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Matti Reinikainen

Hospital Mortality of Intensive Care Patients in Finland

Insights into Prognostic Factors and Measuring Outcomes

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MATTI REINIKAINEN

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ABSTRACT

For patients treated in an intensive care unit (ICU), the main factors determining the risk of death are the severity of the acute illness, age and previous state of health. The aims of this study were to explore the associations between some controversial factors and mortality and to quantify the changes in hospital mortality of ICU patients in Finland in recent years.

The Finnish Intensive Care Consortium is a body co-ordinating a national benchmarking programme in intensive care. The Consortium comprises all general adult ICUs in all main Finnish hospitals; a few highly specialised ICUs are not involved. For all admissions to the participating ICUs, data on characteristics and severity of illness, intensity of care and outcomes are documented in the Consortium's database. Data from this database were used for this study. In five substudies, the number of patients studied varied from 3958 to 85 547. In addition, data from a cohort study on patients with severe sepsis, the Finnsepsis study, were used to investigate the relationship between hospital size and patient outcomes in this group. The number of patients in this substudy was 452.

During the years 2001-2008, the mean hospital mortality rate for Finnish ICU patients was 18.4%. Compared to results from international studies on patient populations with comparable severity of illness, outcomes of Finnish intensive care are good. Moreover, the outcomes further improved during the study period.

Hospital mortality increased with increasing age, being close to 30% in patients aged over 80 years. Mortality was particularly high in the oldest patients admitted to ICUs for non-surgical reasons. Over 60% of all ICU patients were males, and male gender contributed to the risk of poor outcome among the oldest patients. The ageing of the population will most probably increase the demand for intensive care in the near future.

There was a high amount of patients needing intensive care for respiratory failure in the winter season and excess mortality in winter. The severity of illness-adjusted risk of death during the holiday season in July was similar to that in other months.

For surgical patients with severe sepsis, treatment in small ICUs was associated with increased mortality. For patients treated in ICUs after resuscitation from out-of-hospital cardiac arrest, hospital mortality decreased concurrently with the introduction of therapeutic hypothermia for post-resuscitation care.

Improved data completeness and automation of data collection with a clinical information system increase severity-of-illness scores and decrease severity-adjusted mortality rates. This should be taken into account in benchmarking programmes if some ICUs use technology for automatic data collection and others do not.

National Library of Medicine Classification: WA 900, WC 240, WX 218
Medical Subject Headings: Intensive care; Treatment Outcome; Hospital Mortality; Risk Factors; Sex Factors; Age Factors; Seasons; Sepsis; Resuscitation; Hypothermia, Induced; Technology; Automation

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TIIVISTELMÄ

Sairauden vaikeusaste sekä potilaan ikä ja aikaisempi terveydentila ovat tärkeimmät tehohoidossa olevan potilaan kuolemanvaaraan vaikuttavat tekijät. Tämän tutkimuksen tavoitteena oli selvittää tehohoitopotilaiden kuolleisuuden kehitys Suomessa viime vuosina ja tutkia tiettyjen kiistanalaisten tekijöiden yhteyttä kuolemanvaaraan.

Suomen Tehohoitokonsortio on teho-osastojen yhteenliittymä, joka ohjaa tehohoidon kansallista vertaisarviointihanketta. Konsortioon kuuluvat kaikkien suomalaisten yliopisto- ja keskussairaaloiden kaikki yleisteho-osastot. Jotkin pitkälle erikoistuneet teho-osastot eivät ole tässä hankkeessa mukana. Konsortioon kuuluvien osastojen kaikista hoitojaksoista tallennetaan sairauden laatua ja vaikeusastetta, annettua hoitoa ja sen lopputulosta koskevat ydintiedot kansalliseen laatutietokantaan. Tämän tietokannan tietoja käytettiin tässä tutkimuksessa. Viidessä osatutkimuksessa tutkittujen potilaiden määrä oli välillä 3958 – 85 547. Yhdessä osatutkimuksessa käytettiin lisäksi kansallisen Finnsepsis-tutkimuksen tietoja tutkittaessa sairaalan koon vaikutusta vaikeaa sepsistä sairastavien potilaiden hoitotuloksiin. Tässä osatutkimuksessa potilaiden määrä oli 452.

Vuosina 2001-2008 keskimäärin 18,4 % teho-osastojen potilaista kuoli teho-osastolla tai tehohoidon jälkeen saman sairaalahoitojakson aikana. Kuolleisuus oli selvästi alhaisempi verrattuna sellaisiin kansainvälisiin tutkimuksiin, joissa potilasaineiston keskimääräinen sairauden vaikeusaste oli samantasoinen. Hoitotulokset paranivat edelleen tutkimusjakson aikana.

Kuolleisuus lisääntyi iän myötä ja oli liki 30 % yli 80-vuotiailla. Kuolleisuus oli erityisen suurta niiden iäkkäimpien potilaiden ryhmässä, joiden tehohoidon tarpeen syynä oli muu kuin kirurginen sairaus. Miespuolisten potilaiden osuus kaikista tehohoitopotilaista oli yli 60 %. Iäkkäimpien potilaiden ryhmässä miessukupuoli lisäsi kuolemanvaaraa. Väestön ikääntyminen lisännee tehohoidon kysyntää lähitulevaisuudessa.

Hengitysvajauksen vuoksi tehohoitoa tarvinneiden määrä oli suurempi talvella kuin muina vuodenaikoina. Kuolleisuuskin oli suurempi talvella. Sairauden vaikeusasteen suhteen korjattu kuolemanvaara ei ollut heinäkuussa sen suurempi kuin muina kuukausina.

Vaikeaa sepsistä sairastavien kirurgisten potilaiden kuolleisuus oli suurempi pienissä kuin suurissa sairaaloissa. Sydämenpysähdyksen ja elvytyksen jälkeen teho-osastoilla hoidettujen potilaiden kuolleisuus laski samanaikaisesti, kun viilennyshoito otettiin käyttöön osana tämän potilasryhmän hoitoa.

Tiedonkeruun tarkentuminen ja sen automatisointi kliinistä tietojärjestelmää käyttämällä lisäävät mitattua sairauden vaikeusastetta, mikä johtaa laskennallisen vakioidun kuolleisuussuhteen laskuun. Tämä seikka tulisi ottaa huomioon vertaisarviointihankkeissa silloin, kun vain osa yksiköistä käyttää teknologiaa automaattista tiedonkeruuta varten.

Luokitus: WA 900, WC 240, WX 218
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Docent Aarno Kari was the *primus motor* when the Finnish Intensive Care Consortium was established and deserves much of the credit for the development of the benchmarking programme. He was also one of my teachers when I was a medical student and, some years later, my boss. Now as a co-author he presented carefully weighed views that were very helpful. I feel honoured to have been given the chance to work together with a true Grand Old Man of Finnish intensive care medicine.

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Years ago, Professor Hannu Kokki was the first person to introduce me to research in anaesthesiology. That collaboration served as an eye-opener for me: many of our practices are based on beliefs and traditions rather than on scientifically proven facts. Thank you for that lesson and for igniting within me a spark for research.

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Joensuu, March 2012

Matti Reinikainen

List of the original publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Reinikainen M, Niskanen M, Uusaro A, Ruokonen E. Impact of gender on treatment and outcome of ICU patients. *Acta Anaesthesiol Scand* 49: 984-90, 2005.

II Reinikainen M, Uusaro A, Ruokonen E, Niskanen M. Excess mortality in winter in Finnish intensive care. *Acta Anaesthesiol Scand* 50: 706-11, 2006.

III Reinikainen M, Uusaro A, Niskanen M, Ruokonen E. Intensive care of the elderly in Finland. *Acta Anaesthesiol Scand* 51: 522-9, 2007.

IV Reinikainen M, Karlsson S, Varpula T, Parviainen I, Ruokonen E, Varpula M, Ala-Kokko T, Pettilä V; for the Finnsepsis Study Group. Are small hospitals with small intensive care units able to treat patients with severe sepsis? *Intensive Care Med* 36: 673-9, 2010.

V Reinikainen M, Oksanen T, Leppänen P, Torppa T, Niskanen M, Kurola J; for the Finnish Intensive Care Consortium. Mortality in out-of-hospital cardiac arrest patients has decreased in the era of therapeutic hypothermia. *Acta Anaesthesiol Scand* 56: 110-5, 2012.

VI Reinikainen M, Mussalo P, Hovilehto S, Uusaro A, Varpula T, Kari A, Pettilä V; for the Finnish Intensive Care Consortium. Association of automated data collection and data completeness with outcomes of intensive care. A new customised model for outcome prediction. *Acta Anaesthesiol Scand*, in press; electronic publication ahead of print 5th March 2012; doi: 10.1111/j.1399-6576.2012.02669.x

Contents

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CI	Confidence interval
CIS	Clinical information system
CPAP	Continuous positive airway pressure
DRF	Documentation-related factors
FIO_2	Fraction of oxygen in inspiratory gas
HACA	Hypothermia After Cardiac Arrest study
ICU	Intensive care unit
IQR	Inter-quartile range
LOS	Length of stay
MAP	Mean arterial pressure
NYHA	New York Heart Association (classification of the severity of heart failure)
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PaO_2	Oxygen tension in arterial blood
RR	Risk ratio
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SMR	Standardised mortality ratio
SOFA	Sequential Organ Failure Assessment
SPSS	Statistical Package for the Social Sciences
TH	Therapeutic hypothermia
TISS	Therapeutic Intervention Scoring System
VF	Ventricular fibrillation
WBC	White blood cells

1 Introduction

In the summer of 1952, a polio epidemic was raging in Copenhagen, Denmark. The prognosis of patients with paralysis involving respiratory and bulbar muscles seemed to be almost hopeless, as 27 of the first 31 patients (87%) with respiratory insufficiency died, most of them within three days of hospital admission (Lassen 1953). When a 12-year-old girl was desperately ill, gasping for air and apparently not far from dying from respiratory failure, the anaesthesiologist Bjørn Ibsen was called to help. At that time, manual positive pressure ventilation with an anaesthetic bag had already been used for years in operating theatres. Ibsen attempted to save the girl's life with manual bag ventilation via a tracheotomy and with appropriate sedation to cope with bronchospasm – and succeeded (Wackers 1994, Trubuhovich 2004a, Trubuhovich 2004b). According to Ibsen himself, the girl who had been cyanotic, sweating and drowning in her own secretions, "*became warm, dry and pink – a condition which always makes an anaesthetist happy*" (Ibsen 1954). On Ibsen's initiative, this technique was brought into large scale use on polio patients with respiratory insufficiency, and mortality rates declined dramatically (Lassen 1953, Trubuhovich 2004b). It became clear that positive-pressure ventilation could help most polio patients with paralysis of respiratory muscles to survive until recovery started and they regained enough muscle strength for sufficient spontaneous breathing. For some of the over 250 manually ventilated patients, this treatment was needed for several months (Lassen 1953, Berthelsen et al. 2007).

Bjørn Ibsen was not the first one to successfully use positive-pressure ventilation outside operating theatres, not even on a large scale. In 1948-1949, Albert Bower and V. Ray Bennett were faced with a large number of polio patients with respiratory insufficiency in Los Angeles, USA (Trubuhovich 2007). Tank respirators providing ventilatory support with intermittent negative pressure were in use, but in many cases they turned out to be ineffective. Bower and Bennett converted the negative pressure ventilation machine into one that could supply intermittent positive pressure ventilation and achieved remarkably better survival rates than in patients previously treated with negative pressure ventilation alone. Before the historic events in Copenhagen in 1952, Ibsen was aware of the success that Bower and Bennett had achieved earlier using positive pressure ventilation (Wackers 1994).

However, Ibsen's notable achievements were not limited to his contribution in treating polio patients. In 1953, he utilised the experience gained from these patients and from organising their treatment when he created a unit that is generally acknowledged as the first multidisciplinary intensive care unit in the world (Berthelsen and Cronqvist 2003, Reisner-Sénélar 2011). Postoperative recovery rooms for surgical patients had existed before, but usually patients were treated in such units only for a short time post-operatively, until the effects of anaesthesia had vanished. Regarding critically ill medical patients, aggressive treatment was generally not considered useful. Ibsen refused to accept the prevailing fatalism and chose an active and optimistic strategy, paving the way for a new branch in medicine – intensive care medicine (Berthelsen and Cronqvist 2003).

Polio epidemics struck Finland too, until vaccination programmes eradicated the disease in the early 1960s. The largest epidemic occurred in 1954. At that time, the Aurora hospital in Helsinki was rather well prepared. Previous experiences using cuirass respirators (based on negative pressure) had been very disappointing, the mortality rate being roughly 90%, and from the autumn of 1953 the hospital's strategy was to use positive pressure ventilators that had been hurriedly bought (Pettay 1955a, 1955b). During the years 1954-1960, 372 patients with paralytic polio were treated in the Aurora hospital. 100 patients needed ventilator treatment; a tracheotomy was performed on all of these. Though the majority of the patients needed

ventilatory assistance for several months, the one-year mortality was only 16% (Pettay et al. 1964). One patient even gave birth to a healthy baby boy with a forceps-assisted delivery while being treated with a ventilator (Pettay 1955a). After a mean follow-up time of 5.7 years, 74 of the 100 patients were still alive, though 14 of them remained dependent on the ventilator (Pettay et al. 1964).

The ventilator treatment of polio patients suffering from respiratory insufficiency in the 1950s was organised in a dedicated department with special equipment and specially trained personnel, and severely ill patients arriving from long distances were admitted (Pettay et al. 1964); all these features are characteristic of intensive care. However, the terms "intensive care" or "intensive care unit" were not used at that time. Nor were they officially used for the post-operative units for neurosurgical or cardiac surgical patients in the late 1950s and early 1960s (Klossner 2002, Jalonen 2006, Tammisto and Tammisto 2009). Finland's first two intensive care units, called by that name, were opened in January 1964 in Kuopio and Helsinki (Klossner 2002, Tammisto and Tammisto 2009). There is a still unresolved debate about which one was first.

For decades now, the intensive care unit (ICU) has been one of the cornerstones at an acute care hospital. An ICU is an area in a hospital that is staffed with specially trained personnel and is dedicated to the treatment of critically ill patients who have physiological disorders that are acute and life-threatening but still potentially reversible. The ICU provides continuous monitoring and high-intensity care to support or replace failing physiological functions (Moreno et al. 2010a).

By the mid-1980s, clinical experience and research on outcomes from intensive care had revealed the major determinants of short-term prognosis of ICU patients, even to the extent that their relative contributions could be written into a mathematic formula (Knaus et al. 1981, Knaus et al. 1985). The main factors affecting the risk of in-hospital death are age, previous health status (namely, the presence or absence of severe co-morbidities) and the severity of the acute illness, as reflected by the degree of abnormality in the values of essential physiological measurements. In addition, the underlying diagnosis is important: some conditions have a good short-term prognosis even when the values of many physiological measurements are severely abnormal (e.g. diabetic ketoacidosis), whereas others have a rather gloomy prognosis (e.g. admission after resuscitation from cardiac arrest). Among surgical patients, admissions after emergency operations are associated with worse outcomes than admissions after elective surgery (Knaus et al. 1985).

In addition to the well-known major factors influencing the risk of death, many other factors may be of importance. However, the scientific literature is inconclusive for many of these. It has been known for long that gender affects the susceptibility to many diseases: in 1934, Allen concluded from his large study that "*among males there is a higher incidence of most diseases which might permanently influence health or endanger life*" (Allen 1934). Yet, it is unclear whether gender has any independent effect on the patient's ability to recover from critical illness. According to some authors, men fare better than women (Kollef et al. 1997); according to others, male gender is associated with worse outcomes (Moss and Mannino 2002). Some authors have raised the question that there might be a gender bias in the allocation of resources (Valentin et al. 2003, Tilford and Parker 2003).

In the general population, mortality from many conditions is increased in winter (Sheth et al. 1999, Olson et al. 2009). We do not know whether there is a seasonal variation affecting outcomes from intensive care. Nor do we know if a "July phenomenon", i.e. substandard quality of care in July due to staff transition (Inaba et al. 2010), exists in intensive care. There is also uncertainty about the impact of hospital volumes on patient outcomes. For elective high-risk surgery the general rule seems to be the bigger the better (Birkmeyer et al. 2002), but does this apply to intensive care?

Even the impact of chronological age is somewhat controversial. Increasing age is indisputably associated with increased risk of death, and in practice old age is one of the factors associated with refusal of ICU admission (Joynt et al. 2001, Garrouste-Orgeas et al. 2009).

However, many authors have with good reason claimed that age alone is not a good predictor of outcome; premorbid functional status and the severity of acute illness are mainly responsible for the prognosis of the elderly patient (de Rooij et al. 2005, Arsura 2006). Even so, writing evidence-based recommendations about which elderly patients will benefit from ICU care and should thus be admitted has been impossible so far, because we still know too little about the outcomes of intensive care of the elderly (Boumendil et al. 2007). This question is of paramount importance, as there will be an enormous increase in the number of elderly people during the next 20 years (Flaatten 2007).

Two randomised controlled trials showed that mild therapeutic hypothermia improves the chance of survival of patients resuscitated from out-of-hospital cardiac arrest with an initial cardiac rhythm of ventricular fibrillation (Hypothermia after Cardiac Arrest Study Group 2002, Bernard et al. 2002). However, the inclusion criteria in these studies were strictly defined and were met only by a minority of resuscitated patients. It is not known whether the use of hypothermia can bring a major survival benefit also in real life, i.e. outside the context of a controlled clinical trial.

Patient mortality, adjusted for disease characteristics and severity, is a commonly used marker of ICU performance. Comparing that performance with a specified standard, referred to as benchmarking, has become popular in recent years (Moreno et al. 2010b). There is, however, little evidence that benchmarking results in better outcomes (Woodhouse et al. 2009). Moreover, differences in physiological measurements for severity-of-illness calculations may alter predicted probabilities of death and thus change standardised mortality ratios, causing severe bias in the pertinent figures in benchmarking. Studies on small patient populations have clearly shown that both the use of a clinical information system that automatically records physiologic data and increasing the frequency of laboratory tests lead to higher severity-of-illness scores, higher predicted probabilities of death and lower standardised mortality ratios (Bosman et al. 1998, Suistomaa et al. 2000). We do not know to what extent widespread automation of data collection in a large group of ICUs would affect these figures.

The aim of this study was to shed more light on these controversial issues. The study data were derived from the large database of the Finnish Intensive Care Consortium, which is a body co-ordinating a quality assurance and benchmarking programme. Since 2007, the Consortium has included all general adult ICUs in all the main Finnish hospitals; a few highly specialised ICUs are not involved. The database gathers data from every ICU admission to the units participating in the Consortium. In addition, data from a prospective cohort study on patients with severe sepsis, the Finnsepsis study (Karlsson et al. 2007), were used in the present study to investigate the relationship between hospital size and patient outcomes in this group.

2 Review of the Literature

2.1 MAJOR FACTORS AFFECTING THE RISK OF DEATH OF INTENSIVE CARE PATIENTS

The characteristics and severity of the acute illness, the patient's age and the presence or absence of severe co-morbidities are the most important determinants of the short-term prognosis (risk of death during present hospitalisation) of ICU patients. Several severity-of-illness scoring models that take into account the major prognostic factors and quantify the severity with a points-score have been developed. The most commonly used models are APACHE II (Acute Physiology and Chronic Health Evaluation II) (Knaus et al. 1985) and SAPS II (Simplified Acute Physiology Score II) (Le Gall et al. 1993). The newest updated versions of these models are called APACHE IV (Zimmerman et al. 2006) and SAPS 3 (Metnitz et al. 2005, Moreno et al. 2005). The essential prognostic factors according to the models SAPS II, SAPS 3 and APACHE IV are presented in Table 1.

Table 1. Major factors that independently affect the short-term prognosis (risk of death during present hospitalisation) of patients treated in intensive care units.

Factor	**Effect**
Age	After the age of 40 years, increasing risk with increasing age.
Chronic diseases	AIDS, cirrhosis of liver, haematological malignancy, metastatic cancer and severe heart failure (NYHA IV) strongly increase the risk; previous immunosuppressive therapy has a smaller but still significant effect.
Type of admission	Lowest risk for patients admitted for post-operative care after scheduled surgery; considerably poorer prognosis for medical patients (no surgery done) and for emergency surgical patients.
Values of physiological measurements	Abnormal values of the following measurements are associated with increased risk; the more abnormal the value, the higher the risk: Glasgow Coma Score reflecting level of consciousness, heart rate, systolic or mean blood pressure, PaO_2/FIO_2 ratio reflecting severity of oxygenation impairment, body temperature, urinary output, blood haematocrit, white blood cell count and platelet count, blood pH and concentrations of bicarbonate, urea and creatinine, sodium, potassium, albumin and bilirubin.
Diagnostic group	Crude mortality rates are particularly high (over 40%) in the following groups: post cardiac arrest, cardiogenic shock, hepatic failure, severe sepsis of gastrointestinal or pulmonary origin. After adjustment for other factors, the following major diagnostic categories are the strongest independent predictors of outcome: Of non-operative diagnoses, the highest risk of death is associated with the following: pulmonary fibrosis, parasitic / fungal pneumonia, respiratory cancer, intracerebral haemorrhage, subarachnoid haemorrhage, gastrointestinal ischaemia, post cardiac arrest, cardiogenic shock. Of post-operative diagnoses, the highest risk of death is associated with the following: head trauma, non-traumatic intracranial haemorrhage, gastrointestinal ischaemia. The following diagnoses are the strongest independent predictors of good prognosis: diabetic ketoacidosis, drug overdose, acute asthma.

The severity of the acute illness is reflected by the abnormality of the values of the essential physiological variables that are presented in table 1. In general, the more abnormal the value, the more points are given to the severity score, and the higher is the predicted risk of in-hospital death. However, the relationship between the level of abnormality in physiological values and the associated increase in risk is generally not linear. In addition, the relative weights of the different components of the severity models vary. For example, the independent effect of abnormal sodium or potassium values is relatively small, whereas a severely impaired level of consciousness (Glasgow Coma Score < 6), severe hypotension (systolic blood pressure < 70 mmHg) or severely impaired oxygenation (PaO_2/FIO_2 ratio < 100 mmHg) all substantially increase the risk of death. A very low platelet count (< 20 x 10^9/l) strongly increases the risk, as does an age of over 80 years.

In each of these models, the severity-of-illness score can be converted by a mathematical formula into a predicted probability of in-hospital death. The scores or probabilities are not primarily intended to guide decision-making regarding individual patients but to serve as tools in stratifying patient groups according to severity of illness and in measuring ICU performance. The use of the prediction models for benchmarking purposes and the SAPS II scoring system are described in chapter 2.7 of this thesis.

The score given by the commonly used severity models is based on information that is available at the beginning of the intensive care period. The APACHE models and SAPS II take into account the worst value of each physiological measurement during the first 24 hours after ICU admission. SAPS 3 uses a more narrow time window that starts one hour before and ends one hour after ICU admission. These models therefore quantify the severity of illness only at the beginning of the ICU stay. The predictive ability of the models weakens as the length of stay in the ICU increases, and for patients with lengths of ICU stay of over seven days, the predictive ability is poor (Suistomaa et al. 2002).

The SOFA score is a system describing the presence and severity of dysfunction or failure of essential organ systems. The acronym originally stood for "Sepsis-related Organ Failure Assessment" (Vincent et al. 1996). However, as the system is not specific to septic patients, the acronym was soon taken to refer to "Sequential Organ Failure Assessment" (Vincent et al. 1998). SOFA evaluates the function of six organ systems: respiration, coagulation, liver, cardiovascular function, central nervous system, and renal function. For each organ system, a score of 0 (reflecting normal function) to 4 (most abnormal) is given. The worst value for each day is recorded for each organ system. The sum of the organ-specific scores is the SOFA score. The score can be used not only at the beginning of the treatment period but also as a continuous measurement of the severity of organ dysfunctions. The SOFA scoring system is presented in Table 2.

The SOFA score differs from the commonly used prediction models in several ways: Firstly, SOFA was designed not to predict outcome but to describe quantitatively and objectively the degree of organ dysfunction over time both in individual patients and in groups of patients (Vincent et al. 1996). Secondly, SOFA was not based on mathematical modelling but was created by a group of experts in a consensus conference. Nevertheless, studies have shown that high SOFA scores for any individual organ system as well as high total scores are associated with increased mortality. The mortality rate was > 90% among patients whose maximum SOFA score (the highest score during the ICU stay) was > 15, but well below 10% among the patients whose maximum SOFA score was < 7 (Vincent et al. 1998). Several other SOFA-based prediction models have been developed and they work rather well (Minne et al. 2008). Models that combine sequential SOFA scores with the APACHE II/III or SAPS II models have shown particularly good prognostic performance (Minne et al. 2008).

Table 2. The SOFA (Sequential Organ Failure Assessment) scoring system

SOFA score	**1**	**2**	**3**	**4**
Respiration (PaO_2/FIO_2, mmHg)	< 400	< 300	< 200 [a]	< 100 [a]
Coagulation (Platelets, x 10^9/l)	< 150	< 100	< 50	< 20
Liver (Bilirubin, µmol/l)	20-32	33-101	102-204	> 204
Cardiovascular (Hypotension or dose of vasoactive medication)	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose) [b]	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1 [b]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1 [b]
Central nervous system (Glasgow Coma Score)	13-14	10-12	6-9	< 6
Renal (Creatinine, µmol/l, or urine output)	110-170	171-299	300-440 or < 500 ml/day	> 440 or < 200 ml/day

[a] With respiratory support; [b] adrenergic agents administered for at least 1 h (doses are in µg/kg/min); MAP, mean arterial pressure

Intensive care units mainly treat patients who are critically ill but who are still considered to have a reasonable chance of recovery. Patients who are in the terminal phase of an incurable disease or who are otherwise estimated to be too sick to benefit from intensive care are seldom admitted to ICUs (Garrouste-Orgeas et al. 2005, Moreno and Rhodes 2010c). Thus, the prognostic factors presented in this chapter apply to a highly selected group of patients, as the patients treated in an ICU are not a representative sample of the patients in the hospital.

Another important thing to remember is that, although some factor might not appear to be associated with outcome among those patients who have already been admitted to the ICU, that factor may well be the real reason for the critical condition that requires intensive care (and, if the patient dies, the real cause of death). For example, alcohol use is very often the reason for the need of intensive care and the cause of death for some of these patients. Yet, within the group of ICU patients, alcohol use does not seem to be a predictor of death, as there is no difference in mortality between alcohol-related admissions and other admissions (Uusaro et al. 2005). Thus, it is not only important to know what factors have prognostic significance among patients who are treated in ICUs but also to find the factors that lead to the need for intensive care, and this may not be possible by studying only ICU patients.

In addition to the indisputable major determinants of short-term prognosis, many other factors may have some impact. The following chapters will present a review of the current knowledge regarding some of these factors.

2.2 INFLUENCE OF GENDER ON OUTCOMES FROM TRAUMA AND CRITICAL ILLNESS

2.2.1 Animal Studies

Sex hormones affect immune functions and the ability to recover from trauma: Administration of estradiol to male mice improves immune responses after haemorrhagic trauma (Knöferl et al. 2000), while an ovariectomy in female mice before trauma and haemorrhagic shock depresses immune functions (Knöferl et al. 2002). Estradiol administration to male rats improves cardiovascular and hepatocellular functions after trauma (Mizushima et al. 2000). In contrast, testosterone treatment of female mice causes immune depression after haemorrhagic shock (Angele et al. 1998), and castration of male animals before trauma and haemorrhage prevents depression of immune functions (Wichmann et al. 1996a) and improves myocardial function (Remmers et al. 1998).

These results can be summarised as follows: following trauma haemorrhage, female sex hormones seem to enhance immune functions and improve cardiovascular and hepatocellular functions, while male sex hormones seem to be responsible for immunosuppression and depression of myocardial function. This explains the findings of improved immune responses in females and decreased responses in males following haemorrhagic shock. As a consequence, females should be able to immunologically tolerate trauma and major blood loss better than males (Wichmann et al. 1996b). Female mice also seem to be able to tolerate a septic challenge better than male mice, which has been attributed either to the presence of beneficial female sex hormones or the absence of immune-depressive concentrations of testosterone (Zellweger et al. 1997).

2.2.2 Human Studies

Incidence of diseases

Already in the 1930s, careful attention was paid to the fact that for many serious diseases the gender distribution of patients did not match that of the general population. Allen made a large study on the incidence of severe diseases that affect structures common to both sexes (Allen 1934). He noticed that for most serious illnesses of the digestive tract, the lungs and respiratory tract, as well as the blood vessels and heart, males were affected more frequently than females. Diseases of the gallbladder, obesity, arthritis and "hysteria" were among the few diseases that were more common in females. As a result, death rates for men were higher than those for women in all age groups except among persons aged 20 to 34 years, when mortality of females was higher, apparently due to deaths associated with childbirth. Allen pointed out that the mortality of males was higher than that of females already during intra-uterine life and during the very first years of extra-uterine life, so all of the gender-related differences could not be a consequence of some habits of life peculiar to the male. Allen concluded that "*it appears incontrovertible that there exists a sex-linked inferiority of the male; that mere maleness influences unfavorably the resistance of the organism to disease during all ages.*"

The prevalence of illnesses and mortality rates presented by Allen may not be valid any more, but a few of his conclusions may well be: even today, most life-threatening diseases affect males at an earlier age than females. For example, the age-adjusted incidence rate of most cancers, breast and gynaecological cancers excluded, is much higher for males than for females (Cook et al. 2009). Likewise, coronary heart disease is markedly more common in men than in women. Differences in known risk factors, particularly in cholesterol levels and smoking, explain a major part but not all of the gender-based differences (Jousilahti et al. 1999). However, when only patients who already have coronary heart disease are studied, male gender seems to be associated with better outcomes: After an acute myocardial infarction, younger but not older women have higher hospital mortality rates than men (Vaccarino et al. 1999). After coronary

artery bypass surgery, younger women seem to be at a higher risk of death than men, but the sex difference is less marked in the older age categories (Vaccarino et al. 2002). It has been suggested that anatomical differences or differences in thrombotic and fibrinolytic activity may account for the different clinical profiles and outcomes of men and women with acute coronary syndromes (Hochman et al. 1999).

Inflammatory autoimmune diseases are more common in females than in males (Sternberg 2001). Sex hormones modulate the immune system and they are thought to be responsible for the more vigorous immune reactions in females, which leads to a better resistance to some infections but also a higher incidence of autoimmune diseases (Bouman et al. 2005).

Gender distribution of ICU patients

In general ICU patient populations, male patients most often make up the majority. In the multinational study that created the SAPS II prognostic model, 60% of the 13,152 patients were males (Le Gall et al. 1993). ICUs from 35 countries participated in the SAPS 3 study (Metnitz et al. 2005). Overall, 61% of the 19,577 patients were males, and the proportion of females ranged from 37% to 45% across different regions.

Fowler et al. (2007) studied adult patients admitted to hospitals in Ontario, Canada, during the years 2001-2002. Of the 466,792 patients, 57.0% were women. Obstetric diagnoses accounted for 14.0% of all admissions. Of the patients admitted for non-obstetric reasons, 50.1% were women and 49.9% men. The age distribution corresponds to the slight predominance of women (51.1%) in the general population of Ontario in 2001. However, though males accounted for half of the non-obstetric hospital admissions, they accounted for 60.1% of admissions to ICUs. At the time of ICU admission, men and women were of comparable age and had similar severity of illness scores. However, there were some differences in the distribution of patients to different diagnostic categories, with a considerably higher proportion of men than women admitted to ICUs after cardiovascular surgery and elective surgery in general.

Outcomes from trauma

Results from human studies about the association of gender with outcome have been discrepant. Berry et al. (2009) studied patients with traumatic brain injury and found worse outcomes for males than for females among patients aged over 45 years but not among younger patients. Likewise, George et al. (2003) found an increased severity of injury-adjusted risk of death for men compared with women in patients that had sustained blunt trauma; the difference between genders was most apparent for patients aged over 50 years. In some other studies, women had a survival advantage when compared with equally injured men among young adult trauma patients (Wohltmann et al. 2001, Mostafa et al. 2002). According to other studies, however, females with trauma do not have more favourable outcomes than males when patients are appropriately stratified for other variables, including age and severity of injury (Gannon et al. 2002, Rappold et al. 2002).

Incidence and outcome of sepsis

The incidence of severe sepsis is considerably higher for men than for women: Despite an approximately equal number of men and women receiving surgical care in a German study, more than two thirds of the patients who needed intensive care for severe sepsis were males (Wichmann et al. 2000). Men are also more susceptible to septic complications than women following trauma (Oberholzer et al. 2000). In Finland, 67% of adult ICU patients with severe sepsis are males (Karlsson et al. 2007). The incidence of severe sepsis increases with increasing age. An American study found that the age-specific incidence rate of severe sepsis was lower in women than in men: after the age of 30 years, women had a rate similar to that of men who were five years younger (Angus et al. 2001).

Whether male gender is also a risk factor for adverse outcomes in those patients who already have developed severe sepsis is a controversial issue. Results from studies in surgical patients

with sepsis suggest that male gender is associated with increased mortality (Schröder et al. 1998) or with decreased mortality (Eachempati et al. 1999). Schröder et al. (1998) explained that the better outcomes of women might be caused by the observed higher plasma concentrations of anti-inflammatory mediators. Adrie et al. (2007) carried out a case-control study comparing men and women who were treated for severe sepsis. In accordance with other studies, 63% of the patients were men. The authors found a significantly lower in-hospital mortality for women of postmenopausal age (over 50 years) than for equally aged men, whereas there was no difference between the genders among younger patients. One would expect that gender-based differences would be more pronounced among younger patients if they were caused by beneficial effects of female sex hormones. Adrie et al. end the discussion about the possible mechanisms behind their findings by presenting another plausible answer: differences in health-related behaviour over an individual's life span may eventually lead to outcome differences late in life.

Respiratory disorders and general intensive care

Among patients requiring mechanical ventilation, female gender was associated with increased mortality in one study on 357 patients (Kollef et al. 1997), but outcome was not gender-related in another study on 580 patients (Epstein and Vuong 1999), nor in a study on 15,757 patients that were treated in 361 ICUs in 20 countries (Esteban et al. 2002). In the study by Esteban et al., 61% of all patients were males. Kaplan et al. (2002) studied 623,718 hospital admissions for community-acquired pneumonia of patients aged 65 years or older. Men had higher mortality, both unadjusted and after adjustments for confounding factors. Likewise, mortality rates for acute respiratory distress syndrome (ARDS) have been higher for men than for women (Moss and Mannino 2002).

Some authors have studied the impact of gender on treatment and outcome in the heterogeneous patient populations of mixed medical-surgical ICUs. Romo et al. (2004) published a study in which older but not younger women had a higher mortality rate than men. However, severity of illness was not assessed with any scoring system in the study, and therefore no adjustments for disease severity were made. Moreover, Romo et al. only presented ICU mortality rates, not hospital mortality rates. Because of these shortcomings, no firm conclusions can be drawn. Valentin et al. (2003) studied a large cohort of patients admitted to 31 ICUs in Austria and found no statistically significant differences in severity of illness-adjusted mortality rates between men and women. However, male patients received an increased level of care and had a higher probability of receiving several invasive procedures.

Hormonal factors

Animal studies have rather consistently shown beneficial effects of female sex hormones after trauma or a septic challenge. However, it is not at all clear whether high concentrations of estradiol are beneficial or even harmful: May et al. (2008) studied patients who were treated in ICUs for more than 48 hours because of trauma or surgical critical illness. Blood estradiol concentrations at 48 hours after ICU admission were significantly higher in non-survivors than in survivors, with the median value for non-survivors being twice the median for survivors. This ratio was of the same magnitude among both men and women. Similar results were found by Angstwurm et al. (2005), who studied ICU-treated patients with severe infection. Outcome was not influenced by gender. However, blood estradiol concentrations were significantly higher in non-survivors than in survivors, regardless of gender. May et al. (2008) present some fundamental differences between controlled animal studies and critically ill or injured humans: In non-primates, estrogen biosynthesis is limited to the gonads. In humans and other primates, estrogen production takes place also in adipocytes, fibroblasts and osteoblasts. This peripheral production is stimulated by pro-inflammatory cytokines in the presence of glucocorticoids, i.e. stimulated by stress. This means that high estrogen concentrations may be a signal of a strong inflammatory response or a biomarker of the severity of illness.

In addition, the strong inflammatory response associated with female sex hormones in animal studies provided protection against an early death after untreated trauma or untreated septic challenge. A forceful inflammatory response may indeed be beneficial at an early stage, but exaggerated inflammation may also lead to the multiple organ dysfunction syndrome at a later stage. A person with a severe injury or infection would probably benefit from an early strong inflammatory response that is subsequently down-regulated when infections are under control (Fowler et al. 2009). Thus, an appropriate balance between pro-inflammatory and anti-inflammatory mediators in the given temporal context is probably more important than the concentration of any individual mediator. This explains why there is no easy answer to the question whether some extra estradiol would be beneficial or not.

Prolonged critical illness is accompanied by substantial losses of body protein despite feeding (Streat et al. 1987). The catabolism seems to be associated with decreased secretion of anterior pituitary hormones and a decline of pulsatility and regularity in their secretion, which is apparently caused by impaired hypothalamic stimulation (Van den Berghe et al. 1998). Critically ill men seem to be more affected than women by loss of pulsatility of growth hormone secretion (Van den Berghe et al. 2000).

2.2.3 Cellular mosaicism of X-linked genes in females

There has been increasing interest in recent years in genetic factors unrelated to sex hormones as possible mechanisms behind gender differences in the risk of many diseases. Even when environmental differences are insignificant, serious morbidity and mortality are greater in males (Migeon 2006). The protective effect of female gender, for example against infections, is significant in both premenopausal and postmenopausal women, which suggests that factors other than sex hormones play an important role (Sperry et al. 2008). The cellular mosaicism of females may be one such factor. In each cell, apart from reproductive cells and cells without nuclei, females carry two X chromosomes, one maternal and one paternal. Males have a maternal X and a paternal Y chromosome, of which the Y carries the genes responsible for maleness. The Y chromosome is small and has few functional genes (probably less than 100), whereas the X is large and carries more than 1000 genes (Migeon 2006, Spolarics 2007). However, though female cells have two Xs, only one is active in each cell: early in development, cells randomly choose either the maternal or paternal X to be active; the other X chromosome is permanently inactivated (Willard and Carrel 2001). Females are thus cellular mosaics for those X-linked genes that are polymorphic. Many of the genes residing on the X chromosome are important in the innate immune response (Spolarics 2007). Cellular mosaicism offers protection against harmful mutations of X-linked genes and it also seems to be advantageous in the immune response to injury and infection (Migeon 2006, Spolarics 2007, Migeon 2008). On the other hand, cell mosaicism may lead to a larger number of autoantigens and may be the reason for the higher incidence of autoimmune diseases in females (Migeon 2006).

The situation is made even more complex by the recently discovered fact that approximately 15% of the genes on the silenced X chromosome escape inactivation, which means that these genes are expressed from both the active and inactive chromosome (Carrel and Willard 2005). Because of this incomplete X inactivation, many genes are expressed at higher levels in females than in males. Another 10% of genes on the silent X are expressed to varying extents, which suggests a significant amount of heterogeneity of expression among females. The clinical implications of these findings and many other aspects of the function of the X chromosome are still poorly understood. As Gunter (2005) put it, "*She moves in mysterious ways, and we've just been given a preview*."

2.2.4 Summary

- According to animal studies, female sex hormones improve immune functions after trauma, while male sex hormones cause immunosuppression. This suggests that females should tolerate trauma and major blood loss better than males.
- In humans, high estradiol concentrations are associated with increased mortality in critically ill patients. Estradiol may be a marker of the severity of illness and the associated strength of the inflammatory response.
- The age-adjusted incidence rate of most life-threatening diseases is much higher in males than in females. This has been largely attributed to behavioural factors, though these do not however fully explain the differences.
- The incidence rate of most autoimmune diseases is higher in females.
- Males make up the majority of ICU patients fairly consistently across different countries. Roughly 60% of the patients are males.
- Whether gender influences the outcomes of patients who already have a serious illness requiring intensive care is a controversial issue.
- Recent studies suggest that the cellular mosaicism of polymorphic X-linked genes in females may contribute to the lower incidence of many serious diseases in women.

2.3 SEASONAL VARIATIONS IN MORTALITY

2.3.1 Increased Mortality in Winter

In the general population, mortality from acute myocardial infarctions and strokes is increased in winter, with the seasonal variation increasing with increasing age (Sheth et al. 1999). Mortality from respiratory diseases is also higher in winter than in other seasons: Olson et al. (2009) used data from a national registry of death records and studied more than 27 million deaths in the United States in the period 1992-2003. Among files with a code for pneumonia, the mortality rate was 59% higher in winter months (defined as December through February) than in summer months (June through August). According to records with a code for chronic obstructive pulmonary disease, the mortality rate was 29% higher in winter than in summer. The mortality rate of patients with pulmonary fibrosis was 17% higher in winter than in summer. There was notably less seasonal variation in mortality rates from lung cancer: the mortality rate was 3% higher in winter than in summer.

Mortality from ischaemic heart disease, cerebrovascular disease and respiratory disease, as well as all-cause mortality, is increased in winter both in countries with cold winters and in countries with a milder winter climate. Interestingly, the seasonal variations in mortality are larger in regions with relatively warm winters compared to cold regions (Laake and Sverre 1996, The Eurowinter Group 1997). According to the Eurowinter Study, people living in cold areas are better prepared to meet the challenge caused by cold weather: for a given cold temperature, people living in Finland are much more likely to wear warm clothing, including hats, than people living in Italy or Greece. Moreover, thanks to effective heating, people living in Finland have higher indoor temperatures in their homes than people living in southern Europe (The Eurowinter Group 1997).

According to Keatinge (2002), roughly half of the excess deaths in winter are caused by cardiovascular events. These deaths peak about two days after peak cold. Approximately half of the remaining extra winter deaths are caused by respiratory disease. These deaths rise more slowly with a peak at 12 days after the peak of a cold spell. In addition to temperature changes, influenza epidemics, most commonly occurring during winter months, may be a major cause of the excess winter mortality. Reichert et al. (2004) studied the correlations between mortality peaks and influenza. Their conclusion was that the winter-season excess mortality is probably caused by a single factor, which most likely is influenza. Reichert et al. suggest that weather and

other factors may affect the timing and modulate the magnitude of the increase in mortality in winter, but the influenza virus is the primary determinant.

Seasonal variation may affect outcomes from cardiac surgery: Shuhaiber et al. (2008) found increased risk–adjusted odds of hospital mortality in patients having operations in winter compared with the average across all seasons.

It is not clear whether there are seasonal variations in patient outcomes in intensive care. In a study by Harrison et al. (2004a), the hospital mortality rate of ICU patients in the UK was 32.3% in winter (December-February) and 29.3% in non-winter months (March-November). Even after adjustments for APACHE II-based probability of death, the winter season was associated with increased mortality (adjusted odds ratio 1.10, 95% confidence interval 1.05-1.14, $P < 0.001$). However, Harrison et al. also adjusted for other factors reflecting both the case mix of the individual patient and of the patients in surrounding beds. After this, the independent effect of winter season was no longer significant. The authors conclude that the excess winter mortality observed in ICUs in England, Wales and Northern Ireland can be explained by variation in the case mix of admissions.

2.3.2 The July Phenomenon

In some countries, staff transition in teaching hospitals takes place in July, when a new academic year begins. A large number of inexperienced residents thus start to care for patients at the same time. "The July phenomenon", often mentioned in the literature, refers to concerns about the quality of care early in the academic year (Barry and Rosenthal 2003). The study by Inaba et al. (2010) found that admission to a large trauma centre at the beginning of the academic year was associated with an increased risk of errors resulting in complications. However, most other studies addressing this issue, including studies on ICU patients, have not found differences in risk-adjusted outcomes of patients treated in July compared with those treated in other months (Buchwald et al. 1989, Shulkin 1995, Barry and Rosenthal 2003, Finkielman et al. 2004, Bakaeen et al. 2009). Thus, there seems to be little evidence to support the existence of a July phenomenon.

Intensive care patients benefit from being treated by experienced intensivists (Blunt and Burchett 2000, Vincent 2000, Baldock et al. 2001). This raises a question of whether the same standard of care can be achieved continuously. In a study by Uusaro et al. (2003), admissions to Finnish intensive care units during the weekend were associated with a higher mortality than weekday admissions. Likewise, Barnett et al. (2002) found that patients admitted to an ICU on the weekend have a modestly higher risk of death. However, these findings were not confirmed in the study by Wunsch et al. (2004). They found that patients admitted to ICUs on Saturday and Sunday had higher crude hospital mortality compared with mid-week admissions, but this association was no longer significant after adjustments for differences in case mix.

In Finland, there are no particular time points of staff transition; young physicians and nurses start to work in hospitals throughout the year. However, due to the summer holiday season, hospital staff is often less experienced in July than in other months. To what extent this might affect the quality of care delivered is not well known.

2.3.3 Summary

- In the general population, mortality from respiratory diseases, ischaemic heart disease and strokes is increased in winter.
- Some authors attribute the excess winter mortality to cold stress, others to influenza epidemics.
- "The July phenomenon" refers to the idea that the quality of medical care might be worse in July than in other months. Though the term is often mentioned in the literature, there is little evidence to support the existence of such a phenomenon.
- It is not well known whether there are seasonal variations in patient outcomes in intensive care. However, some studies have found an increased mortality of patients admitted to ICUs on weekends compared with weekday admissions.

2.4 INTENSIVE CARE OF THE ELDERLY

The reader of medical texts concerning the elderly may be confused by the fact that the authors of these texts are not unanimous about who should be called "elderly" or "old". The World Health Organization (WHO) uses the term elderly to mean persons aged 60 years or over.[1] According to WHO statistics, the number of these people in the world is 650 million, but it is forecast to triple to 2 billion by 2050. The European Union uses the term elderly for individuals aged 65 years or over.[2] This definition is also most commonly used in the medical literature (Wood and Ely 2003), but not consistently: some authors have used the word elderly for patients aged 70 years or over (Montuclard et al. 2000), some others for patients aged 75 years or over (Walther and Jonasson 2004). Some other terms referring to oldness are also used, again without consistency. Somme et al. (2003) studied elderly patients and divided them into three subgroups: "old" (75-79 years), "very old" (80-84 years) and "the oldest-old" (85 years or over). The term oldest old was also used by Shabot and Johnson (1995), but they referred with it to patients aged 75 years or over. Boumendil et al. (2005) in turn used the term oldest-old for patients aged 80 years or over, while those in the age group 65-79 years were called "young-old". The threshold 80 years as a definition of very high age has been used also by many other authors in recent years. Patients aged 80 years or over have been called "very elderly" (de Rooij et al. 2005, 2006) or "very old" (Bagshaw et al. 2009).

The lack of agreement in terminology can be seen as a reflection of the fact that for any given age there is considerable heterogeneity within populations regarding the presence of chronic diseases and functional capacity. The concept of frailty is used to distinguish old people who are vulnerable to adverse outcomes because of a poor state of health and loss of physiological reserves from those people who are in good shape despite a high chronological age (Boumendil et al. 2007). However, there is no unambiguous definition of frailty either.

2.4.1 Outcomes from Intensive Care

Incidence of severe diseases

Increasing age increases the susceptibility to serious diseases (Wood and Ely 2003). In an American study on the incidence of acute respiratory failure requiring mechanical ventilation, the incidence increased almost exponentially with increasing age until the age of 85 years, resulting in an 88-fold difference in incidence between the youngest age group studied (5-17 years) and the oldest group (85 years and over) (Behrendt 2000). Another study determined the incidence of severe sepsis (Angus et al. 2001). The incidence was rather high in infants,

[1] http://www.who.int/topics/ageing/en/ as accessed on 30th December, 2011

[2] http://ec.europa.eu/health/population_groups/elderly/index_en.htm as accessed on 30th December, 2011

decreased quickly in older children, increased slowly through young adulthood and increased very steeply with increasing age among those aged over 65 years. Among people aged over 85 years, the incidence was more than 100-fold that in children. Hospital mortality rates also increased with increasing age, being 10% for children and 38.4% for patients aged 85 years or over.

Impact of age on short-term outcomes

When the first severity of illness classification systems for intensive care were developed, chronologic age was found to be a risk factor for death from acute illness (Wagner et al. 1983). Yet there has been some controversy regarding the significance of age itself as a predictor of mortality. According to some authors, old age may not be an independent risk factor, once appropriate adjustments for severity of illness or injury are made (Shabot and Johnson 1995, Chelluri et al. 1993). Nevertheless, large studies have confirmed that increasing age is associated with an increasing risk of in-hospital death (Le Gall et al. 1993, Moreno et al. 2005). However, many authors have emphasised that severity of illness, premorbid functional status and co-morbidities have a much greater impact on the prognosis than age per se, and that old age alone should not be used as a reason for withholding intensive care (de Rooij et al. 2005, Boumendil et al. 2007).

Regardless of age, severity of acute illness is the major determinant of short-term prognosis. This severity can be quantified with a score based on the level of abnormality of physiological parameters, i.e. on the level of divergence from normal physiological homeostasis. The severity score can be converted into a probability of in-hospital death (Le Gall et al. 1993, Moreno et al. 2005). The essential physiological variables that are taken into account in the severity-of-illness scores are presented in chapters 2.1 and 2.7 of this thesis.

Bagshaw et al. (2009) made a large registry-based study on 120,123 adult patients who were treated in ICUs in Australia and New Zealand in the years 2000-2005. 15,640 (13%) of the patients were aged 80 years or over, and were termed "very old" by the authors. The hospital mortality rate for the very old patients was 24.0%, as compared with 16.6% for patients aged 65 to 79 years, 11.4% for patients aged 40 to 64 years and 7.1% for patients younger than 40 years. In a multivariate analysis, increasing age was independently associated with increased hospital mortality: for patients aged ≥ 80 years compared with those aged 18-40 years, the adjusted odds ratio (OR) for in-hospital death was 5.4, 95% confidence interval (CI) 4.9-5.9. The following factors were associated with lower survival: admission from a chronic care facility, co-morbid illness, non-surgical admission, greater illness severity, need of mechanical ventilation, and prolonged stay in the ICU.

In a study by Boumendil et al. (2005) from 36 ICUs in France, the hospital mortality rate of ICU-treated patients aged 80 years or over was 28%. For patients aged 65-79 years, hospital mortality was 22%. According to the authors, there seems to be a selection bias against the oldest old patients with severe co-morbidities being admitted to ICUs, as the patients aged 80 years or over had fewer related diagnoses than the patients aged 65-79 years.

Long-term outcomes of elderly ICU patients

In an earlier study, Boumendil et al. (2004) aimed to determine factors that affect long-term survival of oldest old ICU patients. They prospectively studied 233 patients aged 80 years or over who were treated in a medical ICU in France in 1998-1999. These patients accounted for 16% of all ICU patients during the study period. The mean age ± SD was 86.1 ± 3.8 years (range, 80-101 years), and the mean SAPS II score was 45.1 ± 18.9. 105 patients (45.5%) were treated with invasive mechanical ventilation. The ICU mortality rate was 16.3%. Survival rates from the day of ICU admission were 59% at two months, 33% at two years and 29% at 3 years. The median and mean survival times after admission were 231 days and 13 months, respectively. A multivariate analysis identified the following factors as independent predictors of a poor prognosis: the presence of an underlying fatal disease, initial altered level of consciousness, the

need of mechanical ventilation, age over 85 years, and diagnosis of shock. If more than two of these factors were present, median survival time was only 32 days. The authors also determined factors that were predictors of long-term outcome in the subgroup of patients that survived for more than two days after hospital discharge. In this group, survival rates were 71% at two months and 35% at three years. Severe functional limitation before admission and an underlying fatal disease were independent predictors of poor long-term survival.

Kaarlola et al. (2006) studied the long-term survival and quality of life of 882 elderly patients (≥ 65 years of age) who were treated in a medical-surgical ICU in Helsinki, Finland, in 1995-2000. 1827 younger patients made up the control group. The median APACHE II score was 18 for the elderly and 14 for the younger patients. The hospital mortality rate was 36.5% for the elderly and 27.4% for the younger patients. The cumulative three-year mortality was 57% for the elderly and 40% for the younger patients. In the autumn of 2001, the survivors were contacted in order to study their health-related quality of life. The response rate among the elderly was 87%. The median time from ICU discharge to the response was 3.1 years; the inter-quartile range (IQR) was 1.9-5.2 years. 30% of the elderly respondents assessed their present health state as good, 58% as satisfactory and 12% as poor. The elderly had lower values than the younger respondents in indices reflecting physical functioning, but the state of mental health was actually better among the elderly than the younger respondents. When interpreting the results of Kaarlola et al., one should bear in mind that the number of patients aged 80 years or over was rather small (82, i.e. 3.0% of all patients). In addition, none of the elderly patients lived in a nursing home before the ICU admission. It seems that critically ill patients with a very poor premorbid functional status and most very old patients may have been treated in other ICUs of the hospital or may have been refused ICU admission, and thus the study population was rather selected.

In addition to important findings about long-term outcomes, Kaarlola et al. also present some interesting data regarding short-term outcomes: all elderly patients with a day one SOFA score exceeding 15 died in the ICU. The SOFA (Sequential Organ Failure Assessment) score (Vincent et al. 1996) is a system describing the presence and severity of dysfunction or failure of essential organ systems. The score is presented in detail in chapter 2.1 of this thesis.

Roch et al. (2011) studied long-term outcomes of 299 patients aged 80 years or over who were treated in a medical ICU in France in 2001-2006. The mean age was 84 ± 4 years and the mean SAPS II score was 52 ± 22 (which reflects a high severity of illness). 59% of the patients received mechanical ventilation. The hospital, one-year and two-year mortality rates were 55%, 72% and 79% respectively. A high severity of illness (SAPS II score), an underlying fatal disease and a cardiac diagnosis were independent predictors of hospital mortality. Severe acute kidney injury seems to be a strong predictor of a poor outcome in this group of patients: renal replacement therapy was given to 21 patients, and 19 of these (90%) died in hospital; one patient was still alive at two years. The need for mechanical ventilation was also associated with a high mortality rate: of the 176 mechanically ventilated patients, 128 (73%) died in hospital. In 2009, the health-related quality of life was assessed for the 24 individuals who were still alive at that time. The median age of the respondents was 89 years (IQR 87 to 92 years) and the median time between hospital discharge and the evaluation was 63 months (IQR 56 to 85 months). The scores reflecting physical function were poor. However, the scores reflecting emotional and social well-being were rather good and not much different from those of the general population.

Impact of premorbid functional status

Several studies have shown that a poor functional status of elderly people before hospital admission increases the risk of poor outcomes from intensive care regarding both short-term and long-term survival (Bo et al. 2003, Boumendil et al. 2004, Chelluri et al. 2004, Bagshaw 2009). Bo et al. (2003) prospectively studied 659 patients aged 65 years or over who were treated in a medical ICU in Italy in 2000-2001. The mean age was 76.6 ± 7.5 years. The mean severity of illness seems to have been somewhat lower than in many other studies: the mean APACHE II

score was rather low, 13.2 ± 5.3, and only 12.4% of the patients were mechanically ventilated. The hospital mortality rate was 14.7%. In a multivariate analysis, the following factors were independent predictors of an increased risk of in-hospital death: higher severity of illness (APACHE II score), lack of independence in activities of daily living, moderate-to-severe cognitive impairment, and low body mass index (BMI). The hospital mortality rate was 8% for those patients who had been independent in basic activities of daily living, but 30% for those who had been dependent. For patients with no or only slight prior cognitive impairment, hospital mortality was 8%, whereas it was 56% for those who had severe cognitive impairment.

Limitations

When interpreting results of studies that have evaluated the outcomes from intensive care in elderly patients, one has to remember that ICU patients represent a highly selected population. Patients who are estimated to be too sick to benefit from intensive care are often not even referred for ICU admission, and if referred they are often refused admission. Among the elderly, severe co-morbidities (e.g. metastatic cancer) and poor preceding functional status (dependency on help in daily activities) are strongly associated with an increased likelihood of not being admitted to the ICU despite acute critical illness (Garrouste-Orgeas et al. 2005, 2009). Patients with severe co-morbidities and functional limitations may thus be underrepresented in studies on elderly ICU patients, which in turn may lead to an over-optimistic perception of the outcomes of intensive care of the elderly (de Rooij et al. 2005). At the same time one must bear in mind that therapeutic activity may be limited because it is more often presumed to be futile for severely ill old patients than for younger patients. Some authors have suggested that the fact that outcomes for elderly patients are worse than those for younger patients might be partly explained by less aggressive treatment (Grant et al. 2000).

2.4.2 Admission Policies

Principles and practices

In an editorial, Ely (2003) wrote about the principles of appropriate decision-making when considering an ICU admission of an elderly patient. The medical team must estimate the benefits that can be achieved with intensive care, considering baseline disease state, quality of life and acuity of illness. It is also important to find out about the patient's preferences regarding life support. We should be aware of the limitations of medical care and understand that for some severely ill older patients, the right decision is to provide the most peaceful and high quality dying process. If however the acute illness is potentially reversible, and if the patient can benefit from intensive care and has an individual preference for aggressive care, then ICU care is recommended.

In practice, old age is one of the factors associated with refusal of ICU admission (Joynt et al. 2001). In a study by Garrouste-Orgeas et al. (2009), senior emergency physicians first determined ICU admission criteria for patients aged 80 years or over. After this, a prospective study was done in 15 French hospitals in 2004-2006 to find out whether emergency room physicians in these hospitals complied with the criteria. There were 1426 patients aged 80 years or over who met at least one of the definite ICU admission criteria. However, of these patients, the emergency room physicians referred only 31% for ICU admission, and ICU physicians admitted 52% of those referred. The authors concluded that physicians were reluctant to consider ICU admission for patients aged 80 years or over, despite the presence of criteria indicating that ICU admission was certainly or possibly appropriate. It is noteworthy, however, that the preselected criteria only included diagnoses or conditions indicating referral, not conditions that might be considered as relative or definitive contraindications. The likelihood of non-referral was significantly associated with active cancer and with poor functional status in addition to increasing age.

In another study, Garrouste-Orgeas et al. (2005) found that among those patients who were referred for ICU admission the patients for whom admission was refused were older than those who were admitted. However, according to a multivariate analysis, age was not an independent predictor of refusal. Preceding poor functional status (total dependency) and metastatic cancer were strongly associated with an increased likelihood of refusal of admission.

Intercontinental differences

Admission policies in America are somewhat different from those in Europe. A study by Wunsch et al. (2009) compared the use of intensive care during terminal hospitalisations in England and the USA. In England, 50.3% of all deaths occurred in hospital, as compared with 36.6% in the USA. However, only 5.1% of all deaths in England involved intensive care during terminal hospitalisation, whereas 17.2% of decedents had received intensive care in the USA. This means that half of all hospital deaths in the USA involve intensive care, as compared with only one in 10 in England. The difference between the two countries was most notable in the oldest age group: of all decedents aged 85 years or over, the proportion receiving intensive care during terminal hospitalisation was 1.3% in England as compared with 11.0% in the USA.

Angus et al. (2004) studied death registry and hospital discharge data from six US states (representing 22% of the US population). 22.4% of all deaths in 1999 occurred after ICU admission (either in the ICU or during the same hospitalisation). Even 33% of patients who died with metastatic cancer were admitted to the ICU during their terminal hospitalisation. According to the authors nine of ten Americans polled say that they would like to die at home, but in reality more than one in five die using ICU services.

In a study comparing critical care delivery in Japan and the USA, the proportion of patients aged 85 years or older was 4.5 % in the USA and 1.2 % in Japan (Sirio et al. 2002). According to the authors, this difference probably reflects cultural differences regarding health care at the end of life.

Are we aware of the patients' preferences?

The sensibleness of initiating intensive care depends on the outcomes that are likely to be achieved and that can be achieved. When a patient's preferences regarding certain treatments are asked for, the probability of different outcomes may not always be presented. A study by Fried et al. (2002) showed that anticipated outcomes heavily influence patients' preferences. The authors studied 226 persons aged 60 years or over who had a limited life expectancy due to cancer, congestive heart failure or chronic obstructive pulmonary disease. The study participants were asked whether they would want to receive a given treatment; the outcome without treatment was specified as death. For a low-burden treatment with the restoration of current health, 99% of respondents would want the treatment. However, if the anticipated outcome was survival but with severe functional impairment, 74% of the participants would not choose treatment. If the outcome was survival but with severe cognitive impairment, 89% of the participants would not choose treatment. Given the same anticipated outcome, the proportion of respondents who wanted treatment also decreased to some extent as the burden of treatment (length of hospital stay, amount of testing and invasiveness of interventions) increased.

Knowing what a patient wants is a prerequisite for being able to honour those wishes. Unfortunately, physicians may often not be aware of patients' preferences. Hamel et al. (1999) studied adults who had one of several illnesses associated with an average 6-month mortality rate of 50%. The study was done in the USA in the early 1990s. There were 4556 patients who stated a preference about care. For 25% of the patients, physicians stated that they were unaware of the preferences. Moreover, when the physician had a perception about the patient's wishes, it was incorrect in more than one third of cases; the physician had a correct understanding of the patient's preferences in only 45% of all cases. For 19% of all patients, the physician incorrectly believed that the patient wanted care focused on comfort instead of prolonging life, and for 12%, the physician mistakenly believed that the patient wanted care

focused on prolonging life. Increasing age of the patients increased the probability that physicians would erroneously believe that patients did not want life-extending care.

2.4.3 The Need for Intensive Care Resources in the Future

In Finland, persons aged 65 years or older constituted 15.0% of the population in 2000 and 17.5% in 2010. This segment of the population is expected to increase substantially in the near future, as the large post-war generations ("the baby boom generation") reach this elderly age. According to the forecast of Statistics Finland, the proportion of individuals aged 65 years or over will be 23% in 2020 and 26% in 2030.[3] According to Eurostat, the ageing of the population will be a bit slower in most other EU countries than in Finland (partly because of differences in the amount of immigration), but the trend is similar everywhere. In the EU as a whole, individuals aged 65 years or over made up 17.4% of the population in 2010, and this proportion is expected to increase to 24% by 2030.[4] The ageing of the post-war generations, consistently low birth rates and increasing life expectancy will change the age distribution dramatically.

The increasing number of elderly people will increase the demand for intensive care. This fact needs prompt attention in order to avoid shortfalls in the supply of specialists and other components of care (Angus et al 2000a). Facing the challenge will probably be made even more difficult by a shortage of trained personnel, caused partly by the relative smallness of younger cohorts (Flaatten 2007).

In a recent study, Laake et al. (2010) used ICU registry data and population statistics to forecast the demand for intensive care services in Norway in the future. In the calculations they used three different population growth forecasts published by Statistics Norway (the low growth model forecasts population growth to be 11.1% from 2008 to 2025, whereas the high growth model forecasts population growth to be 26.4%). The population growth and the change in age distribution (a marked increase particularly in the age group 60-79 years) will increase the demand for intensive care (ICU bed-days) by roughly one third (between 26% and 37%, depending on the population growth forecast model used).

Increasing age increases the susceptibility to acute respiratory failure requiring mechanical ventilation (Behrendt 2000). Needham et al. (2005) aimed to project the impact of the baby boom generation's ageing on the need for mechanical ventilation in Ontario, Canada. They forecast that the incidence of mechanical ventilation will increase by 80% from 2000 to 2026. This enormous increase is caused partly by the population's ageing, causing a 31% increase in the incidence rate, and by the projected 37% growth of the total population in Ontario.

Caution is needed when interpreting the results of studies of this kind. They are based on the use of intensive care services by different age groups in past years and on population projections. Disease incidence rates, indications and contraindications for treatment, as well as the treatments themselves are all assumed to remain unchanged. Some changes will most probably take place for all of these factors. Nevertheless, it seems obvious that a substantial increase in the need for intensive care is to be expected.

Many studies have shown that old age decreases the likelihood of being admitted to ICUs. This may not be the case so much in the future, as many authors have claimed that old age alone is not an acceptable reason for withholding intensive care. Patients and their families may also request active treatment more often than before. It therefore seems possible that the demand for intensive care services might increase even more than can be forecast based on population projections.

On the other hand, there may also be counteracting factors: The costs of medical care are often high in the last year of life (Lubitz and Riley 1993). However, there are data showing that expenditures in the last year of life decrease with increasing age, particularly for those aged 85

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[3] http://www.stat.fi/tup/suoluk/suoluk_vaesto_en.html as accessed on 30th December, 2011

[4] http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Population_structure_and_ageing as accessed on 30th December, 2011

years or over. The main reason for this is that the aggressiveness of medical care in the last year of life decreases with increasing age (Levinsky et al. 2001). This finding may suggest that if the elderly of tomorrow are healthier and live longer than those of today, possibly a smaller proportion of them would need aggressive care in the ICU.

2.4.4 Summary

- The term elderly most commonly refers to persons aged 65 years or over. Individuals aged 80 years or over are often called very elderly. However, the literature is inconsistent regarding the definitions of old age.
- The incidence rates of many severe disease states, e.g. acute respiratory failure requiring mechanical ventilation and severe sepsis, increase with increasing age.
- Elderly patients have poorer outcomes from intensive care than younger patients.
- Prognosis depends, however, more on severity of illness and premorbid functional status than on age itself. Old age alone is not a contraindication for intensive care.
- Patients admitted after elective surgery generally have a good prognosis despite old age. Elderly patients admitted after emergency surgery tend to have better outcomes than equally aged patients admitted for medical reasons.
- The following factors are associated with a decreased chance of hospital and long-term survival: higher severity of acute illness, severe co-morbidities, preceding poor functional status (as reflected by dependency on help in activities of daily living or by admission from a chronic care facility), failure of multiple organ systems, prolonged ICU stay.
- In patients aged 65 years or over, severe multi-organ failure (SOFA score > 15) predicts a very poor prognosis.
- In patients aged 80 years or over, severe acute kidney injury (need of renal replacement therapy) as part of acute critical illness affecting several organ systems is predictive of poor outcome.
- A majority of elderly long-term survivors from ICU-treated critical illness consider their quality of life as satisfactory or good. Physical functions are limited, but mental well-being is not worse than for younger survivors from critical illness.
- The number of elderly people in society will increase substantially during the next two decades. This will most probably cause a marked increase in the need for intensive care.

2.5 THE RELATIONSHIP BETWEEN HOSPITAL VOLUMES AND PATIENT OUTCOMES

2.5.1 In Surgery, Trauma Care and Cardiology

There is a convincing amount of evidence showing that hospital volumes have an impact on patient outcomes in surgery: the higher the annual number of operations done in a hospital, the better the outcomes. In general, the difference in patient outcomes between high-volume and low-volume hospitals is largest for complex surgical procedures associated with high risks of complications, but a smaller difference seems to be present even for lower-risk procedures. Luft et al. (1979) were the first to do a large-scale study on this issue. They made use of a large registry and studied data on over 800,000 patients operated on during 1974 and 1975 in 1498 hospitals in the USA. For 10 of the 12 surgical procedures studied, they found falling death rates with an increasing number of operations.

Later studies have found that increased hospital volumes are associated with improved survival following major cardiovascular surgery (Goodney et al. 2003) and surgery for several types of cancer (Begg et al. 1998, Sosa et al. 1998, Schrag et al. 2000, Bach et al. 2001). Birkmeyer et al. (2002) studied the mortality associated with six different types of cardiovascular

operations and eight types of major cancer resections between 1994 and 1999 in the USA. The total number of operations studied was 2.5 million. The magnitude of the effect of hospital volume varied considerably according to the type of procedure, with the largest differences between high-volume and low-volume hospitals observed for oesophagectomy and pancreatic resection. However, the direction of the effect was consistent: for all 14 types of procedure, mortality decreased as hospital volume increased. Dudley et al. (2000) made a structured review of studies investigating the association between hospital volumes and mortality rates. They identified 128 studies addressing 40 different conditions, most of which were surgical operations. In 102 of the studies (80%), there was a significant association between high hospital volumes and decreased mortality rates. Moreover, there was a trend towards higher mortality rates in high-volume hospitals in only 4 studies (3%), and none of these differences were statistically significant.

Birkmeyer et al. (2002) present several plausible explanations for the better outcomes in high-volume hospitals: these hospitals may have more surgeons who specialise in specific procedures, more consistent processes for post-operative care, ICUs with better staffing, and better resources for dealing with complications. Surgeon experience indeed has an impact on outcomes, and in many cases surgeon volumes (the annual number of certain procedures done by a particular surgeon) account for a large part of the differences between high-volume and low-volume hospitals (Birkmeyer et al. 2003). In fact, problems associated with "occasional surgeons" have been highlighted more than 50 years ago (Hotchkiss 1960).

In recent years, there has been considerable interest in the USA in concentrating certain high-risk operations in high-volume hospitals. According to a recent study by Finks et al. (2011), median hospital volumes have increased substantially between 1999 and 2008 for several high-risk operations, particularly complex cancer resections. The rise in volumes has been partly caused by an overall increase in the number of operations, but also by a higher concentration of procedures in a smaller number of hospitals. Mortality rates have decreased for all the procedures studied, and the authors attribute the improved outcomes partly to increased hospital volumes and increased regionalisation of care.

Severely injured trauma patients benefit from being treated in designated trauma centres (MacKenzie et al. 2006). However, results from studies investigating the relationship between trauma centre volumes and patient outcomes have been inconsistent. Nathens et al. (2001) defined a high-volume trauma centre as one treating over 650 severely injured trauma patients per year. They studied 1019 patients and found that treatment in high-volume centres was associated with improved survival in subgroups at high risk of adverse outcomes. In contrast, patients who were very severely injured had worse outcomes at the centres with highest volumes in the study by London and Battistella (2003); in the overall population of 98,245 trauma patients hospital volume was not a significant predictor of death. Some other studies have not been able to demonstrate any association between trauma centre volumes and patient outcomes (Glance et al. 2004, Demetriades et al. 2005).

In interventional cardiology, volumes have an impact on outcomes: there is an inverse relation between the number of percutaneous coronary interventions performed at a hospital and mortality rates after the procedure (Jollis et al. 1994, McGrath et al. 2000, Hannan et al. 2005).

2.5.2 In Intensive Care

A few published studies suggest that high patient volumes are also associated with improved outcomes in intensive care. Kahn et al. (2006) studied 20,241 non-surgical patients receiving mechanical ventilation in ICUs and found an association between higher hospital volume and lower risk-adjusted mortality: when compared with patients treated in hospitals in the lowest quartile according to hospital volume (hospitals treating less than 150 patients receiving mechanical ventilation per year), patients treated in hospitals in the highest quartile (more than 400 patients receiving mechanical ventilation per year) had a 34% reduction in the adjusted

odds of in-hospital death (adjusted odds ratio 0.66, 95% confidence interval 0.52-0.83). The relationship between volume and outcome was independent of the hospital's academic status. In contrast to these findings, two other studies found no clear evidence supporting the existence of a relationship between hospital volumes and outcomes of mechanically ventilated patients (Needham et al. 2006, Gopal et al. 2011). A French-American study on ICU patients receiving renal replacement therapy found no association of patient volumes with outcomes despite very large variations in the annual numbers of patients treated (Nguyen et al. 2011).

Glance et al. (2006) studied a heterogeneous population of 70,757 ICU patients. They concluded that "*There is evidence that high patient volumes are associated with lower mortality rates in high-risk critically ill adults*." However, it is debatable whether the data presented justify such a strong conclusion: After adjustments for patient risk factors, there was actually no significant association between ICU volume and mortality rates. The authors also divided the patients into four strata according to severity of illness (reflected by SAPS II scores), and they did not find a volume-outcome association in any of the four groups. A significant association was then found between a high "high-risk ICU volume" (defined as the annual volume of patients with a SAPS II score over 41 points) and decreased mortality rates. However, this association was not significant when patient risk factors were adjusted for; it only reached statistical significance when ICU characteristics in addition to patient risk factors were included in the multivariate model.

Durairaj et al. (2005) studied patients admitted to ICUs because of respiratory, neurologic and gastrointestinal disorders. They compared hospital mortality rates between tertiles of hospital volume (high, medium and low). Among patients treated for respiratory and neurologic disorders, there was no difference in risk-adjusted mortality between hospitals of different size. Among patients treated for gastrointestinal disorders, severity of illness-adjusted risk of death was lower in high-volume hospitals than in low-volume hospitals. In addition, when analysing subgroups based on severity of illness, the authors found better outcomes of more severely ill patients with respiratory disorders in high-volume hospitals than in low-volume hospitals.

In a German study, the hospital mortality rate of ICU-treated patients with severe sepsis was not influenced by hospital size (Engel et al. 2007). Peelen et al. (2007) studied the influence of ICU volume on hospital mortality in patients treated for severe sepsis in the Netherlands. The overall mortality rate was 34.7%. The total number of annual admissions to the ICU had no influence on severity of illness-adjusted risk of death. However, there was a significant association between the annual number of patients admitted with severe sepsis and a decreased hospital mortality rate in this patient group.

Iapichino et al. (2004) studied data from 89 ICUs in 12 European countries and found that a high volume of activity is associated with improved outcomes. However, instead of the number of patients, they used "the number of patients per bed per year" as a parameter reflecting volume of activity. They calculated that hospital mortality decreased by 3.4% for every five extra patients treated per bed per year. Theoretically, one might interpret this result as suggesting that increasing occupancy rates would be beneficial. However, the overall ICU occupancy rate also had an impact in the study by Iapichino et al., but in the opposite direction: a mean occupancy rate of over 80% was a strong predictor of increased mortality. These results raise some questions: If an ICU has both a high number of patients per bed per year and a lower-than-average mean occupancy rate, then lengths of ICU stay must be relatively short. It may not be surprising that short lengths of stay may predict increased survival, as they might simply be a reflection of lower severity of illness, irrespective of the severity scores used.

In conclusion, results from studies addressing the relationship between hospital volumes and patient outcomes in intensive care are inconclusive.

2.5.3 Summary

- Among patients undergoing elective high-risk surgery, higher hospital volumes are associated with improved outcomes.
- For many procedures, differences in surgeon volumes explain a large part of the differences in patient outcomes between high-volume and low-volume hospitals.
- A comparable volume-outcome relationship exists in interventional cardiology: the higher the amount of percutaneous coronary interventions performed at a hospital, the better the outcomes.
- Severely injured trauma patients benefit from being treated in designated trauma centres.
- Some studies suggest that outcomes from intensive care are better in high-volume hospitals than in low-volume hospitals, whereas other studies have not found such a relationship.

2.6 THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST

2.6.1 Prognosis of Patients with Out-of-Hospital Cardiac Arrest

The prognosis of patients with out-of-hospital cardiac arrest (OHCA) is poor. According to Eisenberg et al. (1990), studies conducted on OHCA patients from 1967 to 1988 in 29 different locations reported survival rates to hospital discharge ranging from 2% to 25% for all cardiac rhythms and from 3% to 33% for ventricular fibrillation (VF). Kuisma and Määttä (1996) reported data on cardiac arrest cases encountered by the Helsinki Emergency Medical Services System in 1994. There were 412 patients with confirmed OHCA who were considered for resuscitation. In 344 of these, resuscitation was attempted. Of these patients, 16.6% survived to hospital discharge. When cardiac arrest was bystander witnessed and of cardiac origin with VF as the initial rhythm, survival to hospital discharge was 32.5%. Herlitz et al. (1999) studied cardiac arrest data from five European emergency medical systems: Bonn (Germany), Göttingen (Germany), Helsinki (Finland), Reykjavik (Iceland) and Stavanger (Norway). These regions were chosen for the study because they had shown exceptionally good results in a preliminary survey. For patients with a bystander witnessed arrest of cardiac origin, the proportion of patients surviving to hospital discharge ranged from 21% to 35%.

Survival figures are much worse when also rural areas are included: The study by Pell et al. (2003) was based on the HeartStart (Scotland) register that collects data prospectively on all resuscitation attempts following out-of-hospital cardiopulmonary arrest in Scotland. Of 17,451 patients with OHCA presumably of cardiac origin, 7% survived to hospital discharge; of 3724 patients with OHCA presumably caused by non-cardiac aetiologies, only 2% survived to hospital discharge.

Even after initially successful resuscitation, cardiac arrest victims have high mortality rates: In Scotland, 75% of the patients admitted to emergency departments died in hospital (Pell et al. 2003). In Canada, the in-hospital mortality rate of patients admitted to hospital after OHCA between 1994 and 2004 was 62%, and outcomes did not change during the study period (Redpath et al. 2010). A study from Sweden reported similar results: hospital mortality rates remaining slightly above 60% both in the 1980s and in the 1990s with no improvement in outcome during the 20-year study period (Herlitz et al. 2003). Studies focusing on patients treated in ICUs after resuscitation from cardiac arrest report no better outcomes: hospital mortality rates reported from the USA range from 40% to 80%, with a mean mortality rate of 57% (Carr et al. 2009). In Finland, the prognosis of these patients has been similar and it has not changed much over time: in 1986-87 hospital mortality was 61%, whereas in 1999-2001 it was 59% (Niskanen et al. 2007).

2.6.2 Evidence of the Benefits of Therapeutic Hypothermia

Animal studies have demonstrated that inducing mild hypothermia after resuscitation from cardiac arrest limits neurologic damage (Weinrauch et al. 1992, Safar et al. 1996). Two randomised controlled human trials published in 2002 showed that mild therapeutic hypothermia (TH) improves survival and limits neurologic damage after OHCA (Hypothermia after Cardiac Arrest Study Group 2002, Bernard et al. 2002). The inclusion criteria of the larger of these trials, the Hypothermia After Cardiac Arrest (HACA) Study, are presented in Table 3.

Table 3. The inclusion criteria of the Hypothermia After Cardiac Arrest (HACA) Study

- a witnessed cardiac arrest
- ventricular fibrillation or non-perfusing ventricular tachycardia as the initial cardiac rhythm
- a presumed cardiac origin of the arrest
- an age of 18 to 75 years
- an estimated interval of 5 to 15 minutes from the patient's collapse to the first attempt at resuscitation by emergency medical personnel
- an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation

Only patients with severely impaired level of consciousness after resuscitation were eligible: a response to verbal commands after the return of spontaneous circulation and before randomisation was an exclusion criterion. Nine centres in five European countries participated in the study. A total of 3551 patients were assessed for eligibility, of which 275 (7.7%) met the inclusion criteria and were enrolled. Patients randomly assigned to the hypothermia group were cooled to a target bladder temperature of 32 °C to 34 °C and this temperature was maintained for 24 hours from the start of cooling, after which passive rewarming was allowed. Patients randomised to the normothermia group were treated with standard care with the goal of maintaining normothermia. The primary outcome was a favourable neurologic outcome within six months, defined as good recovery or moderate disability (as opposed to severe disability, vegetative state or death). The physicians responsible for assessing the neurologic outcome were unaware of the treatment assignments. Mortality at six months was 41% (56/137) in the hypothermia group and 55% (76/138) in the normothermia group, $P = 0.02$. One patient in each group was lost to follow-up for neurologic status. 55% of patients in the hypothermia group (75/136) had a favourable outcome at six months, as compared with 39% of patients in the normothermia group (54/137), $P = 0.009$.

The study by Bernard et al. (2002) from Australia included 77 patients who were comatose after having been resuscitated from OHCA with an initial cardiac rhythm of VF. The patients were assigned to treatment with hypothermia (core body temperature reduced to 33 °C and maintained at that temperature for 12 hours) or normothermia. 49% of the patients in the hypothermia group (21/43) survived and had a good neurological outcome (defined as being discharged home or to a rehabilitation facility) as compared with 26% (9/34) of the patients in the normothermia group, $P = 0.046$.

Some methodological issues in the study by Bernard et al. deserve attention. Firstly, the treatment assignment was not randomised in the strict sense of the term. Instead, the day of the month determined the treatment assignment: patients were assigned to hypothermia on odd-numbered days. Secondly, the original plan was to include only 62 patients. After an interim analysis of results from 62 eligible patients, a decision was made to continue the study for a

further 12 months, after which 77 patients had been enrolled. Despite these shortcomings, the study is generally referred to as a high-quality randomised controlled trial and the results from this study and the HACA trial together are considered as high-level evidence supporting the use of TH.

2.6.3 Implementation

In 2003, the International Liaison Committee on Resuscitation (ILCOR) published an advisory statement that recommended:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32 °C to 34 °C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest (Nolan et al. 2003).

TH was promptly implemented in Finnish ICUs: according to a study by Oksanen et al. (2007), 19 ICUs of 20 were using TH in the period 2004-2005. Endovascular cooling is the preferred method in Finland and the target core temperature has been 32-34 °C, applied mostly for 24 h. In the first years of its adoption, TH was used almost exclusively for patients resuscitated from VF: for example, in 2004-2005, all ICUs studied reported that they mainly used the HACA trial's inclusion criteria to select patients for TH.

In many other countries, implementation of TH has been considerably slower. According to a survey done in Germany in the autumn of 2005, 24% of ICUs reported having implemented the treatment (Wolfrum et al. 2007). Likewise, implementation has been quite slow in the UK: by the summer of 2005, 27% of ICUs had implemented TH for patients resuscitated from cardiac arrest (Laver et al. 2006). Nevertheless, the situation has changed in the UK in recent years: in 2009, 86% of ICUs were using TH as part of post-cardiac arrest care; the majority of units had started in 2007 or 2008 (Binks et al. 2010). In Italy, only 16% of ICUs used TH for post-resuscitation care in 2007 (Bianchin et al. 2009).

2.6.4 Summary

- Victims of out-of-hospital cardiac arrest have a poor prognosis: at best, survival to hospital discharge has been slightly over 30% among patients whose cardiac arrest took place in an urban area, was bystander witnessed and of cardiac aetiology.
- When also rural areas and non-cardiac aetiologies are considered, survival figures are much worse, overall survival rates being well below 10%.
- Even after initially successful resuscitation, hospital mortality is high, roughly 60% for ICU-treated patients.
- Two controlled trials published in 2002 showed that mild therapeutic hypothermia improves survival and limits neurologic damage after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation.
- International guidelines recommend that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C – 34°C for 12-24 hours when the initial rhythm was ventricular fibrillation and that cooling should be considered also for patients resuscitated from other initial rhythms or from in-hospital cardiac arrest.
- Implementation of therapeutic hypothermia has been slow in many countries.

2.7 BENCHMARKING IN INTENSIVE CARE

2.7.1 Principles of Comparing Risk-Adjusted Mortality Rates

ICUs treat patients with life-threatening disorders. Thus, mortality is a robust marker of ICU performance (Moreno et al. 2010b). However, crude mortality rates are not very informative if no information is presented about the severity of acute illness, co-morbidities and other factors that affect prognosis. In the early 1980s, Knaus and co-workers presented a severity of illness classification system called APACHE (Acute Physiology And Chronic Health Evaluation) and showed how it could be used to enable comparisons of ICU patient populations and outcomes (Knaus et al. 1981, 1982a, 1982b). Originally developed in America, the system was soon implemented in some other countries. Hospitals from the United States, France, Spain and Finland participated in the first multinational study using this severity scoring model (Wagner et al. 1984).

APACHE was soon followed by SAPS (Simplified Acute Physiology Score), which was developed in France (Le Gall et al. 1983). The second generation versions of these models, APACHE II (Knaus et al. 1985) and SAPS II (Le Gall et al. 1993), have become the most commonly used prediction models in the world (Moreno et al. 2010b). These models are used for measuring severity of illness and predicting vital status at hospital discharge. They may also be useful in clinical trials when patients are stratified into groups according to severity of disease (Le Gall 2005).

The principle is similar in APACHE II and SAPS II: age, severe chronic co-morbidities and abnormal values of physiological measurements are given points to produce a score which is subsequently converted by a mathematical formula into a predicted probability of death during the present hospitalisation. In both scoring systems, the most abnormal value during the first 24 hours in the ICU is taken into account. The physiological variables used are rather similar, though there are some differences. The most important difference between these two models is that for risk prediction the APACHE II needs information about the patient's diagnosis. The SAPS II does not need the specific diagnosis; instead the type of admission (scheduled surgical, unscheduled surgical, medical) affects the score. The SAPS II scoring is presented in Table 4.

When the scoring is ready, the next step is to calculate the logit, i.e. the natural logarithm of the odds of death, for each patient. For SAPS II, the logit is computed as follows:

$$\text{logit} = -7.7631 + 0.0737(\text{SAPS II score}) + 0.9971[\ln(\text{SAPS II score} + 1)] \quad (1)$$

The logit is then converted into a probability of in-hospital death as follows:

$$\text{Probability} = e^{\text{logit}} / (1 + e^{\text{logit}}) \quad (2)$$

Table 4. SAPS II scoring sheet, Part 1. For each physiological variable, the most abnormal value during the first 24-hour period in the ICU is taken into account.

Variable **Points:**	**26**	**13**	**12**	**11**	**9**	**7**	**6**	**5**	**4**	**3**	**2**	**0**
Age, years												<40
Heart rate, beats/min				<40							40-69	70-119
Systolic blood pressure, mmHg		<70						70-99				100-199
Body temperature, °C												<39
PaO_2/FIO_2 (only if ventilated or on CPAP), mmHg				<100	100-199		≥200					
Urinary output, ml/d				<500					500-999			≥1000
Serum urea, mmol/l												<10.0
WBC count, x 10^9/l			<1.0									1.0-19.9
Serum potassium, mmol/l										<3.0		3.0-4.9
Serum sodium, mmol/l								<125				125-144
Serum bicarbonate, mEq/l							<15			15-19		≥20
Bilirubin, µmol/l												< 68.4
Glasgow Coma Score	<6	6-8				9-10		11-13				14-15
Chronic disease												
Type of admission												Scheduled surgical

(Table 4 continuing on next page)

Table 4 (continued). SAPS II scoring sheet, Part 2. For each physiological variable, the most abnormal value during the first 24-hour period in the ICU is taken into account.

Variable **Points:**	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**	**12**	**15**	**16**	**17**	**18**
Age, years						40-59				60-69	70-74	75-79		≥80
Heart rate, beats/min				120-159		≥160								
Systolic blood pressure, mmHg		≥200												
Body temperature, °C			≥39											
PaO_2/FIO_2 (only if ventilated or on CPAP), mmHg														
Urinary output, ml/d														
Serum urea, mmol/l					10.0-29.9				≥30.0					
WBC count, x 10^9/l			≥20.0											
Serum potassium, mmol/l			≥5.0											
Serum sodium, mmol/l	≥145													
Serum bicarbonate, mEq/l														
Bilirubin, µmol/l				68.4-102.5				≥102.6						
Glasgow Coma Score														
Chronic disease								Meta-static cancer	Hematologic malignancy				AIDS	
Type of admission					Medical		Unsche-duled surgical							

Probabilities of death make sense when used as an aggregate measure of risk (Le Gall et al. 1993). In a group of patients with a probability of death of 0.75, approximately 75% of the patients are expected to die, provided that the prediction model fits the population in question. However, we cannot know beforehand which of the patients will die and which ones will be among the 25% who will survive (Le Gall 2005). Even for an individual patient, the severity score (or the associated probability of death) reflects the severity of illness, but the predicted probability is never exactly the same as the actual outcome: the probability is always between 0 and 1 (but never precisely 0 or 1), whereas the outcome for an individual patient is either survival or death. For large groups of patients, the commonly used prediction models have shown a fairly good ability to discriminate survivors from non-survivors and to predict the number of deaths.

Since these risk-adjustment tools became available, comparing ICU performance with a standard, referred to as benchmarking, has become popular. The basic idea is to identify top performing units and to explore the factors associated with good performance (Zimmerman et al. 2003). The ultimate goal is to learn about and to improve the overall performance. ICUs can be compared to each other or to a reference database with respect to many quality indicators, one of which is resource consumption. However, given the primary goal of intensive care, an essential part of the benchmarking process is the comparison of risk-adjusted mortalities (Moreno et al. 2010b). For a group of patients, the sum of individual probabilities equals the number of expected deaths. The number of observed deaths divided by the number of expected deaths, the O/E ratio, is also called the standardised mortality ratio (SMR). If the SMR for an ICU is precisely 1.0, then the number of observed deaths equalled the number of deaths expected by the prediction model. It can be interpreted that the unit performed as well as an average unit performed in the study that created the prediction model. An SMR below 1 means that the observed mortality was lower than predicted by the model; an SMR above 1 indicates excess mortality.

2.7.2 Potential Confounding Factors

Great caution is needed when SMRs are interpreted. No risk-adjustment model can fully control for all differences in patient case mix. Therefore, differences between ICUs in SMRs do not necessarily mean true differences in clinical performance. Even if the confounding factors could be controlled for, SMRs should still be interpreted with caution. A high or low SMR may represent only random variation (Angus 2000b). However, constant differences in SMRs can be interpreted as indicators that one should look more deeply into the situation in different units to identify the factors associated with the differences (Le Gall 2005). This chapter highlights the most important potential confounding factors in comparing risk-adjusted mortalities.

Poor fit of the risk-adjustment model

The risk-adjustment model may fit well the study population that it was derived from. When the model is applied to another patient population, its prognostic performance may be worse (Angus et al 1997). The model may systematically overestimate or underestimate the risk of death. The adequacy of risk estimation may also differ across different levels of risk: the model may e.g. underestimate the mortality of low-risk patients but overestimate the mortality of high-risk patients (Livingston et al. 2000). This is called poor calibration or poor fit of the model (Angus 2000b). When the calibration of the model is poor, comparing SMRs of units with major differences in patient case mix is questionable. If ICUs are ranked according to SMRs, the choice of prognostic model may heavily influence the rank of a unit (Bakshi-Raiez et al. 2007). Nevertheless, risk-adjustment models that have been specifically developed for intensive care are definitely better tools than models derived from administrative data, which are also used in ranking ICUs, particularly in the USA (Keegan et al. 2011, Brinkman et al. 2012).

Over time, treatments change, outcomes tend to improve and prediction models become outdated. If benchmarking programmes use old risk-adjustment models, it is probable that the

SMRs will be low for most, if not all, ICUs. This has been called grade inflation (Popovich 2002). Lower mortality rates than predicted do not mean that there is no need for further improvements.

To solve the problem of worsening prognostic performance of ageing risk-adjustment models, new models have been developed. SAPS has been updated to SAPS 3 (Metnitz et al. 2005, Moreno et al. 2005) and APACHE to APACHE IV (Zimmerman et al. 2006). In the UK, the Intensive Care National Audit & Research Centre (ICNARC) has developed its own prediction model (Harrison et al. 2007). Other models of importance include the Mortality Probability Models (MPMs) (Higgins et al. 2008). However, even if a new model fits perfectly well, its prognostic performance will deteriorate as time goes by (Moreno and Afonso 2008).

An alternative approach to developing a totally new model is to customise an existing model to better fit a regional patient population. First-level customisation means that the variables and their relative weights are kept unchanged but new coefficients to the logit equation are computed. Very good prognostic performance can be achieved with a customised model (Metnitz et al. 2009). Whether a benchmarking programme should use an original risk-adjustment model or a locally customised or even locally created model depends partly on the choice of the reference population that the ICUs are to be compared with (Moreno et al. 2005). An original model gives the possibility to describe the patient population with a severity score that is well-known in the world and to compare the results with those obtained from an international reference population. If it is more important to compare ICUs within the benchmarking programme with each other, then a well-fitting customised model may be a better choice (Angus 2000b, Moreno and Afonso 2008).

The problem of missing data and the impact of sampling rate

Even if the risk-adjustment model fits well, there are several potential confounders. The more abnormal the values of physiological parameters, the higher is the predicted probability. When data are missing, the values of the parameters in question are presumed to be within the normal range. Thus, patient populations with many incomplete datasets may appear less severely ill than they actually are. Consequently, improving data completeness might lead to an increase in mean severity of illness and thus a decrease in SMRs. Accuracy of data is also important. Ensuring data quality is of fundamental importance (Angus 2000b).

Changing the frequency of physiological measurements may affect the severity scores. Automation of data collection with a clinical information system (CIS) increases the sampling rate of physiological data. This increases the probability of obtaining abnormal values and thus leads to higher severity-of-illness scores and lower SMRs (Bosman et al. 1998, Suistomaa et al. 2000). This may cause bias if some ICUs use technology for automatic data collection and others do not. It is not known to what extent widespread automation of data collection in a large group of ICUs would affect measured outcomes.

Hospital mortality is not a perfect marker of outcome

Prediction models have traditionally used hospital mortality as a marker of outcome. This is based on the idea that a critical illness will have resolved before hospital discharge (Angus et al. 1997). Moreover, vital status at hospital discharge is seen as an unambiguous endpoint. Comparing hospital mortalities may still be problematic. Patients discharged into other hospitals or institutional care are calculated as hospital survivors. Some of these patients will nevertheless die within the following weeks. Differences in hospital discharge practices can therefore cause bias (Kahn et al. 2007a). To avoid this bias, it has been recommended that mortality at a fixed time point such as 30-day or 90-day mortality should be substituted for hospital mortality (Angus 2000b, Glance and Szalados 2002). If only hospital mortality is available, Angus (2000b) has suggested doing analyses with and without patients discharged to long-term and rehabilitation facilities.

Care of poor quality can affect severity scores

Severity scores and associated probabilities are thought to reflect severity of illness. However, the scoring systems are not able to differentiate between a patient's poor condition that is caused by a severe disease despite adequate treatment and a poor condition that is partly caused by care of substandard quality prior to ICU admission or in the beginning of the ICU period.

Despite these shortcomings, benchmarking has become increasingly popular during the last two decades. The benchmarking programmes have led to the creation of large databases of ICU treatment periods (Harrison et al. 2004b, Zimmerman et al. 2006, Bakhshi-Raiez et al. 2007, Moran et al. 2008). There is, however, little evidence that benchmarking results in improvements in outcomes (Woodhouse et al. 2009).

2.7.3 Summary

- Benchmarking means comparing the performance of an ICU to other ICUs or to a standard.
- The standardised mortality ratio (SMR) is a basic concept in benchmarking.
- The SMR is calculated by dividing the observed number of deaths by the number of deaths expected by the prediction model.
- The most commonly used prediction models are APACHE II and SAPS II. They quantify the severity of illness with a score of points that is converted to a predicted probability of in-hospital death.
- The prognostic performance of a prediction model deteriorates over time. Old models tend to overestimate the risk of death.
- SMRs should be interpreted with caution because they can be affected by several confounding factors. Differences in data collection for measuring severity of illness and in hospital discharge practices are among the potential confounders.

3 Aims of the Study

The aims of this study were to quantify the changes in the hospital mortality of intensive care patients in Finland in recent years, to improve our understanding about the associations between less well-known or controversial factors and mortality, to assess the mortality of ICU-treated cardiac arrest patients, and to evaluate the effect of automation of data collection on measuring standardised mortality ratios. The specific questions to be answered were the following:

1) Does gender affect the risk of death and length of ICU stay? (Study I)

2) Are there seasonal variations in hospital mortality of Finnish ICU patients? (Study II)

3) To what extent does age influence outcomes and intensity of care? (Study III)

4) Is mortality from severe sepsis influenced by the size of the ICU? (Study IV)

5) Have mortality rates of ICU-treated victims of out-of-hospital cardiac arrest changed in the era of therapeutic hypothermia? (Study V)

6) Have outcomes of patients treated in Finnish ICUs changed in recent years? Are possible changes in standardised mortality ratios caused by changes in measuring severity of illness or do they reflect genuine changes in the quality of intensive care? (Study VI)

4 Methods

4.1 THE FINNISH INTENSIVE CARE CONSORTIUM

The Finnish Intensive Care Consortium (later referred to as "the Consortium") was established in 1994 as a co-operation body coordinating a benchmarking programme. The Consortium originally comprised nine ICUs. Several new units joined in 1998 and subsequently the Consortium grew rapidly: all university hospitals and major non-university hospitals had joined by 2002. Since 2007, the referral areas of the ICUs participating in this benchmarking programme have encompassed the whole Finnish mainland, which is divided into 20 hospital districts. The major hospital in each district is called the central hospital. Five of these are university hospitals. In each of the 15 non-university central hospitals, there is one adult ICU, which is the sole provider of intensive care to adult patients in that hospital and in many cases also treats children older than infants. All these ICUs participate in the Consortium. The major ICUs in all university hospitals participate too. However, in university hospitals, there are, in addition to the participating units, also some specialised units (cardiothoracic surgical, trauma, and neurosurgical ICUs) that are not involved in the Consortium so far.

The purpose of this co-operation is to measure the quality of care, provide regular reports of the performance of participating units and to improve that performance. Detailed data on disease characteristics and severity, intensity of care and patient outcomes are prospectively collected into the database of the Consortium. To describe and quantify the characteristics and severity of disease, APACHE II (Knaus et al. 1985), SAPS II (Le Gall et al. 1993) and SOFA (Vincent et al. 1996) scores are documented for each patient. Intensity of care is measured daily with Therapeutic Intervention Scoring System (TISS) scores (Keene and Cullen 1983). Vital status at ICU and hospital discharge is documented. In recent years, efforts have also been made to document six-month-survival and health-related quality of life, but follow-up is not yet complete enough to evaluate these.

Some data, e.g. data on pre-morbidities and vital status at hospital discharge, are entered manually into the electronic database. Regarding physiological variables, data collection has become highly automated: apart from one single ICU, all units nowadays use clinical information systems (CIS) that automatically collect data from patient monitors, ventilators and laboratory systems. In addition, special software is used for automatic data transfer from the CIS to the central database. Before being submitted to the database, the data are locally validated, both by automatic filters searching for technical artefacts and by trained personnel. The central database was handled by a company called Intensium until 2010 and has been handled by Tieto Healthcare & Welfare since then. Participating ICUs pay a fee for the benchmarking services.

Each ICU receives feedback on its performance compared to other units of similar size and to the whole Consortium regarding data completeness, patient case mix, outcomes and resource consumption. This feedback is provided on a password-protected internet site. In addition, a reporting meeting, providing deeper analyses of the results and an opportunity for discussion, is held twice a year.

Data retrieved from the Consortium's database were used in this study.

4.2 SEVERE SEPSIS

4.2.1 Definition of Severe Sepsis

In 1992, a consensus committee of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published definitions for sepsis that have become widely accepted (Bone et al. 1992). Sepsis is defined as the systemic inflammatory response to infection. This definition required a definition of "the systemic inflammatory response syndrome" (SIRS). The definitions of SIRS, infection, sepsis and severe sepsis are presented in Table 5.

Table 5. Definitions of the systemic inflammatory response syndrome (SIRS), infection, sepsis and severe sepsis, according to the ACCP/SCCM consensus conference committee criteria

Term	**Definition**
SIRS	Systemic inflammatory response, which is manifested by the presence of two or more of the following conditions: 1) Temperature > 38 °C or < 36 °C 2) Heart rate > 90 /min 3) Respiratory rate > 20 /min or $PaCO_2$ < 32 mmHg (4.3 kPa) 4) White blood cell count > 12 x 10^9/l or < 4 x 10^9/l or > 10% of immature forms
Infection	An inflammatory response to the presence of micro-organisms or the invasion of normally sterile tissue by those organisms
Sepsis	SIRS caused by infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.
Sepsis-induced hypotension	Systolic blood pressure < 90 mmHg or a reduction of ≥ 40 mmHg from baseline in the absence of other causes of hypotension
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

SIRS can be caused by a large number of clinical conditions. Besides infectious states that may produce SIRS, non-infectious causes include, among others, pancreatitis, ischaemia, multiple trauma and tissue injury (Bone et al. 1992).

In 2001, the definitions were re-evaluated by experts representing several international societies. The consensus conference concluded that although the diagnostic criteria for SIRS are overly sensitive and non-specific, SIRS remains a useful concept, and the current concepts of sepsis, severe sepsis and septic shock also remain useful (Levy et al. 2003). This meant that the basic definitions were left unchanged.

The ACCP/SCCM criteria did not include a precise definition of "organ dysfunction", and varying criteria have been used in different studies. The SOFA score (Vincent et al. 1996) is commonly used to describe and quantify the presence and severity of organ dysfunction. The scoring system is presented in chapter 2.1 of this thesis. Some authors have defined a SOFA score for an organ system higher than 0 as organ dysfunction (Brun-Buisson et al. 2004) and a score higher than 2 as organ failure (Brun-Buisson et al. 2004, Vincent et al. 2006). This categorisation was also used in the Finnsepsis study (Karlsson et al. 2007, Karlsson 2009).

4.2.2 The Finnsepsis Study

The purpose of the Finnsepsis study was to determine the incidence, treatment and outcome of severe sepsis in the adult Finnish population (Karlsson et al. 2007). Severe sepsis was defined according to the ACCP/SCCM criteria (Bone et al. 1992) as consisting of a systemic inflammatory response, suspected or confirmed infection and acute organ dysfunction. 24 ICUs from 21 hospitals participated in this prospective cohort study. The inhabitants in the referral areas of the participating units accounted for 91% of the total Finnish population. All 4,500 consecutive ICU admission episodes during a 4-month period (1 November 2004 - 28 February 2005) were screened for severe sepsis. The criteria for severe sepsis were fulfilled in 470 adult patients. Detailed data on diagnoses, disease severity, treatments given and outcomes were prospectively collected. The main results of the Finnsepsis study have been published by Karlsson et al. (2007, 2009).

4.3 STUDY PATIENTS

For studies I-III and V-VI, data were retrieved from the database of the Finnish Intensive Care Consortium. To be able to assess hospital mortality correctly, we only included patients admitted for the first time during the hospitalisation in question. However, when lengths of ICU stay, intensity of treatment and ICU mortality rates were assessed in study III, readmissions were also included. The study periods and patient numbers in studies I-III and V-VI are presented in Table 6.

Table 6. The main questions, study periods and patient numbers in studies I-III and V-VI

	Study I	**Study II**	**Study III**	**Study V**	**Study VI**
Main study question	Impact of gender on outcomes	Seasonal variation in outcomes	Intensive care of the elderly	Mortality after re-suscitation from cardiac arrest	Change in outcomes in recent years
Study period	1999-2001	1998-2001	1998-2004	2000-2008	2001-2008
Number of patients	24,341	31,040	79,361	3958	85,547

In study V, patients for whom cardiac arrest was registered as the primary reason for ICU admission and who were admitted from the hospital's emergency department made up the study population. Study VI was designed to determine the changes in severity of illness-adjusted hospital mortality in recent years and to evaluate the possible contribution of automated data collection to changes in measured outcomes. The proportion of cardiac surgical patients was not constant over the years, which was considered a potential confounding factor. Therefore cardiac surgical patients were excluded. A flow chart describing the selection of patients to study VI is presented in Figure 1.

Study IV was different from the other studies as it was not based solely on the Consortium's database. Study IV was a retrospective analysis of data collected for the Finnsepsis study. Some of the data were collected as part of the routine datasets collected for the Consortium's database; some data were specifically collected for the purpose of the study. Of the 470 adult patients with severe sepsis in the study, 18 patients were transferred to the ICU of another hospital during the intensive care period. These patients were excluded from study IV, leaving a study population of 452 patients with ICU-treated severe sepsis.

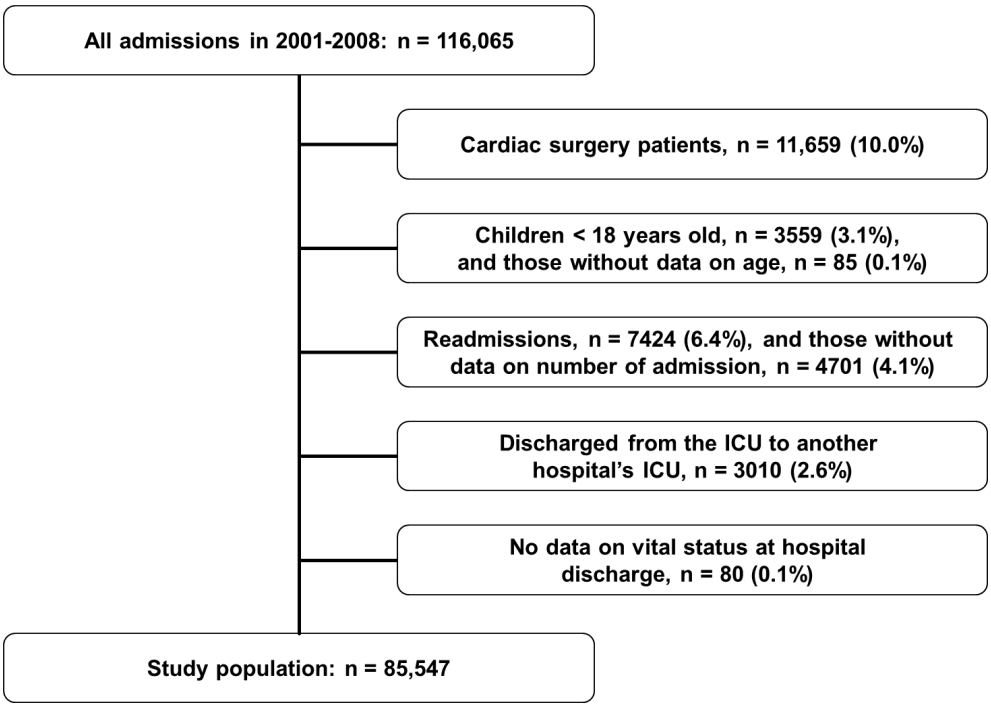

Figure 1. Flow chart describing selection of patients to the study population in study VI

The protocols of studies I-III and V-VI were approved by the Ethics Committee of Kuopio University Hospital and by the board of the Finnish Intensive Care Consortium. The protocol of the Finnsepsis study was approved by the ethics committees in each participating hospital.

4.4 MEASURING SEVERITY OF ILLNESS AND INTENSITY OF CARE

In studies I-II, severity of illness was quantified with APACHE II scores (Knaus et al. 1985). In studies III-VI, SAPS II scores (Le Gall et al. 1993; scoring system presented in chapter 2.7 of this thesis) were used to measure severity of illness. The Glasgow Coma Score, GCS (Teasdale and Jennett 1974, 1976, Teasdale et al. 1979), is a component of both the APACHE II and SAPS II scores, but it was also used as such to describe level of consciousness in study V. In addition, SOFA scores (Vincent et al. 1996; scoring system presented in chapter 2.1 of this thesis) were used in study VI.

Intensity of care was measured with Therapeutic Intervention Scoring System (TISS-76) scores (Keene and Cullen 1983) in all studies. To measure the mean intensity of care, the mean daily TISS score was computed for each patient. TISS scores were first calculated once for each calendar day in the ICU. The mean score was then gained by dividing the total sum of the TISS scores with the number of TISS determinations. For a patient staying a 24-hour period from noon until noon in the ICU, TISS scores were calculated twice, once for each calendar day, and the mean daily TISS score was the sum of those two calculations divided by two.

Length of ICU stay was used as a surrogate for resource consumption. In study III the product of the length of stay and the mean daily TISS score was also used to depict resource use, and in study V the total TISS scores per patient were used for this purpose.

4.5 DATA PROCESSING AND STATISTICAL METHODS

For categorical variables, data are presented as absolute numbers and percentages. For continuous variables, data are presented as means ± standard deviations (SD) or as medians with inter-quartile ranges. To test statistical significance, the χ^2 test was used for categorical variables. The means and distributions of continuous variables were compared with the t test and the analysis of variance. The distribution of the length of ICU stay was highly skewed. Therefore lengths of stay were compared with the Mann-Whitney U test and with the Kruskal-Wallis test.

Multivariate logistic regression analysis, adjusting for severity of illness, was used to assess the independent association of the variable studied with hospital mortality. These variables of interest were gender in study I, seasons in study II, age in study III, hospital and ICU size in study IV, eras before and after the implementation of therapeutic hypothermia for post-cardiac arrest care in study V, and changes over time in study VI. In addition, the following methods were used:

In study I, the study population was split into subgroups based on type of admission, diagnostic categories, age, and severity of illness (with the median of the APACHE II score, 16, as the division line). The logistic regression analysis, assessing the independent association of gender with mortality, was repeated in each subgroup. To compare lengths of ICU stay and the intensity of care of men and women, we used the analysis of covariance to calculate severity of illness-adjusted mean lengths of ICU stay and mean daily TISS scores.

In study II, we divided the year into four seasons, defining "winter" as the period lasting from December to February, "spring" from March to May, "summer" from June to August, and "autumn" from September to November. We defined the month of ICU treatment as the month during which the patient was discharged from the ICU. The choice of the discharge date instead of the admission date was based on the goal to find a possible association between the main holiday season and hospital mortality. In Finland, the main holiday season lasts from Midsummer in late June to the end of July. Thus, most patients discharged in July spend their whole stay in the ICU during the holiday season. Subgroups based on main diagnostic categories were also analysed separately.

In study III, we compared the treatment and outcomes in different age groups using the age groups suggested in the SAPS II scoring system (0-39, 40-59, 60-69, 70-74, 75-79 years and 80 years or over). The SAPS II scores without age points were used to reflect the severity of illness. Based on data about the age distribution of ICU patients in 2004 and about population projections, we also calculated an estimate of how the change in age distribution will affect the need for intensive care resources in Finland by the years 2020 and 2030.

In study IV, the ICUs that participated in the Finnsepsis study were divided into three groups based on their size and academic status. ICUs in university hospitals (n = 7) made up one group. These were from four of the five university hospitals in Finland. All 15 non-university central hospitals participated in the study, as did two regional hospitals from the Helsinki district. These two hospitals are not officially called central hospitals, but as they functioned like central hospitals elsewhere in the country, the two ICUs were classified as non-university central hospital ICUs. Units in non-university central hospitals were divided into two groups: "large central hospital ICUs" (n = 9) and "small central hospital ICUs" (n = 8). Units defined as "small central hospital ICUs" had less than six beds (median 5) and/or a referral population of under 120 000 people. "Large central hospital ICUs" had at least six beds (median

8) and a referral population of over 120 000 people. The groups were compared to each other with regard to patient characteristics and outcomes. Post-operative surgical patients and medical patients were also analysed separately.

In study V, we tested the hypothesis that outcomes of ICU-treated victims of out-of-hospital cardiac arrest might have improved in the era of therapeutic hypothermia (TH). This treatment was implemented in most Finnish ICUs by 2003. We defined the period 2000-2002 as "the pre-hypothermia era" and the years 2003-2008 as "the hypothermia era". To take into account the potential confounding effect of new ICUs that joined the Consortium during the study period, we adjusted for the impact of individual departments in the logistic regression analyses and also repeated the analyses after excluding all the units that had joined during the study period.

In study VI, we calculated standardised mortality ratios (SMRs) for each year by dividing the number of observed in-hospital deaths by the number of deaths expected by the SAPS II prognostic model. We also compared the latter half of the study period (2005 to 2008) to the earlier years (2001 to 2004). To test the hypothesis that SMR changes were caused by new ICUs joining the Consortium, we adjusted for the impact of individual departments in logistic regression analyses and for the impact of new departments as a group in another analysis. We also repeated the analyses including only those departments that participated in the Consortium already at the beginning of the study period. To find out whether SMR changes were caused by changes in discharge practices, we repeated the SMR calculations after excluding all patients that had been discharged from a hospital to other hospitals or institutional care. To investigate whether changes in data completeness were responsible for SMR changes, we repeated the calculations using only complete datasets, i.e. patients with no missing data on SAPS II physiological parameters.

To estimate the relative contribution of automated data collection with the use of a clinical information system (CIS) and improved data completeness, i.e. documentation-related factors (DRF), to the observed change in odds of death between the admission periods, we used a technique similar to that used previously by Birkmeyer et al. (2003) to calculate the relative contribution of surgeon volume to the observed associations between hospital volume and outcome. We first used multivariate logistic regression analysis to calculate the OR_{TIME}, by which we mean the adjusted odds ratio (OR) for in-hospital death in the later period, i.e. in 2005-2008, compared with 2001-2004. The OR_{TIME} is adjusted for severity of illness (SAPS II scores) and the impact of individual ICUs but not for differences in DRFs. We then added the variables "use of CIS" and "number of missing SAPS II physiological parameters" and again calculated the adjusted OR for in-hospital death in 2005-2008 as compared with 2001-2004; this adjusted OR is named $OR_{TIME\text{-}DRF}$. The relative contribution of the DRFs (the use of a CIS and improved data completeness) to the association between admission period and outcome was calculated as

$$[(1 - OR_{TIME}) - (1 - OR_{TIME\text{-}DRF})] / [1 - OR_{TIME}] \quad (3)$$

We also made a new customised model to predict the probability of in-hospital death. Using a stepwise backward procedure in a logistic regression analysis and with death in hospital as the dependent variable, the following variables were entered into the model: SAPS II score, ln (SAPS II score + 1), the SOFA score during the first 24 hours, use of a CIS for documentation, the number of missing SAPS II physiological parameters and the diagnostic groups "drug intoxication", "diabetic ketoacidosis" and "admission for postoperative care after elective surgery" - each of these three groups as a binary variable. The inclusion of these diagnostic groups was based on clinical judgment and previous experience from the Finnish benchmarking programme, which suggest that these groups are associated with a better prognosis than is predicted by the SAPS II model. Based on this customised model, the logit (i.e. natural logarithm of the odds of death) was calculated for each patient. Then the probability of in-hospital death was calculated according to equation (2) in chapter 2.7. The calibration of the

model was tested using the Hosmer and Lemeshow goodness-of-fit $\hat{C}$ test with eight degrees of freedom (Lemeshow and Hosmer 1982), and the discrimination using the area under the receiver operating characteristic curve, ROC (Hanley and McNeil 1982), with 95% CIs. The SMR was then calculated for each calendar year by dividing the number of observed deaths by the sum of individual probabilities obtained with the customised model. Adjusted mortality rates were then calculated for each calendar year by multiplying each year's SMR with the overall mean hospital mortality rate.

P-values < 0.05 were considered statistically significant. All *P*-values are based on two-tailed tests of significance. No corrections for multiple comparisons were made. The SPSS software (SPSS Inc., Chicago, IL, USA) was used in the statistical analyses.

5 Results

5.1 INFLUENCE OF GENDER

5.1.1 Association with Mortality

Of the 24,341 patients in study I, 61.7% were males. Male patients made up the majority in all age groups but the oldest one (Figure 2). The mean age was 57.8 ± 17.9 years for males and 60.4 ± 19.9 for females, $P < 0.001$.

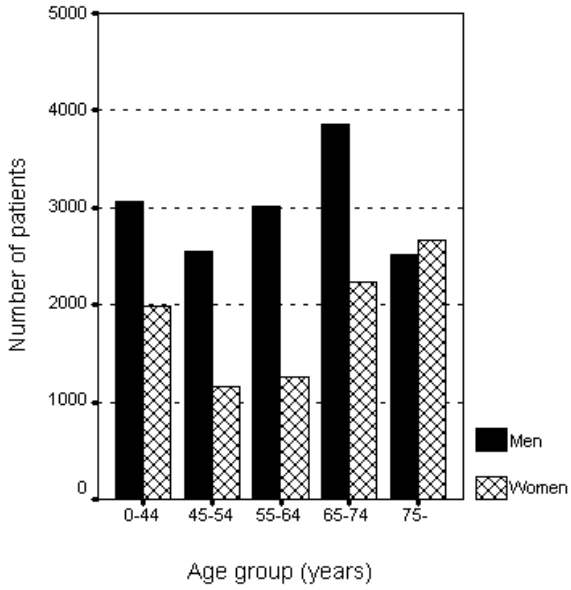

Figure 2. Age and gender distribution of the study population in study I

Overall, there were no differences between genders in unadjusted mortality rates: ICU mortality was 8.9% for men and 8.8% for women, $P = 0.68$; hospital mortality was 16.3% for men and 16.1% for women, $P = 0.71$. Unadjusted hospital mortality rates in different subgroups are presented in Table 7.

Table 7. Unadjusted hospital mortality rates (%) for men and women

	Men	**Women**	***P***
Overall	16.3	16.1	0.71
Among medical admissions	21.5	21.1	0.58
Among postoperative admissions	8.5	8.4	0.91
Elective	4.5	4.9	0.54
Unscheduled	13.6	11.8	0.082
In the diagnostic category			
Respiratory failure	20.1	18.9	0.45
Circulatory failure	31.1	30.0	0.41
Gastroenterological surgery	16.4	14.5	0.19
Vascular surgery	5.1	5.9	0.31
Surgery, other	4.7	3.0	0.13
Neurology / neurosurgery	20.5	18.9	0.31
Trauma	13.3	12.6	0.72
Metabolic / Renal	17.4	19.2	0.24
Intoxication	3.8	2.8	0.29
Miscellaneous	7.6	6.7	0.66
In the age group (years)			
0-44	7.7	6.6	0.12
45-54	12.4	11.5	0.42
55-64	15.5	15.3	0.90
65-74	17.7	18.2	0.61
75 or older	29.6	23.9	< 0.001
Among patients with APACHE II scores			
< 16	4.2	3.2	0.006
≥ 16	28.4	28.2	0.77

When severity of illness and the effect of different diagnostic categories were controlled for, there was no statistically significant difference in the risk of in-hospital death between genders. However, male gender was independently associated with increased hospital mortality in some subgroups, namely postoperative patients, the oldest age group (75 years or older), and patients with relatively low APACHE II scores (Table 8).

Table 8. The independent association of male gender with hospital mortality. Results from multivariate logistic regression analyses with adjustment for severity of illness (as measured with APACHE II scores) and the effect of different diagnostic categories, and for severity of illness within diagnostic categories.

	Adjusted OR	**95% CI**	***P***
Effect of male gender:			
Overall	1.09	1.00-1.18	0.059
Among medical admissions	1.02	0.92-1.13	0.74
Among postoperative admissions	1.33	1.12-1.58	0.001
Elective	1.32	0.96-1.82	0.087
Unscheduled	1.32	1.07-1.64	0.011
In the diagnostic category			
Respiratory failure	0.99	0.80-1.22	0.91
Circulatory failure	1.00	0.85-1.16	0.96
Gastroenterological surgery	1.42	1.12-1.79	0.004
Vascular surgery	0.87	0.62-1.23	0.44
Surgery, other	1.58	0.84-2.99	0.16
Neurology / neurosurgery	1.27	1.02-1.59	0.037
Trauma	1.17	0.78-1.76	0.45
Metabolic / Renal	1.01	0.80-1.28	0.92
Intoxication	0.84	0.45-1.56	0.57
Miscellaneous	1.42	0.66-3.05	0.36
In the age group (years)			
0-44	1.00	0.77-1.31	0.98
45-54	1.01	0.78-1.31	0.96
55-64	1.12	0.90-1.40	0.30
65-74	1.02	0.87-1.20	0.78
75 or older	1.39	1.20-1.61	< 0.001
Among patients with APACHE II scores			
< 16	1.54	1.25-1.89	< 0.001
≥ 16	1.01	0.92-1.11	0.88

5.1.2 Effect on Lengths of Stay and Intensity of Care

The unadjusted mean length of ICU stay was 3.2 ± 5.9 days for men and 2.6 ± 4.4 days for women, $P < 0.001$. ICU stay was prolonged for more than 7 days for 10.6% of male patients, but only for 7.8% of female patients ($P < 0.001$). Table 9 shows the mean lengths of ICU stay of men and women in each diagnostic category after adjustment for severity of illness. Male patients were treated longer than female patients in the overall study population and in most categories. Overall, male patients accounted for 66.0% of the total number of days spent in intensive care.

In the overall study population, unadjusted mean daily TISS scores were 23.8 ± 10.5 for men and 22.5 ± 10.3 for women ($P < 0.001$). However, there were some differences between genders in the distribution of patients to various diagnostic categories. The largest difference was in the proportion of patients belonging to the category "vascular surgery", which comprised 18.2% of male patients but only 12.3% of female patients. Patients in this diagnostic category had the highest TISS scores, and the uneven distribution of patients to this category explains most of the difference in intensity of care that was observed in the overall population. After adjustments for

the effects of different diagnostic categories and severity of illness, the mean daily TISS score was only slightly higher for men than for women (22.6 vs. 22.0, $P < 0.001$). Within most diagnostic categories, differences between the genders in intensity of care were insignificant (Table 9).

*Table 9. A*djusted lengths of ICU stay and mean daily TISS scores of men and women in different diagnostic categories. Analysis of covariance was used to adjust for severity of illness (as measured with APACHE II scores) and the effect of different diagnostic categories, and for severity of illness within diagnostic categories. Data are presented as adjusted means (95% confidence interval of mean).

Adjusted length of ICU stay, days	**Men**	**Women**	***P***
Overall	3.2 (3.1-3.3)	2.6 (2.5-2.7)	< 0.001
In the diagnostic category			
Respiratory failure	4.6 (4.3-4.9)	3.9 (3.5-4.2)	0.002
Circulatory failure	3.3 (3.1-3.5)	3.0 (2.8-3.3)	0.07
Gastroenterological surgery	3.8 (3.5-4.1)	2.6 (2.3-2.9)	< 0.001
Vascular surgery	2.3 (2.1-2.4)	2.1 (1.9-2.4)	0.39
Surgery, other	1.9 (1.7-2.1)	1.6 (1.4-1.8)	0.07
Neurology / neurosurgery	3.1 (2.9-3.3)	2.3 (2.1-2.6)	< 0.001
Trauma	4.3 (3.9-4.7)	3.4 (2.7-4.1)	0.03
Metabolic / Renal	3.7 (3.4-4.0)	2.7 (2.3-3.2)	< 0.001
Intoxication	1.3 (1.2-1.4)	1.3 (1.2-1.4)	0.96
Miscellaneous	3.1 (2.4-3.7)	1.8 (0.9-2.6)	0.01

Adjusted mean TISS score / day	**Men**	**Women**	***P***
Overall	22.6 (22.4-22.7)	22.0 (21.8-22.1)	< 0.001
In the diagnostic category			
Respiratory failure	22.3 (21.9-22.7)	21.6 (21.1-22.0)	0.02
Circulatory failure	22.6 (22.3-22.9)	22.4 (22.0-22.8)	0.44
Gastroenterological surgery	24.5 (24.2-24.8)	23.6 (23.2-24.0)	0.001
Vascular surgery	33.8 (33.4-34.1)	32.3 (31.8-32.8)	< 0.001
Surgery, other	20.2 (19.8-20.7)	19.8 (19.3-20.4)	0.28
Neurology / neurosurgery	21.2 (20.9-21.6)	20.8 (20.4-21.2)	0.14
Trauma	23.3 (22.8-23.8)	22.8 (22.0-23.6)	0.28
Metabolic / Renal	21.4 (21.0-21.8)	21.1 (20.6-21.6)	0.32
Intoxication	13.8 (13.4-14.2)	13.6 (13.2-14.0)	0.47
Miscellaneous	18.1 (17.2-18.9)	17.3 (16.2-18.3)	0.25

5.2 SEASONAL VARIATIONS IN MORTALITY

5.2.1 Excess Mortality in Winter

There were no major differences in total patient numbers between different seasons. 24.7% of all patients in study II were treated in the winter season (December to February). Distribution of patients to different diagnostic categories was somewhat different in winter months than in non-winter months. The most important difference was that patients in the category "respiratory failure" made up 13.6% of the population in winter but only 11.6% in the non-winter period, $P < 0.001$. Patients treated in winter were slightly older than those treated in other seasons. The proportion of patients aged 75 years or over was 22.8% in winter and 20.9% in non-winter, $P < 0.001$.

The mean APACHE II score was 16.9 ± 8.9 in winter and 16.9 ± 8.9 in non-winter, $P = 0.72$. Despite comparable severity of illness, hospital mortality was higher in winter than in non-winter, 17.9% vs. 16.4%, $P = 0.003$. When the effects of age, severity of illness, 10 major diagnostic categories and intensity of care (mean daily TISS scores) were adjusted for, winter compared with non-winter was independently associated with increased hospital mortality (adjusted OR 1.13, 95% CI 1.04-1.22, $P = 0.005$). When patients treated during the summer months (June to August) were left out from the analysis, the independent impact of the winter season on the risk of death was even stronger (adjusted OR 1.17, 95% CI 1.07-1.28, $P = 0.001$.)

When the diagnostic categories were analysed separately, the unadjusted hospital mortality rate tended to be higher in winter than in non-winter in each of the categories, but the difference was not statistically significant in any of them. For the category "respiratory failure", hospital mortality was 22.3% in winter and 19.9% in non-winter, $P = 0.10$. The effect of the winter season remained non-significant in each category also after adjustments for age, severity of illness and intensity of care were made using logistic regression analysis.

As the proportion of patients admitted for respiratory failure was greater in winter, there were proportionately more patients who died because of respiratory failure in winter than in non-winter: in winter, 233 patients (3.0% of all ICU patients) died after being admitted to the ICU for respiratory failure, as compared with 541 patients (2.3%) in non-winter, $P < 0.001$. Compared with the average number of deaths in other seasons, this means 53 extra deaths from respiratory failure in winter. The age-adjusted odds ratio for being admitted to the ICU for an ultimately fatal respiratory failure in winter rather than in non-winter was 1.30 (95% confidence interval 1.11-1.51, $P = 0.001$).

5.2.2 Impact of the Holiday Season in July

The crude hospital mortality rate was at its highest in July (18.8%). However, severity of illness was also at its highest in July (mean APACHE II score 17.7). The mean APACHE II scores and crude hospital mortality rates for each calendar month are shown in Figure 3. When severity of illness and the impact of different diagnostic categories were adjusted for, the risk of death in July was not higher than the risk of death during other months (adjusted OR 1.02, 95% CI 0.90-1.16, $P = 0.79$). The analysis was also repeated after the patients treated during the other summer months (June and August) and the winter months (December to February) had been excluded, which means that the severity of illness-adjusted risk of death in July was compared to the risk in spring and autumn. For July, the adjusted OR for death was 1.08, 95% CI 0.94-1.23, $P = 0.27$.

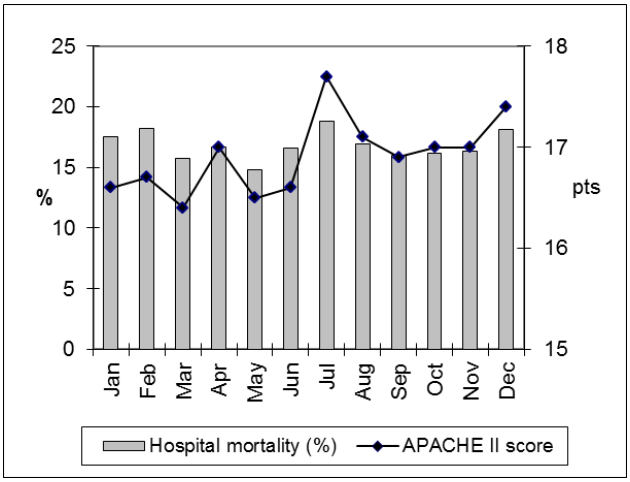

Figure 3. Mean APACHE II scores and hospital mortality rates in different months

Regarding the reason for the need of intensive care, there were differences between July and the other months: 13.8% of the patients treated in July as compared with 18.7% of patients treated in other months were admitted to the ICU after elective surgery. Among these patients, the mean APACHE II score was relatively low, 14.0. This does explain the higher severity of illness in July to some extent, but not fully: among the emergency admissions, the mean APACHE II score was 18.3 in July and 17.6 in other months, $P = 0.004$, despite no significant differences in the age of the patients.

5.3 INTENSIVE CARE OF THE ELDERLY

5.3.1 Impact of Age on Outcomes and Intensity of Care

The mean age in the study population was 58.7 ± 18.5 years; 8.9% of the patients were aged 80 years or older. 62.1% of all patients were males.

The main results of study III are summarised in Table 10. Medical conditions were the most common reasons for admission in the youngest age groups, while almost half of the patients aged over 60 years were admitted for surgical conditions. Scheduled surgery as a reason for ICU admission was most common in the age groups 60-69 years and 70-74 years. In the oldest age group (80 years and older), scheduled surgery was a relatively uncommon cause for admission, whereas the proportion of patients admitted because of unscheduled surgery was high, 30.8%. Mean severity of illness as measured with the SAPS II score without age points increased slightly with increasing age. Overall, the mean SAPS II score, including age points, was 33.4 ± 17.6 (median 30, quartiles 21-43).

The ICU mortality rate increased with increasing age, but the hospital mortality rate increased even more: the hospital mortality / ICU mortality-ratio was 1.3 in the age group 0-39 years, but 2.3 in the age group 80 years and older. Hospital mortality rates for each year of age are presented in Figure 4. Mortality rates were highest for old patients admitted for medical reasons and for old long-stay patients. Hospital mortality rates for various subgroups are presented in Table 11.

Table 10. Characteristics of the study population and figures describing ICU care and outcomes. Data are presented as absolute numbers or percentages, means ± standard deviations or medians (quartiles). For all comparisons between age groups, $P < 0.001$.

	Age group (years)						
	Overall	**0-39**	**40-59**	**60-69**	**70-74**	**75-79**	**≥ 80**
Number of admissions	79,361	12,207 (15.4)	23,454 (29.6)	16,865 (21.3)	10,788 (13.6)	9022 (11.4)	7025 (8.9)
Proportion of females (%)[a]	37.9	41.3	32.2	31.7	38.4	44.7	57.0
Type of admission							
Medical	44,908 (59.3)	8484 (72.8)	14,365 (64.3)	8491 (52.9)	5306 (51.5)	4615 (53.4)	3647 (53.6)
Elective surgical	16,032 (21.2)	1073 (9.2)	4372 (19.6)	4562 (28.4)	2861 (27.8)	2104 (24.4)	1060 (15.6)
Unscheduled surgical	14,838 (19.6)	2100 (18.0)	3604 (16.1)	2987 (18.6)	2138 (20.7)	1918 (22.2)	2091 (30.8)
SAPS II score without age points	23.4 ± 16.4	21.8 ± 14.7	23.4 ± 16.7	22.9 ± 16.6	23.4 ± 16.4	24.4 ± 16.8	25.4 ± 17.0
Mean daily TISS score	25.8 ± 10.9	20.2 ± 9.7	25.3 ± 10.8	27.8 ± 10.9	28.3 ± 11.0	27.8 ± 10.7	25.3 ± 9.9
Length of ICU stay, days	1.3 (0.8-3.0)	1.1 (0.7-2.6)	1.2 (0.8-3.0)	1.4 (0.9-3.2)	1.5 (0.9-3.4)	1.6 (0.9-3.4)	1.2 (0.8-2.9)
ICU mortality (%)	8.5	4.4	7.6	8.6	10.2	11.2	12.5
Hospital mortality (%)[b]	16.2	5.9	12.7	16.6	20.3	24.1	28.4

[a]n = 71,833 (data on gender was not documented before 1999), [b]n = 69,267 (only patients admitted for the first time are included, hospital outcome was unknown for 54 of these patients)

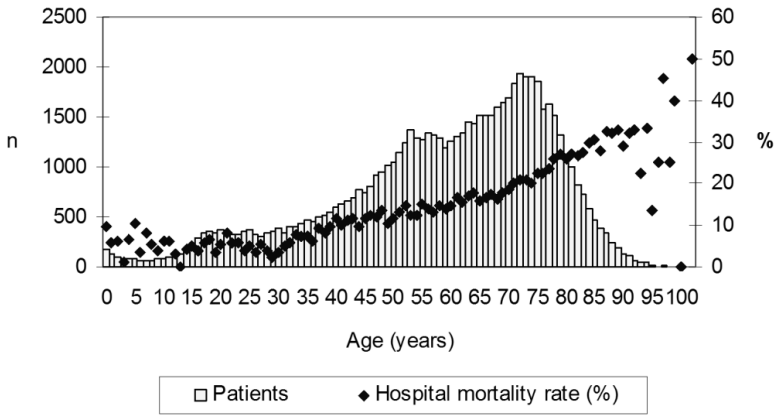

Figure 4. Age distribution of the study population and hospital mortality rates for each year of life

Table 11. Hospital mortality rates (%) for each age group in subgroups according to gender, type of admission and length of ICU stay. For all comparisons between the age groups, $P < 0.001$.

	Age group (years)						
	Overall	**0-39**	**40-59**	**60-69**	**70-74**	**75-79**	**≥ 80**
Males	15.9	6.3	12.6	16.2	19.7	25.4	31.2
Females	16.0	5.3	12.4	16.1	19.4	22.5	25.9
Type of admission							
Medical	21.7	6.9	16.7	25.6	31.5	35.0	37.2
Elective surgical	4.0	1.6	2.0	3.3	5.1	6.2	9.5
Unscheduled surgical	13.7	3.9	10.4	13.1	15.8	19.0	22.7
Length of ICU stay							
< 7 days	14.8	5.5	11.8	14.8	18.0	21.6	26.7
> 7 days	29.4	10.7	20.4	32.0	38.9	45.7	51.4

In the multivariate logistic regression analysis testing the independent effect of age on hospital mortality, the adjusted OR for one additional year of age was 1.035 (95% CI, 1.033-1.037). Among male patients, the adjusted OR was 1.037 (95% CI, 1.035-1.040); among female patients, it was 1.032 (95% CI, 1.029-1.035). However, when only patients aged 65 years or older were included in the analysis, the adjusted OR for one additional year of age was 1.053 (95% CI, 1.045-1.061) for males and 1.035 (95% CI, 1.027-1.044) for females. We also repeated the logistic regression analysis using age groups instead of age as a variable. The results are presented in Table 12.

Table 12. The independent association of age group with hospital mortality. Results from a logistic regression analysis with adjustment for severity of illness (SAPS II scores without age points), intensity of care (mean daily TISS scores), gender, year of admission and the impact of individual departments. $P < 0.001$ for each age group.

Age group	Adjusted OR	95% CI
0-39	Reference	
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

The mean intensity of care was at its highest in the age group 70-74 years (Table 10). The mean daily TISS scores were only slightly lower in the age group 75-79 years, but notably lower for patients aged 80 years or older. Nevertheless, there were patients who were treated with aggressive interventions also in the oldest age group: of patients aged 80 years or older, 17.8% received a pulmonary artery catheter and 2.3% received haemodialysis treatment as compared with 25.5% and 4.6%, respectively, of younger patients. At least two vasoactive drugs were simultaneously infused to 23.1% of patients aged 80 years or older but only to 20.6% of younger patients, $P < 0.001$. For patients aged 80 years or over, as compared with younger patients, the severity of illness-adjusted odds ratio for receiving several vasoactive drug infusions was 1.08 (95% CI, 1.01-1.14, $P = 0.019$).

Overall, the mean length of ICU stay was 3.1 ± 5.3 days (median 1.3, quartiles 0.8-3.0; Table 10). The length of ICU stay was at its longest in the age group 75-79 years, while lengths of stay were considerably shorter in the oldest age group. In particular, the proportion of very long ICU stays was low among the oldest patients: the ICU stay lasted longer than seven days for 10.3% of patients younger than 80 years, but only for 6.8% of patients aged 80 years or older ($P < 0.001$). The decision of whether or not care was restricted was documented in the database for 68,388 admissions (86.2%). Restrictions for future care were set for 15.1% of patients aged 80 years or older, but only for 6.7% of younger patients ($P < 0.001$).

The total amount of time spent in intensive care during the study period was 242,398 days. Figure 5 depicts the proportion of ICU days accounted for by each year of life and the proportion of days taken up by patients older than a given age. Patients aged 63 years or older accounted for 49.9% of all ICU days. The proportion of ICU days was 33.4% for patients aged 70 years or older and 7.1% for patients aged 80 years or older.

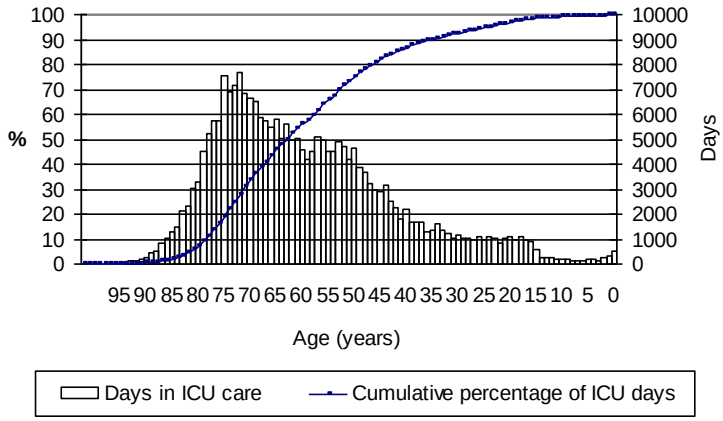

Figure 5. Total number of days spent in an ICU for each year of life and the cumulative percentage of ICU days. Each point on the line shows the proportion of ICU days taken up by patients older than the corresponding age.

We do not know the exact costs of intensive care for individual patients. Instead, we used length of ICU stay and the multiplication of a patient's mean daily TISS score by the exact length of ICU stay to depict resource use. Table 13 presents the amount of resources used in each age group per one hospital survivor. The cost of one life saved was highest in the age group 75-79 years and remarkably lower in the oldest age group.

Table 13. The amount of resources used per one life saved in different age groups

	Age group (years)						
	Overall	**0-39**	**40-59**	**60-69**	**70-74**	**75-79**	**≥80**
Days of ICU care / survivor [a]	3.6	2.8	3.6	3.8	4.1	4.2	3.4
TISS x days / survivor [b]	108.6	73.3	108.2	119.5	128.6	130.5	99.4

[a] *In each age group, the sum of time spent in ICU care was divided by the number of hospital survivors.*
[b] *For each patient, the mean daily TISS score was multiplied by the length of stay to get a score taking into account both the length of stay and the intensity of care. In each age group, the sum of this score was divided by the number of hospital survivors.*

There were large differences between departments in the treatment of the oldest patients. Among those departments that were the sole intensive care units in the hospital, the proportion of patients aged 80 years or older ranged from 3% to 18% (mean 9%). The hospital mortality rate of these patients ranged from 16% to 40% (mean 28%).

5.3.2 Influence of the Ageing Population on the Need for Intensive Care

In 2004, the age group 65 years or older (15.9% of the Finnish population at that time) accounted for 43.0% of all days in intensive care. This age group is predicted to make up 26% of the Finnish population in 2030. Based on data about the age distribution of ICU patients and about population projections, and assuming no changes in the age-adjusted need for intensive care, we calculated that the need for intensive care resources (ICU bed-days) in Finland will increase 19% by the year 2020 and 25% by the year 2030, compared to the number of bed-days in 2004.

5.4 INFLUENCE OF HOSPITAL AND ICU SIZE ON OUTCOMES OF PATIENTS WITH SEVERE SEPSIS

Patient characteristics and outcome data from study IV are presented in Table 14. There were some minor differences between the ICU groups in the case mix. The proportion of postoperative admissions was smaller in large central hospital ICUs than in the other two groups. There were no differences in the total SAPS II scores. Differences between groups regarding the site of infection were small and statistically non-significant. Therapeutic intensity, as measured with the mean TISS score per day, was higher in university hospitals than in non-university central hospitals. Overall, the ICU, hospital and 1-year mortality rates were 15.9%, 29.2%, and 40.7%, respectively. The hospital mortality rate in the group of all central hospital ICUs (30.6%) was not significantly different from that in the university hospital ICUs (27.8%), $P = 0.51$.

The hospital mortality rate was 37.7% for patients treated in small central hospital ICUs and 27.5% for those treated in larger units (including university and large non-university hospital ICUs), $P = 0.073$; risk ratio (RR) 1.37, 95% confidence interval (CI) 0.985-1.91. In post-operative patients, the hospital mortality rate was 42.3% for patients treated in small central hospital ICUs and 22.9% for patients treated in large ICUs, $P = 0.045$; RR 1.85, 95% CI 1.05-3.27. In medical patients, there were no differences between ICU groups in hospital mortality (Table 15). Similarly there was a significant difference in the long-term outcome among post-operative patients, but not among medical patients (Figure 6).

Logistic regression analysis was used to adjust for severity of illness (SAPS II scores). Treatment in small central hospital ICUs as compared with large ICUs was associated with an increased risk of in-hospital death, adjusted OR 1.82, 95% CI 1.03-3.22, $P = 0.038$.

The median length of ICU stay (LOS) was 7.2 days (quartiles, 3.7-12.6) for patients in small central hospital ICUs and 5.6 days (3.0-11.1) in large ICUs, $P = 0.08$. For hospital survivors, there was no difference between the ICU groups in lengths of stay. For non-survivors, the median LOS was 10.0 days (4.6-16.5) in small ICUs and 4.9 days (1.9-12.2) in large ICUs, $P = 0.032$. The sum of all days in ICU care divided by the number of hospital survivors was 15.0 for small central hospital ICUs and 11.1 for large ICUs. Thus, small ICUs used more resources per one life saved when resource consumption is measured by lengths of ICU stay.

Table 14. Patient characteristics and outcomes

	Small central hospital ICUs	**Large central hospital ICUs**	**University hospital ICUs**	***P***
Number of patients, n (%)	77 (17.0)	145 (32.1)	230 (50.9)	
Number of patients per unit, median (range)	10 (3-15)	15 (9-22)	29 (19-53)	
Males, n (%)	48 (62.3)	95 (65.5)	159 (69.1)	0.51
Postoperative admissions, n (%)	26 (33.8)	35 (24.1)	70 (30.4)	0.01
Age, years, mean ± SD	62.3 ± 14.7	59.1 ± 16.2	59.1 ± 15.0	0.24
SAPS II score without age points, mean ± SD	32.7 ± 16.4	37.4 ± 17.0	33.7 ± 14.7	0.04
SAPS II score, mean ± SD	43.7 ± 17.7	47.3 ±18.7	43.6 ± 15.5	0.10
Site of infection, n (%)				0.22
Pulmonary	25 (32.5)	59 (40.7)	97 (42.2)	
Intra-abdominal	32 (41.6)	49 (33.8)	64 (27.8)	
Urinary	5 (6.5)	4 (2.8)	13 (5.7)	
Skin or soft tissue	4 (5.2)	13 (9.0)	27 (11.7)	
Others	4 (5.2)	7 (4.8)	17 (7.4)	
Unknown	7 (9.1)	13 (9.0)	12 (5.2)	
TISS per day, mean ± SD	33.3 ± 6.4	33.7 ± 6.3	39.4 ± 8.0	< 0.001
Length of ICU stay, days				
Mean ± SD	9.3 ± 8.3	7.8 ± 6.8	8.2 ± 8.9	
Median (quartiles)	7.2 (3.7-12.6)	6.0 (3.1-11.3)	5.1 (2.7-11.1)	0.17
ICU mortality, n (%)	16 (20.8)	25 (17.2)	31 (13.5)	0.28
Hospital mortality, n (%)	29 (37.7)	39 (26.9)	64 (27.8)	0.20
SMR (95% CI)	1.03 (0.72-1.49)	0.65 (0.47-0.89)	0.81 (0.64-1.04)	
One-year mortality, n (%)	38 (49.4)	55 (37.9)	91 (39.6)	0.23

SMR, Standardised Mortality Ratio, i.e. the number of observed in-hospital deaths divided by the number of deaths expected according to the SAPS II prognostic model

Table 15. Hospital mortality rates [percentages (n)] in certain subgroups in small central hospital ICUs and in large ICUs. "Large ICUs" include both university hospital ICUs and large non-university central hospital ICUs.

	Small central hospital ICUs	**Large ICUs**	***P***
All patients	37.7 (29/77)	27.5 (103/375)	0.07
Postoperative admissions	42.3 (11/26)	22.9 (24/105)	0.045
Medical admissions	35.3 (18/51)	29.3 (79/270)	0.39
Age			
< 65 years	23.1 (9/39)	21.3 (50/235)	0.80
≥ 65 years	52.6 (20/38)	37.9 (53/140)	0.10
Length of ICU stay			
< 7 days	29.7 (11/37)	25.3 (58/229)	0.57
≥ 7 days	45.0 (18/40)	30.8 (45/146)	0.09
≥ 14 days	61.5 (8/13)	28.3 (17/60)	0.02

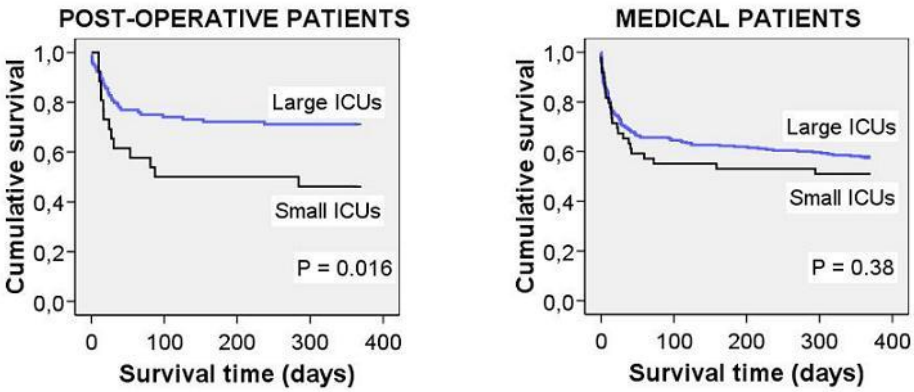

Figure 6. Survival curves of surgical post-operative and of medical patients treated in large ICUs (including university and large non-university central hospital ICUs) and in small central hospital ICUs

5.5 MORTALITY OF PATIENTS RESUSCITATED FROM CARDIAC ARREST

The age distribution of the patients did not change between the two study periods in study V. Severity of illness was higher in the latter period. Despite this, hospital mortality decreased from 57.9% to 51.1%, $P < 0.001$ (Table 16). When logistic regression analysis was used to adjust for severity of illness (SAPS II score), gender and the impact of individual ICUs, treatment in 2003-2008 was associated with a significantly reduced risk of in-hospital death (adjusted OR 0.54, 95% CI 0.45-0.64, $P < 0.001$). When the year of admission (instead of treatment period) was used as an explanatory variable, the severity of illness-adjusted risk of death decreased markedly between the years 2002 and 2003. This improvement has persisted, but there was no further improvement after 2003 (Table 17).

The median age of the patients was 66 years. In patients younger than this, hospital mortality was 52.1% in 2000-2002 and 45.1% in 2003-2008, $P = 0.012$. In patients aged 66 years or over, hospital mortality was 62.7% in 2000-2002 and 57.3% in 2003-2008, $P = 0.036$. After adjustment for SAPS II scores, gender and the impact of individual ICUs, treatment in 2003-2008 had a strong and consistent independent effect on risk of in-hospital death (for patients under 66 years of age, adjusted OR 0.53, 95% CI 0.41-0.69, $P < 0.001$; for patients aged 66 years or over, adjusted OR 0.55, 95% CI 0.42-0.70, $P < 0.001$).

Males made up the majority of patients. For male patients, hospital mortality was 56.1% in 2000-2002 and 49.3% in 2003-2008, $P = 0.003$. For female patients, hospital mortality was 61.8% in 2000-2002 and 56.4% in 2003-2008, $P = 0.12$. After adjustment for SAPS II scores and the impact of individual ICUs, treatment in the latter period was associated with decreased hospital mortality for patients of both genders (for males, adjusted OR 0.55, 95% CI 0.44-0.68, $P < 0.001$; for females, adjusted OR 0.49, 95% CI 0.35-0.70, $P < 0.001$).

The Finnish Intensive Care Consortium grew during the study period: altogether six new ICUs joined. Outcomes of patients treated in these new units were not better than outcomes of patients treated in the Consortium's older units.

Table16. Characteristics of the study population and figures describing ICU care and outcomes

	2000-2002	**2003-2008**	***P***
Hospitals in the Consortium	20	21	
Number of ICUs	21	24	
Number of patients	886	3072	
Males, %	68.8	73.8	0.003
Age	64.4 ± 15.0	63.5 ± 14.7	0.11
SAPS II score	58.1 ± 17.8	61.6 ± 16.9	< 0.001
Worst GCS score during first 24 h	3 (3-6)	3 (3-6)	0.94
Length of ICU stay, days			
Mean ± SD	2.7 ± 3.1	3.2 ± 3.5	< 0.001
Median (quartiles)	1.9 (1.0-3.2)	2.3 (1.2-3.9)	< 0.001
Mean daily TISS score			
Mean ± SD	27.4 ± 8.4	33.0 ± 8.0	< 0.001
Median (quartiles)	26.3 (22.0-31.2)	32.5 (27.5-38.2)	< 0.001
Therapeutic hypothermia, %	1.8	36.2	< 0.001
ICU mortality, %	25.4	21.6	< 0.001
Hospital mortality, %	57.9	51.1	< 0.001
Adjusted OR (95% CI)	Reference	0.54 (0.45-0.64)	< 0.001[a]

Data on continuous variables presented as means ± standard deviation or medians (quartiles). [a]Multivariate logistic regression analysis (the impact of SAPS II scores, gender and individual ICUs was adjusted for).

Table 17. Results of a logistic regression analysis testing the independent effect of SAPS II scores, gender and admission year on risk of in-hospital death. The impact of individual ICUs was adjusted for. Patients treated in ICUs that joined the benchmarking programme during the study period were excluded.

	Adjusted OR	**95% CI**	***P***
SAPS II score (for each additional point)	1.08	1.07-1.08	< 0.001
Male gender	0.72	0.59-0.87	0.001
Admission year			
2000	Reference		
2001	1.03	0.69-1.52	0.90
2002	0.95	0.65-1.39	0.77
2003	0.53	0.37-0.77	0.001
2004	0.54	0.37-0.78	0.001
2005	0.62	0.43-0.89	0.010
2006	0.58	0.40-0.84	0.004
2007	0.54	0.38-0.79	0.001
2008	0.46	0.32-0.67	< 0.001

For all patients treated with therapeutic hypothermia (TH) in 2003-2008, hospital mortality was 36.8%; for patients treated without TH, it was 58.9% ($P < 0.001$). The patients treated with TH were younger and less severely ill than those not treated with TH (mean age 60.1 ± 14.0 vs. 65.4 ± 14.7, $P < 0.001$; mean SAPS II scores 59.0 ± 15.7 vs. 63.1 ± 17.4, $P < 0.001$).

In 2003, the proportion of patients treated with TH was 21.7%. This proportion steadily increased until 2007, when it was 44.0%. In 2008, 43.1% of the patients were treated with TH. However, we found no further improvements in survival rates after the year 2003 despite the increasing use of TH. Over the years, TH was given to more severely ill patients and consequently the mortality of TH-treated patients actually increased: during the years 2003-2004, the mean SAPS II score of TH-treated patients was 54.8 ± 16.3 and the hospital mortality rate was 29.7%; in 2007-2008, the mean SAPS II score was 60.2 ± 14.4 and the hospital mortality rate was 39.5%.

Lengths of ICU stay (LOS) were longer and mean intensity of care was higher in 2003-2008 as compared with earlier years (Table 16). The increase in mean LOS was associated with the use of TH: for patients treated without TH, mean LOS in 2003-2008 was 2.6 ± 3.2 days, which is similar to the mean LOS in 2000-2002. For patients treated with TH in 2003-2008, mean LOS was 4.3 ± 3.6 days. Intensity of care has increased even among those not treated with TH: in 2003-2008, the mean daily TISS score of patients not receiving TH was 30.1 ± 7.4, which is higher than the score of 27.4 ± 8.4 of patients treated in 2000-2002. For patients treated with TH, the mean daily TISS score in 2003-2008 was 38.0 ± 6.3. Overall, the mean total TISS score per patient (the sum of daily TISS score calculations) increased from 105 in 2000-2002 to 142 in 2003-2008, reflecting a 35% increase in resource use in the treatment of this patient group.

5.6 CHANGES IN HOSPITAL MORTALITY OF FINNISH INTENSIVE CARE PATIENTS OVER TIME

5.6.1 Changes in Outcomes

The crude hospital mortality rate decreased from 18.8% in 2001-2004 to 18.0% in 2005-2008. As mean severity of illness increased, risk-adjusted mortality decreased (Table 18, Figure 7). The SAPS II-based SMR was 0.74 (95% CI, 0.72-0.75) in 2001-2004 and 0.64 (95% CI, 0.62-0.65) in 2005-2008. Over the time, outcomes improved in all major admission categories (Table 19). Both crude hospital mortality rates and SMRs were lowest in the youngest age groups. In addition, outcomes improved most in the youngest age group and least in the oldest group (Table 20). The mean intensity of care, as measured with TISS scores, increased over the years. There was no change in mean lengths of ICU stay. A very small, yet statistically significant, decrease in mean lengths of hospital stay was found (Table 18).

Table 18. Patient characteristics and outcomes

	2001-2004	**2005-2008**	***P***
Number of patients	38,482	47,065	
Number of departments	23	24	
In university hospitals	8	8	
Non-university central hospitals	15	16	
Males, %	60.0	61.7	< 0.001
Type of admission, %			< 0.001
Scheduled surgical	14.9	12.0	
Emergency surgical	21.2	21.9	
Medical	63.9	66.1	
Age (years), mean ± SD	59.3 ± 17.1	58.8 ± 17.2	< 0.001
SAPS II score, median (IQR)	33 (22-47)	35 (24-50)	< 0.001
SOFA score, median (IQR)	5 (3-8)	6 (3-9)	< 0.001
TISS / day, median (IQR)	24.7 (18.5-31.3)	27.4 (21.0-33.7)	< 0.001
Length of ICU stay, days			
Median (IQR)	1.5 (0.8-3.3)	1.6 (0.8-3.6)	< 0.001
Mean ± SD	3.2 ± 5.4	3.2 ± 5.2	0.51
Length of hospital stay, days			
Median (IQR)	9 (5-17)	9 (5-17)	< 0.001
Mean ± SD	14.4 ± 17.8	14.1 ± 17.4	0.02
ICU mortality, % (95% CI)	9.9 (9.6-10.2)	8.8 (8.6-9.1)	< 0.001
Hospital mortality, % (95% CI)	18.8 (18.4-19.2)	18.0 (17.6-18.3)	0.002
SMR (95% CI)	0.74 (0.72-0.75)	0.64 (0.62-0.65)	
Adjusted OR (95% CI) [a]	Reference	0.76 (0.73-0.79)	< 0.001

[a] *Severity of illness (SAPS II score) and the impact of individual ICUs were adjusted for.*

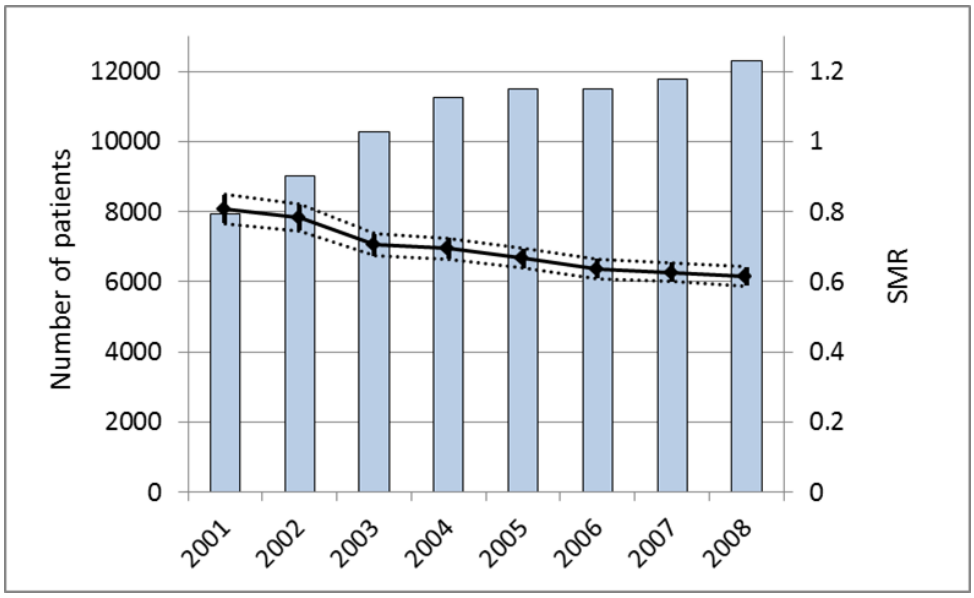

Figure 7. The number of adult patients treated in ICUs participating in the Finnish Intensive Care Consortium and the change in standardised mortality ratio (SMR) during 2001-2008. Bars show the annual number of patients, dots and whiskers show the SMRs with 95% confidence intervals. The SMR was calculated for each year by dividing the number of observed in-hospital deaths by the number of deaths expected by the SAPS II prognostic model.

Table 19. Outcomes for different admission types. Odds ratios (OR) compare the odds of death in 2005-2008 with 2001-2004 (SAPS II scores and the impact of individual ICUs were adjusted for).

		2001-2004	**2005-2008**	***P***
Admission type				
Scheduled surgical	Hospital mortality, %	4.8	3.4	< 0.001
	SMR (95% CI)	0.62 (0.54-0.69)	0.42 (0.37-0.49)	
	Adjusted OR (95% CI)	Reference	0.65 (0.52-0.81)	< 0.001
Emergency surgical	Hospital mortality, %	15.3	14.8	0.36
	SMR (95% CI)	0.62 (0.58-0.66)	0.55 (0.52-0.58)	
	Adjusted OR	Reference	0.78 (0.70-0.86)	< 0.001
Medical	Hospital mortality, %	23.0	21.7	< 0.001
	SMR (95% CI)	0.77 (0.75-0.79)	0.67 (0.65-0.69)	
	Adjusted OR	Reference	0.77 (0.73-0.81)	< 0.001

Table 20. Outcomes in different age groups. Odds ratios (OR) compare the odds of death in 2005-2008 with 2001-2004 (SAPS II scores and the impact of individual ICUs were adjusted for).

		2001-2004	**2005-2008**	***P***
Age group, yrs				
< 40	Hospital mortality,%	6.3	5.1	0.004
	SMR (95% CI)	0.58 (0.52-0.64)	0.44 (0.40-0.49)	
	Adjusted OR (95% CI)	Reference	0.63 (0.53-0.76)	< 0.001
40-59	Hospital mortality,%	14.5	13.7	0.04
	SMR (95% CI)	0.69 (0.65-0.72)	0.58 (0.55-0.60)	
	Adjusted OR (95% CI)	Reference	0.75 (0.69-0.81)	< 0.001
60-69	Hospital mortality,%	20.1	20.0	0.87
	SMR (95% CI)	0.72 (0.69-0.76)	0.63 (0.61-0.66)	
	Adjusted OR (95% CI)	Reference	0.80 (0.73-0.88)	< 0.001
70-74	Hospital mortality,%	24.5	23.9	0.51
	SMR (95% CI)	0.76 (0.72-0.80)	0.66 (0.62-0.70)	
	Adjusted OR (95% CI)	Reference	0.78 (0.70-0.87)	< 0.001
75-79	Hospital mortality,%	28.6	26.9	0.07
	SMR (95% CI)	0.83 (0.78-0.88)	0.70 (0.67-0.74)	
	Adjusted OR (95% CI)	Reference	0.75 (0.67-0.84)	< 0.001
80-	Hospital mortality,%	30.1	31.5	0.17
	SMR (95% CI)	0.80 (0.76-0.85)	0.75 (0.71-0.79)	
	Adjusted OR (95% CI)	Reference	0.84 (0.75-0.94)	0.002

5.6.2 Influence of Possible Confounding Factors

Influence of new ICUs joining the Consortium

The observed decrease in severity of illness-adjusted hospital mortality was not caused by new ICUs joining the benchmarking programme. When SAPS II scores and the year of admission were adjusted for, treatment in departments that joined the Consortium after 2001 was associated with increased hospital mortality (adjusted OR for death 1.12, 95% CI 1.07-1.18). When only those departments that participated in the Consortium already in 2001 (18 ICUs, 61,280 patients) were included, the decrease in SMR over time was comparable to that observed in the overall patient population: the SMR (95% CI) was 0.73 (0.71-0.75) in 2001-2004 and 0.63 (0.61-0.64) in 2005-2008.

Influence of changes in hospital discharge practices

In addition to vital status, the hospital discharge data included information of whether a surviving patient was discharged home or to another healthcare institution. Overall, 35.8% of the patients (n = 30,594) were discharged from a hospital to another hospital or institutional care. This proportion was 37.0% in 2001-2004 and 34.8% in 2005-2008, $P < 0.001$. For 7 patients, the database lacked discharge information. When we excluded from the analyses those patients that were discharged to other institutions (leaving 54,946 patients), the SMR (95% CI) was 1.12 (1.09-1.14) in 2001-2004 and 0.96 (0.94-0.98) in 2005-2008.When SAPS II scores and the impact of

individual ICUs were adjusted for, the odds of death were lower in the latter period, adjusted OR 0.71 (95% CI 0.67-0.75).

Influence of hospital size

The odds of death decreased in all hospital groups: when SAPS II scores and the impact of individual departments were adjusted for and the period 2001-2004 was the reference, the adjusted OR for death in 2005-2008 was 0.87 (95% CI 0.78-0.96, $P = 0.005$) in small central hospital ICUs, 0.73 (95% CI 0.68-0.78, $P < 0.001$) in large central hospital ICUs and 0.75 (0.70-0.80, $P < 0.001$) in university hospital ICUs. When severity of illness, diagnostic categories and year of admission were adjusted for and university hospital ICUs made up the reference category, treatment in small central hospital ICUs had no independent effect on the risk of death (adjusted OR 1.02, 95% CI 0.96-1.08, $P = 0.53$), whereas treatment in large central hospital ICUs was associated with decreased mortality (adjusted OR 0.90, 95% CI 0.86-0.94, $P < 0.001$).

Data completeness and automation of data collection

In the overall study population, the median number of missing SOFA parameters was 0 (inter-quartile range, 0-1). The median number of missing SAPS II physiological parameters was 1 (0-2). The most commonly missing physiological measurements were the concentrations of bilirubin (missing in 46.6% of cases) and urea (missing in 39.3% of cases). These measurements are commonly made only when clinically indicated, not just for severity-of-illness scoring. Apart from bilirubin and urea concentrations, mean data completeness on other SAPS II physiological parameters was 96.6%. Data completeness improved over time. The proportion of patients with no missing data on any SAPS II physiological parameters was 26.8% in 2001 and 49.2% in 2008.

After adjustments for SAPS II scores, the impact of individual ICUs and the treatment period, the binary variable "dataset fully complete on SAPS II physiological parameters" had a mathematically independent association with decreased hospital mortality (adjusted OR 0.77, 95% CI 0.73-0.81).

A clinical information system (CIS) automatically collects data from patient monitors and the hospital's laboratory systems. Of the 24 participating ICUs, 12 had a CIS installed already at the beginning of the study period. 11 ICUs installed a CIS during the study period and one ICU continued with manual documentation at the end of 2008. After adjustments for SAPS II scores, the impact of individual ICUs and the treatment period, the CIS was independently associated with decreased hospital mortality (adjusted OR 0.80, 95% CI 0.73-0.88).

When severity of illness (SAPS II score) and the impact of individual ICUs were adjusted for, treatment in the latter half of the study period (2005-2008), as compared with the period 2001-2004, was associated with a decreased risk of in-hospital death: adjusted OR (OR_{TIME}) 0.76, 95% CI 0.73-0.79. When the documentation-related factors (DRF) "use of CIS" and "number of missing SAPS II physiological parameters" were added into the model, the adjusted OR for death in the latter period as compared with the early period ($OR_{TIME\text{-}DRF}$) was 0.81, 95% CI 0.78-0.85. Thus, the relative contribution of the documentation-related factors to OR_{TIME} was

$$[(1 - 0.76) - (1 - 0.81)] / [1 - 0.76] = 0.208, \text{ i.e. } 21\%.$$

This means that after adjustments for SAPS II scores and the impact of individual ICUs but without attention paid to documentation-related factors, the odds of death were 24% lower in 2005-2008 than in 2001-2004. However, five percentage points (i.e. 21%) of this computational difference is explained by automated data collection with the use of a CIS and improved data completeness. When differences in these factors were also adjusted for, the odds of death were 19% lower in 2005-2008 than in 2001-2004.

The new customised prediction model yielded the following equation:

logit = −9.7618 + 0.03417×(SAPS II score) + 1.6429×[ln(SAPS II score + 1)] + 0.07372×(SOFA score) − 0.3939 (only if admission after elective surgery) − 1.7945 (only if admission for diabetic ketoacidosis) − 2.0687 (only if admission for drug intoxication) + 0.2416×(number of missing SAPS II physiological parameters) − 0.1269 (only if data documented with a CIS)

The probability of in-hospital death was then calculated as

$e^{logit} / (1 + e^{logit})$.

In the Hosmer and Lemeshow goodness-of-fit test, $\hat{C} = 14.9$ and $P = 0.061$. The AUC was 0.860 (95% CI, 0.857-0.863). Hospital mortality rates for each calendar year, adjusted for differences in case mix and in documentation with this customised model, and adjusted ORs of death for each year are presented in Table 21. The adjusted hospital mortality was 19.4% in 2001-2004 and 17.5% in 2005-2008. When admission period was added as a variable to the model, the adjusted OR for death in 2005-2008 as compared with 2001-2004 was 0.82 (95% CI 0.79-0.86).

Table 21. Adjusted hospital mortality rates and odds ratios for death based on the customised prediction model

Year	Adjusted hospital mortality (%)	Adjusted OR (95% CI)
2001	21.1	Reference
2002	20.4	0.95 (0.86-1.04)
2003	18.6	0.80 (0.73-0.87)
2004	18.5	0.79 (0.72-0.87)
2005	17.9	0.74 (0.68-0.81)
2006	17.7	0.72 (0.66-0.79)
2007	17.2	0.69 (0.63-0.75)
2008	17.3	0.69 (0.63-0.76)

The adjusted mortality rates were calculated as follows: First, multivariate logistic regression was used to develop a model adjusting for differences in case mix and for differences in data collection and to calculate a probability of in-hospital death for each patient. The precise equation is presented in the text. For each calendar year, the standardised mortality ratio (SMR) was calculated by dividing the observed number of deaths by the sum of individual probabilities. Finally, the adjusted mortality rates were calculated for each year by multiplying the overall hospital mortality rate (18.35%) by the SMR. The adjusted odds ratios of death for each year, compared with the year 2001, were calculated by adding the calendar year as a variable to the customised prediction model.

6 Discussion

6.1 IMPACT OF GENDER ON TREATMENT AND OUTCOMES

Male patients made up 62% of the study population. Quite similar gender distributions have been reported in other large studies on heterogeneous ICU populations (Valentin et al. 2003, Metnitz et al. 2005, Fowler et al. 2007). The reason for the disproportionately high numbers of male patients is unknown. Are males more susceptible to conditions requiring intensive care, or is there a bias against admitting females to ICUs? In this study we measured severity of illness with APACHE II scores, which were similar between men and women. Thus, it seems that the need for intensive care has been assessed irrespective of the patients' gender. Men have higher age-adjusted incidence rates of most severe diseases than women (Jousilahti et al. 1999, Angus et al. 2001, Cook et al. 2009), which is probably reflected in the male majority in age groups other than the oldest group, where females made up the majority.

Even if there were a causal relationship between some factor and the critical illness that requires treatment in an ICU, that factor would not necessarily prove to be an independent predictor of poor outcome when the population studied consists only of patients that have already been admitted to ICUs. In the overall study population of ICU patients, gender had no impact on outcome. However, male gender was associated with increased hospital mortality among postoperative patients and in the oldest age group.

Male patients were treated longer than female patients. Even after adjustment for severity of illness, the mean length of stay was higher for men than for women both overall and within most diagnostic categories. These results together with the higher risk of death of male patients in certain subgroups imply that women may have a better ability than men to recover from critical illness or surgery.

In some previous large studies, outcomes of men have not been worse than outcomes of women (Valentin et al. 2003, Fowler et al. 2007). However, in these studies, proportionately more men than women were admitted to ICUs after cardiovascular surgery, which is a diagnostic group with a relatively good prognosis. The possible effects of different diagnostic categories were not adjusted for.

The reasons for gender-based differences are not evident. Sex hormones (Bouman et al. 2005), other hormonal mechanisms (Van den Berghe et al. 2000) and the cellular mosaicism of X-linked genes in females (Spolarics 2007) may play some role. Most probably behavioural factors, smoking and heavy alcohol use in particular, are also important. The need of intensive care is often related to alcohol use, and this particularly affects males (Uusaro et al. 2005). Whatever the reasons behind the differences, this study supports the conclusion of Edgar V. Allen (1934): "*The male is fundamentally the weakling of the two sexes.*"

If the differences between genders in outcome were caused primarily by sex hormones, one would expect these differences to be more pronounced in people of premenopausal age. This hypothesis is supported by the study of Wohltmann et al. (2001), in which young women seemed to have a survival advantage when compared with equally injured young men, whereas outcome was not gender-related in patients older than 50 years. In our study, however, male gender was associated with an increased risk of death in patients aged 75 years or older but not in the younger age groups. It is possible that men in the oldest age group have a higher incidence of concomitant cardiovascular disease or chronic pulmonary disease and thus a higher risk of cardiovascular or pulmonary complications than women.

In the study by Valentin et al. (2003), men received an increased level of care and had a higher probability of receiving several invasive procedures. In our study, the intensity of care

was higher for men than for women in the overall study population. However, the diagnostic category "vascular surgery" comprised a higher proportion of men than women. Patients in this category were treated more intensively than patients of other diagnostic categories. This fact explains most of the difference found between genders in intensity of care. When severity of illness and the effects of different diagnostic categories were adjusted for, the difference between genders was small. Moreover, there were only insignificant differences between genders in the intensity of care within most diagnostic categories. These results do not support the hypothesis that a patient's gender would influence the intensity of ICU care in Finland.

6.2 SEASONAL VARIATIONS IN MORTALITY

The winter season is associated with excess mortality in the general population due to an increased incidence of myocardial infarctions, strokes and respiratory problems (Sheth et al. 1999, Keatinge 2002, Olson et al. 2009). Some authors attribute the extra deaths to cold stress (Keatinge 2002), others to influenza epidemics (Reichert et al. 2004). In this study, hospital mortality of patients treated in Finnish ICUs was higher in winter than in other seasons.

Conditions inside the walls of an ICU remain rather constant regardless of season-related changes in conditions outdoors. Thus, one would not expect severity of illness-adjusted outcomes to vary much between different seasons. In this study, the independent effect of the winter season was non-significant when each diagnostic category was analysed separately, which means that outcomes of patients with a given severity of disease were not worse in the winter season. However, there was a higher amount of seriously ill patients needing intensive care for respiratory failure in winter than in other seasons and this led to extra deaths in winter.

These findings are in accordance with the results of Danai et al. (2007). They analysed hospital discharge data on over 12 million patients that were hospitalised because of sepsis in the USA in 1979-2003 and found that both the incidence and mortality of sepsis are seasonal and consistently highest during winter. The seasonal variability is mainly related to respiratory sepsis.

In this study, the proportion of patients aged 75 years or older was higher in winter than in other seasons. This partly explains the higher crude mortality rates in winter. The finding implies that winter increases old people's susceptibility to conditions requiring intensive care.

"The July phenomenon" refers to the idea that the quality of medical care might be substandard in July. However, according to previously published studies, this phenomenon seems to be fiction rather than fact, at least in intensive care (Barry and Rosenthal 2003, Finkielman et al. 2004). Our study found similar results: Crude hospital mortality was higher in July than in other months, but this difference seems to be entirely explained by differences in case mix, the most important of which is the lower amount of patients admitted after scheduled surgery in July. After differences in case mix were adjusted for, outcomes of patients treated in July were not different from outcomes of patients treated in other months.

An increase in the mean daily TISS score was an independent predictor of increased hospital mortality. This finding is not surprising: the mean daily TISS score reflects the intensity of the care needed in the particular case and thus is a measure of the severity of illness. Some previous studies have shown that high TISS scores at the time of discharge from the ICU mean an increased risk of death after intensive care (Smith et al. 1999, Beck et al. 2002). Our findings agree well with these previous results: patients needing care of high intensity are at a high risk of death.

6.3 INFLUENCE OF OLD AGE

This study showed that old age is indeed a risk factor for death: with a given severity of illness, old patients have a far higher risk of in-hospital death than younger patients. Particularly the oldest patients admitted for medical reasons are at a high risk of death, as are those elderly patients whose ICU stay is long. These findings are in accordance with the results of a large study from Australia and New Zealand: old age, non-surgical admission, greater illness severity, and prolonged stay in the ICU are associated with poor outcomes (Bagshaw et al. 2009). In our study, the hospital mortality rate seemed to rise in quite a linear way with increasing age. However, elderly women seem to be less sensitive than elderly men to the effects of further aging: the impact of one additional year of age on risk of death was smaller among elderly women than men.

Among the youngest patients, deaths after intensive care, during the same hospitalisation, were rather uncommon. Among the oldest patients, even more deaths occurred after intensive care than in the ICU. This may reflect the limited ability of many elderly patients to recover from serious illnesses. It has been shown previously that elderly trauma patients are more likely than younger patients to die later because of the combination of injury and pre-existing diseases and complications (Perdue et al. 1998). The high amount of post-ICU deaths is probably also associated with restrictions of future care because further aggressive treatment is considered to be futile. Restrictions (which may include for example orders not to attempt resuscitation or the refusal of a new ICU admission) were quite often imposed on the oldest patients.

The mean intensity of care was at its highest among patients aged 60-79 years. Younger patients as well as the oldest patients were treated less aggressively. However, in the youngest age groups also the mean severity of illness was at its lowest, whereas the severity of illness was at its highest in the oldest age group. It seems that the care of the oldest patients has been notably limited. The data about lengths of ICU stay support the same conclusion: the length of stay was at its highest in the age group 75-79 years, but markedly shorter for patients aged 80 years or over. It seems that the average Finnish ICU keeps on treating ageing patients with full intensity until approximately 80 years of age, after which the mean intensity declines. That said, it should be noted that even in the oldest age group, a significant proportion of patients received treatment of high intensity. In particular, the use of several vasoactive drug infusions was even more common in the oldest age group than among younger patients.

Withdrawal of aggressive life-sustaining therapy is generally considered appropriate in a situation where the patient's condition deteriorates despite active treatment and the prognosis gives no hope for recovery (Chelluri et al. 1995). At times, the right decision is to not even start aggressive treatments that would be futile (Ely 2003). However, a major problem in the intensive care of severely ill elderly people is to reliably identify those patients for whom therapy is futile. It is incorrect to restrict therapeutic activity in all old patients. Even after prolonged intensive care, a reasonable proportion of elderly patients survive. Most elderly survivors consider their quality of life as satisfactory or good a few years after ICU discharge (Kaarlola et al. 2006, Roch et al. 2011).

The mean length of ICU stay was at its longest in the age group 75-79 years and the mean intensity of care was also high in this age group. Still, the hospital mortality rate was rather high, namely 24%. Thus, a relatively high amount of ICU resources was consumed in relation to the number of surviving patients. The cost of one life saved was almost double in the age group 75-79 years as compared with the youngest age group. Given the relatively low life expectancy of people over 75 years old, the cost of life years gained becomes much higher than in younger age groups. On the other hand, the amount of resources consumed per one survivor was rather low in the oldest age group.

An important question is whether intensive care resources are used correctly in the treatment of old patients. Many elderly patients do benefit from intensive care. On the other hand, ICU services may be superfluous. According to a study from Sweden, reduction of intensive care

resources because of cost containment in the 1990s led to shorter lengths of ICU stay and lower TISS scores for elderly patients without any significant change in 180-day mortality (Walther and Jonasson 2004). According to the authors, ICU services were probably over-dimensioned during the early years of the study period. Among the ICUs in our study, the proportion of patients aged 80 years or older varied a lot, from 3% to 18%. A major reason for these differences probably lies in the character of the individual departments and hospitals: in some hospitals, there are relatively many ICU beds but otherwise relatively few high-dependency beds. However, the magnitude of the differences suggests that there may be differences between hospitals within Finland in treatment strategies regarding the oldest old patients. Based on this study, it is not possible to estimate what an ideal proportion would be. Nevertheless, these differences give reason to speculate that in some hospitals equally good outcomes might be achieved with less intensive treatment and with less costs, whereas in other hospitals there may have been patients who might have benefited from more aggressive therapy.

The ageing of the population will most probably increase the demand for intensive care in the near future. Projections based on studies in other countries anticipate an even larger increase in the demand for ICU services (Needham et al. 2005, Laake et al. 2010). The difference in forecasts is mainly caused by the differences in projections for population growth, which is predicted to be very low in Finland. Otherwise the results of this study are in agreement with the forecasts based on other studies. The baby boom generation of the post-war years is approaching the years of life most commonly associated with the need for intensive care, causing a substantial increase in the need for ICU resources.

6.4 THE RELATIONSHIP BETWEEN HOSPITAL SIZE AND OUTCOMES

In the overall population of ICU-treated adult patients with severe sepsis, there were no statistically significant differences between university and non-university hospital ICUs or between large and small ICUs in unadjusted hospital mortality rates. However, after adjustment for severity of illness, treatment in small central hospital ICUs as compared with large ICUs was associated with an increased risk of death. The mortality of postoperative patients was higher for small ICUs than for large ICUs. Mortality rates were especially high among patients with long lengths of stay in small ICUs.

The number of patients in our study was rather small. Further studies are needed to find the patient groups that would benefit from treatment in large hospitals. Our results are however in concordance with some previous studies suggesting that higher patient volumes are associated with better outcomes in intensive care (Kahn et al. 2006, Peelen et al. 2007). That said, one has to bear in mind that the literature on this topic is controversial: several studies have found no evidence for a volume-outcome relationship (Engel et al. 2007, Gopal et al. 2011, Nguyen et al. 2011).

When a relationship between higher patient volumes and improved outcomes has been found, a common explanation has been that a higher number of patients gives the staff more experience, which may benefit subsequent patients. Another plausible explanation is that high-volume centres may be better at adopting new useful therapies or more probably have in place organisational factors that are associated with improved outcomes (Kahn 2007b). One such factor that may improve patient outcomes is the availability of multidisciplinary expertise. Rothen et al. (2007) defined a very efficient unit as one with both a low standardised mortality ratio and low standardised resource use. The presence of multiprofessional clinical rounds was associated with the probability of an ICU belonging to the group of most efficient units.

The need for multidisciplinary expertise may be a problematic issue in many small Finnish hospitals, especially during out-of-office hours. Broad expertise, e.g. in the different specialities

of surgery, may not be continuously available. In this study, treatment in small central hospital ICUs was associated with a worse outcome in surgical but not in medical patients. Severely ill surgical patients often need experts from several specialities (e.g. radiology, gastroenterological surgery, anaesthesiology and intensive care medicine) to get the right diagnosis and adequate treatment. One might speculate that surgical patients may be more vulnerable than medical patients to the limited availability of expertise in small hospitals.

According to Kahn (2007b), regionalisation of critical care may be the best solution when a volume-outcome relationship exists and the reasons behind it are related to organisational factors not easily exportable to small units. However, regionalisation of medical care may also have drawbacks. Already more than 25 years ago, Luft (1985) and Maerki et al. (1986) recommended regionalisation of many surgical procedures to high-volume hospitals, but also highlighted some problems potentially resulting from regionalisation of care: In small hospitals, it might lead to situations where medical services urgently needed for emergencies are not available. For some procedures or diagnoses, regionalisation of care to distant hospitals may not be feasible because of the emergency nature of the problem.

Results from studies done in densely populated urban areas and recommendations based on these studies do not necessarily apply to rural areas. According to Luft (1985), "*In the US, many hospitals within sight of each other often provide the same services.*" In California, 58% of patients treated in low-volume hospitals could have gone to a high-volume hospital without having to travel more than 16 km (10 miles) farther and 76% could have reached a high-volume hospital without having to travel more than 40 km (25 miles) farther (Dudley et al. 2000). Obviously, the situation is different in sparsely populated Finland. Thus, both study results and local circumstances should be considered when regionalisation of care is discussed.

6.5 THERAPEUTIC HYPOTHERMIA FOR POST-RESUSCITATION CARE

Survival of out-of-hospital cardiac arrest (OHCA) patients treated in Finnish ICUs was better in 2003-2008 than in 2000-2002. This finding was consistent for both younger and older patients and for both genders. A plausible explanation for this improvement in outcome is the use of therapeutic hypothermia (TH), which became widespread in Finland after publication of the studies by Bernard et al. (2002) and the Hypothermia after Cardiac Arrest Study Group (2002).

The improvement in outcome took place concurrently with the implementation of TH in most Finnish ICUs, supporting the interpretation that TH is the main reason for the improvement. Regarding changes in other treatments, tight glycaemic control with intensive insulin therapy has to be considered as a potential confounding factor, as it became common at about the same time, after Van den Berghe et al. (2001) published positive results of this treatment in surgical patients. However, later studies have failed to show a reduction in mortality of medical patients with intensive insulin therapy (Van den Berghe et al. 2006, NICE-SUGAR Study Investigators 2009). As the usefulness of tight glycaemic control is questionable (Marik and Varon 2007), it is unlikely that implementation of intensive insulin therapy would explain the results of our study.

A recent study from the Netherlands showed a significant reduction in hospital mortality of ICU-treated cardiac arrest patients after implementation of TH (van der Wal et al. 2011). The crude hospital mortality rates were higher (72.0% before TH, 65.4% after implementation of TH) than in our study, but so was the mean severity of illness as reflected by the SAPS II scores. The absolute risk reduction achieved after implementation of TH (6.6%) was of the same magnitude as in our study (6.8%). These figures correspond to a number needed to treat (NNT) of around 15.

A study from Sweden found a significantly improved survival of patients resuscitated from ventricular fibrillation in 2003-2006 as compared with 1980-2002: one-year survival 57% vs. 37%

(Martinell et al. 2010). However, the percentage of patients whose initial rhythm was ventricular fibrillation decreased during the study period and for all patients resuscitated from OHCA, there was no statistically significant change in survival.

We found that an improvement in outcome took place in 2003 and it has persisted ever since. However, although the use of TH has increased even after 2003, there seem to have been no further improvements. According to a survey (Oksanen et al. 2007), TH was at first used in Finland almost exclusively for patients resuscitated from ventricular fibrillation, and the inclusion criteria of the HACA trial (Hypothermia after Cardiac Arrest Study Group 2002; the criteria also presented in chapter 2.6.2 of this thesis) were used to select patients for the treatment. In this study we found that over the years TH was given to more severely ill patients. This is in accordance with the fact that many ICUs no longer strictly stick to the HACA trial's inclusion criteria. It seems possible that patients fulfilling these criteria are the ones most likely to benefit from TH and loosening the criteria for patient selection brings little additional benefit. This view is supported by the results of two newly published studies that found no benefit of TH in patients resuscitated from cardiac arrest with a non-shockable initial rhythm (Dumas et al. 2011, Storm et al. 2012). Nevertheless, it is still possible that sporadic resuscitated patients may benefit from TH although the initial rhythm was non-shockable. Based on this idea and on the fact that harm caused by TH is usually manageable, current Scandinavian guidelines recommend TH for all comatose resuscitated patients, if active treatment is considered justifiable (Castrén et al. 2009).

Lengths of ICU stay were longer in 2003-2008 than in 2000-2002. This change is explained by the relatively long lengths of stay of patients treated with TH. We also found an increase in intensity of care. It seems that the overall approach towards post-resuscitation patients has become more active. Considerably more resources were used in the treatment of patients resuscitated from cardiac arrest in 2003-2008 than in previous years.

In many countries that there are published reports from, implementation of TH for post-resuscitation care has been quite slow (Laver et al. 2006, Wolfrum et al. 2007, Bianchin et al. 2009). In addition to obstacles caused by resource issues, unawareness of the level of evidence regarding the usefulness of the treatment or lack of consensus about it have been mentioned as common reasons for not using TH in the UK (Laver et al. 2006). There have even been outbursts of scepticism in recent years (Fisher 2008). In 2007, the vast majority of Italian ICUs were not using TH (Bianchin et al. 2009). The two most common reasons for this were "*No experience, need more info*" and "*Never thought about it*".

In Finnish ICUs, TH was promptly implemented. A certain author once considered the love of progress as typical of the Finns: In the 1890s, Ángel Ganivet was the Spanish consul in Finland, at that time the Grand Duchy of Finland, an autonomic part of the Russian Empire. He wrote, "*The enthusiasm with which all innovations of practical utility are accepted, and the speed and perfection with which they are assimilated, are characteristic of Finland*" (Ganivet 1905).

6.6 THE NATIONAL BENCHMARKING PROGRAMME: THE FINNISH INTENSIVE CARE CONSORTIUM

During the years 2001-2008, the mean hospital mortality rate for patients treated in Finnish ICUs, cardiac surgical patients excluded, was 18.4%. Based on severity scores, the mean severity of illness in this study population was comparable to the mean severity of illness in a large study from the UK (Harrison et al. 2004b) and to that in the multinational SAPS 3 study (Metnitz et al. 2005). Despite this, mean hospital mortality rates were considerably higher both in the UK (28.6%) and in the SAPS 3 study (28%). Based on these figures, it can be concluded that the outcomes of Finnish intensive care patients are rather good.

Moreover, outcomes improved during the study period: both the crude hospital mortality rate and severity of illness-adjusted mortality decreased. Outcomes improved in all age groups, for all admission types and in both small and large hospitals. The impact of new departments joining the benchmarking programme did not explain the improvements.

Though hospital mortality is commonly used as an outcome measure, it may be problematic. Patients discharged to other institutions are calculated as hospital survivors. However, some of these patients will die within the following months. Thus, discharges to other hospitals or institutional care may cause bias (Kahn et al. 2007a). It has been recommended that mortality at a fixed time point such as 30-day or 90-day mortality should be substituted for hospital mortality (Glance and Szalados 2002). For situations where only hospital mortality is available, Angus (2000b) has suggested doing analyses with and without patients discharged to long-term and rehabilitation facilities. We did this and found that the observed decrease in SMRs over the years cannot be attributed to changes in hospital discharge practices.

The more abnormal the values of physiological measurements, the more points are given to severity-of-illness scores. When data are missing, the values of the parameters in question are presumed to be within the normal range. Thus, patient populations with many incomplete datasets may appear less severely ill than they actually are. Consequently, improving data completeness might lead to an increase in mean severity of illness and thus a decrease in SMRs. Data completeness improved during the study period and this does partly explain the observed improvements in SMRs.

Automation of data collection with a CIS increases the sampling rate of physiological data. This increases the probability of obtaining abnormal values and thus leads to higher severity-of-illness scores and lower SMRs, which has been confirmed in previous studies (Bosman et al. 1998, Suistomaa et al. 2000). In this study, the use of a CIS had an independent mathematical association with decreased severity of illness-adjusted mortality. The severity-adjusted odds of death were 24% lower in 2005-2008 than in 2001-2004, but roughly one fifth of this difference between the admission periods is explained by automated data collection with the use of a CIS and improved data completeness.

We developed a new customised prediction model that takes into account both differences in case mix and differences in documentation-related factors (i.e. the use of a CIS and the number of missing SAPS II physiological parameters). The goodness of fit of this model was satisfactory, as was the discrimination. Based on this model, the adjusted mortality rate decreased from 21.1% in 2001 to 17.3% in 2008. If a difference of this magnitude were achieved with some new intervention, then the corresponding number needed to treat (NNT) would be around 26.

This means that outcomes improved considerably over the years. Most probably, genuine improvements in the quality of intensive care have taken place. It is also possible that patient selection may have improved: ICUs may have learnt to better allocate intensive care to patients that are able to benefit from aggressive treatment. Based on this study, it is not possible to answer the question whether the improved outcomes can be attributed to the benchmarking programme per se. According to lessons learnt from manufacturing industries, an essential step in striving for quality improvements is measuring the results of one's processes. Moreover, as David T. Kearns, former CEO at the Xerox Corporation, put it, "*Quality improvement can't be measured in a meaningful way against standards of your own internal devising*" (Kearns 1990.) This study shows that outcomes have improved concurrently with the benchmarking programme. However, as there was no control group in the study, it is not possible to prove any causality between the programme and the changes in outcomes.

Nevertheless, the benchmarking programme has had an impact in the generation of a network of communication and of collaboration within the Finnish intensive care community, which in turn has influenced the harmonisation of clinical practices and the implementation of treatments proven to be beneficial. This may have had a positive effect on the quality of care.

This study confirms that improving data completeness and automation of data collection do decrease severity-adjusted mortality rates. This should be taken into consideration in

benchmarking programmes if some ICUs use technology for automatic data collection and others do not. In Finland, this issue has no longer any major significance as a confounding factor, because a CIS for automated data collection is used in practically all ICUs.

6.7 LIMITATIONS OF THE STUDY

The main strength of this study is the high number of patients and rather good data completeness. The study populations represent well the patients treated in Finnish ICUs. There are some important limitations, though. The main weaknesses of this study are those that are inherent in retrospective studies. A mathematical association between two factors does not necessarily prove any causal relationship, as it may be impossible to completely control for all potential confounding factors.

There were no uniform criteria for ICU admission. Admission depended on the decision of the attending physicians, and the availability of other high-dependency units has also had some impact. Thus, there was heterogeneity between ICUs and also changes over time. Severity scores were used to adjust for differences in case mix, but it is well known that no severity-of-illness model is perfect in controlling for these differences (Moreno and Afonso 2008). In addition to severity scores, we also adjusted for the impact of different diagnostic categories. However, category grouping is not always unambiguous.

For each patient treated in an ICU participating in the Finnish Intensive Care Consortium, vital status at hospital discharge is registered into the Consortium's database. For comprehensive follow-up even after that, registering the personal identity number of each patient would be necessary. That is possible in Finland only if consent is obtained prospectively. Thus, only data on hospital mortality were available for studies I-III and V-VI. The lack of data on fixed-time mortality is a shortcoming but it does not invalidate the main findings of the studies. Efforts to improve long-term follow-up have already been made in the Consortium.

In Study III, severity of illness was measured with the SAPS II scoring system, which does not take into account most chronic diseases nor the functional status of the patient. The lack of adjustment for these factors may have influenced the impact of chronological age on prognosis, most probably leading to an overestimation of the influence of age. On the other hand, it is possible that very severely ill old patients may have been refused ICU admission more often than younger patients because of a gloomy prognosis and the subsequent assumption that intensive care would be futile. This in turn would lead to an underestimation of the impact of old age on the risk of death.

The major weakness of Study IV is the low number of patients. Therefore the results should be interpreted with caution. Another limitation is that the definitions of "small" and "large" ICUs may be regarded as somewhat arbitrary. The units classified as "large" in this study might be classified as small somewhere else.

There are also several limitations to Study V. The Consortium's database contains no information about the initial cardiac rhythm of the cardiac arrest patient, nor about the quality and length of resuscitation. Some changes may have taken place in these factors during the study period. In addition, we know nothing about patients that may have been taken alive to hospital but not admitted to the ICU. However, it is not likely that any major changes occurred in pre-hospital factors or in ICU admission policies between the years 2002 and 2003. Thus it is unlikely that a change in patient characteristics would account for the observed improvement in hospital mortality rates. Another important limitation is that we do not have information about the neurological outcomes of survivors.

6.8 IMPLICATIONS AND FUTURE PERSPECTIVES

Male gender is a risk factor for conditions requiring intensive care. It also increases the risk of poor outcome in some groups of ICU patients. More studies are needed to fully understand the reasons for this. However, the gender-based differences are probably caused partly by genetic and partly by behavioural factors, of which alcohol consumption is of importance (Uusaro et al. 2005). Factors that are effective in reducing excessive use of alcohol would probably also result in a decrease in untimely ICU admissions and deaths. Sex hormones also influence the resistance to severe infections (Bouman et al. 2005). However, all too little is known about their effects, and based on current knowledge no sex hormone treatments of severely ill patients can be proposed.

There is excess mortality in intensive care patients in the winter season. Severe respiratory failure is more frequent in winter than in other seasons. This should be taken into consideration when resource allocation is planned. Mortality is increased in winter also in the general population, which has been attributed to cold stress (Keatinge 2002) and influenza epidemics (Reichert et al. 2004). Avoiding harmful cold exposure with adequate clothing and indoor heating in conjunction with vaccination programmes and antiviral therapy against influenza are probably the most effective means of fighting against the winter-related risk of death.

Because of a reduced number of elective surgical patients during the holiday season, the case mix of Finnish ICU patients in July is different from that in other months. Crude mortality is increased in July, but the severity of illness-adjusted risk of death is not increased. It seems that the ICUs can keep their performance at a good level also during the holiday season.

The risk of death of intensive care patients increases in quite a linear way with increasing age. Particularly the oldest patients admitted for medical, i.e. non-surgical reasons are at a high risk of death, as are those elderly patients whose ICU stay is prolonged. Nevertheless, even in the oldest age group a reasonable proportion of patients survive after intensive care. Previous studies have shown that most elderly survivors consider their quality of life as satisfactory or good (Kaarlola et al. 2006, Roch et al. 2011). This means that intensive care is worthwhile also for many old patients.

Future studies are needed to learn more about long-term outcomes of severely ill old patients in various diagnostic groups. Being able to identify the patients that can benefit from aggressive treatment and those for whom intensive care is futile will be increasingly important in the years to come, as the ageing of the population will substantially increase the number of elderly people in society and also increase the demand for intensive care.

For surgical patients with severe sepsis, outcomes were worse in small ICUs than in large ICUs. However, because of the rather small number of patients in Study IV, this result must be interpreted with caution. Further studies are needed to explore the relationship between hospital volumes and patient outcomes and to identify those patients that might benefit from regionalisation of care to large hospitals.

Despite evidence-based international guidelines (Nolan et al. 2003), implementation of TH for post-resuscitation care has been slow in many countries. This study showed that concurrently with the implementation of TH, hospital mortality of patients treated in Finnish ICUs after resuscitation from out-of-hospital cardiac arrest decreased. Hopefully these results together with comparable results from other studies (van der Wal et al. 2011) will encourage hesitant ICU leaders to implement this treatment in their departments.

However, there are still unanswered questions regarding TH. There is uncertainty about the usefulness of the treatment in patients resuscitated from non-shockable initial rhythms (asystole, pulseless electrical activation) and about the optimal target temperature, timing and duration of cooling (Sunde and Søreide 2011). More research is needed to find the answers.

Hospital mortality rates of Finnish ICU patients are rather low compared to results of international studies. Moreover, the outcomes of Finnish intensive care have further improved during the years 2001-2008. However, we should beware of self-satisfaction because there is still

plenty of room for improvements. A major shortcoming in the benchmarking programme of the Finnish Intensive Care Consortium is the lack of comprehensive long-term follow-up. The true benefits of intensive care can only be measured when long-term outcomes are known. Many hospitals have already made efforts to improve in this respect. This should be seen as a key factor for development in the Consortium.

Improved data completeness and automation of data collection increase severity-of-illness scores and thus decrease standardised mortality ratios. It is advisable that this should be taken into consideration in benchmarking programmes in other countries, if some ICUs use technology for automatic data collection and others do not.

7 Conclusions

Based on these studies, the following conclusions can be drawn:

1) Males make up a majority of ICU patients. Male gender is associated with increased hospital mortality among post-operative patients and in the oldest age group. Lengths of ICU stay are longer for men than for women.

2) Because of a high amount of patients suffering from respiratory failure in winter, there is excess hospital mortality in intensive care patients in the winter season. The severity of illness-adjusted risk of death is not higher in July, the main holiday season, than in other months.

3) The risk of death of intensive care patients increases with increasing age. Mortality is particularly high among the oldest patients admitted for medical reasons and among those elderly patients whose ICU stay is prolonged. The intensity of care is lower for the oldest patients than for patients aged less than 80 years.

4) For surgical patients with severe sepsis, treatment in small ICUs was associated with increased hospital mortality. Because of the small sample size, further studies are needed to confirm or refute this association.

5) For patients treated in Finnish ICUs after resuscitation from out-of-hospital cardiac arrest, hospital mortality decreased concurrently with the implementation of therapeutic hypothermia.

6) Outcomes of Finnish intensive care patients are rather good. The outcomes further improved during the years 2001-2008. Improved data completeness and automation of data collection with a clinical information system do decrease severity of illness-adjusted mortality rates. However, this explains only one fifth of the improvement in measured outcomes in recent years.

8 References

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Appendix

INTENSIVE CARE UNITS THAT WERE PARTICIPATING IN THE FINNISH INTENSIVE CARE CONSORTIUM AT THE END OF THE STUDY PERIOD (IN ALPHABETICAL ORDER):

The number of beds refers to the situation in 2005.

Hospital	Number of beds	In the Finnish Intensive Care Consortium from
Helsinki University Central Hospital, Jorvi Hospital, Espoo	8	1998
Helsinki University Central Hospital, Meilahti Hospital, Helsinki (three departments)	9 + 8 + 10	2002, 2003, 2004
Kainuu Central Hospital, Kajaani	8	1998
Kanta-Häme Central Hospital, Hämeenlinna	5	1998
Keski-Pohjanmaa Central Hospital, Kokkola	4	2000
Keski-Suomi Central Hospital, Jyväskylä	8	1994
Kuopio University Hospital, Kuopio	15	2000
Kymenlaakso Central Hospital, Kotka	5	2000
Lappi Central Hospital, Rovaniemi	8	1999
Länsi-Pohja Central Hospital, Kemi	5	2007
Mikkeli Central Hospital, Mikkeli	5	1994
North Karelia Central Hospital, Joensuu	8	1994
Oulu University Hospital, Oulu (two departments)	10 + 10	2000
Päijät-Häme Central Hospital, Lahti	8	1994
Satakunta Central Hospital, Pori	8	1994
Savonlinna Central Hospital, Savonlinna	6	1994
Seinäjoki Central Hospital, Seinäjoki	7	1994
South Karelia Central Hospital, Lappeenranta	6	1994
Tampere University Hospital, Tampere	18	2002
Turku University Central Hospital, Turku	22	2002
Vaasa Central Hospital, Vaasa	10	1998

Matti Reinikainen

Hospital Mortality of Intensive Care Patients in Finland

Insights into Prognostic Factors and Measuring Outcomes

The Finnish Intensive Care Consortium co-ordinates a benchmarking programme in intensive care. The Consortium comprises all general adult intensive care units in all main Finnish hospitals. For every admission to these units, data on severity of illness, intensity of care and outcomes are documented in the Consortium's database. Data from this database were used for this study. This dissertation presents new information about the outcomes of Finnish intensive care, prognostic factors and factors affecting the calculation of severity of illness-adjusted mortality rates.

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