

Linköping University Medical Dissertations No. 1117

Health related quality of life in adult former intensive care unit patients

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Linköping 2009-05-08

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Cover picture:

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Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2009

ISBN 978-91-7393-651-4

ISSN 0345-0082

*To Madeleine and Liselotte
and
In memory of Hasse*

*“Life is what happens to you while you’re busy making other plans”
- John Lennon*

*“Everything should be as simple as it is, but not simpler”
- Albert Einstein*

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ABSTRACT

Background: Patients treated in an intensive care unit (ICU) are seriously ill, have a high co-morbidity, morbidity and mortality. ICUs are resource – demanding as they consume significant hospital resources for a minority of patients. The development of new medical procedures for critical care patients has over the years led to survival of larger numbers with more complex illnesses and extensive injuries. Improved survival rates lead to needs for outcome measures other than survival. The present study examines health-related quality of life (HRQoL) and factors assumed to be important for the long term HRQoL for former ICU patients.

Methods: This is a multicenter cohort study of 980 adult patients admitted to one of three mixed medical-surgical ICUs in Southern Sweden, during 2000 to 2004. The patients were studied at four different occasions after their critical illness: 6, 12, 24, and 36 months after discharge from the ICU and hospital. HRQoL was assessed by the EuroQol 5-Dimensions (EQ-5D) and Medical Outcome Short Form (SF-36), sleep disturbances by the Basic Nordic Sleep questionnaire (BNSQ), and pre-existing diseases was collected by self-reported disease diagnosis. Data from a large public health survey (n=6093) of the county population were used as reference group.

Results: Compared with the age and sex adjusted general reference group the patients who had been in the ICU had significantly lower scores on EQ-5D and in SF-36 all eight dimensions. This was seen both for the general ICU patients as well as for the multiple trauma patients. Significant improvement over time was seen only in single and separate dimensions for the general ICU group, and for the multiple trauma group. Long term effects of ICU care on sleep patterns were found minor as 70 % reported an unchanged sleep pattern and only 9% reported worse sleep after the IC period. Pre-existing diseases were found to be the factor that had the largest influence on HRQoL in both the short- and long term perspective for the general ICU patients as well as for the multiple trauma patients. It was also found to have negative impact on sleep. IC -related factors showed only a minor influence on HRQoL or sleep patterns after the ICU stay.

Conclusions: This multicenter study shows that pre-existing diseases influence the HRQoL short- and long-term after IC, and it must be accounted for when HRQoL and outcome after IC are studied. Approximately, 50% of the decline in HRQoL for the ICU patients could be explained by pre-existing diseases. Future research needs to focus on the remaining factors of importance for the total HRQoL impairment for these patients.

LIST OF PAPERS

This thesis is based on the following papers, referenced in the text by their roman numerals I – IV

- I. Orwelius L, Nordlund A, Edell-Gustafsson U, Simonsson E, Nordlund P, Kristenson M, Bendtsen P, Sjöberg F. Role of preexisting disease in patients' perceptions of health-related quality of life after intensive care. *Crit Care Med* 2005; 33:1557-1564.
- II. Orwelius L, Nordlund A, Nordlund P, Edell-Gustafsson U, Sjöberg F. Prevalence of sleep disturbances and long-term reduced health-related quality of life after critical care: A prospective multicenter cohort study. *Crit Care* 2008; 12:R97.
- III. Orwelius L, Nordlund A, Nordlund P, Simonsson E, Bäckman C, Samuelsson A, Sjöberg F. Pre-existing disease: the most important factor for health related quality of life after critical illness (submitted).
- IV. Orwelius L, Nordlund A, Nordlund P, Simonsson E, Bäckman C, Bergkvist M, Sjöberg F. Pre-existing disease is an important contributor to reduced health related quality of life after critical care in Swedish trauma patients (in manuscript).

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ABBREVIATIONS

APACHE II	Acute physiological and chronic health evaluation
BNSQ	Basic Nordic sleep questionnaire
BP	Bodily pain
EQ-5D	EuroQol 5-dimensions
GH	General health
HRQoL	Health related quality of life
IC	Intensive care
ICU	Intensive care unit
ISS	Injury severity score
LoS	Length of stay
MH	Mental health
PF	Physical functioning
RE	Role-emotional
RP	Role-physical
SF-36	MOS 36-item short-form health survey
SF	Social functioning
SOFA	Sequential organ failure assessment
VT	Vitality

BACKGROUND

The focus of this thesis is the health and health related quality of life (HRQoL) in adult patients who were treated in an intensive care unit (ICU). The focus is on long-term outcomes, and the relation between outcome and different patient-related variables.

Care of the critically ill in an intensive care unit

Critical care medicine and critical care nursing evolved in Scandinavia in the early 1950s to coordinate respirators and healthcare professionals with special skills in advanced life support. The term *intensive care unit* was coined in the United States in 1958, in connection with the organisation of the first special care units. Initially the critical care was focused on problems of the heart and lungs and on life-support efforts for patients who other disciplines considered being “hopelessly ill” (1). The development of new medical procedures, expensive technology, specialised clinical care, and pharmacological treatment of critical care patients over the years has allowed the survival of more patients with complex illnesses and extensive injuries. Precise definitions of “ICU patients” and “intensive care” are lacking, but intensive care is mainly a concept indicating a specific level of care. The patients in the ICU are seriously ill, are usually a heterogeneous group of patients, and have high morbidity. ICUs are organised in many different ways depending on the underlying patient groups and where they are located in a hospital or worldwide. The ICU is a resource-intense and labour-demanding environment that consumes substantial hospital and social resources for a minority (1).

Follow-up after critical illness, various perspectives

Measuring outcome after critical illness is important for many reasons, particularly of all it is one measure of the effectiveness of the intensive care treatment and support that has been offered, and for the standard of care.

Outcomes after critical illness can be viewed from at least three separate perspectives; that of the patients and relatives, the clinical staff, and the

managers of the health care system (Figure 1). Most important is the patient's perspective as the consumer of the healthcare. This perspective can be divided into mortality, and survival. The later perspective may be further examined in for example health related quality of life and functional ability. The staff perspective is more complex as the capabilities and capacity of the ICU is influenced by the heterogeneous nature of the patients and their particular needs and expectations. Outcome data can be a guide and a tool for the staff to assess the quality of the care and provide the background for improvements. From the staff perspective outcome may be assessed as for example, the incidence of adverse and serious events, in a medical as well as an ethical sense. From the perspective of society the outcome measure can be used for economic evaluation of the health care costs, and can be used as a measure to set social and economic priorities. The professionals involved in IC need to produce accurate and reliable information to allow rational decision-making to ensure that the hospital resources are not used in a profligate manner.

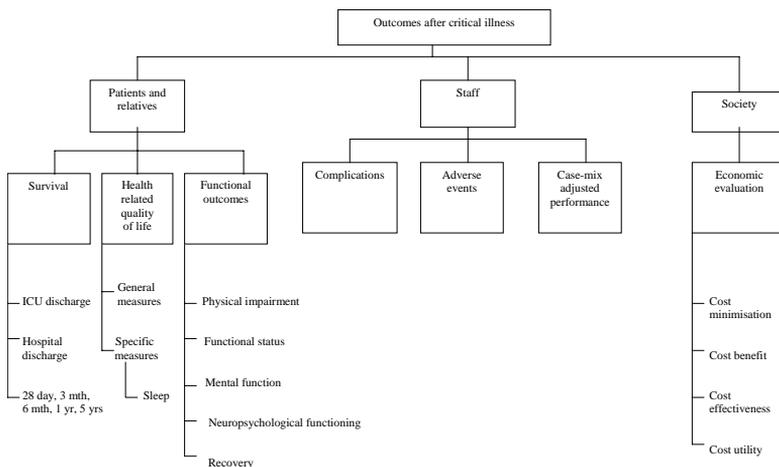


Figure 1 Outcomes on interest after critical illness (modified from Ridley and Duncan (2)) This thesis will focus on the patient-centred outcome: survival and patient-perceived health related quality of life.

Mortality

Traditionally the outcome after intensive care has focused largely on mortality (3). This may not be an adequate overall measure as the mortality rate for

patients in the ICU depends on many of reasons including the underlying diagnostic category. A large study that included 27 103 patients in IC, who were compared with 41 308 patients admitted to hospitals but not cared for in an ICU, showed that the association between the admission to ICU and mortality after discharge was overshadowed by the effect of the underlying diagnosis (4).

The mortality increases during and after intensive care, but after two years it parallels that of the general population (5). The ICU mortality is often described to be in the range of 11%-29% (6-13). For hospital mortality the range is 5%-38% (6-12). The mortality examined at the 6-month follow up after IC is in the range of 5%-7% (7-9, 14) (11) (Table 1).

Table 1 Mortality among ICU patients

First author, year	Patients (n)	ICU mortality (%)	Hospital Mortality (%)	Mortality at 6 Months (%)	Follow-up time (months) †	ICU designation
Wehler 2003 (7)	318	25	8	7	6	Multiple organ dysfunction
Vedio 2000 (8)	341	17	9.7	5	6	General
Hofhuis 2008 (9)	451	10.7	5.2	4.7	6	General
Korosec Jagodic 2006 (12)	98	26	38	NA	24	Trauma
Eddleston 2000 (10)	370	28.9	8.1	NA	12	General
Graf 2003 (13)	714	11.5	NA	NA	9	Cardiovascular Pulmonary
Granja 2002 (6)	355	19	6	6.4	6	General
Granja 2005 (11)	1414	21	6.6	7.3	6	General

NA: not available; †Follow-up time after ICU or hospital discharge

Patient perspective

Short-term outcomes such as ICU and hospital mortality are not adequate surrogates for subsequent patient-centred outcomes as they fail to address the

issue of what it means to survive intensive care (3), and survival needs to be interpreted more broadly in terms of the impact and consequences of treatment (15). Many potential ICU-related factors before, during, and after admission affect the patients in many ways, and influence the outcome after discharge. During the last decade interests in outcome measures after critical care have turned towards examining subjective measures of function (Table 2) (16-21).

Table 2 Morbidity after critical care

First author, Year	No of patients	ICU designation	Factor	Follow-up period	Mean age (years)	Instruments used for measurement
Scragg 2001 (16)	142	General	Anxiety, depression, PTSD	NA	57	HADS, IES
Evans 2003 (17)	109	Mechanically ventilated	Disability	5 years	25	OPCS
Samuelsson 2006 (18)	206	Mechanically ventilated	Memory	3-5 days	62	ICUM, MAAS, CAM-ICU, HADS, IES
Ulvik 2008 (21)	156	Trauma	Sexual function	3-8 years	46	British instrument
Jones 2007 (20)	238	Mechanically ventilated	PTSD Memories	3 months	61 (median)	MAAS, CAM-ICU, PDS, PTSS-14,

NA; Not available, PTSD; Post traumatic stress disorder, HADS; Hospital anxiety and depression scale, IES; Impact of events scale, OPCS; Office of population census and surveys, ICU; Intensive care unit, ICUM; ICU memory tool MAAS; Motor activity assessment scale, CAM-ICU Confusion assessment method, PDS; Post traumatic diagnostic scale, PTSS-14; Post traumatic stress scale

The prevalence of post traumatic stress disorder (PTSD) in ICU survivors is high and studies of risk factors for symptoms of PTSD identified female sex, younger age, prolonged sedation, delusional memories, and previous psychiatric illness (20) as important predictors of long-term outcome. The outcomes of a cohort of mechanically-ventilated ICU patients showed that longer ICU stay, higher baseline values of the severity of illness, worse MAAS scores, and more sedation were significantly associated with delusional memories (18). Sexual dysfunction was common 3 to 8 years after the acute

illness in a group of critically ill patients after trauma and it was also associated with depression (21).

Health related quality of life

Definition

The term "quality of life" appeared in the mid-1950s as a political slogan in the United States and is now generally accepted as a concept in clinical research, being used generally to sum up various health-related components (22). There is no homogeneous definition and the concept is sometimes used incorrectly as a synonym for health. Health related quality of life (HRQoL) is a multidimensional concept including aspects of life that are not generally considered as "health", such as income, freedom, and quality of the environment. When a patient is ill or diseased, almost all aspects of life can become health related (23), because it affects their overall quality of life. HRQoL can be defined as the level of well being and satisfaction associated with a person's life and how it is affected by disease, accident, and treatments (2). The most important aspects of HRQoL are physical and mental health, social function, role function, and general well being (24), because the goal of health care is to maximize the health component of quality of life (25). The overall aims of IC are to reduce morbidity and mortality, to maintain functional capacity, and to ensure that the patients regain or maintain their HRQoL. The survivors of critical illness are at risk of permanent physical and functional deficits that may affect psychological and social functioning, which is known to reduce HRQoL significantly. The ideal outcome is for the patient to return to their pre-existing state or to that expected for a person of the same age and medical condition (26). Recently it has been generally accepted that the most important variable for assessing the outcome and the effectiveness of intensive care is HRQoL (3, 27), and interest in this area has grown particularly during the last decade.

Scoring systems for health related quality of life in health care

There are many different ways of measuring HRQoL and they may be classified as direct and indirect. Direct methods are, for example, time trade-

off (TTO), standard gamble (SG), and rating scale (RS) (28). The indirect methods use some type of questionnaire (instrument) which can be divided into disease-specific or generic instruments. A disease-specific instrument is adapted for special groups and examines dimensions specific for an illness or treatment for a single disease group of patients or area of function. An example of such a measure is the Abbreviated Burn Specific Health Scale (BSHS-A)(29). Generic instruments include health profiles and instruments that generate health utilities that can be applied to any groups and is not related to disease. Example of generic instruments are EuroQol 5-D (EQ-5D), Medical outcomes Study 36-item Short-form Health Survey (SF-36), Nottingham Health Profile (NHP), and Sickness Impact Profile (SIP), and these have all been used repeatedly in critical care research (30) (Table 3). HRQoL questionnaires are made up of a number of items or questions. These items are added up in a number of domains or dimensions. A domain or dimension refers to the area of behaviour or experience that the investigator is trying to measure. For some instruments the evaluation exercises are of importance for each item rates in relation to the others. For other instruments items are equally weighted, which assumes that their value is equal. The HRQoL questionnaires can be administered by trained interviewers or self-administered, and there are strengths and weaknesses with both techniques. By using interviewers the response rates are usually improved and the errors caused by misunderstanding are reduced. A drawback is that they consume resources and the interviewer needs to be specially trained. Self-administered questionnaires are less demanding and usually lead to high response rates but there may be missing items and misunderstandings in response patterns (23). A compromise between the two approaches to optimise outcome is to telephone the patients to remind them of the inquiry in cases of no reply in the self-administrated questionnaire. Computer and web-based provisions of HRQoL measures are under development and they may be good options for the future. Today there is no doubt that the ultimate evaluation of any treatment or procedure for any given patient is the evaluation made by the patient himself (15). In this aspect it is important to underline that the patients' ratings have been found to be different to those made for the patient by the treating physicians, health care personnel, or by a proxy (25, 31-33). These findings have led us to prefer to use instruments that are constructed for self-assessment.

Table 3 Instruments commonly used to assess health related quality of life after intensive care

Instrument	Purpose	Description	Concepts measured
EuroQol-5D (34)	State of health	5 items assessed at 3 levels	Mobility, personal care, usual activities, pain/discomfort, anxiety/depression
Short Form 36 (26)	General health	36 items in 8 dimensions, and physical and mental summary scores	Physical: functioning, role limitations, pain, general health Mental: vitality, social, role limitations, mental health
Nottingham Health Profile (35)	Perceived physical, social and emotional health	First part 38 items, second part 7 items	Sleep: physical mobility, energy, pain, emotional reactions, social isolation Employment: home- social-sex life, hobbies and holidays
Sickness Impact Profile (36)	Health-related dysfunction	136 items in 12 categories	Physical: body movement, mobility, ambulation Psychosocial: intellectual, social interaction, emotional behaviour, communication Other: sleep and rest, daily work, household, leisure and recreation

Scoring instruments

EQ-5D

The EQ-5D (34) was developed by a multidisciplinary group of research workers from five European centres. It was designed to serve as a complement to other more comprehensive or disease-specific instruments (37). In short it contains two parts. The first is a five-item questionnaire that elicits one of three responses (“no”, “some”, or “extreme”) for problems with mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Taken together these define a total of 243 (=3⁵) possible health states. The index value of a particular health state indicates the preference for being in that health state in relation to death, which has been set as equal to 0, and the best possible health value that

has been set at 1.0. The second part of the EQ-5D is a visual analogue scale (VAS) ranging from 0 (worst possible health state) to 100 (best possible health state), on which the respondents rate how they perceived their health on that particular day. The EQ-5D has not been comprehensively validated for ICU patients (30).

SF-36

The SF-36 (26) (Figure 2) was developed in the early 1990s by an American science group under the direction of John Ware Jr. SF-36 is based on WHO's broad health concept and was constructed to satisfy the minimum psychometric standards necessary for group comparisons. It contains multi-dimensional indicators of health concepts and measurement of the full range of health states, including behavioural function and dysfunction, distress and wellbeing, objective reports, and subjective ratings, and both favourable and unfavourable self-evaluations of general health. SF-36 uses 36 items to measure eight domains: physical functioning (10 items), role limitations as a result of physical problems (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations as a result of emotional problems (4 items) and mental health (5 items). All but one of the 36 items (self-reported health transition) is used to score the eight SF-36 scales.

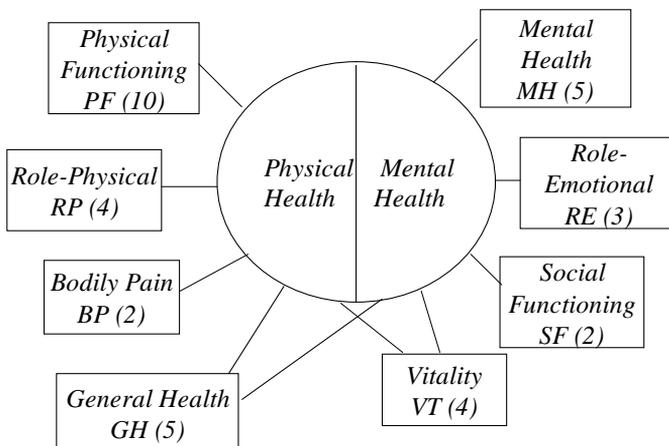


Figure 2 The MOS 36-item short-form health survey (SF-36) (26)

An overall score and a sum score for each category are obtained where the scores on all subscales are transported to a scale from 0 (worst score) to 100 (best score). At least 50% of the items in a given scale must be present for estimating that particular scale, and to complete data for all eight SF-36 scales in estimating the summary scores. The instrument works favourably in separating psychiatric and physical illnesses and in discriminating severe major medical illness groups from moderately ill and healthy groups. It is one of the few HRQoL instruments that are brief enough to use in clinical trials without any loss of essential psychometric quality and clinical validity (38). The SF-36 has been validated in critically ill patients (39). It is suitable for self computerised- or interviewer administration, to persons aged 14 years and older, and is most often completed in 5-10 minutes.

NHP

The NHP (35) was developed in England and is a measure of perceived distress related to severe or potentially disabling health conditions. It is self-administered and can be used as a questionnaire sent out by post. The NHP contains 38 yes/no statements in six domains of distress: energy level, pain, emotional reactions, sleep, social isolation, and physical abilities. Summed scores are obtained for each NHP domain, but an overall score is not provided. The disadvantage of NHP is its inadequate ability in diseases involving minor to mild levels of physical disability (38), and NHP has not been comprehensively validated for ICU patients (30).

SIP

The SIP was developed in the USA as a behaviourally-based assessment of the impact of illness on everyday life (36). It covers a wide range of functioning in different areas of activity and is intended to be broadly applicable across diverse demographic groups because of its focus on behaviour. The SIP contains 136 yes/no statements describing limitations or recent change in 12 dimensions of functioning: social interactions, communication, alertness, emotional behaviour, body care, mobility, ambulation, work, eating, sleep, home management, and recreation. An overall score and a summed score for each category is provided. SIP can be administered by interviewer, self-administered, or by postal version. The instrument has been validated in critically ill patients (40). It is more sensitive to declines in functioning than improvements, and its precision and sensitivity to clinically important changes

in patient functioning (both positive and negative changes in performance) is uncertain (38).

The EQ-5D and SF-36 have been recommended as the best-suited instruments for measuring HRQoL in multicentre critical care trials (3). SF-36 is the most often used instrument for assessing HRQoL in critical care, and 93% of studies using SF-36 or EQ-5D were published in 2000 or later, compared with 14% using SIP or NHP (30). In the present study HRQoL was measured by EQ-5D and SF-36.

Table 4 Health related quality of life studies in ICU survivors

First author	No	Instrument	Follow-up time (months)	Result (reduction %)
Granja 2002 (6)	275	EQ-5D	6	25
Badia 2001 (41)	334	EQ-5D	12	35
Kvåle 2003 (42)	223	SF-36	6	44
Flaatten 2001 (43)	51	SF-36	144	14
Tian 1995 (40)	3655	SIP	12	9
Combes 2003 (44)	87	NHP	36	15
Capuzzo 2000 (32)	84	QOL-SP	12	58

EQ-5D; EuroQol 5-dimension, SF-36; Medical outcomes Study 36-item Short-form Health Survey, SIP; Sickness impact profile, NHP; Nottingham Health Profile, QOL-SP; Spanish quality of life questionnaire

Several studies have shown that the HRQoL for survivors after IC is significantly lower than in the general population up to one year after the critical care period measured with different questionnaires (Table 4)(6, 32, 40-44), and EQ-5D (Table 5), and SF-36 (Table 6). In a review of HRQoL adult survivors of ICU HRQoL improved over time, but was significantly lower than that in the general population during the long-time follow-up (30). Few studies have followed general ICU patients for a longer period of time and the median follow-up time has until now been 7 months (30). This rather short follow-up time raises the question of whether the impairments for HRQoL remains consistent over longer periods of time or returns to normal.

Table 5 Health related quality of life measurements in adult ICU survivors versus age and sex adjusted general population or comparison with pre-ICU scores, or other patient groups (ICU intensive care unit, EQ-5D EuroQol 5 Dimension)

First author (year)	No ‡	Follow-up time (months)	ICU category	HRQoL comparison	EQ-5D index mean
Granja (2003) (49)	29	6	ARDS	ARDS and non-ARDS	–
Granja (2002) (6)	275	6	general	pre-existing and healthy	↓*
Holtslag (2006) (50)	335	6 and 18	trauma	pre-existing and healthy	↓*
Badia (2001) (41)	334	12	general	before and after ICU	↓*
Ulvik (2008) (21)	210	2-7 years	trauma	before and after the tra	↓*

‡ sample size at first follow-up

↓* statistically significant ($p < 0.05$) decreament in HRQoL, – ; not statistically significant differences, ARDS; acute respiratory distress syndrome

An important question is what factors predict HRQoL. Studies have investigated associations of different factors before, during, and after ICU; a) patient-related factors such as age and sex and b) patient-acquired factors such as previous health state, social factors, sleep, and c) intensive-care-related factors such as type of admission, diagnosis on admission, severity of illness, length of stay in ICU, sedation, time in ventilator, severity of injury, or organ dysfunction, and d) factors after ICU such as length of stay in hospital, sleep-disturbances, pain, and memories with HRQoL in ICU survivors (Table 7 only age and ICU related factors included in the table)(7-11, 13, 24, 42, 45-51). In these studies most found significantly lower physical functioning in elderly compared with younger ICU survivors (7, 13, 24, 47, 48, 50). No study found a significant association between age and mental health (SF-36) or anxiety/depression (EQ-5D). Physical functioning was associated with severity of illness, length of stay in ICU, and severity of injury in some of the studies (9, 24, 45, 47, 48). For time in ventilator and organ dysfunction both physical and mental health were affected (7, 46, 48).

Table 6 Health related quality of life measurements in adult ICU survivors, age-and sex general population or comparison with before ICU scores, or other patient groups (ICU intensive care unit, SF-36 Medical Outcomes study 36-item Short Form General Health Survey)

First author (year)	N †	Follow-up time (months)	ICU category	HRQoL comparison with	Physical domains			Mental domains				
					Physical function	Role physical	Bodily pain	General health	Vitality	Social function	Role emotional	Mental health
Eddleston (2000) (10)	143	3	General	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	-
Hofhuis (2008) (9)	257	3 and 6	General	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Kvale (2003) (42)	223	6	General	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Vedio (2000) (8)	109	6	General	pre-existing vs healthy	↓*	-	-	↓*	↓*	-	-	-
Ridley (1997) (24)	95	6	General	pre-existing vs healthy	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Graf (2003) (13)	153	1 and 9	CaP	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Wehler (2003) (7)	171	6	MOD	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Ringdal (2007) (48)	239	6 and 18	Trauma	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Michaels (2000) (65)	126	6 and 12	Trauma	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Pettila (2000) (46)	299	12	MOD	GRG	↓*	↓*	-	↓*	↓*	↓*	↓*	↓*
Heyland (2000) (66)	26	16	Sepsis	GRG	↓*	↓*	-	↓*	↓*	↓*	↓*	-
Sluys (2005) (47)	205	5 years	Trauma	GRG	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Flaatten (2001) (43)	51	12 years	General	GRG	↓*	↓*	-	↓*	↓*	↓*	↓*	↓*

† sample size at first follow-up

GRG; general reference group, CaP; Cardiovascular and pulmonary, MOD; multiple organ dysfunction

↓* clinically relevant and significant ($p < 0.05$) decrement in HRQoL; - non-clinically relevant (< 5 -point) change in HRQoL

Table 7 Age and ICU factors associated with health related quality of life in adult ICU survivors

First author (year)	Age	Severity of illness	LoS ICU (days)	Diagnosis on admission	Type of admission	Time in ventilator (days)	Sedation	ISS	Maximum SOFA
SF-36									
Graf (2003) (13)	PF	No				No			No
Ridley (1997) (24)	Older	Yes	Yes						
Eddleston (2000) (10)	Younger	No				No			Physical
Wehler (2003) (7)	Physical	No	No			No			
Kvale (2003) (42)		No							
Hofhuis (2008) (9)	No	No	Yes						
Kleinpell (2003) (45)	No	Yes							
Pettita (2000) (46)	Physical	No	Yes	Yes				No	PF,BP, VT, RE
Sluys (2005) (47)	Older		Yes						
Vedio (2000) (8)	No		No		Yes				
Ringdal (2007) (48)	PF, RP	PF, RP	PF, RP			PF, RP, VT, SF, MH	Yes	PF, RP	PF, RP
EQ-5D									
Granja 2003(49)	No	No	No			No			
Holtslag 2006 (50)	Yes							Yes	
Ulvik 2008 (21)	No							Yes	Yes
Granja 2005 (6)				Yes	Yes				

ICU; intensive care unit, LOS; length of stay, ISS; Injury severity score, SOFA; Sequential organ failure assessment SF-36; Outcomes study 36-item Short Form General Health Survey, EQ-5D; EuroQol 5 Dimension) PF; Physical functioning, RP; Role physical, BP; Bodily pain, VT; Vitality, SF; Social functioning, RE; Role emotional, MH; Mental health

Difficulties experienced in follow-up after critical illness

Several factors are known to affect HRQoL which by themselves may lead to methodological difficulties when examining HRQoL in ICU patients. A risk group, such as those patients admitted with a physical trauma, has been claimed to significantly reduce their HRQoL after the ICU stay (6, 41, 43). Before the trauma, patients often reflected the norm for healthy adults but up to 5 years after injury the patients have reported considerable physical (68%) and psychological (41%) disabilities (47). Pre-existing chronic diseases and the health before admission to the ICU are claimed to be associated with impaired HRQoL, as chronic diseases are well known to influence HRQoL (7, 52). For example diabetes is associated with poor HRQoL in both the medical and psychosocial aspects (53). Chronic disease is also well-known to impair sleep (54). Many IC patients, irrespective of their diagnosis, have been found to have disturbed sleep during the ICU period and after discharge from ICU (55). Survivors of IC may therefore have reduced HRQoL caused by both the pre-existing chronic diseases and effects caused by the period of critical care.

Proxies for perception of patient's health related quality of life

Several investigators have tried to validate the use of proxies instead of the patients for assessing patient-perceived HRQoL. Some have found good agreement (7, 9, 52) and others have reported poor correlation between proxy and patient perceived HRQoL. Relatives are claimed to overestimate the patient's physical dysfunction and to underestimate the mental limitations relative to the measures presented by patients themselves (31, 33). From a philosophical point of view, HRQoL is a unique personal perception and therefore the best description of the HRQoL most certainly will have to come from the person himself.

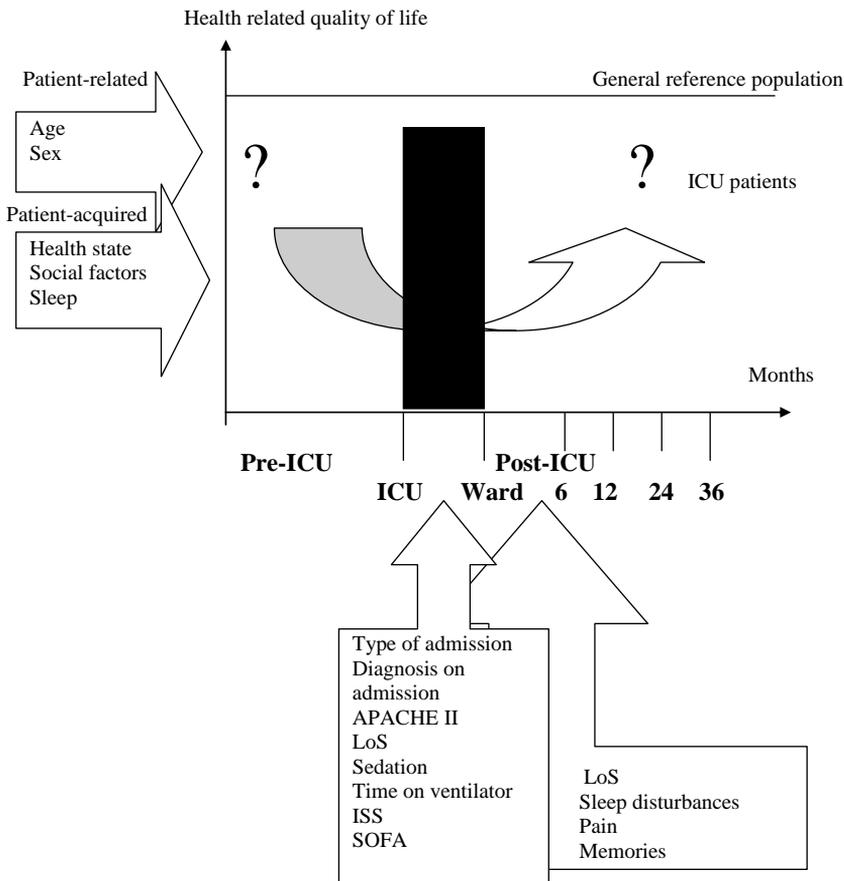


Figure 3 Hypothetical model for this hypothesis

We know that HRQoL is reduced up to two years after intensive care compared with that in the general population. However it is not known if the decrease is already present in the period before the intensive care, or if it is to the result of the circumstances of the intensive care period. It is also unknown when the HRQoL returns to the pre-ICU level. Factors that have been found to have an impact on the HRQoL for the ICU patient are patient related; age and sex, patient acquired factors; health state, social factors and sleep, intensive-care-related factors; type of admission, diagnosis on admission, APACHE II score, length of stay in ICU, sedation, time on ventilator, severity of injury, and organ dysfunction, and factors after the critical care period; length of stay on hospital, sleep disturbances, pain, and memories.

AIMS OF THE THESIS

The general aim of this thesis was to investigate the long-term HRQoL in a large cohort of adult survivors after critical illness and a period of intensive care.

The specific aims in the different papers were:

I. To investigate the short-term (paper I) and long-term (paper III) HRQoL after intensive care, and compare the HRQoL of ICU survivors with that of the general population, with particular emphasis on the effects of pre-existing disease, age, sex, and factors related to ICU care.

II. To depict the short and long-term (6 and 12 months) sleep patterns after critical illness, and to examine specifically the relation between sleep disturbances and HRQoL. To investigate also whether pre-existing disease and factors related to intensive care affected the long-term sleep patterns of these patients.

III. To assess the rate of pre-existing diseases and to examine their possible long term (2 years) affects on HRQoL in a group of adult trauma patients who require intensive care.

PATIENTS AND METHODS

Setting and study population

Data were collected from two (paper I) and three (paper II-IV) mixed medical-surgical ICUs in the southeast of Sweden: one university, and two general hospitals. The regional referral area of the hospitals covers roughly 1 million people. The ICU at the university hospital has eight beds, and 500 to 750 patients are admitted annually. Adult postoperative patients, those after open-heart surgery, neurosurgery, and burns are treated in other specialised units, and were not included in this study. The two general hospitals both have six-bed ICUs, and admit 500 to 700 patients annually. The units are the only ICUs at the general hospitals apart from the neonatal ICU.

All patients aged 18 years and older, who remained in the ICU for more than 24 hours and were alive 6 months after discharge from the hospitals, were included in the study. Patients who were readmitted were included on only their first admission. After the national Swedish Social Security register had been checked to avoid sending inquiries to patients who had died, information and a request to participate were sent to each patient by mail, together with a structured questionnaire and a preaddressed and prepaid envelope. Patients who had not responded within about 10 days were contacted by telephone by one of the investigators from each hospital (LO, ES, or CB). If telephone or first mailing achieved no answer two reminders were sent out (at 3 and 6 weeks).

All admissions to ICU at the hospitals are recorded electronically in databases (LINDA 2000, Kneippen Datakonsult AB, Norrköping Sweden in Linköping and Norrköping, and FENIX 1.3.5, System/Udac AB, Uppsala Sweden in Jönköping). From these databases, data were extracted about patients' sex, age, reasons for admission to, and length of stay in ICU, APACHE II score on admission, and outcome (dead or alive).

The questionnaire contained questions about the patients' civil state, children living at home, education, employment before and after admission to the ICU, and pre existing disease (self-reported diagnosis). The questionnaire asked, "Do you have any of the following illnesses and have had for more than 6 months with the pre-specified alternatives: cancer, diabetes, heart failure, asthma/allergy, rheumatic-gastrointestinal, blood, kidney, psychiatric,

neurological disease, thyroid, or any other metabolic disturbance, or other long term illness?"

Reference group

Data from a public health survey of the population of the county of Östergötland (the area in which the university hospital and the general hospital of Norrköping is situated and adjacent to the county where the general hospital of Jönköping is located) were used as reference group (56). The survey aimed at monitoring health and health-related risk factors in the general population and was completed during 1999 (57). Questionnaires were mailed to a random sample of 10 000 people aged 20 to 74 years. After two reminders, 6093 (61%) had responded. Apart from lower percentages of immigrants and single households, the responders differed only marginally from the reference population of the county. The questionnaire included, apart from questions on background characteristics, a wide array of questions about health problems. These questions assessed the frequency (daily, weekly, monthly, and rarely/never) of specific symptoms of ill-health during the previous 12 months, some of which were specific to certain health problems and diseases such as asthma and cardiovascular disease. This section of the survey was concluded with an open question that asked about "other health problems". Although different from the questions used to assess pre existing disease in the ICU patients, the questions about health problems made it possible to classify the reference population into disease groups corresponding to those reported by the ICU patients. This was done in the following way. One of the authors (MK) transformed the free-text information regarding such "other health problems", which were basically in two categories; one Latin names of diagnoses that were well-defined, the other to a large extent, symptoms, that corresponded to the International Classification of Diseases-10 nomenclature. Milder symptoms (low intensity and uncommon) were overlooked. Classification of the reference group into disease-specific subgroups were based on symptoms reported as daily or weekly on one or more questions within the same disease category, or the International Classification of Diseases-10 labels put on the "other health problems" reported. As no questions about symptoms of cancer and diabetes were included in the questionnaire, the cancer and diabetes subgroups were based solely on the second question, whereas the other disease-specific subgroups, namely cardiovascular disease, gastrointestinal disease, and asthma, were based on either one, or a combination of the two. In most cases, the

classification of respondents as having a disease was based on only the information from the open-ended question (mainly a Latin diagnosis).

Patient inclusions and follow-up

The patients were included in the study and studied 1 August 2000 to 30 June 2007 at four different occasions after their critical illness; 6, 12, 24, and 36 months after discharge from the ICU and from the hospital. The questionnaires contained all instruments at the same time, and were identical at all times. From that, HRQoL was first assessed from the 6 months measure and from the patients who had been included in the study until 2002 (Paper I). Secondly, sleep disturbances were assessed from the 6 and 12 months measure and from the patients who had been included until November 2003 (Paper II). Thirdly, HRQoL was assessed from all four occasions and the whole study period (Paper III). Fourth, HRQoL questionnaires of the patients with the admission diagnosis "multiple trauma" that were gathered in study III were examined separately (Paper IV).

Ethics

This study was approved by the Local Committee for Ethical Research, and the Data Inspection Board approved the protocol. Informed consent was obtained from all participants.

Questionnaires and scoring systems used

Health related quality of life was evaluated by EQ-5D (34) (paper I, III and IV) and SF-36 (58) (paper I-IV). Sleep disturbance was evaluated by BNSQ (59). The APACHE II assessed severity of illness (60) (paper I-IV). Injury severity was measured by ISS (paper IV) (61). The SOFA score quantified organ dysfunction failure (paper IV) (62).

Sleep questionnaire

The questions of sleep disturbances were taken from the Swedish version of the Basic Nordic Sleep Questionnaire (BNSQ) (59). The instrument has been shown to be valid (59, 63).

Three questions included in the BNSQ were used: were there difficulties in falling asleep; what was the quality of sleep like, and; was there a difference between the reported need for sleep and that achieved. These questions were also used in the public health survey. To the second question above (“what was the quality of sleep like”) yet another, single non validated question (64) was added asking about the quality of sleep prior to the ICU stay. This question was only asked to the ICU group.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 11.0-15.0) was used to help with the statistical analyses. Categorical variables are presented as numbers and percentages and continuous data are presented as means and standard deviations or 95% confidence intervals. Unadjusted two-sample comparisons using Pearson’s chi square, Kruskal Wallis (paper II), and Student’s t test were used to assess differences in background characteristics between groups. As eight to 10 different HRQoL measures were used by SF-36 eight subscales (paper I-IV) and the EQ-5D two overall measures (paper I, III and IV) the number of comparisons involved became rather large. No formal adjustments for multiple testing were made. Instead focus was directed on the size of the numerical differences and the consistency of differences seen across the different HRQoL measures. The 95% CI were used to illustrate the uncertainty associated with the observed differences.

A general population of the county of Östergötland was used as a reference group, (containing 6093 people aged 20-74 years). When ICU patients were compared with the reference group, patient’s over 75 years old were excluded. Probabilities lower than 0.05 were regarded as significant.

Paper I

The focus was on assessing the impact of in the burden of pre existing diseases on HRQoL in ICU patients and in reference population. In addition to overall comparisons disease-specific subgroups were compared, the choice of which was based on judgements regarding the comparability of the disease-specific subgroups formed.

Multiple linear regression analysis, adjusted for age and sex, was used to evaluate the independent effects of concurrent disease, APACHE II scores on admission, and length of stay at the ICU on HRQoL among the ICU patients.

Paper II

The focus was on examining the frequency of sleep disturbances in the ICU patient group and to assess the impact of sleep disturbances on HRQoL. Comparisons were made with the reference population. Three questions about sleep were used from the BNSQ. The answers were dichotomised and compared as follows: the severity of difficulties in falling asleep at least weekly rather than less than weekly; poor quality of sleep or worse compared with, good or better; time slept less than required compared with time slept equal to or more than required. Logistic regression analysis, adjusted for age, sex, and pre-existing disease was used to evaluate the difference between the patients and the reference group. Logistic regression was also used to evaluate the independent effects of age, sex, concurrent disease, APACHE II scores on admission, length of stays in ICU and hospital and diagnoses on admission of sleep disturbances among the patients and the relation between sleep disturbances and HRQoL.

Paper III

The focus was on assessing changing in HRQoL over time for the ICU patients, and to evaluate the effect of pre-existing diseases and ICU-related factors. A general linear model (GLM) adjusted for age and sex was used to analyse the impact on HRQoL of ICU related factors; diagnosis at admission, APACHE II score, length of stay in ICU and hospital, time on ventilator, and background factors; sick leave before ICU, employment before ICU, born in Sweden, and pre-existing diseases. Marginal means were estimated from the model including all variables with an effect that yielded a p-value lower than 0.05. To maximize the statistical power, the 6 month' follow-up data were used for this purpose. GLM was also used to assess changes in HRQoL (all SF-36 eight variables and EQ-5D) over time within groups, total and divided in those with pre-existing diseases and previously healthy. In analyses that compared HRQoL over time, only survivors with answers at all the follow-ups were used in the comparison.

Paper IV

The focus was on assessing the incidence of pre-existing diseases in the multiple trauma patients and to compare their HRQoL with other ICU admission diagnostic groups. A multiple regression analysis, adjusted for age and sex, was made to identify how pre-existing disease and ICU factors (ISS-score, Maximal SOFA score, admission APACHE II score, length of stay in

ICU, and hospital, and time on ventilator) were related to problems reported in EQ-5D and in each SF-36 dimension. In the model, all variables were continuous apart from pre-existing disease and sex.

RESULTS

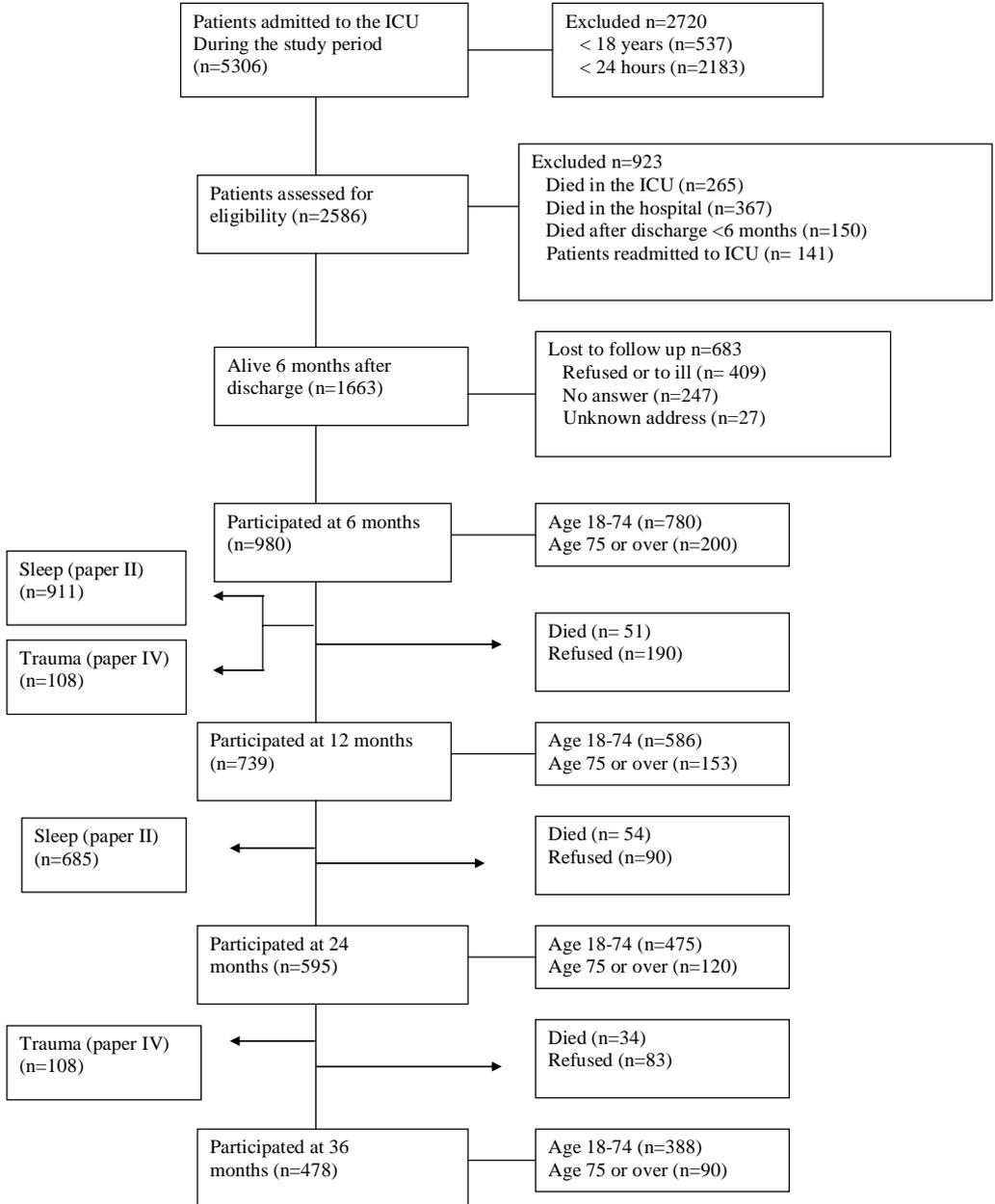


Figure 4 Flow diagram of the patients who were and were not included in the study (paper I-IV)

Lost to follow up

Papers I-IV

Of the 2586 patients who were assessed for eligibility 923 patients (36%) were excluded (Figure 4). Of these one hundred forty-one (15%) were re-admissions, 265 (28.7%) died in the ICU, 367 (39.8%) died in hospital, and 150 (16.2%) died up to six months after discharge from hospital. Of the survivors 683 patients were lost to follow up. Four hundred and nine patients (25%) refused or were too ill to participate, and 274 (17%) did not answer or could not be traced. The non-responders were significantly younger than the patients who participated in the study (52 compared with 58 years) ($p=0.02$), had higher APACHE II scores (16.3 compared with 15.6) ($p=0.04$), stayed a shorter time in the ICU (93 compared with 123 hours) ($p<0.001$), and spent a shorter time on mechanical ventilation (33.5 compared with 62.0) ($p<0.001$). The clinical details for these patients are presented in table 8.

Table 8 Clinical details for the patients who were lost to follow up (n=683)

	Mean	SD	Range	N (%)
Age	57.7	19.6	18-99	
APACHE II score	16.3	7.6	0-44	
Time on ventilator, hours	33.5	81-6	0-610	
LoS ICU, hours	93.2	105.4	24 -958	
LoS hospital, days	14.8	19.9	1-246	
Diagnosis				
Multiple trauma				69 (10)
Sepsis				53 (8)
Gastrointestinal				104 (15)
Respiratory				147 (22)
Miscellaneous				309 (45)

Demographic and clinical variables

Papers I and III

The entire study comprises 980 patients that replied at the 6 month measure (Figure 4). The patients in the ICU group were older, more likely to be men, more likely to have retired, and more likely to have frequent sick leave than

the reference group (Table 9). In paper I patients from two of the hospitals participated; the university hospital in Linköping and the general hospital of Jönköping. The patients from this study (I; n=343) are part of the data included later in the results of the total 6 months measure in paper III. The underlying clinical and demographic details of these two papers are similar and are presented in Table 10.

The mean age of all patients if taken together in study I (n=343) and III (n=980 and n=478), was 58.0 years, and 57.3% were male. Mean length of stay in the ICU was 5.1 (SD 7.0) days. Of these 294 (30.0%) of the patients remained in the ICU for more than 2 days and 226 (23%) for more than 6 days. Median length of stay in the hospital was 9 days (range 1-231). Median APACHE II score was 15.0 (range 0-43) and 165 (22%) had an APACHE II score of ≤ 9 , 344 (35%) of the patients had 16-25, and 108 (11%) had ≥ 26 . Of those who had been on mechanical ventilation 403 (41%) more than one third 129 (32%) were mechanically ventilated for seven days or more; 105 (26%) for three to six days and 170 (42%) for one to two days. For the diagnoses at admission the patients were divided in the most frequent diagnostic groups, which together represented 61% (n=595). These diagnoses were; multiple trauma, sepsis, gastrointestinal disease, and respiratory disease. In the remaining group, the "miscellaneous", the most common diagnosis was cardiovascular disease 9% (n=86). In paper II the patients with this diagnosis are examined separately. Further diagnoses were intoxication n=32 (3%), renal failure n=31 (3%) and HELLP/eclampsia n=27 (3%). In the entire ICU group 725 (74 %) had pre-existing diseases, and of these 225 (31%) had two or more chronic diseases at least 6 months before admission to the ICU. For the patients who were healthy before critical care, more than half 156 (62%) had APACHE II scores of ≤ 15 whereas the patients who had two or more pre-existing diseases had APACHE scores of ≥ 16 . There were no significant relations between having a pre-existing disease and length of stay in the ICU or time on mechanical ventilation.

Table 9 Sociodemographic characteristics of patients in intensive care unit (ICU) and reference groups

Characteristic	ICU group (n=980)	Reference group (n=6093)	p Value
Male gender	567 (58)	2833 (46)	<0.001
Age, yrs			<0.001
20-39	181 (18)	2197 (36)	
40-59	263 (27)	2504 (41)	
60-74	324 (33)	1392 (23)	
Education			0.06
Basic school †	380 (39)	1757 (29)	
High school/university †	217 (22)	1350 (23)	
Other †	383 (39)	2885 (48)	
Marital state			<0.001
Single †	257 (27)	1312 (22)	
Married/cohabit †	598 (62)	4114 (74)	
Other †	110 (11)	275 (5)	
Children at home	172 (18)	2316 (39)	<0.001
Employment			<0.001
Employed/leader ‡	371 (38)	3538 (59)	
Unemployed ‡	39 (4)	366 (6)	
Retired ‡	491 (50)	1132 (19)	
Student ‡	27 (3)	396 (7)	
Other ‡	52 (5)	504 (8)	
Sick leave	110 (11)		<0.001
Reported sick 100%‡	71 (7)	64 (1)	
Reported sick <100%‡	26 (3)	11 (0.2)	

† Not all patients answered the question; ‡ before ICU.

Data are number (%) of totals.

Paper II

The study of the ICU patients' long term sleep-disturbances after critical care consisted of 685 patients who answered the questionnaires at both 6 and 12 months (Figure 4). Of these 45% had difficulties in falling asleep, poor sleep quality, or slept for shorter periods than needed. The mean age of all patients in the group was 56 years, and 55% were male (Table 10). APACHE II score, length of stay in ICU or in hospital, and time on mechanical ventilation were in line with what has seen for the patients in papers I and III. There were no significant associations between long term sleep disturbances and APACHE II score, length of stay in ICU or in hospital, admission diagnosis or the extent of mechanical ventilation. For the patients with sleep disturbances, 41% had been on mechanical ventilation, 9% for three to six days and 14% for seven days or more. For the patients with sleep-disturbances 324 (77 %) had pre-existing diseases.

Paper IV

Paper IV is based on 108 patients with the admission diagnosis of multiple traumas (Figure 4). Of these, 51 answered the questionnaire at 6, 12 and 24 months. Their mean age was 44 years and 68% were male (Table 10). Of the total group 89% had ISS ≥ 9 and 62% had ISS ≥ 15 . Maximum-SOFA score in 77% was ≥ 3 , and in 13% ≥ 10 . Nearly half (47%) of these patients had been on mechanical ventilation, 19% for three to six days and 11% were mechanically ventilated for seven days or more. Most of the patients (77%) were exposed to blunt trauma after traffic- (56%), falls- (10%), working accidents (7%), or assaults (4%). There were significant differences between the patients from the three hospitals. The trauma patients from Norrköping had significantly lower scores on maximum-SOFA than the other two hospitals Jönköping ($p=0.02$), and Linköping ($p=0.04$). Lower ISS ($p=0.04$), and APACHE II scores ($p=0.02$) were seen for the general hospitals compared with the university hospital. At the university hospital, the patients were younger ($p=0.005$). Of the patients with multiple trauma 33% ($n=36$) had combined body and skull trauma. Of these, three patients were admitted to a neurosurgical intensive care unit prior to admission to the general ICU.

Table 10 Clinical and demographic variables (paper I-IV)

	Paper I 6 months n=343	Paper III 6 months n=980	Paper III 36 months n=478	Paper II Sleep disturbances (n=419)	Paper IV Trauma group (n=108)
	min-max	min-max	min-max	min-max	min-max
Male (%) a	196 (57)	567 (58)	274 (57)	231 (55.1)	74 (68)
Age (years) b	57.0 (19.1)	58.2 (18.2)	58.8 (17.0)	55.7 (18.4)	44.4 (18.3)
APACHE II c	15.9 (15.0;16.8)	15.6 (15.1;16.1)	15.3 (14.7;16.0)	15.2 (14.4; 16.0)	10.8 (9.6;12.1)
LoS ICU hour c	126.4 (106.5;141.6)	123.1 (112.6;133.6)	24-1845	122.7 (106.6;138.9)	131.1 (93.5;168.6)
LoS hospital Day c	15.6 (13.1;18.0)	15.1 (13.8;16.3)	1-231	15.2 (13.2;17.1)	17.6 (12.3;22.8)
Time on ventilator, hour c	56.2 (42.0;70.3)	62.0 (52.3;71.7)	0-1753	62.4 (47.0;77.7)	63.7 (28.2;99.2)
Maximal SOFA c			0-1753	0-1753	0-1753
ISS c					5.3 (4.7;6.0)
Diagnose at admission a					18.8 (16.8;20.8)
multitrauma	50 (15)	114 (12)	57 (12)	49 (12)	
sepsis	36 (10)	84 (9)	37 (8)	38 (9)	
gastrointestinal disease	65 (19)	201 (20)	101 (21)	80 (19)	
respiratory disease	68 (20)	197 (20)	85 (18)	84 (20)	
cardiovascular				29 (7)	
miscellaneous	124 (36)	384 (39)	198 (41)	134 (33)	
Pre-existing disease a	262 (76)	725 (74)	340 (71)	324 (77)	76 (70)

Data are given as n (%), b mean (standard deviation), or c mean (95% confidence interval) APACHE II, Acute Physiology and Chronic health Evaluation; LoS, Length of stay; ICU, Intensive Care Unit; SOFA, Sequential organ failure assessment; ISS, injury severity score

Mortality

During the study period 423 died on the ICU (8%), and of these, 184 (44%) patients died during the first 24 hours. Mean age for those who died were 70 years, mean length of stay 4 days and mean APACHE II score 24.7. Up to six months after discharge from ICU and hospital 150 patients 18 years old or more had died. In the trauma group two patients died 12 to 24 months after discharge from hospital. For both of them they were physically abused on admission, and committed suicide.

Health related quality of life (HRQoL)

Papers I and III

HRQoL, examined with both EQ-5D and SF-36 showed minor improvements over time. For the entire group (n=980), significant or clinical important improvement (>5 units) was seen only in physical function (PF) between 6 and 36 months with units of 5.8, role limitations due to physical problems (RP) between 6 and 12 months with units of 8.9 and role limitations due to emotional problems (RE) between 6 and 12 months with units of 6.4 improvement (Table 11 a). For the group who answered on all four occasions (n=478) there were no significant or clinical important (>5 units) improvements apart from role limitations due to physical problems (RP) between 6 and 12 months which showed an improvement with 9.0 units (Table 11 b).

Table 11a HRQoL EQ-5D and SF-36 mean score (95% Confidence interval) for all patients answered at each measure time (with withdrawals)

Variable	6 months (n=980)		12 months (n=739)		24 months (n=595)		36 months (n=498)	
EQ-5D	0.62	(0.60:0.64)	0.66	(0.64:0.69)	0.67	(0.67:0.69)	0.68	(0.66:0.71)
PF	59.3	(57.4:61.3)	62.7	(60.5:64.9)	63.8	(62.5:67.39)	65.1	(62.6:67.8)
RP	41.6	(38.8:44.4)	50.5	(47.4:53.7)	53.6	(49.6:56.6)	55.7	(51.9:59.7)
BP	59.8	(57.9:61.8)	62.7	(60.6:64.9)	61.7	(60.0:64.7)	63.8	(61.1:66.3)
GH	53.6	(52.0:55.2)	56.2	(54.5:58.1)	55.5	(53.8:58.0)	58.1	(55.9:60.3)
VT	53.2	(51.6:54.8)	56.7	(54.9:58.4)	54.5	(53.5:57.5)	56.4	(54.3:58.59)
SF	70.1	(68.3:72.0)	74.2	(72.3:76.2)	74.1	(72.6:77.0)	75.1	(72.8:77.4)
RE	60.2	(57.4:63.1)	66.6	(63.6:69.7)	67.5	(64.4:71.2)	70.4	(67.0:74.1)
MH	70.4	(69.0:71.9)	72.9	(71.4:74.5)	72.1	(71.4:74.9)	73.4	(71.6:75.3)

EQ 5D; EuroQol 5-dimension, SF-36; Medical Outcomes Study 36-item Short Form Health survey;

PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain;

GH, general health; VT, vitality; SF, social functioning;

RE, role limitations due to emotional problems; MH, mental health

Table 11b HRQoL EQ-5D and SF-36 and mean score (95% Confidence interval) for the patients that answered all measures (n=478) (without withdrawals)

Variable	6 months (n=478)		12 months (n=478)		24 months (n=478)		36 months (n=478)	
EQ-5D	0.67	(0.64:0.69)	0.68	(0.66:0.71)	0.68	(0.65:0.71)	0.68	(0.66:0.71)
PF	64.3	(61.7:67.0)	65.5	(62.8:68.2)	67.2	(64.6:69.8)	65.2	(62.5:67.9)
RP	45.6	(41.6:49.7)	54.6	(50.7:58.6)	55.5	(51.6:59.4)	55.6	(51.6:59.5)
BP	62.5	(59.8:65.2)	64.1	(61.4:66.8)	63.9	(61.3:66.5)	63.8	(61.1:66.4)
GH	57.2	(55.0:59.4)	59.3	(57.1:61.69)	57.7	(55.4:60.0)	57.8	(55.5:60.0)
VT	55.8	(53.6:58.1)	58.1	(55.9:60.3)	56.7	(54.5:58.9)	56.1	(53.9:58.3)
SF	73.2	(70.7:75.6)	76.9	(74.5:79.2)	76.3	(73.9:78.6)	74.9	(72.5:77.2)
RE	66.7	(62.8:70.6)	70.6	(66.9:74.3)	69.1	(65.4:72.99)	70.9	(67.2:74.5)
MH	72.7	(70.7:74.7)	74.4	(72.5:76.3)	73.9	(72.0:75.9)	73.3	(71.4:75.1)

Compared with the age and sex adjusted general reference group the patients who had been in IC had significantly lower scores on both EQ-5D and in SF-36 all eight dimensions. This was seen both in the short-term perspective (6 months; paper I) and in the long-term perspective (3 year; paper III).

When dividing the ICU patients and the reference group into those with or without co-existing diseases the significant differences observed remained ($p < 0.001$) apart from mental health (MH) in both the previously healthy group (at 6 months) and the group with co-existing diseases (at 12 months) for SF-36. When we compared the scores over time (paper III) for the ICU group that answered on all four occasions with or without pre-existing diseases, there were small improvements over time. The group who were previously healthy scored higher on role physical (RP) at 12 months and on physical functioning (PF) at 24 months compared with 6 months. The group with pre-existing disease scored higher on three dimensions; role physical (RP), social functioning (SF), and role emotional (RE), all between six and 12 months (Figure 5a and b).

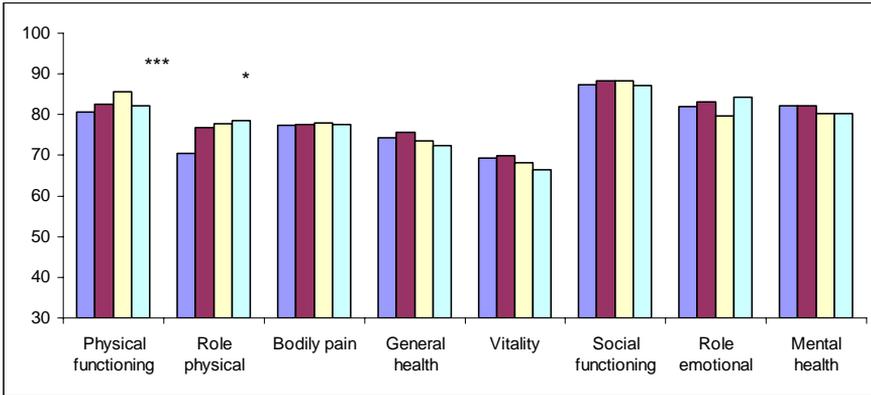


Figure 5a Changes in SF-36 scores over time at 6, 12, 24, and 36 months in ICU patients without pre-existing diseases (n=138) *p<0.05, ***p<0.001

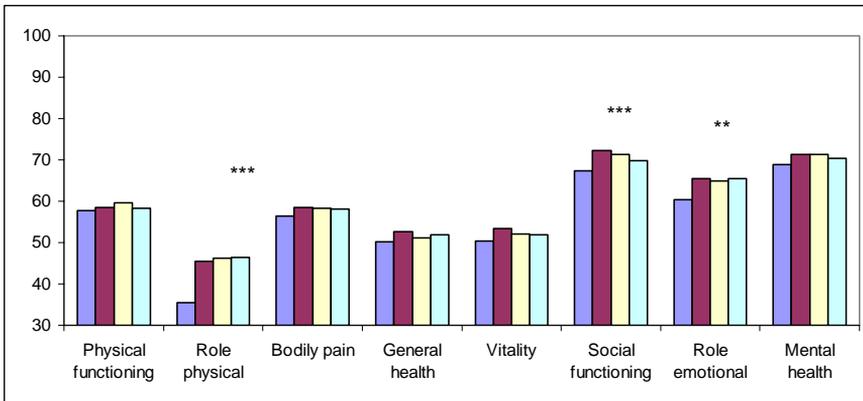


Figure 5b Changes in SF-36 scores over time at 6, 12, 24, and 36 months in ICU patients with pre-existing disease (n=340) **p=0.02, ***p<0.001

In Figure 6 the results from EQ-5D are shown for 36 months. The previously healthy patients that were cared for in an ICU ended up with a HRQoL after ICU that is almost identical to the group in the reference population that had concurrent disease.

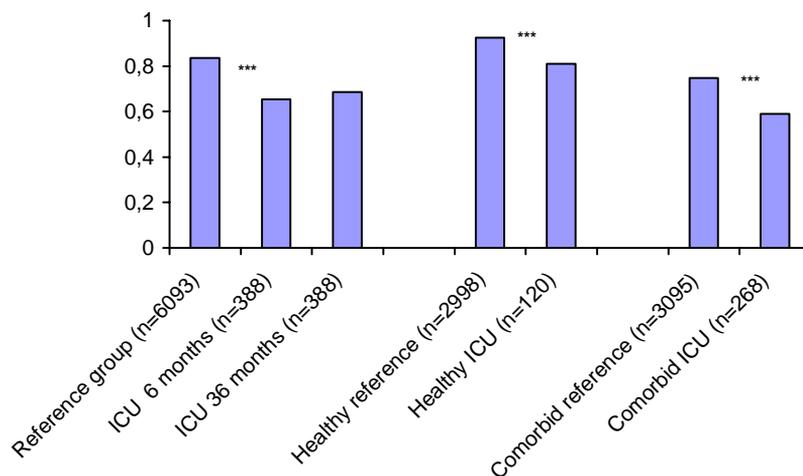


Figure 6 Health related quality of life (EuroQol-5D) for the total reference group, healthy or with coexisting diseases compared with the total group of intensive care patients <75 years old who answered on all four occasions and healthy or with coexisting diseases *** $p < 0.001$ reference group compared with the ICU group. ICU; Intensive care unit

In the multivariate analysis (paper III), pre-existing diseases had a significant impact on HRQoL both in EQ-5D and all eight dimensions of SF-36 (Table 12). When pre-existing diseases were excluded from the analysis, length of stay in hospital, sick leave before ICU, marital status (single or widower), and born in Sweden also were found to significantly affect the EQ-5D and six to seven dimensions for SF-36, depending on which dimension that is investigated.

Table 12 Associations between EQ-5D and SF-36 and different variables (paper III)

Source	EQ-5D	PF	RP	BP	GH	VT	SF	RE	MH
Preexisting disease	x								
APACHE II score									
Los ICU									
Los hospital	x	x	x		x	x	x	x	x
Diagnosis	x		x	x					
Time on ventilator									
Sick leave before ICU	x		x		x	x	x	x	x
Marital status	x	x		x		x	x	x	x
Employment before ICU				x	x			x	
Employment now	x	x	x		x		x		
High school/university									
Born in Sweden	x	x		x	x	x	x	x	x
Sex		x	x						
Age	x	x	x	x	x			x	

x = significant correlation in the multivariate analysis with all factors, x = significant correlation in the multivariate analysis without pre-existing diseases

EQ-5D, EuroQol 5-dimension; SF-36, Medical Outcome Short Form; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health

Sleep disturbances and HRQoL

Paper II

The ICU patients had significantly reduced HRQoL in all eight dimensions of SF-36 compared with the age and sex-adjusted reference group at both 6 and 12 months. No improvements were seen up to 12 months after discharge from ICU and hospital apart from role physical (RP) with an increase in 6.1 units. Of the ICU patients who had good quality of sleep before the critical care period, 70% (n=459), and for those who had poor sleep before the critical care period 13% (n=85) this remained at 6 month after IC (Table 13).

Table 13 Comparison of quality of sleep before the ICU period and 6 month after (n=911)

Before ICU a	6 months after ICU b	
	Good	Bad
Good	459 (70)	60 (9)
Bad	56 (8)	85 (13)

72% of the patients answered the questions:

- a) Rate your overall sleep quality before the intensive care period and b) Rate your overall sleep quality during the last month

Data are number (%) of totals

Seventeen percent (n=164) of the patients used sleeping pills daily or almost daily during the last month at the 6 month follow-up measure, and at 12 month the consumption remained almost the same (15.9%) whereas 73% (n=538) reported that they never used sleeping pills.

In the logistic regression analysis adjusting for age, sex, and sleep difficulties, (measured as difficulties in falling asleep, bad quality of sleep, and difference between the reported need for sleep and that achieved (sleep deficit)), had impact on HRQoL (SF-36).

At the lower scores for bodily pain, general health, vitality, or mental health, more sleep related problems were reported (difficulties in falling asleep (OR 0.98 to 1.01) ($p<0.01$) and bad quality of sleep (OR 0.97 to 0.99) ($p<0.001$)). When the scores on physical functioning or role physical were decreased, more problems with sleep deficit were reported (OR 1.01 compared with 1.00 respectively) ($p<0.02$). Women had more difficulties in falling asleep than did men (OR 1.13) ($p<0.03$). ICU patients had less problems with difficulties in falling asleep than the reference group (OR 0.67) ($p<0.001$), but on the other hand they reported a greater sleep deficit (OR 1.70) ($p<0.001$). Pre-existing disease was significantly associated with difficulties in falling asleep and poor quality of sleep ($p<0.001$).

Trauma and HRQoL

Paper IV

The trauma patients perceived their HRQoL as being significantly lower than the reference group in EQ-5D and in all eight dimensions of SF-36, with only small improvement over time. Compared with the other ICU admission diagnostic groups the patients with multiple trauma had significantly lower scores in EQ-5D up to 24 months after discharge from the ICU and in the SF-36 dimensions bodily pain and vitality up to 12 months. The burden of pre-existing diseases in the trauma group was high. Seventy percent had one or more chronic diseases at admission to the ICU. The trauma group with pre-existing diseases had, apart from general health, social functioning, and mental health significant lower scores on SF-36 dimensions up to 24 months after discharge from ICU and hospital compared with the trauma patients who were healthy before the trauma. There were no significant differences over time (24 months) when the previously healthy trauma group was compared with the previously healthy other diagnostic groups. For the corresponding

groups with pre-existing diseases the trauma group had significantly higher scores for general health at 24 months (Figure 7).

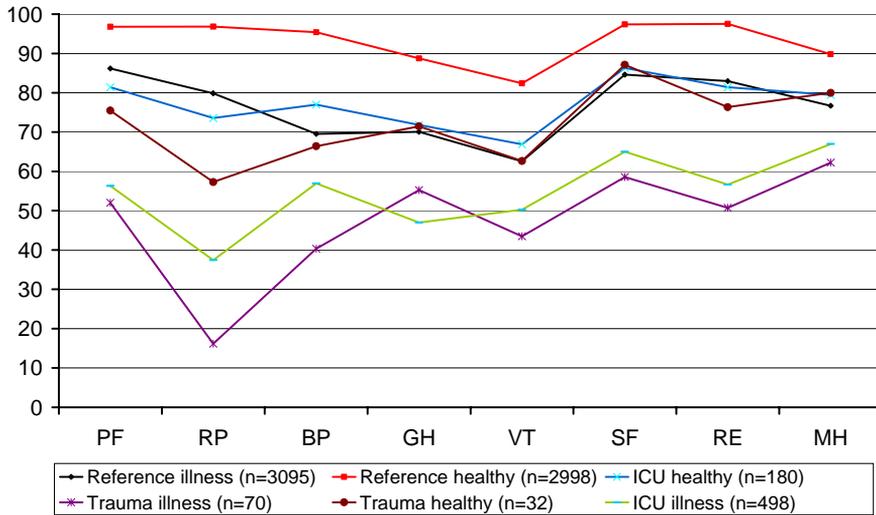


Figure 7 Medical Outcome Short Form results in the eight scales in the reference group compared with the intensive care unit (ICU) group, trauma diagnosis and other diagnosis than trauma, divided in with or without co-morbidity.

The multivariate analyses showed that ISS, time on ventilator, length of stay in ICU, age and sex had no effects on the long term HRQoL of trauma as measured by EQ-5D and SF-36. Maximum--SOFA had an effect on physical function and social functioning in SF-36, and length of stay in hospital had effect on EQ-5D. APACHE II score had an effect on vitality, social functioning, and mental health. Pre-existing disease had an effect on EQ-5D and all SF-36 eight dimensions (Table 14).

Table 14 Impact of different factors on HRQoL (EQ-5D and SF-36 mean) for the trauma patients at 6 months (n=108)

Factor	EQ-5D	SF-36 PF	RP	BP	GH	VT	SF	RE	MH
ISS									
Maximum-SOFA		X					X		
APACHE II						X	X		X
Time on ventilator									
LoS ICU									
LoS hospital	X								
Pre-existing disease	X	X	X	X	X	X	X	X	X
Age									
Sex									

HRQoL: Health related quality of life, SF-36: Medical Outcome Short Form- 36, EQ-5D: EuroQol 5 dimensions, PF: physical functioning, RP: role limitations due to physical problems, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems, MH: mental health, ISS; injury severity score, SOFA: sequential organ failure, APACHE II: acute physiology and chronic health evaluation, LoS: length of stay

DISCUSSION

The overall aim of this thesis was to investigate the long term (3 years) HRQoL in a large cohort of adult patients (>17 years) after critical illness and a period of intensive care. Several possible factors affecting the long term HRQoL after critical care were explored: e.g. socio-demographic characteristics, previous quality of sleep and pre-existing diseases, intensive care related factors and injury characteristics. Overall, pre-existing diseases exerted a greater influence on perceived HRQoL than any other factor investigated.

Short and long-term health related quality of life

As described in paper III the patients after intensive care perceived only a small improvement in HRQoL over time, and they reported significant poorer HRQoL up to 36 months compared with the age and sex adjusted reference group. Improvements in HRQoL in the period after intensive care are often described but patients who survive critical illness are at risk of permanent physical and functional deficits which decreases the HRQoL. ICU patients have been found to report significantly lower ($p<0.05$) mean scores assessed both by EQ-5D and SF-36 after ICU admission compared with the general population (7, 9, 10, 13, 24, 41-43, 46-48, 51, 65, 66) In some of these studies HRQoL increased 6 to 9 months after ICU discharge compared with at baseline. However, HRQoL in these studies were retrospectively examined prior to the ICU admission from the patients' description or from a proxy (9, 13, 24, 41, 51). Such techniques have been claimed to have flaws in that a poor health status in the ICU may lead to a false overestimation of HRQoL status before the critical illness. Families of former ICU patients tend to provide higher estimates on the physical dimensions and lower on the mental dimensions than the patient himself (33, 67).

A new and very important finding in the present study is the large effect that the high frequency of pre-existing diseases has on the HRQoL reported by the critical care patients. Pre-existing diseases in the present study was found to be the factor that had the largest influence on HRQoL (EQ-5D and all SF-36 eight dimensions) in: both the short- (paper I) and long term perspective (paper III); for the general ICU patient (paper I and III) as well as for the

multiple trauma patient (paper IV); and furthermore, it was found to have negative impact on sleep (paper II).

Although there are several previous studies that have reported a significant incidence of pre-existing diseases for ICU patients' (6, 8, 24, 48, 50, 68) surprisingly few have particularly assessed this factor when examining the HRQoL after critical illness. When these authors divide their patients into groups of with, or without pre-existing diseases the HRQoL decreases for the IC patients with pre-existing diseases (general intensive care) 6 months (6, 8, 24), as well as for the patients (trauma) 18 months after discharge from ICU (48, 50) compared with the corresponding IC patients without pre-existing diseases. In these studies 7%-72% of the patients had pre-existing diseases. In one of these, EQ-5D values were significantly lower for the patients with pre-existing diseases apart from "anxiety/ depression". However in that study the patients pre-existing diseases were listed from a validated questionnaire from which the authors excluded depression as they only wanted to describe "physical co-morbidity" (50).

When looking at other factors of importance for HRQoL with the factor pre-existing diseases excluded, new and more dimensions on the SF-36 evaluation became statistically significant; longer length of hospital stay was found to significantly affect all SF-36 dimensions apart from bodily pain. Not born in Sweden significantly affected all SF-36 dimensions apart from limitation of role because of emotional problems. A recent study examining HRQoL five years after major trauma found that the patients with a length of stay in hospital >5 days reported lower SF-36 scores compared with those with shorter length of stay (47).

ICU factors that did not have significant effect for HRQoL in the current study are: APACHE II score, length of stay in the ICU, time treated on ventilator, and education. Higher APACHE II score (11, 46, 47), longer length of stay in the ICU (11, 47), lower education (47, 50) and prolonged mechanical ventilation (48) has previous been found to significantly affect the HRQoL after the IC period, whereas others have been unable to find such effects (7, 9, 13, 42, 49).

Sleep disturbances

In paper II the longer term sleep pattern of the former IC patients was examined. The new finding in the study is that a surprisingly high percent

(70%, n=459) reported unchanged, good quality of sleep 6 months after discharge from ICU and hospital compared with before the ICU period. Only 9% (n=60) changed their sleeping quality from good to bad. On the other hand 8% (n=56) changed from bad prior to the ICU period to good quality of sleep after.

ICU patients are known to have sleep disturbances in the short time perspective after discharge from the ICU (55, 69). However, we have been unable to find studies with a follow up period longer than 3 months after discharge from the ICU. Six months after discharge from the ICU and from hospital the sleep patterns seemed to return to normal. The decrease or low HRQoL was found to be associated with sleep disturbances, or vice versa. Patients with difficulties in falling asleep, poor quality of sleep or sleep deficit reported lower scores on SF-36, because of limitations of role because of physical problems, bodily pain, general health, vitality or mental health compared with the patients without these sleeping problems. It is well known that sleep is important for the overall wellbeing and that sleep disturbances in the general population leads to decreased quality of life and premature mortality (70). Sleep disturbances are significantly affected by pain. Patients with pain after critical illness perceived significantly more sleep disturbances and lower scores on EQ-5D compared with those without pain (11). In a study examining quality of sleep and HRQoL for individuals with chronic pain conditions, lower scores on the physical dimensions on SF-36 were correlated with sleep disturbances and difficulties in falling asleep (71).

Relevant factors for sleep disturbances in the current study were: as also pointed out in the earlier studies; i.e., the presence of pre-existing diseases and female sex; whereas ICU related factors were found less important. No study that we know of has been found that assesses the impact of sleep disturbances on long term HRQoL after ICU and at the same time adjusts for pre-existing diseases. This makes data and outcome comparisons difficult. The predisposition for women to have sleep disturbances in the general population is well known (72) and in our study, the women in the large reference group reported more sleep disturbances than did the men. Three years after IC the patients with sleep disturbances and effects on physical mobility reported impaired HRQoL measured with the NHP, but with no differences between sexes (44).

Trauma

During 2008 approximately 3200 patients required IC in Sweden because of multiple traumas (73). In Sweden as in the rest of the western world, trauma is the major cause of mortality before the age of 45 and a significant number of patients die: at the site of the accident, transport, during the IC or shortly after being discharge from the ICU.

A new and interesting finding in this study is the high prevalence of pre-existing diseases even for the IC patients admitted because of multiple traumas, (paper IV). Trauma patients are often claimed to reflect the norm for the healthy adult population before the trauma, and their HRQoL is often found to decrease significantly after the trauma (47, 48, 65). Most importantly, and in line with other studies (14, 41, 48, 74) physical function and pain is decreased and increased after trauma when comparisons are made with the other admission diagnoses or with healthy reference groups. After 24 months however, the trauma patients have reached the same level of HRQoL as the other diagnoses. As the rest of the admission diagnoses, the burden of pre-existing diseases was found to significantly affect the HRQoL in both EQ-5D and all eight dimensions on SF-36. Opposite to other studies (7, 46, 50, 51) ISS did not seem to affect HRQoL whereas maximal-SOFA did in the SF-36 dimensions: physical functioning and social functioning. However, in these studies no adjustments for pre-existing diseases were made. Contrary to our pre study beliefs ISS was found not to be related with HRQoL measured with EQ-5D or SF-36, and after adjusting for pre-existing diseases. Previously, maximal-SOFA has been found to affect limitations of role because of physical problems (48).

In this study the patients with an isolated or a significant concomitant traumatic brain injury where excluded, as it is recognized as a negative predictor of functional outcome (75). Furthermore head injuries are known to affect the HRQoL outcome data (51) and it may be debated whether HRQoL is adequately assessed by EQ-5D and SF-36 in patients with significant brain injuries where cognitive dysfunctions also may be anticipated.

Disease burden

In the present study 74% of the patients had pre-existing diseases and for this group the HRQoL was significantly decreased compared with: the previously healthy IC patients, and the reference group. Interestingly, the previously healthy patients that were cared for in an ICU ended up with a HRQoL post ICU that is almost identical to the group in the reference population that has

concurrent disease. Furthermore, these patients remained largely at this level and did never regain the same level in HRQoL as is described by the healthy reference population.

If the factors related to intensive care have none or minor impact on the HRQoL decrease for the IC patients, what is then the cause for this lasting decline for the previously healthy patient group?

Angus (76) suggest that an episode of critical illness begins when the patient leaves his/hers previous state of health prior to the IC period. And it ends when either the patient recovers fully from the event or when the improvement in the health state is stabilized at a new and most often a lower level. In other words, the extra burden of the acute critical illness for the patients with pre-existing disease is added on top of the present disease burden (imposed by the critical illness) and it can then explain the larger decrease in HRQoL for this group. This is presented graphically in Figure 8.

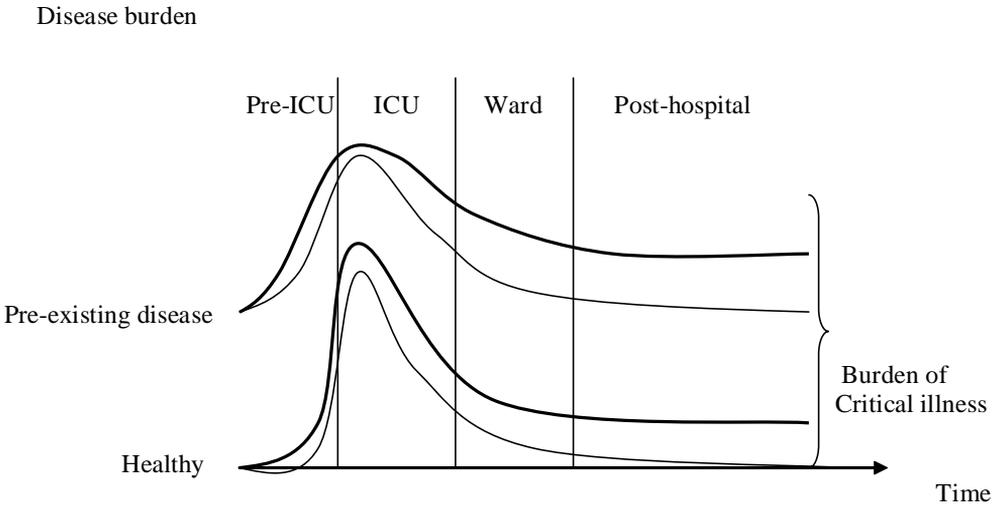


Figure 8 The episode of critical illness (modified from Angus (76))

There are theoretically a multitude of other reasons and factors that may explain the decreased HRQoL seen in the former IC patients and it is difficult to isolate and to investigate all possible factors. For instance disturbed memory and amnesia during and after IC have shown effects on the IC patient’s psychological morbidity (77), and patients with delusional memories after trauma had a significantly decreased HRQoL in all eight dimensions of SF-36 (78). The level of sedation during the mechanical ventilation is claimed a significant reason for obtaining delusional memories (18). This and the

addition of a traumatic event with a reaction of intense fear, helplessness and horror may lead to development of post traumatic stress disorder (PTSD) (20), which has been found in 4%-32% of the former IC patients (79-81). The first 3 months following the injury appear to be the most critical period for development of PTSD (80). Significant association between low HRQoL and poor information during the acute in-hospital care stay have also been found (47), and there is a need for the critically ill patients to talk about their experiences from the period in the ICU (82, 83).

Methodological considerations and limitations

Study design

This thesis is based on studies which use a quantitative, prospective, dual- (paper I) and multicenter (paper II-IV) study approach. The results in the studies with the long-term follow-up (paper II-IV) appear consistent over time, especially for different subgroups and only small improvements in separate measures of HRQoL are registered over time. Furthermore, the HRQoL values registered are in the range reported by others using the same instruments and applied to similar patient groups. This suggests that the data presented are relevant and has an acceptable reproducibility.

Patients who are admitted for critical care are clearly different from a general population as they have a significant rate of pre-existing diseases, often in the range of 70% or more, which is to be compared to the 50% concurrent disease rate that was prevalent in the general reference population sampled from the uptake area of the hospitals and that was used for comparison in this study. Therefore, in the comparisons with the ICU patients, the reference group data was adjusted for age, sex and especially co-morbidity in all papers.

A central issue for this thesis is the effect of pre-existing diseases on the long term HRQoL for the ICU patients. Using a proper control group that has specified concurrent diseases may be a help in the process of finding and adjusting for any effects of the differences in these concurrent (reference person) and pre-existing diseases (patients). There are however, some methodological issues that are relevant for the interpretation of the data and that needs to be commented on:

Firstly, although the reference population has concurrent diseases that are used for the comparison, the disease burden for any specific disease may not be the same as for the ICU patient group. In other words, diabetes for the ICU

patient may be of a different severity (more severe) than that encountered in the control population (reference population). We think this reason provides a significant effect and contributes to why the HRQoL was consistently lower for the patient group compared to the reference group although we did adjust for pre-existing disease/concurrent disease.

Secondly, there may be people in the reference group that are ill, but are yet undiagnosed. This issue was addressed for the present study as the reference group had been asked also to list significant symptoms that later were converted to a diagnosis, which then was added to the list of concurrent diseases (57).

Thirdly, as there seem to be a distinct HRQoL effect that can be related to the period of critical illness, but that was not related to any separate IC parameter examined (Apache II, time on ventilator, or LoS) a suspicion of a cause effect relationship may still be anticipated e.g., for either the admission or the discharge diagnosis. This was addressed in the present study as admission diagnoses registered by the APACHE II system were collected and in single and separate examinations were found significant for the post ICU HRQoL level, albeit the magnitude of this factor appeared minor (paper I-IV) and did not provide an explanation for the changes in HRQoL that remained after adjustments for pre-existing diseases were performed. We believe that the discharge diagnose better describes what the patient has experienced in the ICU, and therefore would have a larger impact on the long term HRQoL. This will be further explored in the future.

Fourth, one important issue for HRQoL studies are the possible effect and consequences of non-responders or drop outs when collecting the HRQoL questionnaires. In the present study a response rate of approximately 60% (at 6 months) both in the ICU group and for the reference population is in line with what is usually described in similar investigations. However, the dropout rate in the long term perspective (study III) was quantitatively larger and as anticipated in a long term follow-up study. This should lead to a more cautious approach when drawing conclusions from the material.

Fifth, there are other factors that are related to personal characteristics of each patient that are known to affect HRQoL (e.g. coping strategies and feeling of hopelessness) and that may be of importance for the interpretation of the long term HRQoL results in this thesis. The magnitude of such an effect is difficult to predict, however we assume it to be relatively minor based on data presented for these factors in other studies (81, 84, 85).

Sixth, the reference group had answered the same HRQoL instruments as the ICU patients, however the questionnaires on sleep disturbances were not

identical. Therefore, in order to make the comparisons more reliable, only the questions (three) that were identical between the groups (ICU patients/reference population) were used.

Observations included in the analyses

It is a strength of the present study that it is one of the larger long term follow-up studies yet made in the IC setting.

In all comparisons over time, only the patients that have answered at all of these occasions were included in the analyses rather than all that answered at each occasion. This is usually the approach chosen as it reduces the risk of obtaining significant effects related to differences in the populations examined. The reason for including only those who answered at all occasion is that those only answering at one of the occasions may be different in some respect. Thus, including them at only one of the occasions may introduce bias.

In paper IV the trauma patient group that was examined over time became relatively small. It needs to be stressed however, that in comparisons with other multiple trauma follow up studies the present study group size was not exceptional (19, 47, 48).

Methods

The HRQoL instruments used in the papers (EQ-5D and SF-36) are well validated and reliable and are the ones that have been recommended for use in the IC setting by international experts (3). For the corresponding sleep questionnaires there are few consensuses on which type of sleep disturbances to investigate and what protocols to use. This makes comparisons to other studies more difficult.

In general, self-report questionnaires are considered valuable, although there is a risk of bias in that the respondent can misunderstand or misinterpret the questions. However, postal questionnaires allow written anonymous answers to intimate questions which may facilitate patient participation (25). Furthermore, the significant length of time that was present between the different HRQoL assessments in the study (first 6 months and then one year each time), reduces the likelihood for the recall bias that may affect the HRQoL estimate of each patient (86).

Both for the IC patients and the reference group the pre-existing/concurrent diseases were self-reported. In the present investigation the incidence of concurrent disease for the reference group was based both on reports on

diagnosis and symptoms converted to diagnoses. In the IC patients it was based on diagnosis reported only. This may introduce an error when comparing the two groups. We believe this error to be minor as any significant concurrent symptom reported in the ICU patient group would have been investigated further and in parallel diagnosed and treated. Unfortunately, the diagnosis for such an event would most probably appear first in the discharge note and would not be reported and registered in the present study. This will be further investigated in the planned next studies of the present patient population.

Implications and future aspects

The data of our study suggest that the intensive care period itself only has minor impact on the long term HRQoL reported by former ICU patients. This finding should be further investigated and explored in several aspects as e.g., listed below:

Firstly, further investigations need to be done to explain why previously healthy ICU patients do not regain their HRQoL status that we assume they had prior to the period of critical illness. Our hypothesis is that they have acquired a significant illness (burden of illness) prior to or leading to the critical care comparable to that of e.g., the group having concurrent diseases. This conclusion is supported by our finding that this group ends up at the level of the reference group that has a one significant concurrent disease.

Secondly, and very importantly, after an adjusting for pre-existing disease there are still significant HRQoL decreases that remain unexplained. This needs to be further addressed.

Thirdly, an important area to investigate is also the HRQoL effects that post ICU may be due to the characteristics of each individual. This and possible areas for intervention in order to support and improve the long term HRQoL level of former ICU patients is urgent

CONCLUSIONS

The frequency of pre-existing diseases was high among the intensive care patients in this study. Of all the factors investigated pre-existing diseases was overall most important for the long term HRQoL in former adult intensive care patients. It contributed to approximately 50% of the HRQoL reduction registered for the ICU patients compared with the general population. The intensive care patients with pre-existing diseases perceived significantly lower HRQoL compared with both the general population with or without comorbidity, as well as the intensive care patients who were previously healthy. Furthermore, the intensive care patients had impaired HRQoL both in the short-term (6 months) and in the long-term (36 months) perspective compared with the general population.

Sleep disturbances was common after critical care with only minor improvements over time (12 months), although changes in quality of sleep prior to compared with after the ICU and hospital seemed to be minor. The patients with pre-existing diseases reported higher frequency of sleep disturbances compared with the previously healthy patients.

After multiple trauma and a period in intensive care the trauma patients perceived considerably reduced HRQoL both when compared with a general group of ICU patients, and healthy controls. Impaired physical function and increased pain was most affected. After 24 months the degree of HRQoL for the trauma patients treated in ICU reached the same level as that of general ICU patients.

SVENSK SAMMANFATTNING

Patientskattad hälsorelaterad livskvalitet hos vuxna som överlevt intensivvård – en 3-årig uppföljningsstudie

På en intensivvårdsavdelning (IVA) vårdas svårt sjuka patienter som har såväl hög morbiditet som mortalitet. Detta kräver noggrann övervakning, avancerad behandling och specialiserad omvårdnad. Patientvården är resurskrävande bl.a. pga. att personaltätheten på en IVA är högre än på allmänna vårdavdelningar.

Utvecklingen av de medicinska behandlingarna, förfinad teknologi, fler avancerade läkemedel och specialiserad klinisk sjukvård har möjliggjort en ökad överlevnad för patienter även med komplexa sjukdomar och omfattande skador. Intensivvården är idag en av de största konsumenterna av sjukhusens ekonomiska resurser och uppges konsumera 20 % av sjukhusens totala budget eller nästan 1 % av BNP i ett västerländskt I-land (USA). För att fastställa effektiviteten och resultatet av intensivvården används idag huvudsakligen mortalitet och långtidsöverlevnad som effektivitetsmått. Mortalitet är dock inget idealiskt mått för att mäta långtidsresultatet av intensivvård. Vi vet att mortaliteten efter intensivvårdstillfället är ökad, men efter 2 år är t.ex. överlevnadskurvorna parallella med en "normal" population.

Internationellt sätt används hälsorelaterad livskvalitet (HRQoL) som ett mått för att mäta behandlingseffekter och det har föreslagits som ett viktigt, om inte det allra viktigaste verktyget för utvärdering av intensivvård. Det används i dessa sammanhang huvudsakligen tillsammans med överlevnadsmått. Internationella rekommendationer är därför att mätningar av behandlingseffekt och utvärdering av effektiviteten av intensivvård måste inkludera HRQoL mätningar. Sådana data kan dessutom hjälpa till för prioriterings och policybeslut på kohortnivå. Viktigt är dock att de undersökningar som internationellt hitintills gjorts är baserade på jämförelser med *friska* kontroll populationer. I dessa jämförelser har man visat att intensivvårdspatienterna har kraftigt sänkt HRQoL efter intensivvård.

Trots att forskningen avseende HRQoL efter intensivvård internationellt sätt har ökat de senaste åren finns det få Svenska studier inom området. Med tanke på att vården blir mer sofistikerad, att vi har en förväntad konsumtionsökning av sjukvård och en ökad population av äldre och med det

ökade krav på intensivvårds service är det av vikt att vi har en bättre uppföljning och förståelse av långtidsresultatet för våra före detta intensivvårdspatienter. Överlevnadsmåttet är viktigt men inte utan en acceptabel HRQoL.

Upp till ett år efter intensivvård upplever patienterna en signifikant lägre HRQoL jämfört med en ålder- och kön justerad allmän population. Det sker en gradvis förbättring av den HRQoL över tid, men det finns få långtidsuppföljningar för denna patientgrupp. Anledningen till den sänkta HRQoL efter intensivvårdstiden kan vara många, då faktorer både före- under och efter intensivvårds perioden påverkar HRQoL.

Som exempel kan nämnas ålder, kön och social bakgrund, och dessutom vet man att sömnproblem och sjukdom har stark koppling till sänkt HRQoL. Tidigare forskning har dessutom visat att patienter som har vårdats på IVA för multipelt trauma skattar sin HRQoL lägre än övriga intensivvårdspatienter ända upp till 5 år efter utskrivningen.

Den svåra sjukdomen och den livsnödvändiga behandlingen på IVA påverkar patienten fysiskt såväl som psykiskt samt kan leda till kvarstående smärttillstånd. Detta kan ha inverkan på den fysiska, psykiska och sociala funktionen efter intensivvårds tiden med symtom som sömnstörningar, amnesi, ångslan, vanföreställningar, hopplöshet, underlägsenhet och sexuella problem. Dessa kan i sin tur leda till en generellt sänkt långsiktig HRQoL.

Ett antagande som låg till grund för avhandlingsarbetet var att den sänkta HRQoL och de sömnstörningar som finns beskrivna efter intensivvård till största delen är orsakade av patientens tidigare förvärvade sjuklighet och inte primärt härrör från de direkt intensivvårdsrelaterade faktorerna. Antagandet gällde såväl intensivvårdsgruppen som patienterna med intagningsdiagnos multipelt trauma.

Avhandlingens resultat är baserade på en grupp intensivvårdspatienter, äldre än 17 och som vårdats mer än 24 timmar på en allmän intensivvårdsavdelning vid något av sjukhusen: Universitetssjukhuset i Linköping, sjukhuset Ryhov i Jönköping eller Vrinnevisjukhuset i Norrköping. Ett frågeformulär avseende sociodemografisk situation, tidigare kroniska sjukdomar, HRQoL och sömn skickades till patienten 6, 12, 24 och 36 månader efter utskrivning från sjukhuset. HRQoL mättes med hjälp av EuroQol 5-dimensions (EQ-5D) och Short Form-36 (SF-36), och sömnstörningarna undersöktes med en modifierad form av Basic Nordic Sleep Questionnaire (BNSQ). Dessutom tillfrågades

patienterna om sömnkvaliteten före, respektive efter intensivvårdsperioden. Som kontrollgrupp användes en ålder- kön och sjukdomsjusterad population från Östergötland, bestående av 6093 individer.

Studien visade att 74 % av intensivvårdspatienterna har väsentliga pre-existerande, kroniska sjukdomar innan intensivvårdsperioden. I artikel I och III studerades HRQoL i ett kort (6 månader) perspektiv hos 980 patienter, samt i ett långt (36 månader) perspektiv hos 478 patienter. Patienterna som deltog vid 36 månads uppföljningen hade svarat på samtliga fyra enkätutskick (6,12, 24 och 36 mån). HRQoL var signifikant lägre i gruppen av intensivvårdspatienter jämfört med kontroll gruppen både vid 6- och 36 månader, med endast en ringa förbättring över tid. Uppdelat på patienter med tidigare sjukdomar respektive friska innan intensivvårdstiden visade resultaten en signifikant lägre HRQoL hos båda intensivvårdsgrupperna, dvs., med och utan tidigare sjukdomar jämfört mot både en frisk och en sjuk kontroll grupp. De största generella effekterna som uppmättes på HRQoL var de som kunde förklaras av tidigare sjukdomar.

I artikel II studerades sömnkvaliteten. Den största delen (70 %) av patienterna upplevde god sömn både före och efter intensivvården. Jämfört med referensgruppen hade intensivvårdspatienterna mer sömnstörningar upp till 12 månader efter utskrivningen. Dessa sömnproblem var huvudsakligen relaterade till de pre-existerande sjukdomarna.

I artikel IV undersöktes HRQoL hos de intensivvårdspatienter som vårdats för multipelt trauma. Jämfört med både övriga intagningsdiagnoser på IVA samt mot kontrollgruppen skattade trauma patienterna sin HRQoL signifikant lägre, framför allt i den fysiska dimensionen, samt att de också upplevde mer smärta. Efter 2 år var traumagruppen ifatt de övriga diagnosgrupperna i dessa avseenden. Sänkningen i HRQoL var i huvudsak relaterad till de pre-existerande sjukdomarna.

Av alla i studien undersökta bakomliggande faktorer, så var det de pre-existerande sjukdomarna som var de som påverkade HRQoL mest, både i det korta såväl som långa uppföljningsperspektivet, och de stod för ca 50 % av sänkningen i HRQoL för intensivvårdspatienterna.

Sammanfattningsvis kan sägas, utifrån denna undersökning, att pre-existerande sjukdomar befanns vara den mest betydande faktorn för den

långsiktiga HRQoL som intensivvårdspatienterna beskriver. En väsentlig del av sänkningen i HRQoL som patienterna beskriver tillkommer emellertid i samband med intensivvårdsperioden, men är inte beroende av hur kritiskt sjuk patienten varit just då. Troligen beror den kvarvarande sänkningen i HRQoL efter intensivvård, och som inte beror på pre-existerande sjukdomar, på det nya sjukdomstillståndet som patienten förvärvat/genomgått och som föranlett intensivvårdsbehovet. Fortsatta undersökningar bör riktas framför allt mot att kartlägga detta och därigenom förhoppningsvis bättre kunna förklara hela HRQoL sänkningen.

ACKNOWLEDGEMENTS

This thesis is the result of collaboration between the Intensive Care unit's at Linköping University Hospital, Ryhov Hospital in Jönköping, and Vrinnevi Hospital in Norrköping. Many people made important contributions, and I would like to express my sincere gratitude to everyone who has had any part in this work. In particular I am grateful to:

All the respondents for participating in the studies, who tirelessly answered the questionnaires, and provided me with knowledge of and a greater understanding of the life situation after being critically ill and requiring intensive care treatment.

Above all, I wish to thank Professor *Folke Sjöberg*, my excellent supervisor and tutor for all his patience and fruitful discussions. Thank you for believing in me from the very beginning. You were the one who once upon a time introduced me to critical care outcome research, saw the potential in my master thesis, and with careful guidance and outstanding scientific knowledge helped me to attain goals far beyond what I ever thought possible. I am impressed by your capability to always see "around the corner", by your way of giving me support when most needed, your remarkable capacity to turn negative feelings to positive ones, and your consistently supportive attitude that give me a feeling of growing with the task.

I also want to express my sincere gratitude to;

Anders Nordlund, my co-supervisor for your useful knowledge in health and society. Thank you for the support and necessary help with the data, and your irreplaceable help solving statistical problems. When you later had to move to Lund you kept providing your valuable support suggesting useful statistic analyses and answering my never ending questions day and night.

My co-supervisor *Ulla Edéll-Gustafsson* for the introduction in sleep and its impact for well-being and health.

Ebba Lundén, my friend and colleague, for necessary help and support with all the data for endless hours with the computer, kindness and support in my research and for many good laughs. In some strange ways you always knew when I needed a cup of coffee or a hug.

Eva Simonsson, my co-author and colleague for your friendship and carefully help with data from Jönköping. You're encouraging and resourceful support has been of great help.

Carl Bäckman, my colleague and PhD student friend for help and support with the data from Norrköping, and for your never ending enthusiasm in critical care research. Your interest in my research and for our mutual work has given many fruitful discussions concerning the outcome after critical care.

My co-authors *Peter Nordlund*, *Anders Samuelsson*, *Margareta Kristenson*, and *Preben Bendtsen* for your guidance and for sharing your expertise and *Max Bergkvist* for useful help with the trauma data.

My department heads, *Claes Lennmarken* and *Peter Kimme* for your support and encouragement, and for your great enthusiasm regarding this study and valuable understanding off the importance for the critical care outcome research. To my *colleagues* at the Department of Anaesthesia and Intensive care Linköping University hospital for your interest, kindness and support in my research. Special thanks to all the departments' hard workers *Lena Sjögren*, *Anita Stjernberg*, and *Anette Karlsson* for skilful assistance over the years.

To Professor *Jan Person* and Professor *Per Carlsson* at the Center for Medical Technology Assessment (CMT), Linköping University, for giving me a great opportunity to complete my PhD. To *Magnus Husberg* and *Lars Bernfort* for all your support in the health-economic field, and to all other *colleagues and PhD students* at the CMT for good friendship.

...All the *doctoral students and lecturers* at the Institution of Medicine and Health (IMH), division of Nursing Science, Linköping University for sharing their knowledge and for great interest and helpful comments during seminars.

To the *Linqest group* at the Centre for public health at the county Council of Östergötland for letting me use the database of the reference population.

Olle Ericsson at The Department of Computer and Information Science Linköping University, division of statistics, for statistical advice.

...To *Mary Evans* for excellent revision of the English texts.

To my friend *Lars Hoffsten* for greatly appreciated help and artistic ideas regarding the outward presentation of my dissertation.

And last and most important;

All my close friends (none forgotten), particularly *Marianne*, my oldest friend, and *Håkan* who have been my link to reality during this time who forced me to slow down during many late Fridays evening discussions.

My wonderful daughters, *Madeleine* and *Liselotte*, for all your boundless love and support, for all the fun and wonderful discussion times we have had and

for your company during necessary, relaxing vacation trips. You are good listeners with hearts “as big as Texas”. I love you! And to my late, loving husband *Hasse*, who supported me from the very beginning, but unfortunately could not follow my work to the end. I know that you always believed in me and supported my dreams and that you are with me all the time.

My dear son-in-law *John*, and my sisters *Margareta* and *Gunilla*, with husbands *Luiz* and *Jan*, and my mother *Runa*, for your support and believing in me and my dreams, and in memory of my father *Arne*.

The investigation was supported by the Health Research Council in the South-East of Sweden (FORSS), the County Council of Östergötland, Sweden, the Center for Medical Technology Assessment (CMT), Linköping University, Sweden, and the University of Linköping.

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