patients accounted for 12.6% of all admissions throughout the entire study period. The proportion of elderly ICU patients increased slightly from 11.7% (898/7653) in 2005 to 13.8% (845/6104) in 2011, which corresponds to a PPR of 1.18 (95% CI 1.08–1.29) during the 7-year study period. By comparison, a smaller increase in hospital admissions of the elderly was seen from 13.4% in 2005 to 14.3% in 2011, corresponding to a PPR of 1.06 (95% CI 1.05–1.08).‡ During our study period, there was no increase in the proportion of

‡*Statens Serum Institut. Health data and ICT. http://www.ssi.dk/Sundhedsdataogit/Dataformidling/Sundhedsdata/Behandling%20ved%20sygehuse/Sygehusaktivitet%20Offentlig%20og%20privat.aspx [Accessed 4 June 2013]*

Table 1

Characteristics of 49,938 admissions to an intensive care unit in Northern Denmark from 2005–2011 according to age groups, *n* (%).

Age groups (years)	15–49	50–64	65–79	≥ 80
Number of patients	13,001 (26.0)	13,305 (26.6)	17,366 (34.8)	6,266 (12.6)
Median age, years (IQR)	35 (25–44)	59 (55–62)	72 (69–76)	84 (82–87)
Sex				
Men	7,011 (53.9)	8,340 (62.7)	10,361 (59.7)	2,988 (47.7)
Admission type				
Medical patients	6,223 (47.9)	4,655 (35.0)	5,523 (31.8)	2,332 (37.2)
Elective surgical patients	2,025 (15.6)	4,372 (32.9)	6,690 (38.5)	1,353 (21.6)
Acute surgical patients	4,753 (36.6)	4,278 (32.2)	5,123 (29.7)	2,581 (41.2)
Preexisting morbidity				
Myocardial infarction	165 (1.3)	915 (6.9)	1,728 (10.0)	589 (9.4)
Congestive heart failure	184 (1.4)	736 (5.5)	1,829 (10.5)	950 (15.2)
Peripheral vascular disease	171 (1.3)	776 (5.8)	1,984 (11.4)	599 (9.6)
Cerebrovascular disease	374 (2.9)	1,085 (8.2)	2,097 (12.1)	919 (14.7)
Dementia	4 (0.0)	50 (0.4)	177 (1.0)	179 (2.9)
Chronic pulmonary disease	556 (4.3)	1,275 (9.6)	2,821 (16.2)	954 (15.2)
Connective tissue disease	187 (1.4)	295 (2.2)	626 (3.6)	262 (4.2)
Ulcer disease	223 (1.7)	492 (3.7)	747 (4.3)	370 (5.9)
Mild liver disease	358 (2.8)	581 (4.4)	254 (1.5)	25 (0.4)
Diabetes mellitus	595 (4.6)	1,201 (9.0)	1,889 (10.9)	527 (8.4)
Hemiplegia	127 (01.0)	84 (0.6)	61 (0.4)	6 (0.1)
Moderate/severe renal disease	272 (2.1)	480 (3.6)	808 (4.7)	336 (5.4)
Diabetes mellitus with chronic complications	311 (2.4)	724 (5.4)	1,105 (6.4)	304 (4.9)
Any tumor	572 (4.4)	2,088 (15.7)	3,144 (18.1)	891 (14.2)
Leukemia	54 (0.4)	85 (0.6)	124 (0.7)	23 (0.4)
Lymphoma	85 (0.7)	198 (1.5)	229 (1.3)	44 (0.7)
Moderate/severe liver disease	142 (1.1)	287 (2.2)	93 (0.5)	12 (0.2)
Metastatic solid tumor	217 (1.7)	520 (3.9)	549 (3.2)	84 (1.3)
AIDS	27 (0.2)	16 (0.1)	8 (0.1)	0 (0.0)
Any preexisting morbidity	3,098 (23.8)	7,050 (53.0)	11,143 (64.2)	3,865 (61.7)
Charlson comorbidity index				
Low (0)	9,903 (76.2)	6,255 (47.0)	6,223 (35.8)	2,401 (38.3)
Medium (1–2)	2,190 (16.8)	4,703 (35.4)	7,266 (41.8)	2,596 (41.4)
High (> 2)	908 (7.0)	2,347 (17.6)	3,877 (22.3)	1,269 (20.3)
Mechanical ventilation	3,632 (27.9)	6,093 (45.8)	8,877 (51.1)	2,420 (38.6)
Acute dialysis	397 (3.1)	696 (5.2)	1,230 (7.1)	273 (4.4)
Inotropics/vasopressors	2,082 (16.0)	4,915 (36.9)	8,137 (46.9)	2,440 (38.9)
Admission diagnosis				
Infectious diseases	1,347 (10.4)	1,327 (10.0)	1,694 (9.8)	796 (12.7)
Cardiovascular diseases	1,558 (12.0)	4,398 (33.1)	7,042 (40.6)	1,833 (29.3)
Respiratory diseases	298 (2.3)	648 (4.9)	1,154 (6.7)	435 (6.9)
Gastrointestinal/liver	729 (5.6)	1,151 (8.7)	1,512 (8.7)	1,070 (17.1)
Endocrine diseases	373 (2.9)	234 (1.8)	190 (1.1)	77 (1.2)
Neoplasms	905 (7.0)	2,260 (17.0)	2,794 (16.1)	596 (9.5)
Trauma/poisoning	4,275 (32.9)	1,527 (11.5)	1,310 (7.5)	826 (13.2)
Other	3,516 (27.0)	1,760 (13.2)	1,670 (9.6)	633 (10.1)

AIDS, acquired immunodeficiency syndrome; IQR, interquartile range.

elderly people in the general population as people aged 80 years or older accounted for 4.1% of the population in both 2005 and 2011.§ The annual proportion of ICU admissions by age group is illustrated in Fig. 1. LOS was available in 11,259 of 13,271 admissions during 2010–2011. Median LOS did not differ between age groups (data not shown).

Cumulative mortality according to age groups

Figure 2 presents the cumulative 1-year mortality among ICU patients stratified by age groups. The risk of dying within 1 year after ICU admission rose with advancing age. Forty-nine percent of the elderly died within 1 year compared with only 11.7% (average mortality during the study period) of the elderly from the general population.¶ Mortality

§*StatBank Denmark. Population and elections. http://www.statbank.dk/statbank5a/default.asp?w=1280 [Accessed 13 February 2013]*

¶*StatBank Denmark. Population and elections. Deaths. http://www.statbank.dk/statbank5a/default.asp?w=1280 [Accessed 5 June 2013]*

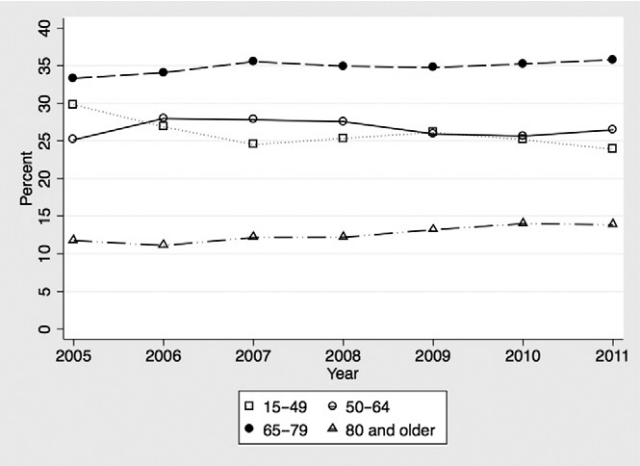

Fig. 1. Proportion of ICU admissions of ICU patients by age group and calendar year.

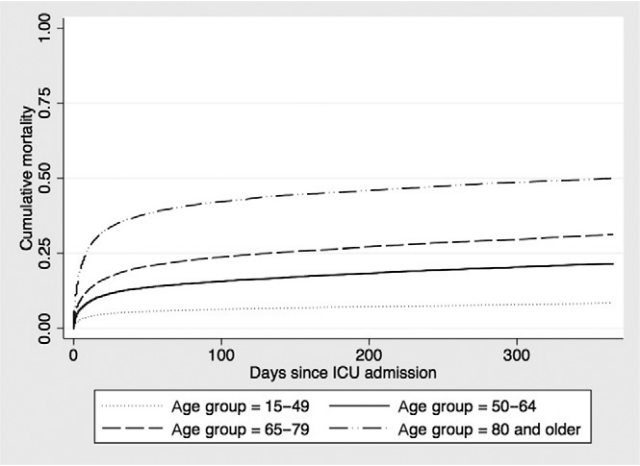

Fig. 2. Cumulative mortality curves among ICU patients according to age groups.

among patients aged 65–79 years was 31%, 21% among patients aged 50–64 years, and 8% among patients aged 15–49 years compared with 2.7%, 0.77%, and 0.10% among the same age groups in the general population.

Thirty-day and 31–365-day mortality stratified on type of admission

The 30-day and 31–365-day mortality are shown in Table 2. Elderly patients had a higher mortality than younger patients irrespective of type of admission. While the absolute mortality was higher in medical patients and acute surgical patients among all age groups than among elective surgical patients (Table 2), the 30-day adjusted MRRs were higher among elderly patients with elective surgical admissions with an adjusted MRR of 5.2 (95% CI 4.1–6.6) than the adjusted MRR of 2.7 (95% CI 2.5–3.0) and 2.7 (95% CI 2.4–3.0) in medical and acute surgical patients, respectively, indicating that when the absolute 30-day mortality was low, the relative risk of dying increased with advancing age. By comparison, even though the absolute 31–365-day mortality was higher among medical and acute surgical patients compared with elective surgical patients (Table 2), the relative risk of dying among the elderly was approximately the same.

Standardization to the distribution of preexisting morbidity in the age group of 50–64-year-old patients did neither change the 30-day nor the 31–365-day mortality substantially (Table 2).

Differences in level of preexisting morbidity did not have any major influence on our results. When omitting the preexisting morbidity variable from the Cox model, there was no significant change in the MRRs (Table 2).

The smoothed age–mortality curve (Fig. 3) indicated an almost linear increase for 30-day and 1-year mortality until approximately age 75, and thereafter a steeper increase was seen. This was the case for all three levels of preexisting morbidity.

Discussion

In this large cohort study of ICU patients, we found an approximately 18% increase in the proportion of elderly patients from 11.7% in 2005 to 13.8% in 2011. Furthermore, we found that elderly ICU patients had a more than doubled 1-year mortality compared with younger ICU patients. Stratification by type of admission showed higher mortality among elderly ICU patients with acute medical and surgical admissions compared with elective surgical admission.

The 18% increase of the proportion of elderly ICU patients during our 7-year study period is lower than the 5.6% annual increase shown by Bagshaw et al.[3] Thus, the prediction of a 72% rise in ICU and hospital bed days of patients aged 80 or older by 2015 stated by Bagshaw et al. may be an overestimation, at least in Denmark. However, the 18% increase of elderly patients admitted to the ICUs did not reflect the corresponding 6% increase of elderly patients admitted to hospital in general during the same study period/study setting. Furthermore, there was no increase in the proportion of elderly people in the general population, indicating that the increase in elderly patients admitted to our ICUs is not only due to the aging population, but also

Table 2

Crude and adjusted risk of death and mortality rate ratio (MRR) within 30 days or 31–365 days among intensive care unit patients admitted (a) for medical (nonsurgical) reasons by age, (b) after acute surgery by age, and (c) after elective surgery by age.

Age group, *n*	Dead, *n*/*N*	Mortality, %	Standardized mortality, % (95% CI)	Crude MRR (95% CI)	Adjusted* MRR (95% CI)	Adjusted† MRR (95% CI)
(a)						
30 days						
≥ 80 years	1,019/2,332	43.7	43.2 (41.0–45.4)	3.0 (2.8–3.3)	2.8 (2.6–3.1)	2.7 (2.5–3.0)
65–79 years	1,529/5,523	27.7	26.0 (24.8–27.2)	1.7 (1.6–1.9)	1.6 (1.4–1.7)	1.5 (1.4–1.6)
50–64 years	789/4,655	17.0	17.0 (15.9–18.0)	1 (ref.)	1 (ref.)	1 (ref.)
15–49 years	318/6,223	5.1	7.3 (6.5–8.2)	0.3 (0.2–0.3)	0.4 (0.3–0.4)	0.4 (0.4–0.5)
31–365 days						
≥ 80 years	333/1,313	25.4	23.4 (21.0–25.8)	2.8 (2.5–3.3)	2.7 (2.3–3.1)	2.5 (2.1–2.9)
65–79 years	681/3,994	17.1	14.9 (13.8–16.0)	1.8 (1.6–2.1)	1.6 (1.5–1.9)	1.5 (1.3–1.7)
50–64 years	381/3,866	9.9	9.9 (8.9–10.8)	1 (ref.)	1 (ref.)	1 (ref.)
15–49 years	177/5,905	3.0	5.2 (4.4–6.0)	0.3 (0.2–0.4)	0.4 (0.3–0.4)	0.5 (0.4–0.5)
(b)						
30 days						
≥ 80 years	1,021/2,581	39.6	39.4 (37.3–41.5)	2.7 (2.5–3.0)	2.8 (2.6–3.1)	2.7 (2.4–3.0)
65–79 years	1,354/5,153	26.3	25.2 (24.0–26.4)	1.6 (1.5–1.8)	1.6 (1.5–1.8)	1.5 (1.4–1.7)
50–64 years	725/4,278	17.0	17.0 (15.8–18.1)	1 (ref.)	1 (ref.)	1 (ref.)
15–49 years	320/4,753	6.7	10.1 (8.9–11.3)	0.4 (0.3–0.4)	0.4 (0.4–0.5)	0.5 (0.4–0.5)
31–365 days						
≥ 80 years	419/1,560	26.9	26.8 (24.3–29.3)	2.4 (2.1–2.7)	2.4 (2.1–2.8)	2.2 (1.9–2.5)
65–79 years	764/3,799	20.1	18.5 (17.3–19.8)	1.7 (1.5–1.9)	1.7 (1.5–1.9)	1.6 (1.4–1.7)
50–64 years	447/3,553	12.6	12.6 (11.5–13.6)	1 (ref.)	1 (ref.)	1 (ref.)
15–49 years	145/4,433	3.3	6.7 (5.6–7.8)	0.2 (0.2–0.3)	0.3 (0.2–0.3)	0.3 (0.3–0.4)
(c)						
30 days						
≥ 80 years	157/1,353	11.6	11.5 (9.8–13.2)	4.5 (3.6–5.8)	5.2 (4.1–6.7)	5.2 (4.1–6.6)
65–79 years	308/6,690	4.6	4.5 (4.0–5.0)	1.7 (1.4–2.1)	2.0 (1.6–2.5)	1.9 (1.5–2.3)
50–64 years	117/4,372	2.7	2.7 (2.2–3.2)	1 (ref.)	1 (ref.)	1 (ref.)
15–49 years	33/2,025	1.6	2.2 (1.4–3.0)	0.6 (0.4–0.9)	0.5 (0.3–0.8)	0.6 (0.4–0.9)
31–365 days						
≥ 80 years	142/1,196	11.9	11.7 (9.9–13.6)	1.5 (1.2–1.8)	1.9 (1.6–2.3)	1.9 (1.6–2.3)
65–79 years	684/6,382	10.7	10.3 (9.6–11.0)	1.3 (1.2–1.5)	1.6 (1.4–1.8)	1.5 (1.3–1.7)
50–64 years	354/4,255	8.3	8.3 (7.5–9.1)	1 (ref.)	1 (ref.)	1 (ref.)
15–49 years	85/1,992	4.3	6.3 (4.9–7.6)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.6 (0.4–0.7)

*Adjusted for sex and primary diagnosis of current hospital stay.
†Adjusted for sex, primary diagnosis of current hospital stay, and Charlson comorbidity score.
CI, confidence interval; ref., reference.

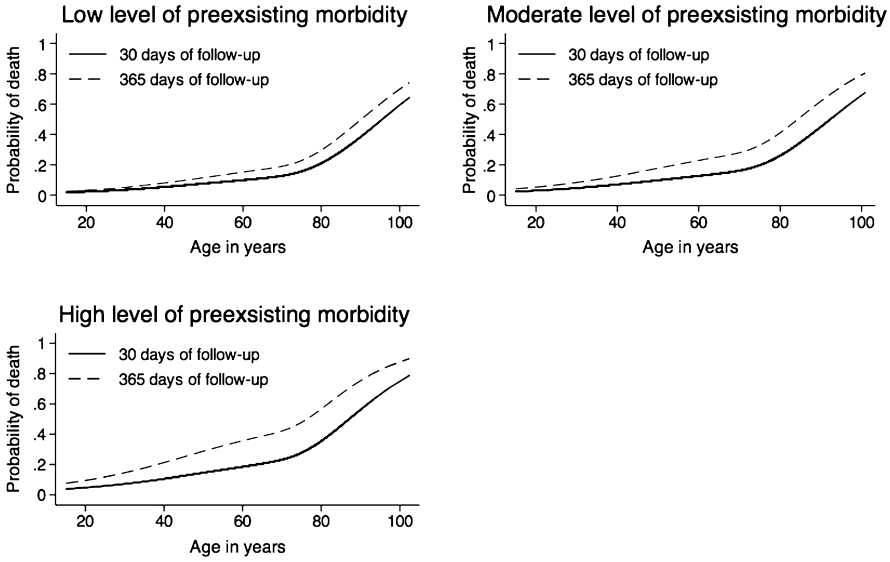

Fig. 3. Estimated 30-day and 1-year mortality among ICU patients with the three levels of preexisting morbidity in relation to age. Preexisting morbidity is defined according to Charlsons comorbidity index (CCI): low: CCI = 0, moderate: CCI = 1–2, high: CCI > 2.

because of a change in the ICU admission policy in regard to age.

Our findings of increased mortality among elderly patients are supported by the recent study by Fuchs et al.[11] who found age as risk factor of 28-day mortality among ICU patients. We found that the association between age and mortality after ICU admission persisted even when we controlled for preexisting morbidity, suggesting that differences in preexisting morbidity between age groups did not explain the observed difference in mortality. Furthermore, the standardization of mortality to the distribution of preexisting morbidity in the age group of 50–64-year-old in order to bear a better comparison between age groups did not influence the results, thus substantiating the association between age and mortality.

In our study, elderly ICU patients admitted due to medical or acute surgical reasons had higher mortality than elderly patients admitted following elective surgery, which is supporting previous studies.[19,20] A recent review, focusing on the challenge of admitting elderly patients (defined as aged 80 years or older) to the ICU, suggested ICU admissions to be limited to elective surgical patients and only selected medical or acute surgical elderly patients because of the poor prognosis.[21] Yet the survival benefit of treatment in the ICU as opposed to treatment in the ward is greater among elderly patients compared with younger patients.[22] In addition, our findings indicate that when ICU admission is because of elective surgery, the relative risk of dying within 30 days is also markedly increased among elderly patients compared with younger age groups that have very low mortality. The reason for this might be that elderly patients are more vulnerable to any adverse effect of surgery because of age-related decrease in physiological reserve.[23]

Our study was conducted in a population-based hospital setting with use of routinely and prospectively collected data and complete follow-up. The Danish health care sector provides centralized, tax-supported universal medical coverage to each Danish citizen, which limits potential selection and information bias. Still, several issues must be considered in the interpretation of our data. We included all ICU admissions during our study period, thereby allowing individual persons to contribute with more than one ICU admission if these admissions were more than 1 year apart. Because different admissions of one individual may not be entirely independent, our estimated CIs could consequently be too narrow. However, because less than 5% of the patients contributed with more than one admission, we do not expect that this could affect our conclusions. We defined our cohort while relying on routine procedure code registration in the DNPR. In a previous study conducted in the North Denmark Region, we found a PPV of 87.2% (95% CI 75.6–94.5) of the coding of ICU admission in the DNPR.[14] In addition, Christiansen et al. found a higher PPV of 98.7% (95% CI 95.3–99.8%) of ICU admission coding registered in the DNPR with an ICU admission to ICUs in a single university hospital.[10] Nevertheless, we do not expect any miscoding to be dependent of patient age, and therefore we expect such misclassification to bias our findings towards no association. We lacked measures of severity of illness, which could have informed our results further. It is possible that severity of illness differed among the different age groups as the increased level of preexisting morbidity together with decreased physiologic reserves in elderly may increase the risk of acute organ failure during critical illness.[23] ICU beds account for only 5% of European hospital beds, and the demand for ICU admissions often exceeds the number of available ICU beds. This often forces ICU physicians to perform ICU triage.[24] Furthermore, the ICU refusal rate increases with increasing age.[22]

Elderly patients admitted to the ICU may therefore be in good preadmission condition, as shown by Boumendil et al.[1] On the other hand, they also found that the elderly (aged 80 years or older) received less intensive care therapy than the matched younger-old (65–79 years).[1] This is supported by a recent Swedish study[25] and is on par with our findings that elderly patients receive less therapy in terms of mechanical ventilation, acute dialysis, and inotropics/vasopressors than patients aged 65–79 (Table 1). Because of this selection into the ICU, findings from this, and other ICU studies, should not be generalized to critically ill patients outside the ICU.

In conclusion, we found an 18% increase in the proportion of elderly patients admitted to the ICU during the 7-year period. In addition, we found that advancing age is associated with increased mortality among ICU patients irrespective of admission type. Furthermore, the mortality among the elderly patients was increased compared with younger patients irrespective of adjustment for preexisting morbidity, indicating that preexisting morbidity did not entirely explain the association.

Acknowledgements

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Short title: Bacteremia in ICU patients

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Competing interests

Henrik C. Schønheyder participates in a project on rapid identification of blood culture isolates funded by the Danish National Advanced Technology Foundation. The authors declare that they have no competing interests.

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Abbreviations list

CCI: Charlsons comorbidity index

CI: Confidence interval

CRP: C-reactive protein

DNPR: Danish National Patient Registry

ICU: Intensive care unit

IQR: Inter quartile range

HR: Hazard ratio

POR: Prevalence odds ratio

WBC: White blood cell

Abstract

Background: Bacteremia is a severe infection. We examined the association between age and bacteremia and associated biochemical markers of organ dysfunction among ICU patients.

Methods: Our study cohort consisted of 47,579 ICU patients admitted in Northern Denmark during 2005-2011. We estimated the proportion of patients with bacteremia (first positive blood culture) from 2 days before to 7 days after ICU admission and compared 1) bacteremia prevalence odds ratios (PORs) at ICU admission and 2) the bacteremia risk days 2-7 after ICU admission accounting for death as competing risk between age groups (15-49, 50-64, 65-79, 80+ years). Inflammatory response and organ dysfunction was described using C-reactive protein (CPR), white blood cell count (WBC), serum creatinine, bilirubin, and platelet count.

Results: Only 1,872 (3.9%) of the 47,579 patients had bacteremia. Bacteremia prevalence at admission was 1.9% in patients aged 15-49 years rising to 4.1% in patients 80+ years (adjusted POR= 1.8 (95% CI 1.5-2.2)). During days 2-7 the bacteremia risk was 0.7% (95% CI 0.5-0.8) in patients aged 15-49 years rising to 1.1% (0.8-1.4) in patients aged 80+ years (adjusted hazard ratio= 1.4 (95% CI 0.9-2.0)). Bacteremia patients aged 80+ had more frequently high CRP, WBC and creatinine but less frequently liver and coagulation dysfunction.

Conclusions: Only 1 in 25 ICU patients had bacteremia from 2 days before to 7 days after ICU admission, and prevalence at admission increased with increasing age. The risk of acquiring bacteremia during the first week after ICU admittance was 1.0% with little variation by age.

Introduction

Bacteremia is a severe infection with a 30-day mortality exceeding 15%.[1,2] The incidence of bacteremia rises with advancing age.[3,4] Following the aging of populations in Western countries admissions of patients aged 80+ years in intensive care unit (ICU) are increasing.[5,6] Patients in the ICU are at increased risk of acquiring infection because of use of intraluminal devices, pre-existing morbidity, and a compromised immune system.[3] Ultimately, exposure to nosocomial pathogens plays a role.[7] The cross-sectional EPIC-II study revealed that half of all ICU patients had an infection on the study day, and 15% of infected ICU patients had bacteremia.[8] Among infected patients in the study, elderly patients (≥85 years) presented less often with bacteremia than younger patients.[9] Similarly, a Belgian cohort study on the impact of age on nosocomial bacteremia in the ICU, found decreasing incidence of bacteremia with increasing age.[10] Yet, a Canadian study including all patients with a positive blood culture showed a relative risk of bacteremia requiring ICU admission of 7.0 (95 % confidence interval (CI), 5.6-8.7) in patients aged ≥65 years compared with patients aged <65 years.[4] Few studies have focused on the bacteremia burden at ICU admission in relation to age, which is important given the increase in bacteremia incidence and the aging world population. Elderly patients with bacteremia or sepsis may more often than younger patients present with non-distinctive clinical manifestations such as anorexia, malaise, and urinary incontinence[3,11–13]. This may lead to a delay of the correct diagnosis making comparison of clinical manifestations between age groups of major clinical relevance. We therefore examined the impact of age on the burden of bacteremia during ICU admission and described the biochemical markers of organ dysfunction at ICU admission in bacteremia patients by age.

Materials and methods

We conducted this study in Northern Denmark (population ~ 1.15 million). The study area is mixed urban-rural including 12 ICUs.[6] We linked prospectively collected data from population-based medical registries using the unique civil registration number assigned to all Danish citizens at birth.

Through the Danish National Patient Registry (DNPR) we identified all patients aged 15+ with a first-time admissions to an ICU in Northern Denmark from 1 January 2005 to 31 December 2011. The DNPR has

recorded individual-level data on dates, diagnoses and procedures from admissions to non-psychiatric hospitals since 1977 and emergency room visits and outpatient clinic visits since 1995.[14,15] Since 2005, ICU admissions and treatments are accurately registered in DNPR.[16,17] We classified the patients as either acute surgical, elective surgical or non-surgical using surgical procedures performed within 7 days before ICU admission.[6] We categorized the patients into eight major disease categories based on the primary diagnosis of the current admission (see Additional file 1 for categories and codes).[18]

Bacteremia was defined as the presence of viable bacteria or fungi in the bloodstream evidenced by blood cultures in which contamination had been ruled out.[1] Coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., and *Propionibacterium acnes* were regarded as contaminants unless isolated from two or more separate blood culture sets. We used the laboratory information system, maintained at the Departments of Clinical Microbiology, Aalborg University Hospital and Aarhus University Hospital, to identify ICU patients with bacteremia defined by the first positive blood culture obtained from 2 days before to 7 days after ICU admission. This date was also regarded as first date of infection.

Using the clinical laboratory information system (LABKA) research database,[19] we obtained information on the level of C-reactive protein (CRP) and white blood cell (WBC) count at date of ICU admission. We obtained data on serum creatinine, serum bilirubin, and platelet count using the laboratory cut-off values for the respective organ dysfunctions in the Sequential Organ Failure Assessment (SOFA) score.[20] If routine laboratory measurements on the day of ICU admission were missing, we used measurements from one day before or after ICU admission. From the DNPR we obtained information on treatment with mechanical ventilation, renal replacement therapy, and inotropes/vasopressors.

To compute the Charlson Comorbidity Index (CCI) for each patient[21] we retrieved all diagnoses registered in DNPR within five years before the current hospital admission. Morbidity levels were divided into low (CCI score 0), moderate (CCI score 1-2), and high (CCI score $\geq$3). We obtained information on patients with previous filled prescriptions for immunosuppressive therapy within 1 year prior to ICU admission using the Aarhus University Prescription Database. Data includes information on reimbursed medications dispensed at all pharmacies of the North and Central Denmark Region.[22] We excluded patients with less than one-year residency in the study area before admission.

Statistical analyses

Patient characteristics, the proportion of patients with bacteremia from 2 days before to 7 days after ICU admission, and the clinical manifestations were described by age group; 15-49 years, 50-64 years, 65-79 years and 80+ years. Bacteremia prevalence at ICU admission (defined as a positive blood culture obtained from 2 days before to 1 day after ICU admission) was compared between age groups by prevalence odds ratios (PORs) estimated using logistic regression and adjusting for sex, CCI level, primary diagnosis of current hospital stay, and preadmission use of immunosuppressive drugs. We stratified the analysis by type of admission (non-surgical, acute/elective surgical) and by CCI level. To evaluate the bacteremia risk after admission to the ICU, we estimated and plotted graphically the bacteremia risk during days 2-7 after ICU admission using the cumulative risk method treating death as a competing risk.[23] We used a Cox proportional hazards model to compare the hazard ratios (HRs) for bacteremia between age groups, adjusting for sex, CCI score, and immunosuppressive therapy. The 15-49 year-old age group was reference. The assumption of proportional hazards was checked graphically and found acceptable. As patients dying shortly after ICU admission are no longer at risk of bacteremia, we performed a sensitivity analysis of bacteremia PORs, re-defining the time period to a positive blood culture obtained from 2 days before to the day of ICU admission. All statistical analyses were performed using Stata software (version 11.2; StataCorp LP, College Station, TX). The study was conducted in accordance with the amended Declaration of Helsinki. According to Danish legislation the study does not require ethical approval or informed consent. The study was approved by the Danish Data protection Agency (record no. 2009-41-3987).

Results

We included 47,579 adult ICU patients. Table 1 presents patient characteristics by age groups. From 2 days before to 7 days after ICU admission, a total of 15,304 patients (32.2%) had a blood culture drawn of which 1,872 (3.9% of all and 12.2% of those tested) were positive. The bacteremia burden increased from 2.6% among patients aged 15-49 to 4.1% in patients aged 50-64, 4.5% in patients aged 65-79, and 5.0% in patients aged 80+ years. Figure 1A+B displays the bacteremia burden occurring pre- and post- ICU admission.

The proportion of patients with CRP > 250 mg/L and WBC > 12 x 10^9 /L increased by age (Table 2). In addition, an age-related increase in serum creatinine was seen whereas serum bilirubin and platelet count decreased by age (Table 2). Patients aged 80+ years less frequently received mechanical ventilation, renal replacement therapy, and inotropes/vasopressors than the younger age groups (Table 2).

Bacteremia prevalence at ICU admission

Bacteremia prevalence at ICU admission increased from 1.9% among patients aged 15-49 to 4.1% in patients aged 80+ years with corresponding adjusted POR of 1.8 (95% CI 1.5-2.2) (Table 3). The bacteremia prevalence was lower among surgical than among non-surgical patients and was less than 1% for elective surgical patients regardless of age (Table 3). Stratification by CCI level revealed no substantial age-related differences in bacteremia prevalence in patients with moderate and high morbidity level (Table 3). Among patients with a low CCI level, however, the bacteremia prevalence nearly tripled in patients aged 80+ years (3.9%) compared with the youngest age group (1.4%) corresponding to a POR of 2.8 (95% CI 2.1-3.6) (Table 3).

Bacteremia risk day 2-7 after ICU admission

Among the 44,034 patients who did not present with bacteremia from 2 days before to 1 day after ICU admission, 4,859 (11.1%) had a blood culture drawn during day 2-7 after ICU admission of which 422 (1.0% of all and 8.7% of those tested) were positive. The bacteremia risk treating death as a competing risk was approximately 1% in all age groups (Table 4). We observed, however, an age-related increased risk among acute surgical patients and patients with low levels of pre-existing morbidity; yet, a decrease was seen in patients aged 80+ years. Figure 2 presents the risk of developing bacteremia by age with death as competing risk.

Sensitivity analysis

Changing the definition of bacteremia at ICU admission from 2 days before to the day of ICU admission (instead of the day after) did not change the adjusted PORs considerably. (Data not shown)

Discussion

This is the first study to investigate the impact of age on bacteremia burden in an ICU cohort discriminating between bacteremia present at time of admission and acquired after admission. We found an overall bacteremia burden of 3.9%. In both non-surgical and acute surgical patients aged 50+ years the bacteremia prevalence at ICU admission was 2-3-fold higher than in patients aged 15-49 years. Yet, above the age of 50 years we observed no further increase in the bacteremia prevalence. During days 2-7 after ICU admission an age-related increase in the bacteremia risk was seen until the seventies, thereafter a decrease was noted. Patients aged 80+ years had higher serum creatinine at admission, but less frequent low platelet count and increased level of serum bilirubin.

The previous ICU studies showed both lower prevalence of bacteremia among the elderly[9] and a decreasing risk of acquiring bacteremia with increasing age.[10,24] In contrast, we found an age-related increase in bacteremia incidence until the seventies, and thereafter a decrease was seen. In accordance with our findings, a Belgian study found decreasing incidence of nosocomial bacteremia in elderly ICU patients with increasing age (8.4 per 1000 patient days for age 45-64, 5.5 per 1000 patient days for age 65-74, and 4.6 in 1000 patient days for age 75 years or older).[10] In contrast to our finding of a highest risk of acquiring bacteremia in patients aged 65-79 years, a cohort study from Canada found younger age (<65 years) to be associated with an increased risk of developing ICU-acquired bacteremia compared with older patients (relative risk=1.77 (95% CI 1.01-3.11)).[24] The difference may at least partly be explained by the fact that we accounted for death as a competing risk. Our results are supported by a recent study showing an increasing prevalence of ventilator-associated pneumonia with advancing age until age 75 years.[25]

Strain on ICU capacity may influence on decisions to transfer elderly patients to treatment to the ICUs[26] which may result in admission to the ICU being most likely for elderly patients in a good pre-admission condition,[27] which is confirmed by our finding of a lower morbidity level among patients aged 80+ years compared with those aged 65-79 years. This is, however, consistent with the comorbidity level found in community-acquired bacteremia in Denmark in general, in which 35% of patients aged 80+ years had a CCI level of 0 compared with 31% of those aged 65-79 years[28]. This supports at least some healthy ageing effect.

Interestingly, we found a lower bacteremia risk after admittance to the ICU in patients aged 80+ years within each morbidity level than patients aged 65-79 years.

Previous studies of bacteremia patients in ICU showed no major age-related differences in organ dysfunction. [9,10] Based only on serum creatinine measurements we found increased levels of renal impairment among patients aged 80+. An increased risk of renal failure among elderly patients with bacteremia was also found in a single center study from Taiwan.[29]

The strengths of our study include the large size, the well-defined study population within a uniform health care system with equal access. This, together with the use of prospectively collected data and virtually complete follow-up, reduced risk of both information and selection bias to a minimum. In the analyses we were able to adjust for a number of pre-specified potential confounders. Still, several limitations should be considered when interpreting our data. First, blood cultures were obtained only in patients suspected of infection and therefore some bacteremias could have been missed, but this is not different from other studies.[10,29–32] The indication for drawing blood cultures may differ according to age due to non-specific clinical symptoms in elderly patients with bacteremia or sepsis, e.g. anorexia, malaise, and urinary incontinence.[3,11–13] In addition, fever may more often be absent in the elderly bacteremia population.[11–13] This may lead to differential misclassification with regard to bacteremia status. Nonetheless, we observed that patients aged 50+ years more often had a blood culture drawn than patients aged 15-49 years and more important, the proportion of patients aged 80+ years with a blood culture drawn did not differ substantially from patients aged 50-79 years. In relation to the patients with a drawn blood culture, the proportion turning positive was marginally higher in patients aged 50+ years compared with the youngest age group. This speaks in favor of only minor variation in the indication for drawing a blood culture. Second, our data did not include information on decisions on withholding treatment and do not resuscitate orders which may influence clinicians upon ordering a blood culture or not. Previous studies have shown, that elderly critically ill patients are more likely to receive less intensive care therapy compared with younger patients[6,27,33] and older age is associated with lower hospital costs and resource intensity.[34] This could explain our finding of a lower incidence of bacteremia among patients aged 80+ than among those aged 65-79 years. Still, as mentioned above this finding of a lower bacteremia incidence did not vary by morbidity level which would

have been expected if it was caused solely by less intensive diagnostic work-up among the most critically ill elderly patients. Finally, we did not have information on treatment with antibiotic therapy during hospital/ICU stay, which may result in negative blood cultures despite the presence of bacteremia. This could lead to an underestimation of the bacteremia burden. However, we do not expect treatment with broad-spectrum antibiotics to differ between the age groups studied here.

Conclusion

The bacteremia prevalence at ICU admission was increased in ICU patients aged 50+ years with no further increase with advancing age above 50 years. Except for increased serum creatinine at admission, the elderly less frequently presented with organ dysfunction at ICU admission compared with younger patients. Once admitted to the ICU, the bacteremia risk was very low (~1%), and an age-related increase was seen until the seventies, thereafter a decrease was seen.

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MN, ET, BSR, and MSN conceived the study idea. MSN, CFC, and MN designed the study. MSN analyzed the data. All authors interpreted the findings. MSN reviewed the literature. MSN wrote the first draft, and all authors critically reviewed and edited the manuscript and approved the final version.

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Table 1. Characteristics of 47,579 ICU patients admitted to an ICU during 2005-2011 by age group, n (%)

Age groups, (years)	**15-49 n=12,373**	**50-64 n=12,640**	**65-79 n=16,525**	**80+ n=6,041**
Median age, years (IQR)	35 (25-44)	59 (55-62)	72 (69-76)	84 (82-87)
Sex				
Men	6,668 (53.9)	7,925 (62.7)	9,824 (59.5)	2,862 (47.4)
Admission type				
Non-surgical patients	5,582 (45.1)	3,944 (31.2)	4,696 (28.4)	2,161 (35.8)
Elective surgical patients	2,027 (16.4)	4,405 (34.9)	6,748 (40.8)	1,352 (22.4)
Acute surgical patients	4,764 (38.5)	4,291 (34.0)	5,081 (30.8)	2,528 (41.9)
Primary diagnosis of current hospitalization				
Infectious diseases	1,295 (10.5)	1,247 (9.9)	1,582 (9.6)	765 (12.7)
Cardiovascular diseases	1,508 (12.2)	4,284 (33.9)	6,839 (41.4)	1,793 (29.7)
Respiratory diseases	281 (2.3)	576 (4.6)	1,036 (6.3)	404 (6.7)
Gastrointestinal or liver diseases	680 (5.5)	1,065 (8.4)	1,427 (8.6)	1,033 (17.1)
Endocrine diseases	325 (2.6)	213 (1.7)	178 (1.1)	76 (1.3)
Cancer	857 (6.9)	2,184 (17.3)	2,691 (16.3)	576 (9.5)
Trauma or poisoning	4,072 (32.9)	1,454 (11.5)	1,232 (7.5)	792 (13.1)
Other diseases	3,355 (27.1)	1,617 (12.8)	1,540 (9.3)	602 (10.0)
Charlson Comorbidity Index				
Low (0)	9,596 (77.6)	6,112 (48.4)	6,132 (37.1)	2,380 (39.4)
Medium (1-2)	2,117 (17.1)	4,556 (36.0)	7,060 (42.7)	2,513 (41.6)
High (> 2)	660 (5.3)	1,972 (15.6)	3,333 (20.2)	1,148 (19.0)
Immune status				
Immunosuppressive therapy	740 (6.0)	1,444 (11.4)	2,679 (16.2)	981 (16.2)

Table 2. Clinical manifestations at ICU admission and ICU treatment among the 1,872 bacteremia patients by age group, n (%)

Age groups, (years)	**15-49 n=316**	**50-64 n=519**	**65-79 n=737**	**80+ n=300**
C-reactive protein (CRP)				
CRP <10 mg/L	25 (7.9)	28 (5.4)	37 (5.0)	15 (5.0)
CRP 10-99 mg/L	84 (26.6)	126 (24.3)	162 (22.0)	56 (18.7)
CRP 100-249 mg/L	71 (22.5)	115 (22.2)	191 (25.9)	73 (24.3)
CRP > 250 mg/L	123 (38.9)	232 (44.7)	316 (42.9)	145 (48.3)
CRP missing	13 (4.1)	18 (3.5)	31 (4.2)	11 (3.7)
White blood cell count (WBC)				
WBC <3.5 x 10^9/L	38 (12.0)	75 (14.5)	88 (11.9)	19 (6.3)
WBC 3.5-10 x 12^9/L	104 (32.9)	186 (35.8)	235 (31.9)	93 (31.0)
WBC > 12 x 10^9/L	159 (50.3)	234 (45.1)	374 (50.8)	179 (59.7)
WBC missing	15 (4.8)	24 (4.6)	40 (5.4)	9 (3.0)
Laboratory cut-of values modified from SOFA-score				
Renal				
Creatinine <110 μmol/L	174 (55.1)	253 (48.8)	317 (43.0)	95 (31.7)
Creatinine 110-299 μmol/L	101 (32.0)	173 (33.3)	310 (42.1)	169 (56.3)
Creatinine >300 μmol/L	30 (9.5)	83 (16.0)	102 (13.8)	33 (11.0)
Creatinine missing	11 (3.5)	10 (1.9)	8 (1.1)	3 (1.0)
Liver				
Bilirubin <20 μmol/L	152 (48.1)	241 (46.4)	360 (48.9)	157 (52.3)
Bilirubin 20-101 μmol/L	85 (26.9)	155 (29.9)	178 (24.2)	73 (24.3)
Bilirubin >102 μmol/L	19 (6.0)	33 (6.4)	33 (4.5)	10 (3.3)
Bilirubin missing	60 (19.0)	90 (17.3)	166 (22.5)	60 (20.0)
Coagulation				
Platelet count >150 x 10^9/L	152 (48.1)	245 (47.2)	401 (54.4)	183 (61.0)
Platelet count 50-149 x 10^9/L	95 (30.1)	156 (30.1)	211 (28.6)	79 (26.3)
Platelet count <50 x 10^9/L	49 (15.5)	90 (17.3)	76 (10.3)	15 (5.0)
Platelet count missing	20 (6.3)	28 (5.4)	49 (6.7)	23 (7.7)
ICU treatments				
Mechanical ventilation	174 (55.1)	308 (59.3)	423 (57.4)	127 (42.3)
Renal replacement therapy	54 (17.1)	113 (21.8)	148 (20.1)	36 (12.0)
Inotropes/vasopressors	151 (47.8)	318 (61.3)	450 (61.1)	166 (55.3)

Table 3: Bacteremia prevalence present at admission and prevalence odds ratios (PORs) during 2005-2011, n (%)

Age groups, (years)	**15-49 n=12,373**	**50-64 n=12,640**	**65-79 n=16,525**	**80+ n=6,041**
Overall				
Patients with a blood culture drawn	2,346 (19.0)	3,153 (24.9)	4,208 (25.5)	1,781 (29.5)
Bacteremia at admission	238 (1.9)	413 (3.3)	549 (3.3)	250 (4.1)
Prevalence odds ratios (95% CI)	1 (ref.)	1.5 (1.3-1.8)	1.5 (1.3-1.7)	1.8 (1.5-2.2)
Admission type				
Non-surgical patients				
Patients with a blood culture drawn	1,084(19.4)	1,421 (36.0)	2,075 (44.2)	946 (43.8)
Bacteremia at admission	132 (2.4)	224 (5.7)	291 (6.2)	139 (6.4)
Prevalence odds ratios (95% CI)	1 (ref.)	2.1 (1.7-2.6)	2.0 (1.6-2.6)	2.2 (1.7-2.8)
Acute surgical patients				
Patients with a blood culture drawn	1,083 (22.7)	1,378 (32.1)	1,656 (32.6)	729 (28.8)
Bacteremia at admission	96 (2.0)	158 (3.7)	221 (4.4)	103 (4.1)
Prevalence odds ratios (95% CI)	1 (ref.)	1.7 (1.3-2.2)	1.9 (1.5-2.4)	1.8 (1.3-2.4)
Elective surgical patients				
Patients with a blood culture drawn	179 (8.8)	354 (8.0)	477 (7.1)	106 (7.8)
Bacteremia at admission	10 (0.5)	31 (0.7)	37 (0.6)	8 (0.6)
Prevalence odds ratios (95% CI)	1 (ref.)	1.3 (0.6-2.8)	1.0 (0.5-2.1)	1.1 (0.4-2.8)
Pre-existing morbidity				
CCI* = low (0)				
Patients with a blood culture drawn	1,516 (15.8)	1,399 (22.9)	1,382 (22.5)	667 (28.0)
Bacteremia at admission	137 (1.4)	170 (2.8)	174 (2.8)	93 (3.9)
Prevalence odds ratios (95% CI)	1 (ref.)	2.0 (1.6-2.5)	2.0 (1.6-2.5)	2.8 (2.1-3.6)
CCI* = moderate (1-2)				
Patients with a blood culture drawn	597 (28.2)	1,133 (24.9)	1,762 (25.0)	732 (29.1)
Bacteremia at admission	68 (3.2)	138 (3.0)	210 (3.0)	108 (4.3)
Prevalence odds ratios (95% CI)	1 (ref.)	0.9 (0.7-1.3)	0.9 (0.7-1.2)	1.3 (1.0-1.8)
CCI* = high (>2)				
Patients with a blood culture drawn	233 (35.3)	621 (31.5)	1,064 (31.9)	382 (33.3)
Bacteremia at admission	33 (5.0)	105 (5.3)	165 (5.0)	49 (4.3)
Prevalence odds ratios (95% CI)	1 (ref.)	1.1 (0.7-1.6)	1.0 (0.7-1.4)	0.8 (0.5-1.3)

* CCI: Charlson Comorbidity Index

Table 4: Bacteremia risk accounting for competing risk by death during days 2-7 after ICU admission and hazard ratios (HRs) during 2005-2011, n (%)

Age groups, (years)	**15-49 n=11,884**	**50-64 n=11,743**	**65-79 n=15,052**	**80+ n=5,128**
Overall				
Patients with a blood culture drawn	1,034 (8.7)	1,546 (13.1)	1,941 (12.8)	567 (11.0)
Bacteremia (days 2-7), n / % (95% CI)	78 / 0.7 (0.5-0.8)	106 / 0.9 (0.8-1.1)	188 / 1.2 (1.1-1.4)	50 / 1.0 (0.7-1.3)
Hazard ratios (95% CI)	1 (ref.)	1.2 (0.9-1.6)	1.6 (1.2-2.1)	1.4 (0.9-2.0)
Admission type				
Non-surgical patients				
Patients with a blood culture drawn	279 (5.2)	312 (9.0)	345 (8.8)	146 (8.8)
Bacteremia (days 2-7), n / % (95% CI)	31 / 0.6 (0.4-0.7)	31 / 0.9 (0.7-1.1)	28 / 1.2 (1.1-1.4)	13 / 1.0 (0.7-1.3)
Hazard ratios (95% CI)	1 (ref.)	1.4 (0.9-2.4)	1.1 (0.6-1.9)	1.3 (0.6-2.5)
Acute surgical patients				
Patients with a blood culture drawn	536 (11.7)	660 (16.6)	741 (16.3)	251 (11.5)
Bacteremia (days 2-7), n / % (95% CI)	33 / 0.7 (0.5-0.8)	48 / 0.9 (0.7-1.1)	82 / 1.2 (1.1-1.4)	26 / 1.0 (0.7-1.3)
Hazard ratios (95% CI)	1 (ref.)	1.6 (1.0-2.5)	2.4 (1.5-3.6)	1.7 (1.0-2.9)
Elective surgical patients				
Patients with a blood culture drawn	219 (10.9)	574 (13.2)	855 (12.8)	170 (12.9)
Bacteremia (days 2-7), n / % (95% CI)	14 / 0.7 (0.5-0.8)	27 / 0.9 (0.7-1.1)	78 / 1.2 (1.1-1.4)	11 / 1.0 (0.7-1.3)
Hazard ratios (95% CI)	1 (ref.)	0.7 (0.3-1.3)	1.2 (0.7-2.1)	0.9 (0.4-2.1)
Pre-existing morbidity				
CCI* = low (0)				
Patients with a blood culture drawn	779 (8.4)	726 (12.6)	739 (12.0)	219 (10.7)
Bacteremia (days 2-7), n / % (95% CI)	48 / 0.7 (0.5-0.8)	44 / 0.9 (0.7-1.1)	61 / 1.2 (1.1-1.4)	14 / 1.0 (0.7-1.3)
Hazard ratios (95% CI)	1 (ref.)	1.4 (1.0-2.2)	2.1 (1.5-3.1)	1.4 (0.8-2.6)
CCI* = moderate (1-2)				
Patients with a blood culture drawn	191 (9.6)	578 (13.5)	811 (12.5)	255 (11.8)
Bacteremia (days 2-7), n / % (95% CI)	24 / 0.7 (0.5-0.8)	37 / 0.9 (0.7-1.1)	87 / 1.2 (1.1-1.4)	28 / 1.0 (0.7-1.2)
Hazard ratios (95% CI)	1 (ref.)	0.7 (0.4-1.2)	1.1 (0.7-1.7)	1.2 (0.7-2.0)
CCI* = high (>2)				
Patients with a blood culture drawn	64 (10.6)	242 (13.6)	391 (13.1)	93 (9.7)
Bacteremia (days 2-7), n / % (95% CI)	6 / 0.7 (0.5-0.8)	25 / 0.9 (0.7-1.1)	40 / 1.2 (1.1-1.4)	8 / 1.0 (0.7-1.3)
Hazard ratios (95% CI)	1 (ref.)	1.4 (0.6-3.5)	1.4 (0.6-3.3)	0.9 (0.3-2.7)

*CCI: Charlson Comorbidity Index

Figure 1A+B: Flowchart displaying the patients with blood cultures drawn from A) 2 days before to 1 day after ICU admission (prevalence), and B) 2 days after ICU admission to 7 days after ICU admission (cumulative risk)

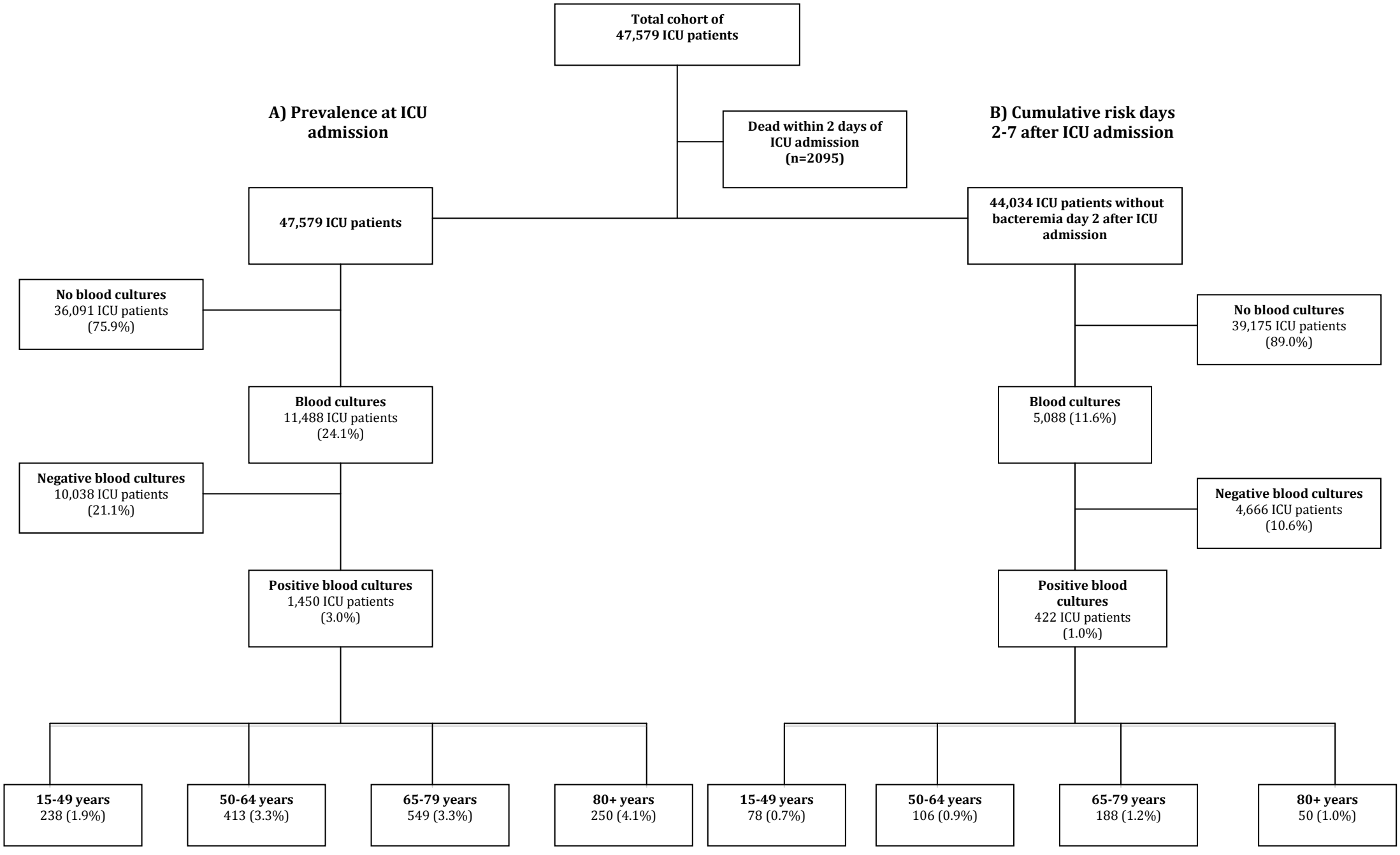
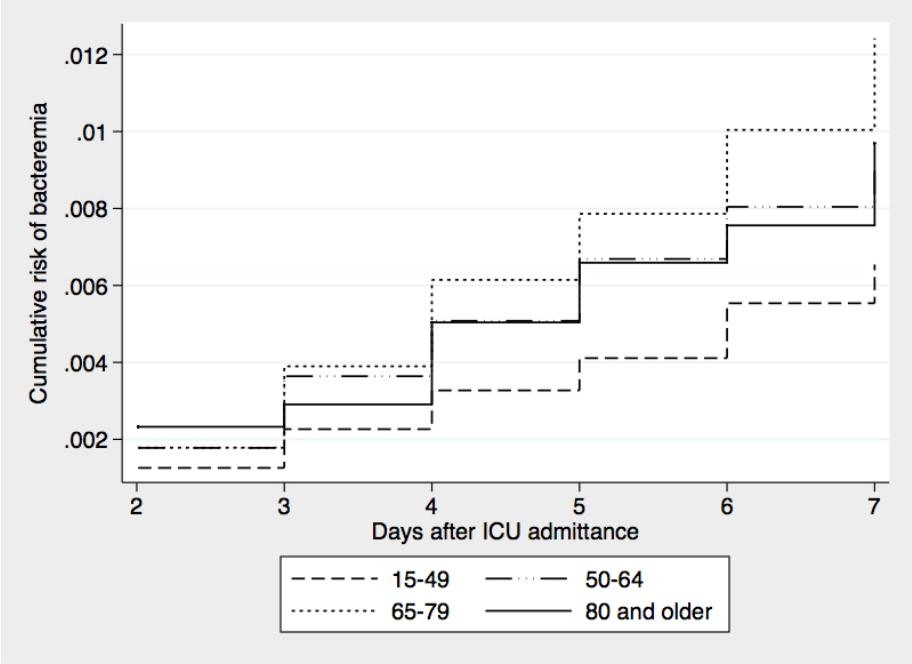


Figure 2: Cumulative 2-7- day risk of bacteremia acccounting for competing risk by death in relation to age, 2005-2011



Study IV

Mortality in elderly intensive care patients with early bacteremia: a Danish cohort study

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Abstract

Introduction: Age is a predictor for death in bacteremic patients. Yet, studies on the effect of age on 1-year mortality in intensive care unit (ICU) patients with bacteremia remain sparse. We examined the association between age and mortality in ICU patients with bacteremia taking pre-existing morbidity into account.

Methods: We linked population-based medical registries to identify a cohort of 1,348 bacteremic patients admitted to an ICU in Northern Denmark during 2005-2011. We estimated 7-day, 8-30-day, and 31-365-day mortality and mortality rate ratios (MRRs) according to age groups (15-49, 50-64, 65-79, ≥80 years) and stratified by pre-existing morbidity (Charlsons Comorbidity Index (CCI): low (CCI score 0), moderate (CCI score 1-2) and high (CCI score 3+)), admission type, immunosuppressive therapy, and type of bacteremia. Mortality was compared between age groups using the age group of 15-49 years as reference, adjusting for sex, type of bacteremia, immunosuppressive therapy, and pre-existing morbidity.

Results: Of the entire cohort, 49% died within 1 year. The 7-day mortality was 39.7% in patients aged ≥80, 25.6% in patients aged 65-79, 21.7% in patients aged 50-64, and 9.8% in patients aged 15-49 years with corresponding adjusted MRRs of 4.2 (95% confidence interval, CI 2.6-6.7), 2.5 (95% CI 1.6-3.8), 2.1 (95% CI 1.3-3.4), respectively, compared with patients aged 15-49. A similar age-related pattern was seen for 8-30-day mortality, although less pronounced. Among 30-day survivors, the 31-365-day risk of dying increased with increasing age until age 80 whereafter a decrease was seen. Mortality was 21.4% in patients aged ≥80, 28.2% in patients aged 65-79, 19.2% in patients aged 50-64 compared with 8.4% in patients aged 15-49 years with corresponding MRRs of 2.1 (95% CI 1.2-3.7), 3.1 (95% CI 1.8-5.3), and 2.3 (95% CI 1.2-4.5), respectively. An age-related increase in mortality was seen within all three levels of pre-existing morbidity.

Conclusion: Short-term mortality was associated with advancing age. Yet, among those who survived the first 30-days, the elderly had a lower 1-year mortality than patients aged 65-79 years.

Key words: Bacteremia, Bloodstream infection**,** Critical care, Elderly, Intensive Care Unit, Mortality, Prognosis

Introduction

Bacteremia is a severe infection associated with intensive care unit (ICU) admissions. Mortality following bacteremia remains substantial. A recent review estimated at least 158,000 deaths per year in Europe and at least 79,000 deaths per year in North America following bacteremia placing it among the top seven causes of death in many European countries and North America (1). During recent decades, ICU admissions of patients aged ≥80 years have been increasing (2,3). Bacteremia incidence has increased too (4), and the incidence rises with advancing age (5,6). Furthermore, advancing age is associated with increased in-hospital and short-term mortality in bacteremia patients (7-11), and previous studies have found age as an important predictor of both 1-year (12) and 3-year mortality (13) following bacteremia. Another important predictor of mortality is pre-existing morbidity (12,14-15). Pre-existing morbidity is present in nearly half of ICU patients and is associated with a worsened prognosis (16). Admittance to the ICU, however, may differ in relation to age, and a Danish cohort study found that only 3% of patients aged ≥80 years with community-acquired bacteremia were admitted to the ICU compared with 4% of patients aged 65-79 years, and 8% of patients aged 15-65 years (9). This selection into the ICU may minimize any difference in pre-existing morbidity between age groups. Still, Blot et al found that the risk of in-hospital death among ICU patients with nosocomial bacteremia was 56% in patients aged ≥75 years compared with 49% in patients aged 65-74, and 43% in patients aged 45-64, with corresponding adjusted hazard ratios (HRs) of 1.76 (95% confidence interval (CI) 1.33-2.33) in patients aged ≥75 and 1.20 (95% CI 0.97-1.48) in patients aged 65-74 compared with the youngest age group (7). Few studies, if any, have investigated the impact of age on 1-year mortality in bacteremic ICU patients taking pre-existing morbidity into account. We therefore examined the association between age and 7-day, 8-31-day, and 31-365-day mortality among bacteremic ICU patients. In addition, we examined the impact of age on mortality at different levels of pre-existing morbidity.

Materials and methods

Study design and settings

We conducted this cohort study in Northern Denmark (former counties of Aarhus and North Jutland) with a population of approximately 1.15 million. All Danish citizens are guaranteed free tax-supported universal

medical coverage, including access to treatment in intensive care units. In addition, most prescribed medication in Denmark is qualified for full or partial general reimbursement by the National Health Service. The study area is mixed urban-rural including 12 ICUs (2 neurosurgical ICUs, 2 cardiothoracic/multidisciplinary ICU, 8 multidisciplinary ICUs). We linked population-based medical and administrative registries with prospectively collected data using the unique civil registration number (CPR-number) assigned to all Danish citizens at birth.

Study cohort

We identified all adults (age ≥15 years) with a first-time ICU admission in Northern Denmark during 1 January 2005-31 December 2011 (n=47,579), using the Danish National Patient Registry (DNPR). Thereafter, we used the Laboratory Information System maintained at the Departments of Clinical Microbiology in Aarhus and Aalborg to identify bacteremia, defined as the first positive blood culture obtained at date of ICU admission or within the first seven days after ICU admission. Thus, by linking these databases, we ended up with a total cohort of 1,348 bacteremia patients with a first-time ICU admission.

Bacteremia

Bacteremia was defined as the presence of viable bacteria or fungi in the bloodstream, evidenced by blood cultures in which contamination had been ruled out (17). Coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., and *Propioni-bacterium acnes* were regarded as contaminants unless they were isolated from two or more separate blood culture sets. We used the Laboratory Information System maintained at the Departments of Clinical Microbiology in Aarhus and Aalborg to identify bacteremia among ICU patients living in the former North Jutland and Aarhus County. Data includes information on bacterial isolates, dates of drawn blood culture, patient's age, gender, and the CPR number. The blood culture system used during our study period was the BacT/Alert system (bioMérieux). In the former North Jutland County, the nominal volume per blood culture was 28-32 ml (adult patients), and a blood culture set comprised 3 bottles. In the former Aarhus County, a blood culture set, however, comprised 2 bottles, and the drawing of two sets was recommended for adult patients.

Pre-existing morbidity, primary diagnosis, and immune status

We obtained data on pre-existing morbidity from the DNPR to compute the Charlson Comorbidity Index (CCI) for each patient (18). The DNPR has been recording all discharges from all non-psychiatric hospitals since 1977 and visits to emergency rooms and outpatient clinics were included in 1995 (19,20). Data contained in this registry include the patient's CPR-number, dates of admission and discharge, procedure codes, one primary diagnosis and up to 19 secondary diagnoses coded by physicians. Diagnoses were classified according to the *International Classification of Diseases* (ICD), 10th revision. Information on ICU admission and treatments was included in 2005, and is registered with high accuracy (16,21). We categorized morbidity levels as: low (CCI score = 0), moderate (CCI score 1 and 2) and high (CCI score 3 or more). The CCI was based on all ambulatory and hospital discharge codes registered within five years before the current hospital admission. Furthermore, we categorized the patients´ primary cause of admission into eight major disease groups (infectious diseases, cardiovascular diseases, respiratory diseases, gastrointestinal or liver diseases, endocrine diseases, cancer, trauma or poisoning, other diseases) by using the information on the primary diagnosis of the current hospital stay. Finally, we obtained information on patients with previous filled prescriptions for immunosuppressive therapy within 1 year prior to ICU admission (ATC: L01, L04, H02A, H02B) as a proxy for compromised immune system from the Aarhus University Prescription Database (22,23). Data includes information on reimbursed medications dispensed at all pharmacies of the North and Central Denmark Region.

Clinical manifestations associated with bacteremia

To assess clinical manifestations associated with bacteremia we used the LABKA research database to obtain information on organ-specific dysfunction (24). Data contains test results from every blood sample drawn at any public or private hospital or by any general practitioners analyzed at any clinical chemistry department located in the North and Central Denmark Regions (approximately 1.8 million inhabitants). We determined level of C-reactive protein (CRP) and of white blood cell count (WBC) as a marker of inflammation. In addition, we determined level of serum creatine, platelet count and serum bilirubin using

laboratory cut-off values in the Sequential Organ Failure Assessment (SOFA) score (24). Information on treatment with mechanical ventilation, renal replacement therapy, and treatment with inotropes or vasopressors was obtained from the DNPR.

Statistical analyses

Patient characteristics and clinical manifestations were described in contingency tables by age group; 15-49, 50-64, 65-79, ≥80 years. We defined elderly as patients aged ≥80 years. Follow-up began on the date of the first positive blood culture, and the patients were followed until death, emigration, for 365 days, or until 1 January 2012, whichever came first. We used the Kaplan-Meier method to estimate the 1-year mortality probability as 1 minus the survival probability with 95% CI and plotted cumulative mortality for bacteremia patients according to age groups and pre-existing morbidity level. We estimated mortality rate ratios (MRR) by using a Cox proportional hazards model comparing mortality between patients aged 15-49, 50-64, 65-79, ≥80 years, adjusting for sex, CCI score, type of bacteremia, and immunosuppressive therapy using the age group of 15-49-year-old as a reference group. Bacteremia requiring an ICU admission is often associated with organ dysfunction and we expected the risk of death to be highest during the first days-weeks of infection. Consequently, our 1-year follow-up was split into three time periods; 0-7-day, 8-30-day, and 31-365-day. The assumption of proportional hazards in each period was checked graphically and found acceptable. To evaluate the impact of pre-existing morbidity on the association between age and mortality, we made a separate analysis stratifying by the three levels of pre-existing morbidity. Furthermore, we stratified by admission type, type of bacteremia, and immunosuppressive therapy in order to evaluate whether or not the effect of age on mortality differed within these subgroups (effect measure modification). All statistical analyses were performed using Stata software (version 11.2; StataCorp LP, College Station, TX). The study was approved by the Danish Data protection Agency (record no. 2009-41-3987).

Results

Descriptive data

Patient characteristics of the 1,348 bacteremia patients with a first-time ICU admission are displayed in Table 1, stratified on age groups. Median age was 67 years (interquartile range (IQR) 55-76 years), 57.6% of the patients were men, and 53.7% were surgical patients.

Approximately 34% of the ICU patients had an infectious disease recorded as their primary diagnosis. Among patients younger than 65 years, however, nearly 40% had a primary diagnosis of infectious diseases compared with only 30% of patients aged ≥65 years (Table 1). The prevalence of preexisting morbidity increased with age until age 80 (Table 1).

Microorganisms and bacteremia-associated clinical manifestations, and level of treatment by age groups

Approximately 42% of the patients presented with Gram-negative microorganisms, whereas 40.5% presented with Gram-positive microorganisms, 9% with yeasts, and 8.6% with poly-microbial microorganisms. The distribution of microorganisms in relation to age is displayed in Figure 1. The proportion of patients presenting with Gram-negative bacteremia or fungemia increased with age. The opposite was seen for Gram-positive and poly-microbial bacteremias.

Table 2 presents clinical manifestations and the level of treatment in relation to age. The elderly presented with higher levels of CRP and WBC at ICU admission compared with younger patients. Serum creatinine was increased among the elderly at ICU admission, whether as platelet count and serum bilirubin was lower compared with younger patients. Level of treatment during ICU stay differed markedly between age groups, with the elderly less frequently treated with mechanical ventilation, renal replacement therapy, and inotropes/vasopressors.

Cumulative mortality according to age groups and level of pre-existing morbidity

The 1-year cumulative mortality in relation to age and preexisting morbidity is displayed in Figure 2 and 3, respectively. A total of 49.4% of the patients died within 1 year. The 1-year risk of dying increased notably with age (Figure 2) with a mortality of 63.2% in the elderly compared with 57.2% in patients aged 65-79, 45.3% in patients aged 50-64, and 26.0% in patients aged 15-49. In addition, patients with high levels of

preexisting morbidity were in greater risk of dying within 1 year than patients with moderate or low levels of preexisting morbidity (Figure 3).

7-day, 8-30-day, and 31-365-day mortality

The 7-day, 8-30-day, and 31-365-day mortality according to age group are shown in Table 3. Mortality was highest during the first 7 days after bacteremia diagnosis, and 7-day mortality among the elderly (39.7%) increased fourfold compared with patients aged 15-49 years (9.8%) (Table 3). The corresponding adjusted MRR was 4.2 (95% CI 2.6-6.7) in the elderly, 2.5 (95% CI 1.6-3.8) in patients aged 65-79 years, 2.1 (95% CI 1.3-3.4) in patients aged 50-64 years compared with patients aged 15-49 years. Among 7-day survivors, an age-related increase in 8-30-day mortality was seen, even though less pronounced than for 7-day mortality (Table 3). In patients who survived 30 days, the 31-365-risk of dying increased with increasing age until age 80 whereafter a decrease was seen (Table 3). Mortality in the elderly was 21.4%, 28.2% in patients aged 65-79 years, 19.2% in patients aged 50-64 years compared with 8.4% in patients aged 15-49 years with corresponding MRRs of 2.1 (95% CI 1.2-3.7), 3.1 (95% CI 1.8-5.3), and 2.3 (95% CI 1.2-4.5), respectively, compared with patients aged 15-49 years (Table 3).

Mortality by pre-existing morbidity level and additional subgroups

Table 4a-c presents 7-day, 8-30-day, and 31-365-day mortality stratified by pre-existing morbidity level, admission type, type of bacteremia, and immunosuppressive therapy. The 7-day mortality increased with increasing age within all three levels of pre-existing morbidity (Table 4a). The age-related difference in 8-30-day mortality was less pronounced; yet, a tendency of increasing mortality with increasing age was seen within the three levels of pre-existing morbidity (Table 4b). Among 30-day survivors, only patients with moderate levels of pre-existing morbidity had an age-related increase in risk of death within 1 year. In patients with low or high levels of pre-existing morbidity, risk of death within 1 year increased until age 80, whereafter a decrease was seen (Table 4c). The association between age and 7-day mortality was evident within the different subgroups (Tables 4a) except for patients with fungemia who had little variation in mortality between age groups (adjusted MRRs of 1.0 (95% CI 0.2-4.3) in the elderly, 1.3 (95% CI 0.4-4.8) in

patients aged 65-79 years, 0.9 (95% CI 0.2-3.7) in patients aged 50-64 years compared with patients aged 15-49 years). The association of age on 8-30-day mortality was less pronounced within the different subgroups (Table 4b). The increased 31-365-day mortality risk until age 80 remained evident within the different subgroups (Table 4c) except the non-surgical patients that had an increased mortality in patients ≥50 years (adjusted MRRs of 2.7 (1.0-7.7) in the elderly, 2.7 (95% CI 1.0-6.8) in patients aged 65-79, and 3.3 (95% CI 1.3-8.3) in patients aged 50-64 compared with patients aged 15-49 years).

Discussion

In this cohort study of bacteremic patients within 0-7 days of their first-time ICU admission, we found that half of the patients had died within 1 year. As expected, the mortality rate was highest in the first week after the first positive blood culture was obtained, and 7-day mortality was fourfold higher among the elderly compared with the youngest age group. The same pattern regarding age was seen for 8-30-day mortality, although less pronounced. The elderly actually had a 25% lower 31-365-day mortality than patients aged 65-79 years. Yet, as stated above, mortality in the elderly was markedly increased within the first week/month of infection compared with younger patients, which may imply a discard of the frailest elderly. In addition, the elderly were less frequent treated with mechanical ventilation, renal replacement and inotropes/vasopressor and this may be a marker of withholding or the withdrawal of treatment. We assessed the effect of age within the three levels of pre-existing morbidity, and we found an age-related increase in mortality within all three levels of preexisting morbidity.

Existing studies

Our study extends previous research of bacteremic ICU patients by examining 1-year mortality in relation to age. Intuitively, one would expect long-term mortality to increase with advancing age, as prediction studies assessing 1-3-year mortality following bacteremia have revealed age as an important predictor (12,13). These studies, however, were conducted in patients irrespective of admission to the ward or an ICU, whereas our study was restricted to critically ill ICU patients representing only approximately 9% of all hospitalized bacteremia patients (4). In addition, the ICU refusal rate increases with increasing age (25), which, as mentioned above, may imply a selection of the elderly critically ill with only the elderly in good pre-

admission condition being admitted (26). Still, elderly patients are more vulnerable and may be unable to compensate during critical illness due to an age-related decrease in physiological reserves (27). Our findings of increased 7-day and 8-30-day mortality in the elderly compared with younger age groups are supporting previous studies. Among 30-day survivors, however, 1-year mortality was higher in patients aged 65-79 years compared with the elderly patients. This may be explained by the presence of higher levels of pre-existing morbidity, and a primary diagnosis of current hospital stay of cancer as well as treatment with immunosuppressive therapy being more frequent in patients aged 65-79 compared with the elderly (Table 1). However, 1-year mortality was decreased in the elderly compared with patients aged 65-79, even among patients with low level of pre-existing morbidity. Our findings extend the findings in a previous Danish study by Søgaard et al. They investigated the effect of age at different levels of pre-existing morbidity on 30-day mortality among patients with community-acquired bacteremia (9). According to our findings, they found higher mortality with advancing age with HRs of 2.0 (95% CI 1.6-2.5) in patients aged ≥80 years compared with patients aged 15-64 years, and increased levels of pre-existing morbidity among patients aged ≥80 years did not fully explain differences in mortality between age groups.

Strengths and limitations

Our study was conducted within a population-based hospital setting. We used prospectively collected data with virtually complete follow-up thereby limiting potential selection and information bias. Nonetheless, several limitations must be considered in the interpretation of our results. We defined our cohort as being 1) all patients with a first-time ICU admission during our study period and 2) having a positive blood culture obtained within the first 7 days after ICU admission relying on the capture of all ICU patients with bacteremia within the defined time period. The coding for ICU admission is registered with high accuracy in the DNPR (16,20), and we do not expect any miscoding to be dependent on patients age. Hence, any misclassification would bias our results towards no association. In our study, as well as previous other studies (4,5,7-15), blood cultures were obtained only on suspicion of infection. This could bias our results if indications for drawing a blood culture differed between age groups. Elderly infected patients may more frequently than younger patients present with atypical clinical manifestations of infection (6,28,29) with the potential of more often being misclassified as non-infected. In our cohort, however, patients aged ≥ 80 years

presented with higher levels of CRP and white blood cell count than the younger age groups (Table 2), and in a previous study, we found that patients aged ≥ 50 years more often had a blood culture drawn than patients aged 15-49 years. Furthermore, the proportion of patients aged ≥ 80 years with a blood culture drawn did not differ essentially from patients aged 50-79 years. Thus, we do not expect any major age-related difference in ordering a blood culture. We did not have information on pathogen susceptibility, nor on potential inadequate antibiotic treatment during ICU/hospital stay, both of which are predictors of increased 30-day mortality (30,31). Finally, we lacked information on severity of illness scores at ICU admission, e.g. the Simplified Acute Physiology (SAPS) II score. These scores were developed to predict in-hospital mortality and represent a measure of the degree of organ dysfunction (32). In our study cohort, any organ dysfunction may represent host response to infection, thereby being a step in the causal pathway, and any attempt to control for severity of illness may weaken any true association.

Conclusion

We found an age-related increase in 7-day and 8-30-day mortality in ICU patients with bacteremia, whereas the elderly had a lower 31-365-day mortality compared with patients aged 65-79 years. The effect of age on mortality was evident within all three levels of pre-existing morbidity.

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Table 1. Characteristics of the 1,348 bacteremia patients admitted to an ICU during 2005-2011 by age group, n (%)

Age groups, (years)	**15-49 n=235**	**50-64 n=369**	**65-79 n=535**	**80+ n=209**
Median age, years (IQR)	41 (32-47)	59 (55-62)	73 (69-76)	84 (82-86)
Sex				
Men	143 (60.9)	214 (58.0)	305 (57.1)	114 (54.6)
Admission type				
Non-surgical patients	128 (54.5)	182 (49.3)	209 (39.1)	105 (50.2)
Elective surgical patients	23 (9.8)	50 (13.6)	103 (19.3)	17 (8.1)
Acute surgical patients	84 (35.7)	137 (37.1)	223 (41.7)	87 (41.6)
Primary diagnosis of current hospitalization				
Infectious diseases	91 (38.7)	144 (39.0)	160 (29.9)	68 (32.5)
Cardiovascular diseases	18 (7.7)	34 (9.2)	74 (13.8)	32 (15.3)
Respiratory diseases	7 (3.0)	21 (5.7)	30 (5.6)	11 (5.3)
Gastrointestinal or liver diseases	20 (8.5)	43 (11.7)	84 (15.7)	32(15.3)
Endocrine diseases	7 (3.0)	1 (0.3)	3 (0.6)	3 (1.4)
Cancer	20 (8.5)	56 (15.2)	102 (19.1)	23 (11.0)
Trauma or poisoning	35 (14.9)	30 (8.1)	26 (4.9)	13 (6.2)
Other diseases	37 (15.7)	40 (10.8)	56 (10.5)	27 (12.9)
Charlson Comorbidity Index				
Low (0)	136 (57.9)	160 (43.4)	178 (33.3)	76 (36.4)
Medium (1-2)	71 (30.1)	120 (32.5)	215 (40.2)	95 (45.5)
High (> 2)	28 (11.9)	89 (24.1)	142 (26.5)	38 (18.2)
Immune status				
Immunosuppressive therapy	31 (13.2)	54 (14.6)	108 (20.2)	36 (17.2)

Table 2. Bacteremia-associated clinical manifestations and level of treatment by age groups

Age groups, (years)	**15-49 n=236**	**50-64 n=369**	**65-79 n=534**	**80+ n=209**
C-reactive protein (CRP)				
CRP <10 mg/L	25 (10.6)	28 (7.6)	35 (6.5)	14 (6.7)
CRP 10-99 mg/L	69 (29.4)	111 (30.1)	146 (27.3)	50 (23.9)
CRP 100-249 mg/L	52 (22.1)	79 (21.4)	132 (24.7)	49 (23.4)
CRP > 250 mg/L	79 (33.6)	135 (36.6)	191 (35.7)	86 (41.2)
CRP missing	10 (4.3)	16 (4.3)	31 (5.8)	10 (4.8)
White blood cell (WBC)				
WBC < 3.5 x 10^9 L	28 (11.9)	48 (13.0)	63 (11.8)	12 (5.7)
WBC 3.5-10 x 10^9 L	48 (20.4)	97 (26.3)	135 (25.2)	49 (23.4)
WBC > 10 x 10^9 L	148 (63.0)	204 (55.3)	301 (56.3)	140 (67.0)
WBC missing	11 (4.7)	20 (5.4)	36 (6.7)	8 (3.8)
Laboratory cut-of values modified from SOFA-score				
Renal				
Creatinine < 110 μmol/L	124 (52.8)	185 (50.1)	243 (45.4)	70 (33.5)
Creatinine 110-299 μmol/L	80 (34.0)	123 (33.3)	218(40.8)	117 (56.0)
Creatinine >300 μmol/L	24 (10.2)	53 (14.4)	66 (12.3)	20 (9.6)
Creatinine missing	7 (3.0)	8 (2.2)	8 (1.5)	2 (1.0)
Liver				
Bilirubin < 20 μmol/L	115 (48.9)	176 (47.7)	261 (48.8)	107 (51.2)
Bilirubin 20-101 μmol/L	65 (27.7)	103 (27.9)	118 (22.1)	48 (23.0)
Bilirubin > 102 μmol/L	15 (6.4)	23 (6.2)	27 (5.1)	8 (3.8)
Bilirubin missing	40 (17.0)	67 (18.2)	129 (24.1)	46 (22.0)
Coagulation				
Platelets >150 x 10^9/L	122 (51.9)	191 (51.8)	303 (56.6)	132 (63.2)
Platelets 50-149 x 10^9/L	68 (28.9)	110 (29.8)	156 (29.2)	53 (25.4)
Platelets < 50 x 10^9/L	32 (13.6)	44 (11.9)	41 (7.7)	8 (3.8)
Platelets missing	13 (5.5)	24 (6.5)	35 (6.5)	16 (7.7)
ICU treatments				
Mechanical ventilation	131 (55.7)	230 (62.3)	328 (61.3)	89 (42.6)
Renal replacement treatment	43 (18.3)	82 (22.2)	119 (22.2)	27 (12.9)
Inotropes/vasopressors	116 (49.4)	226 (61.3)	334 (62.4)	117 (56.0)

Table 3: 7-day, 8-30-day, and 31-365-day risk of death and crude and adjusted mortality rate ratios (MRR) among the 1,348 bacteremia patients admitted to an ICU by age

Age group	Dead, n / N	Mortality, %	Crude MRR (95%CI)	Adjusted* MRR (95%CI)
7-day				
15-49	23 / 235	9.8	1 (reference)	1 (reference)
50-64	80 / 369	21.7	2.4 (1.5-3.8)	2.1 (1.3-3.4)
65-79	137 /535	25.6	2.9 (1.9-4.5)	2.5 (1.6-3.8)
80+	83 /209	39.7	4.8 (3.0-7.6)	4.2 (2.6-6.7)
8-30-day				
15-49	22 / 212	10.4	1 (reference)	1 (reference)
50-64	39 / 289	13.5	1.3 (0.8-2.3)	1.2 (0.7-2.0)
65-79	79 / 398	19.9	2.0 (1.2-3.2)	1.6 (1.0-2.6)
80+	28 / 126	22.2	2.3 (1.3-3.9)	1.9 (1.1-3.3)
31-365-day				
15-49	16 / 190	8.4	1 (reference)	1 (reference)
50-64	48 / 250	19.2	2.4 (1.4-4.3)	2.1 (1.2-3.7)
65-79	90 / 319	28.2	3.8 (2.2-6.4)	3.1 (1.8-5.3)
80+	21 / 98	21.4	2.7 (1.4-5.3)	2.3 (1.2-4.5)

* Adjusted for sex, pre-existing morbidity level, type of bacteremia, and immunosuppressive therapy

Figure 1: The distribution of microorganisms by age group (%), 2005-2011

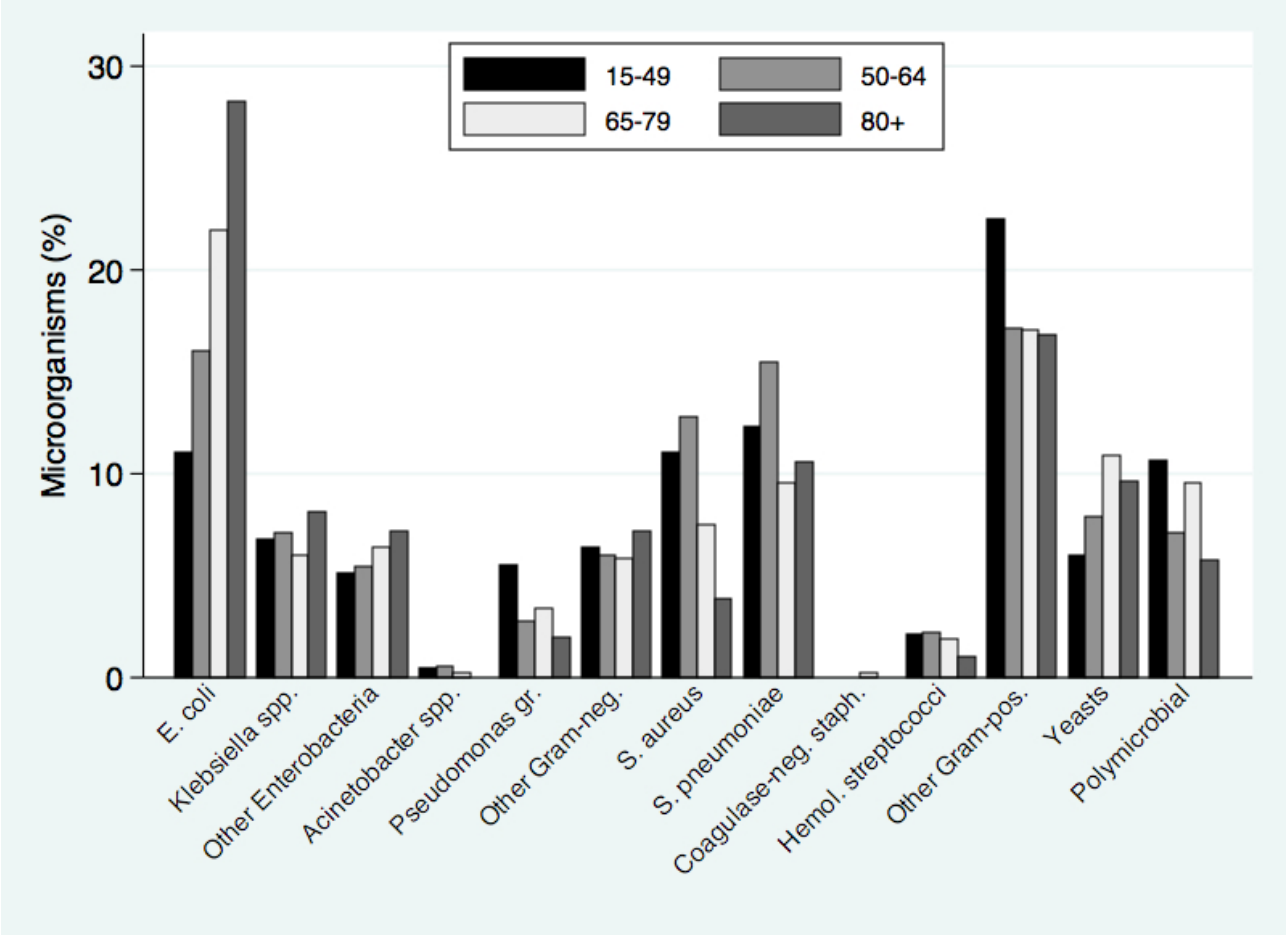


Figure 2: Cumulative 1-year mortality by age group, 2005-2011

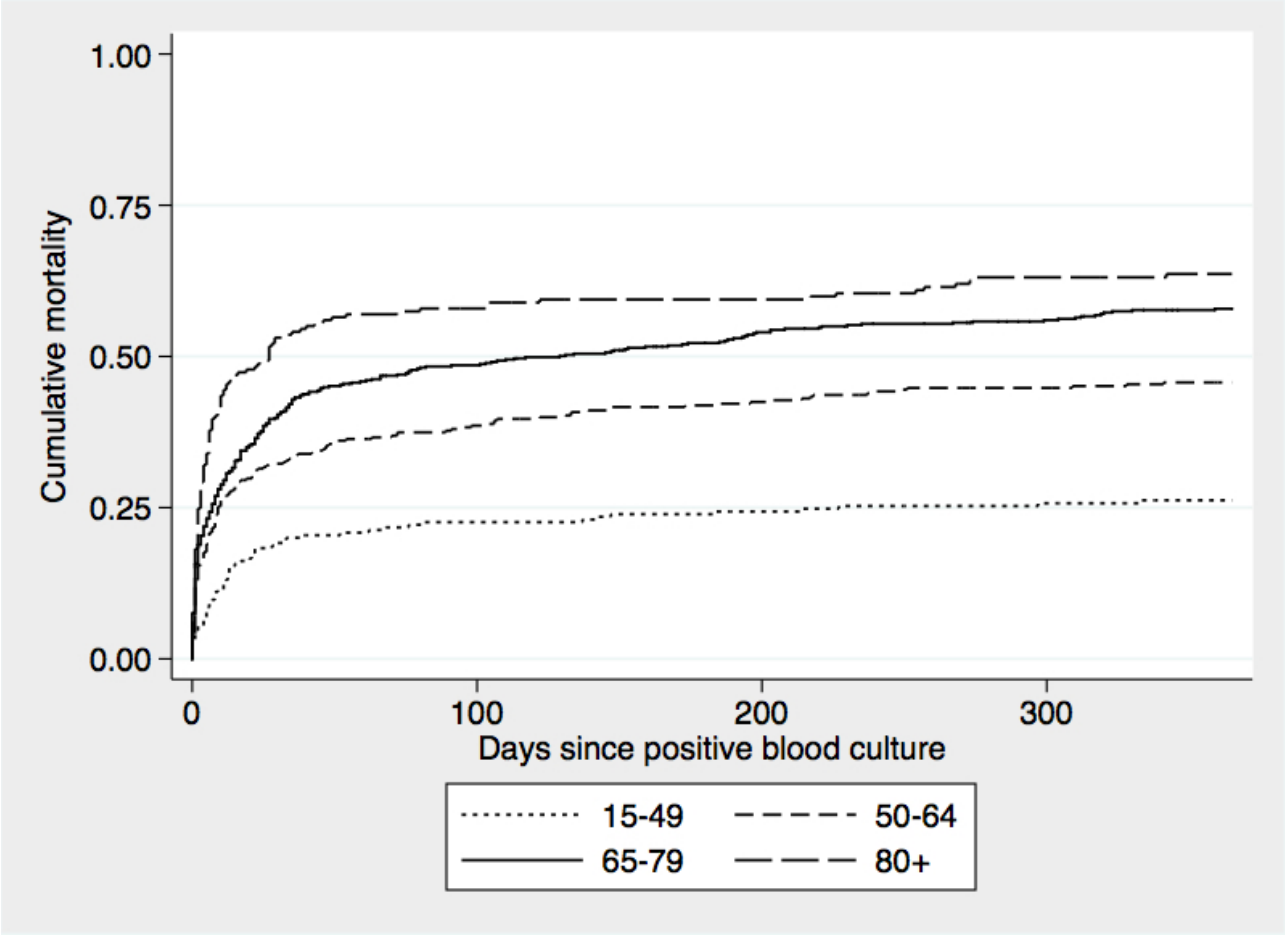
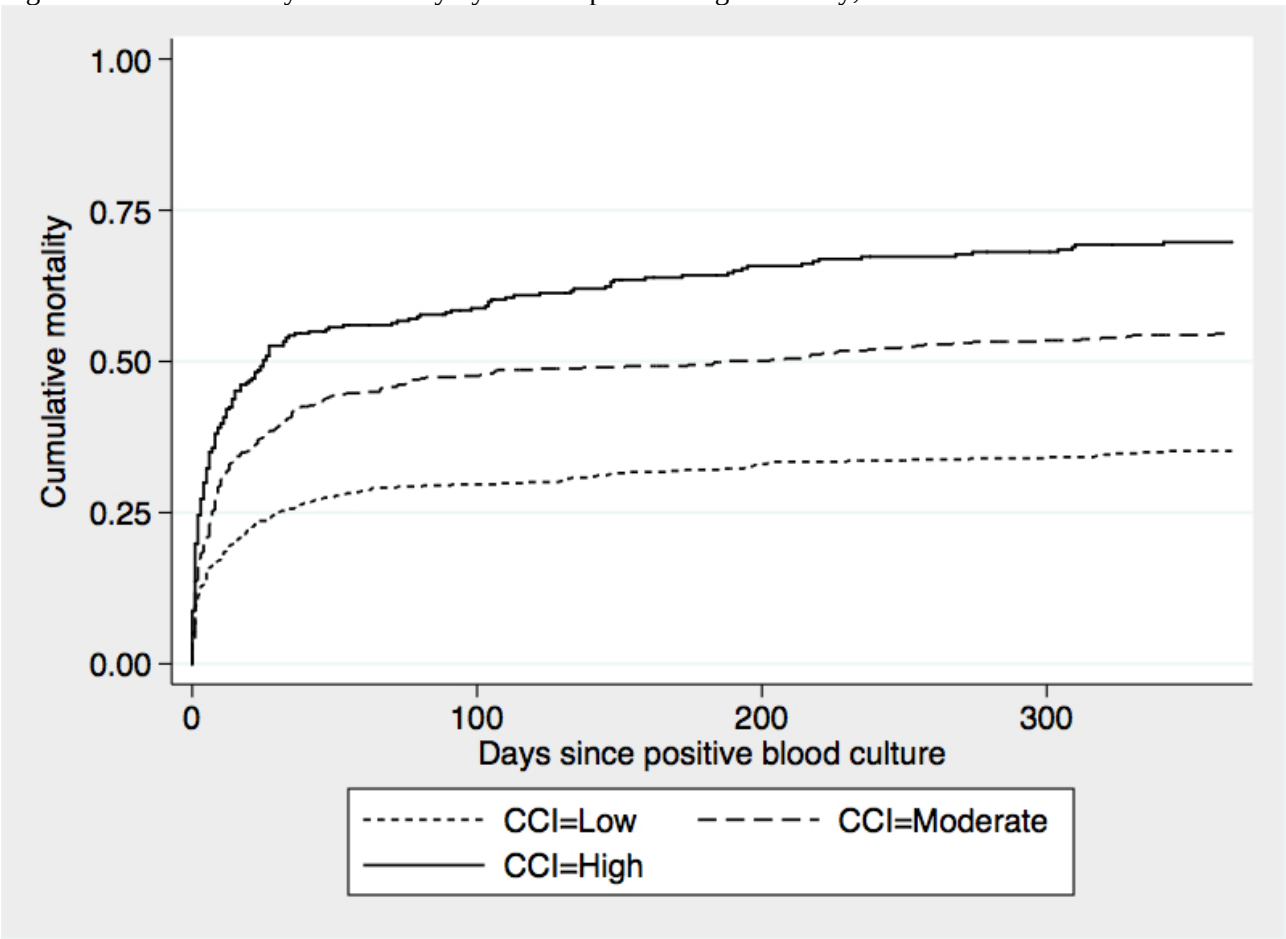


Figure 3: Cumulative 1-year mortality by level of pre-existing morbidity, 2005-2011



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