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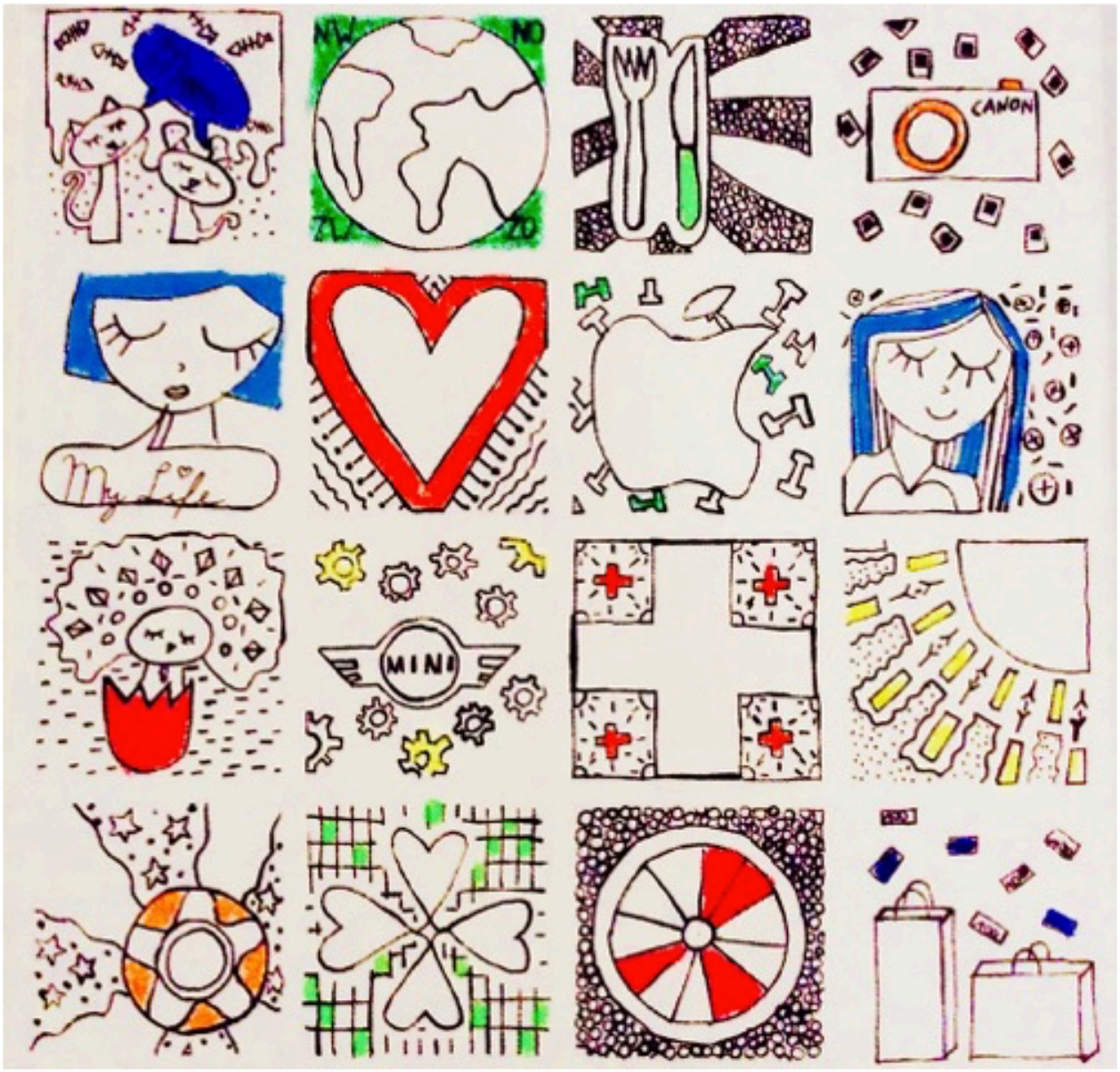

Long-term Outcomes and Quality of Life In Critically Ill Patients

Sandra Oeyen

GHENT
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Every day you may make progress. Every step may be fruitful.
Yet there will stretch out before you an ever lengthening, ever ascending,
ever improving path. You know you will never get to the end of the journey.
But this, so far from discouraging, only adds to the joy and glory of the climb.

Winston Churchill

Cover: Sandra's quality of life by Aline Hartgers

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aan mijn lieve man Alain
aan onze katten
voor jullie onvoorwaardelijke steun

aan mijn ouders
aan Annick, Jeroen en Aline

aan Daniella, Patsy, Patrick en Jo

“Life is like riding a bicycle. To keep your balance you must keep moving.”

Albert Einstein

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Sandra Oeyen, 27 juni 2018

Part One

Long-term outcomes and Quality of Life: Introduction and Research Questions

I. Introduction

1. Moving towards long-term outcomes and quality of life

The intensive care unit (ICU), as a dedicated area in the hospital, emerged around 1960. Main and only focus at that time and in the following decades was reducing ICU-mortality [1]. Hospital mortality became the most important parameter to report outcome, especially with the introduction of the first general severity of illness score, the Acute Physiology and Chronic Health Evaluation II (APACHE II score) [2] that could estimate the probability of hospital mortality.

It was by the end of the 80s and 90s that critical care physicians started to be aware of the need to evaluate other endpoints beyond short-term mortality [3-5]. An important development in the field of healthcare at that time was the recognition of the central role of the patient's view regarding the quality of medical care outcomes. A medical outcome became "the extent to which a change in a patient's functioning or well-being meets the patient's needs and expectations" [6]. Earlier, Lembcke stated that "the best measure of quality is not how well or how frequently a medical service is given, but how closely the result approaches the fundamental objectives of prolonging life, relieving distress, restoring function and preventing disability" [7]. European and American critical care societies were founded and held roundtable conferences and workshops concerning "outcomes research" and "surviving intensive care" [8, 9].

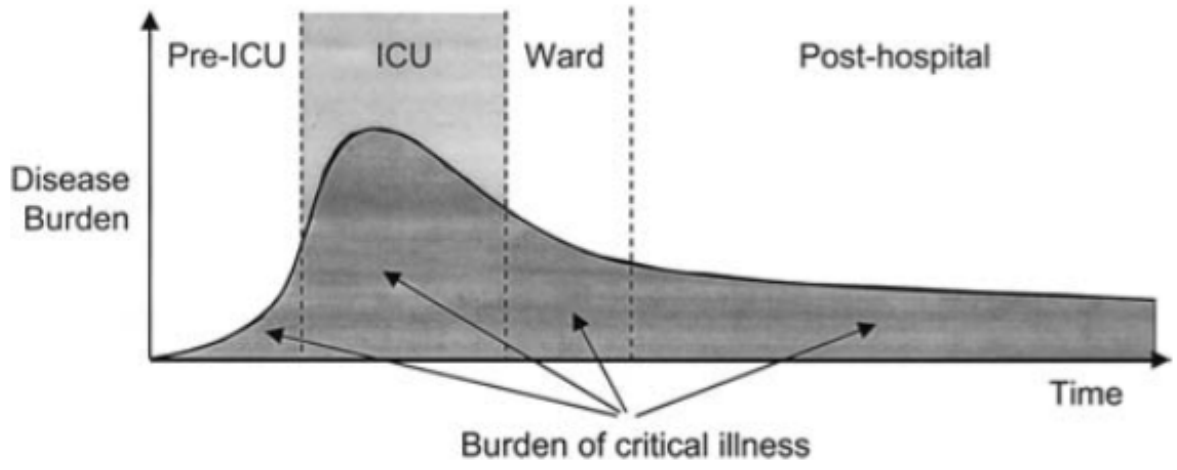
It was only since the 90s that clinical investigators began to use information about functional status and well-being of patients. Earlier, data from patients regarding their experiences of disease, treatment, and outcome had not been routinely collected. Several advances in the methods for assessing patient perspectives occurred in these years. Some of these advances were an improved understanding of the major dimensions – physical, mental, and cognitive - of health and the validity of specific measurements in relation to these dimensions, a demonstration of the usefulness of standardized health surveys in clinical trials, and the development of general population health surveys. Techniques for constructing health measures and content of these measures improved over time.

Some 10 years ago, a chapter in the yearbook of the European Society of Intensive Care Medicine (ESICM) was dedicated to long-term outcomes [14], which was the proof that more efforts had been put on measuring outcomes other than only survival. Gradually, the focus on outcome had shifted from ICU to hospital mortality, from hospital mortality to post-hospital functionality and well-being, and to the (very) long-term-outcome.

Measuring and understanding the outcome of a treatment from the patients' perspective captures the essence of patient-centred care and incorporating this information in medical decision-making is essential. Although this change in outcome interest seems rather late in time, it is logical that for many years the traditional goal of critical care medicine has been to decrease short-term mortality

because critical care medicine per definition treats the most critically ill patients with an inherent high risk of mortality. The majority of randomized controlled trials in the field of critical care medicine still have as primary endpoint short-term mortality and some very well known key-studies have focused on this [10-13]. While reducing short-term mortality is worthy, extremely important, and the core business of a critical care physician, this goal however fails to address the issue of what it means to survive intensive care [9].

The main reason for the increasing and still expanding interest in long-term outcomes is that advances in diagnostic, supportive and therapeutic options make that more and more patients nowadays survive their critical illness [15,16]. There is also an increasing acknowledgment that the episode of critical illness is not just the period of time the patient spends in the ICU but is the period that begins with the onset of deterioration and ends when the patient's risk of late sequelae returns to a baseline level of risk of a similar patient who has not been critically ill [9]. Critical care can therefore be identified as one important piece in a complex continuum of care. For this reason, we have to question whether and to what extent critical illness will affect the long-term (≥ 12 months after ICU discharge) functionality and quality of life (QOL) in survivors.



From: Angus DC, Carlet J, 2002 Brussels Roundtable Participants Surviving Intensive Care: A report from the 2002 Brussels Roundtable. Intensive Care Med 2003; 29: 368-377

As QOL incorporates a patient' values and preferences, it distinguishes itself from other health outcome measures [17]. Hence, next to survival or mortality rate, indices regarding long-term morbidity and QOL after ICU discharge should be taken into account as well to fully appreciate long-term outcomes in critically ill patients. QOL considerations may be particularly important in the critical care setting, where interventions can save lives but where the final outcome may be valued as worse than death [18].

A better understanding of how critical care affects the long-term health and QOL of its survivors can help critical care physicians when deciding on allocation therapeutic efforts in the future, and can help in a better and efficient advanced care planning and communication with patient and family.

2. Quality of life

2.1 Definition

One of the difficulties in QOL research is defining exactly what one means by "QOL" as there is no universally accepted or applied definition. QOL, health status, functional status, functionality, and health-related QOL (HRQOL) are all terms that are often used in literature, but which may reflect quite different aspects of an individual's well-being. Differences in conceptualization of QOL may lead to different measurement approaches, which may lead to other results [18,19].

The World Health Organization defines "QOL" as "*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment"* [20]. According to Wikipedia, QOL is "*the general well-being of individuals and societies, outlining negative and positive features of life. It observes life satisfaction, including everything from physical health, family, education, employment, wealth, religious beliefs, finance and the environment"* [21].

Theoretically, it is important not to mix up the concept of QOL with HRQOL. An assessment of HRQOL is effectively an evaluation of how an individual's well-being or QOL may be affected over time by a disease, disability, or disorder. However, this distinction between QOL and HRQOL seems far too theoretical since it is hardly imaginable that an individual's well-being and perception of life, which is defined as QOL, will not be influenced by health, which is defined as HRQOL. In literature, both terms are often used interchangeably. Through our research we will always refer to the term "QOL", which should theoretically be "HRQOL".

2.2 Quality of life assessment in the critically ill patient

QOL measures will either be specific or generic. Specific QOL measures are designed to be relevant to a particular disease, to a certain patient population, to a certain function (for example sleep), or to a specific condition (for example pain). As critically ill patients are a very heterogenic group of patients, generic instruments that can be used across a wide range of diagnostic categories are needed [22]. They may however be less sensitive to changes in certain conditions or symptoms as compared to specific QOL instruments. Generic instruments should be reliable, valid, and contain a high responsiveness.

Reliability is the repeatability of observations (test-retest) when instruments are administered by different individuals and at different points in time.

Validity refers to an instrument that measures what it claims to measure. The way a QOL measure is validated falls generally onto one of three categories: construct validity, content validity, and criterion validity.

Construct validity is the degree to which a test measures what it claims to be measuring. It is the overarching concern of validity research, subsuming all other types of validity evidence. Construct validity examines if the measure behaves like the theory says that the measure should behave. For example, the construct validity of a questionnaire can be checked to ensure that certain groups (older, lower social classes, those with illnesses) will gain worse scores than other groups (younger, higher social classes, those without illnesses).

Content validity refers to choice of, and relative importance given to, items on a questionnaire. It is important that items appropriate to the phenomenon under investigation are chosen and if they are weighted in some way, that the weights reflect the perceived level of difficulty or health problem. Referring to QOL surveys, it reflects how well a QOL questionnaire effectively and comprehensively can measure all different health domains. Content validity is different from face validity, which refers not to what the test actually measures, but whether items on a questionnaire appear both appropriate to the phenomenon being measured and to make sense, as well as being easily understood. Face validity assesses whether the test "looks valid" to the examinees that take it. Content validity requires experts to evaluate whether test items assess defined content and more rigorous statistical tests than does the assessment of face validity.

Criterion validity refers to the ability of a QOL survey to be systematically related to the gold standards of one or more outcome criteria, which is difficult as gold standards are hard to find in the area of QOL research.

Other forms of validity examine the extent to which individual items in a domain measure the same underlying (internal consistency) or different aspects of QOL (factor analysis) [19, 22].

The sensitivity to change or “responsiveness” of an instrument is a very important criterion to consider when selecting measures. It is essential that evaluative instruments are able to detect change and the level of this change over time [22].

Examples of generic QOL instruments are the Nottingham Health Profile (NHP) [23], the Sickness Impact Profile (SIP) questionnaires [24, 25], the Quality of Well-Being (QWB) Scale [26], the EuroQol-5 Dimensions (EQ-5D) [27, 28], the RAND-36 Item Health Survey (RAND-36) [29], and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36®) [30-34]. All these instruments are commonly used and/or cited in the English language literature.

The NHP was developed to reflect lay rather than professional perceptions of health. It contains 38 yes/no statements in 6 domains: mobility, pain, sleep, energy, emotional reactions, and social isolation. Validity is good, but its reliability and responsiveness in critically ill patients are less well-known [22]. The SIP survey was constructed as a measure of sickness in relation to impact on behavior. It contains 136 items in 12 categories: work, recreation, emotional behavior, alertness, home management, sleep, body care, eating, ambulation, mobility, communication, and social interaction. Test-retest reliability (r = 0.92) and internal consistency (r - 0.94) are high [24, 25]. The QWB is, equal to the EQ-5D, a preference-based measure designed to measure QOL over the previous three days in four areas: physical activities, social activities, mobility, and symptom/problem complexes. It consists of 71 items and takes 20 minutes to complete. The four domain scores of the questionnaire are combined into a total score that ranges from 0 to 1, with 1 representing optimum function and 0 representing death [26]. The RAND-36 is a validated, profile-based QOL measure based on the SF-36. Questions in the RAND-36 and in the SF-36 are similar and the correlation between the measures is excellent (r=0.99) [29]. Scoring systems differ slightly.

There are no uniformly 'worst' or 'best' performing generic instruments. The decision to use one over another, to use a combination of 2 or more, or to use a generic measure along with a preference-based measure will be driven by the purpose of the measurement. The choice will also depend on a variety of factors including the characteristics of the population (age, health status, language/culture) and the environment in which the measurement is undertaken (clinical trial, routine physician visit) [35].

Examples of generic and specific outcome measurements

Generic instruments	
QOL	Nottingham Health Profile (NHP) Sickness Impact Profile (SIP) Quality of Well-Being (QWB) EuroQoL-5D (EQ-5D) RAND-36 Item Health Survey (RAND-36) Medical Outcome Study Short Form-36 Health Survey (SF-36® and SF-36v2®)
Functional status	Katz's Activities of Daily Living (ADL) Karnofsky Index Barthel Index
Mental status	Hospital Anxiety and Depression Scale (HADS)
Specific instruments	
Disease specific	New York Heart Association (NYHA) Functional Class American Thoracic Society (ATS) Respiratory Questionnaire Glasgow Coma Score (GCS)
Patient group specific	Clinical Frailty Score in older patients
Condition specific	Numeric rating scale (NRS) for pain assessment Mini-Mental State Examination (MMSE) for neuropsychological function
Function	Pittsburgh Sleep Quality Index (PSQI) for assessment of sleep quality

We chose to use the EQ-5D and the SF-36® questionnaires through our research. We preferred the combination of a respectively preference-based score with a single index value, reflecting the preference of being in a health state and to be used in future economic evaluations, together with a comprehensive short-form generic QOL measure with a better discriminative power [36]. They are commonly used in critical care outcome research, are well validated and have population norms. Both questionnaires will now be explained more in detail.

2.2.1 The EQ-5D questionnaire

The EQ-5D is a standardized, generic and preference-based measure of health state developed by the EuroQol group (www.euroqol.org) [27, 28]. It is a simple and short questionnaire that is easily understood and answered by patients. Furthermore, its usefulness and validity have been tested in different patient groups and in the critically ill patient population [9, 37-39]. It can assess QOL in face-to-face interviews, interviews by phone or by sending the questionnaire by regular mail. It consists of 3 parts:

The first part is a simple descriptive part where health status can be assessed in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: 1=no problems, 2=moderate problems or 3=severe problems. The decision per dimension results in a 1-digit number (1, 2 or 3) expressing the level selected for that dimension. The digits for the 5 dimensions can be combined in a 5-digit number describing the respondent's health state. Therefore, patients can be classified into 1 of 243 (3^5) possible health states.

The EQ-5D

Mobility	
I have no problems in walking about	□
I have some problems in walking about	□
I am confined to bed	□
Self-Care	
I have no problems with self-care	□
I have some problems washing or dressing myself	□
I am unable to wash or dress myself	□
Usual activities (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	□
I have some problems with performing my usual activities	□
I am unable to perform my usual activities	□
Pain/Discomfort	
I have no pain or discomfort	□
I have moderate pain or discomfort	□
I have extreme pain or discomfort	□
Anxiety/Depression	
I am not anxious or depressed	□
I am moderately anxious or depressed	□
I am extremely anxious or depressed	□

The second part is the EQ-visual analogue scale (EQ-VAS), which is a 20-cm vertical hash-marked scale where patients can rate their perceived overall health between two anchors "0" (worst imaginable health state) and "100" (best imaginable health state). The EQ-VAS score is patient-based and can be used as a quantitative measure of health status as judged by the individual respondents. VAS has long been used in the measurement of health status and QOL in diverse populations [40, 41]. It can also be used to measure specific aspects of QOL such as pain [42]. Measuring VAS has a good validity, and an excellent reliability. The EQ-VAS score has a good anchor-based responsiveness, meaning that the score has the ability to detect clinically important changes over time between its two "0-100" anchors. The level

of responsiveness calculated by distribution-based methods - using statistical analysis (i.e. standardized response mean, effect size) to calculate whether the magnitude of change in score over time should be considered significant – is however moderate, especially for mental health, meaning that there is a better distribution-based responsiveness for the physical compared to the mental health subscales. VAS can be an alternative to a multi-item measure, depending on the research question [43].

In the third part of the EQ-5D, the health status – as assessed in the first part – can be converted by the researcher into a single index value, which indicates the preference of being in a health status, hence the name "utility index" (UI). This conversion is done by applying a formula that essentially attaches values (=weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, which is the value for full health (health state 11111). Converting a health state towards a UI requires thus general population-based value sets. The rationale behind this is that the values are supposed to reflect the preferences of local taxpayers and potential receivers of healthcare. The UI reflects therefore the opinion of the general population, whereas the EQ-VAS score is patient-based and not representative for the general population.

General population-based value sets have been derived for EQ-5D in several countries using the time trade-off (TTO) valuation technique or the EQ-5D VAS-technique. In the TTO technique, respondents from the general population are asked, for example, to imagine they live in a health state (e.g. 22222) for 10 years and then asked to specify the amount of time they are willing to give up to live in full health instead (i.e. 11111). For example, someone might find 8 years in 11111 equivalent to 10 years in 22222. The VAS technique on the other hand, asks people to indicate where, on a vertical thermometer-like scale ranging from best imaginable health ("100") to worst imaginable health ("0"), they think a health state should be positioned. Although there is still an ongoing discussion which of both techniques is preferable, there is now more or less a consensus that the TTO is a more reliable valuation technique but that the VAS technique is more practical and feasible in use and therefore an accepted technique for preference value measurement.

For Belgium, 722 value sets based upon the EQ-VAS technique as valuation method were used [44]. The index value of the EQ-5D is thus a preference-based measure of health status - reflecting the preference to be in a certain health state - ensuring that consequences that are more preferred will receive a greater weight in the analysis than less preferred ones. It makes the EQ-5D suitable for quantifying health outcomes, which can be useful in clinical and economical evaluations of health care interventions.

The UI can range from -0.1584 (which is the index value for a health status indicating severe problems on all 5 dimensions: the 5-digit number in part 1 will be 33333) to 1.000 (which indicates a health status with no problems on the 5 dimensions: the 5-digit number in part 1 will be 11111). An index value of 0.0000 equals dead. In 17 of the 243 possible health states the corresponding UI is below zero, so

it becomes negative. This indicates a health status that is considered to be worse than dead, so a health status no one prefers to be in. In that case, the patient has severe problems in at least 3 or 4 or in all 5 dimensions, mainly in the pain/discomfort and anxiety/depression dimension. Coma also corresponds to a UI below zero [45].

The EQ-5D has now been translated into more than 170 languages – including Dutch - and is used worldwide free of charge.

However, ceiling effects, meaning that certain variations no longer could be captured, were reported and a Task Force was established within the EuroQol Group [46] to investigate methods to increase reliability and sensitivity while maintaining the same feasibility. A new version of the EQ-5D was developed which included five levels (5L) of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems) in each of the existing five EQ-5D dimensions. It was called the "EQ-5D-5L". The existing EQ-5D was renamed the "EQ-5D-3L", referring to the 3 levels of severity on each of the 5 dimensions. As we used the EQ-5D-3L throughout our research, we still will use the name "EQ-5D" for simplicity reasons

2.2.2 The SF-36 questionnaire

The SF-36® questionnaire is another example of a generic QOL-survey [30]. It is the most commonly used QOL measure. The SF-36® was first published in 1992 and further developed and validated in 1993 and 1994 [31, 32]. It was developed as a short-form measure of functioning and well-being in the Medical Outcomes Study (MOS). The MOS was a 4-year longitudinal observational study of the variations in practice styles and of the health outcomes for chronically ill patients. Over 23000 US patients participated in this study [47]. The MOS provided the opportunity for al large-scale test of the feasibility of self-administered patient questionnaires and generic health scales. The MOS surveys were based on a multidimensional model of health and assessed 40 health concepts in a comprehensive way.

The SF-36® questionnaire contains 11 sections holding a total of 36 questions or items measuring QOL at 8 multi-item health domains or scales. The 8 health domains representing in the SF-36® were selected from the 40 health domains that were included in the MOS. Those 8 represent the health domains most frequently measured in health surveys and those believed to be most affected by disease and health conditions. These 8 domains are: general perceptions of health, physical functioning, role limitations due to physical-, or emotional problems, social functioning, bodily pain, vitality, and mental health. The 36th item, health transition, provides information about perceived changes in health status compared to one year ago. Two component summary measures, a physical and a mental, are calculated summary measures where respectively the physical or the mental domains will account more in the measure and where respectively the mental and physical scales weight negatively.

Although the SF-36® proved to be useful for many purposes, 10 years of experience revealed the need and potential for improvements. At the end of the 90s and beginning of the years 2000, the SF-36v2® was developed [33]. It is also a 36-item health survey yielding the same 8 health domain scales and the same 2 component summary measures. Compared to the SF-36® it has improved item wording without ambiguity or bias, improved lay-out of questions, and increased comparability in relation to other cultures. Response choices for the role limitation due to physical health domain and role limitation due to emotional problems domain were increased and decreased for the mental health and vitality domains. All these matters led to a survey which was easier to understand and which had a better validity and reliability.

Although the 8 health domains of the SF-36v2® are assessed in 36 questions, it is a comprehensive and rather short QOL measure. Patients or other respondents are not tired of completing the survey, which is certainly an advantage in the critically ill population.

Each of the 8 health domains of the SF-36v2® has a raw score, which can be converted to 0-100 scores through a simple scoring algorithm. The higher the score, the better the condition on that domain. General population norms provide a basis for meaningful comparisons across the health scales. The "physical functioning" general population norm is between 80 and 90 while the "vitality" norm is around 60. Differences in norms for each health domain must be kept in mind which can make a correct interpretation difficult.

The interpretation of SF-36v2® results has been greatly simplified with the norm-based scoring of its health domain scales and component summary measures. These norm-based scores are based upon the mean and standard deviations (0-100 scores) for each health domain of the US general healthy population in 1998. It is recommended that users base their interpretations on norm-based scores, where all domains have the same mean (50) and the same standard deviation (10). Norm-based scoring does not only allow to compare with a general healthy population (the 1998 US general population) but it also allows to compare the results of one domain with other domains, since all domains have the same mean and standard deviation.

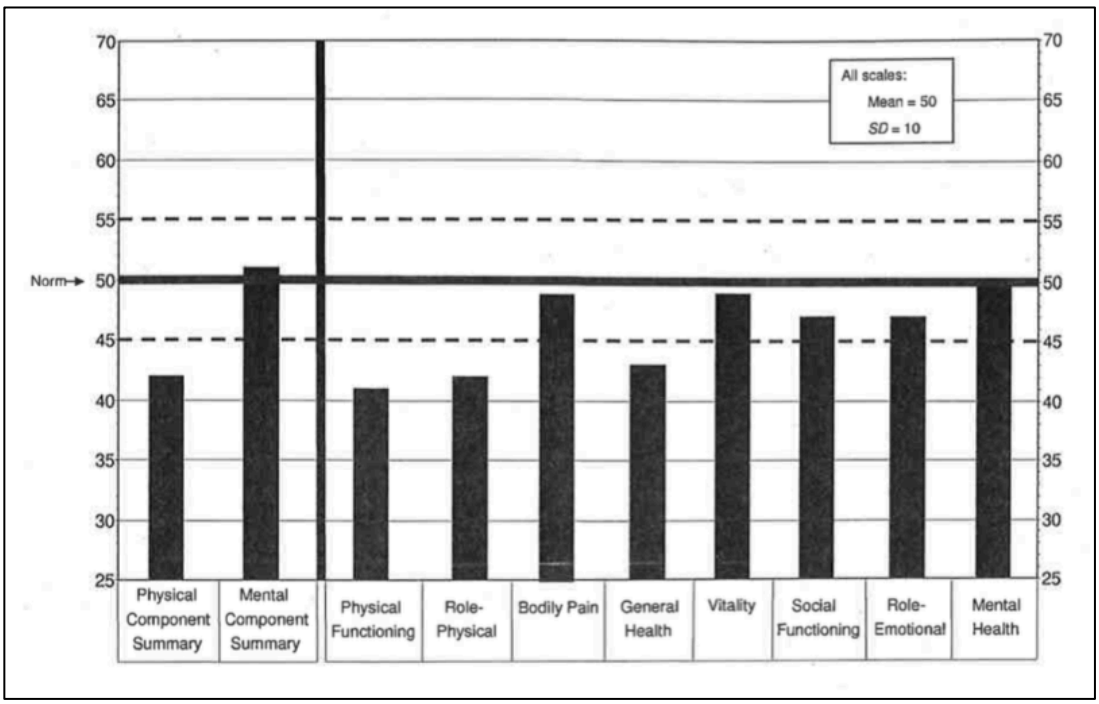
The first step of transforming 0-100 scores to norm-based scores consists of standardizing each SF-36v2® health domain scale using a z-score transformation. A z-score for each domain is calculated by subtracting the 1998 US general population mean for that respective domain from the 0-100 score, and then dividing the difference by the corresponding standard deviation of the 1998 US general population on that domain. The next step is to transform the standard z-scores to norm-based scores by a T-score transformation (mean 50; SD 10). This is accomplished by multiplying each z-score by 10 and then adding 50 to the resulting product. The result is the norm-based score for that respective health domain. The transformation towards physical and mental component norm-based scores goes in an analogue way.

We assessed SF-36v2® as norm-based scores to be able to compare them directly with the general

healthy population, with a group-level range of 47-53 considered as average or normal. Group scores less than 47 indicate impaired functioning within that health domain; group scores greater than or equal to 53 should be considered above the normative sample [33]. Individual patient data are considered as average or normal within a range of 45-55. Scores less than 40 or above 55 indicate an impaired or better health condition than that of the general population. Scores between 40-44 should require further investigation to determine the presence of impaired functioning for the individual patient.

Apart from the advantage of norm-based scoring for interpretation of the study results, it is also important to examine visually the profile of the domain scores. This profile, representing the scores of an individual patient or the means or medians of a group provides a broad overview of the health status. Therefore, the first scores in the profile should always be the physical and mental component scores. These should be placed on the left side, emphasizing the importance of first considering the overall results in the physical or mental health domains. The 8 health domains of the SF-36v2® should then be placed from left to right in this specific order: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Hence, the health domains reflecting mainly physical functioning are on the left side of the profile, while health domains mainly reflecting mental health are on the right.

A very quick interpretation of a health status at first sight is thus possible.



Adapted from Ware JE Jr, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: Quality Metric Incorporated. Optum's Table Abbreviated Item Content for the SF-36v2® Health Survey Health Domain Scale, Figure 7.1, page 74.

The reliability, validity and responsiveness of the SF-36v2® has been confirmed in the critically ill population, and its use is validated in face-to-face interviews, interviews by phone, computer administered or by sending the questionnaire by regular mail [33, 34]. The SF-36v2® is currently available in more than 250 language translations, including Dutch. It may provide more information and may be more sensitive and discriminative than the EQ-5D [9, 18, 31-34, 37]. However, in the older patient population, where brevity of QOL measures is preferred, lower completion rates of the SF-36v2® can be a problem [38].

The SF-12v2® and SF-8™ health surveys are abbreviated versions of the SF-36v2® containing respectively 12 and 8 questions. They measure the same 8 health domains, and each survey provides also the physical and mental component summary scores. Their discriminative power is however less. A preference-based utility index, the SF-6D is also available to help understand economic benefit.

The SF-36®, SF-36v2®, and their shorter versions, are registered trademarks of the Medical Outcomes Trust and are used under license. The SF-36v2® Health Survey is copyrighted © 1992, 1996, 2000, by Medical Outcomes Trust and QualityMetric Incorporated. Permission to reproduce and to use the SF-36v2® Health Survey for both scholarly and commercial purposes can be obtained by completing a Survey Information Request Form at: http://optum.com . We used the SF-36v2® throughout our research, and will refer to it as "SF-36" for simplicity reasons.

Abbreviated questions from the SF-36

Question/ section	Domain	Abbreviated content
1	General perception of health	Is your health excellent, very good, good, fair, poor
2	Health transition	How health is now compared to 1 year ago
3a	Physical functioning	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
3b	Physical functioning	Moderate activities, such as moving a table, pushing a vacuum, bowling, playing golf
3c	Physical functioning	Lifting or carrying groceries
3d	Physical functioning	Climbing several flights of stairs
3e	Physical functioning	Climbing one flight of stairs
3f	Physical functioning	Bending, kneeling, or stooping
3g	Physical functioning	Walking more than one kilometer
3h	Physical functioning	Walking several hundred meters
3i	Physical functioning	Waling one hundred meters
3j	Physical functioning	Bathing or dressing oneself
4a	Role limitations due to physical problems	Cut down the amount of time spent on work or other activities because of physical health
4b	Role limitations due to physical problems	Accomplished less than you would like because of physical health
4c	Role limitations due to physical problems	Limited in kind of work or other activities because of physical health
4d	Role limitations due to physical problems	Had difficulty performing work or other activities because of physical health (It took extra time)
5a	Role limitations due to	Cut down the amount of time spent on work or other activities because of

	emotional problems	emotional problems
5b	Role limitations due to emotional problems	Accomplished less than you would like because of emotional problems
5c	Role limitations due to emotional problems	Did work or other activities less carefully than usual because of emotional problems
6	Social functioning	Extent health problems interfered with normal social activities
7	Bodily pain	Intensity of bodily pain
8	Bodily pain	Extent pain interfered with normal work
9a	Vitality	Feel full of life
9b	Mental health	Been very nervous
9c	Mental health	Felt so down in the dumps that nothing could cheer up
9d	Mental health	Felt calm and peaceful
9e	Vitality	Have a lot of energy
9f	Mental health	Felt downhearted and depressed
9g	Vitality	Feel worn out
9h	Mental health	Been happy
9i	Vitality	Feel tired
10	Social functioning	Frequency health problems interfered with normal social activities
11a	General perception of health	Seem to get sick a little easier than other people
11b	General perception of health	As healthy as anybody I know
11c	General perception of health	Expect my health to get worse
11d	General perception of health	Health is excellent

Adapted from Ware JE Jr, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: Quality Metric Incorporated. Optum's Table Abbreviated Item Content for the SF-36v2® Health Survey Health Domain Scale, Table 2.1, page 15.

2.3 Quality of life research in the critically ill patient

QOL research studies the effects of treatments on endpoints important to the patient. The goal of QOL research is not only to discriminate between who has a good or worse QOL at long-term but also to evaluate how QOL will change over time. Although QOL has now been accepted to be valuable regarding outcome, it is still not routinely included in studies [48]. This has many reasons.

Firstly, assessing QOL with specific questionnaires is more labour intensive and time consuming and will always be more ambiguous for interpretation than the unequivocal "death" or "alive" outcome binary parameter, which has the advantage of being unambiguous and very easy to measure. As critical care physicians, we are not very familiar with handling such a personal and subjective parameter as QOL. QOL depends on a lot of different issues and will not only differ from patient to patient but also from the time point of assessment within the same patient.

Secondly, as QOL incorporates a patient' personal values and preferences, QOL questionnaires should ideally only be answered by the patient himself at every QOL assessment time point. However, many ICU patients cannot complete QOL questionnaires because they are too ill, too weak, too confused, or sedated. Asking the patient to complete QOL surveys after the ICU admission holds the risk of recall bias [17, 49, 50]. Yet, proxies can complete QOL questionnaires on behalf of the patient. They can provide a reasonably accurate estimate of QOL of ICU patients, although they tend to underestimate QOL but differences are usually small and not clinically important [17, 49-52]. The emotional dimensions seem to

be assessed less accurately and are often underestimated by proxies compared to the physical ones, that are frequently overestimated, which means that relatives tend to think that a patient has less mental power and a better physical health than the patient actually has [50-54]. Nevertheless, QOL assessments by proxies at any time, even with possible inherent small under- or overestimations, could be considered as more important and more informative than no QOL assessment at all.

Thirdly, when QOL measures are used as discriminative instruments (who has a good and who has a poor QOL?), possible confounders, which could influence QOL, should be eliminated. Therefore, QOL in ICU patients can be compared to an age- and gender- matched general population. The study findings can also be compared with an appropriate control group eliminating the influence of specific health conditions. More important, long-term QOL should also be compared with QOL before ICU admission, to discriminate whether poor long-term QOL is a result of the severity of illness, or due to confounding factors such as co-morbid disease, poor pre-admission QOL, age, gender, or acquired complications. Baseline assessment of QOL (=QOL 2 weeks before ICU admission) is difficult but of great value to examine the true burden of the critical illness. Evidence for poorer health status among patients discharged from the ICU may be misleading if the prior health status of the ICU patient is not taken into account [49]. In that case, it will be difficult to make honest comparisons or to draw strong conclusions as the impact of the critical illness may be large and may last for a long time. We will however never be able to separate the acute illness from the predisposition to the acute illness.

Fourthly, long-term outcomes and QOL research will always be observational. The prospective observational cohort study is therefore the most powerful research design to maximize the impact of this kind of research [55]. This should be coupled with the need to examine data longitudinally without optimal time intervals for measurement of long-term QOL being known or defined [22, 39]. A very complete picture of outcomes after critical care might require a long follow-up period, and one can wonder when QOL measures will no longer give additional information. The shorter the follow-up intervals for QOL assessments, the less informative results will be and the higher the risk of “assessment-fatigue” in patients. The longer the follow-up periods however, the higher the risk that more patients will be lost to follow-up, which could lead to important bias of the study results. While optimal time intervals for QOL assessments are not known, it is important to keep these intervals as strict and uniform as possible so evolutions in QOL over time between different patients can be evaluated in a correct way.

Fifthly, to assess QOL over time, it is necessarily to track patients after they are discharged from the ICU and from the hospital. This can be difficult and is labour intensive. Validated QOL questionnaires can access QOL by face-to-face interview, by phone, or by regular mail. Although a high response rate to QOL questionnaires is the aim of every QOL study, there will always be non-responders. If this is a numerous group, it is important to describe these non-responders to find out if the reason for non-responding can be clarified [56].

Sixthly, evaluations of long-term QOL always imply survival bias as QOL can only be assessed in survivors [57]. It should be acknowledged that long-term QOL might be modified by events happening to the patient after hospital discharge.

Seventhly, the increasing interest in patients' perceptions of health status has led to huge variations in applied methodology to measure functional status and QOL, which hampers the ability to compare results or draw strong conclusions out of outcome research. As QOL is a subjective parameter by itself, it should therefore always be preferred to use standardized QOL questionnaires, which have a well-known validity, reliability, and are responsive to real changes in health [22]. As already been said, there are no uniformly 'worst' or 'best' performing generic instruments and the decision to use one over another or to use a combination of 2 or more, will depend upon the characteristics of the population and the environment in which the measurement is undertaken [35]. However, It should be encouraged to uniform outcome research so that QOL evaluations could be easier compared and placed in a broader perspective.

3. Costs and Outcome Study in the ICU (COSI study)

3.1 Design, setting, patients, and QOL assessments

With the knowledge that QOL is a subjective parameter, that we have to use standardized questionnaires, preferentially completed by the patient, that baseline QOL should be assessed, that it would be difficult to track patient at long-term, that there will be a survival bias and that outcome research implied an observational study design, we performed a prospective observational cohort study in which we, during a one-year period (March 3rd 2008 - March 3rd 2009) included all adult (≥ 16 years) critically ill patients consecutively admitted to the 14-bed medical and 22-bed surgical ICU and the 6-bed burn unit of the Ghent University Hospital, Ghent, Belgium. Our main purpose was to gain data concerning long-term outcomes and QOL in our own critically ill patient population. Within the total patient cohort, we also predefined some subgroups namely patients admitted to the ICU due to oncological or hematological disease, patients with liver cirrhosis Child-Pugh B or C, patients developing acute kidney injury (AKI) with need for renal replacement therapy (RRT), patients with a prolonged ICU length of stay (LOS) (≥8 days) or older (≥ 80 years) patients.

In case of multiple ICU admissions during the same hospitalization period, we only included the first admission. We did not include cardiac surgery patients as these patients represent a very specific patient population, where ICU admission is needed mainly after elective cardiac surgery, where ICU stays are often short, and where QOL at long-term is likely to be very good [58]. Due to the high turnover in these patients, they would otherwise have become the major patient group in our study cohort, which could have led to bias in our main study results.

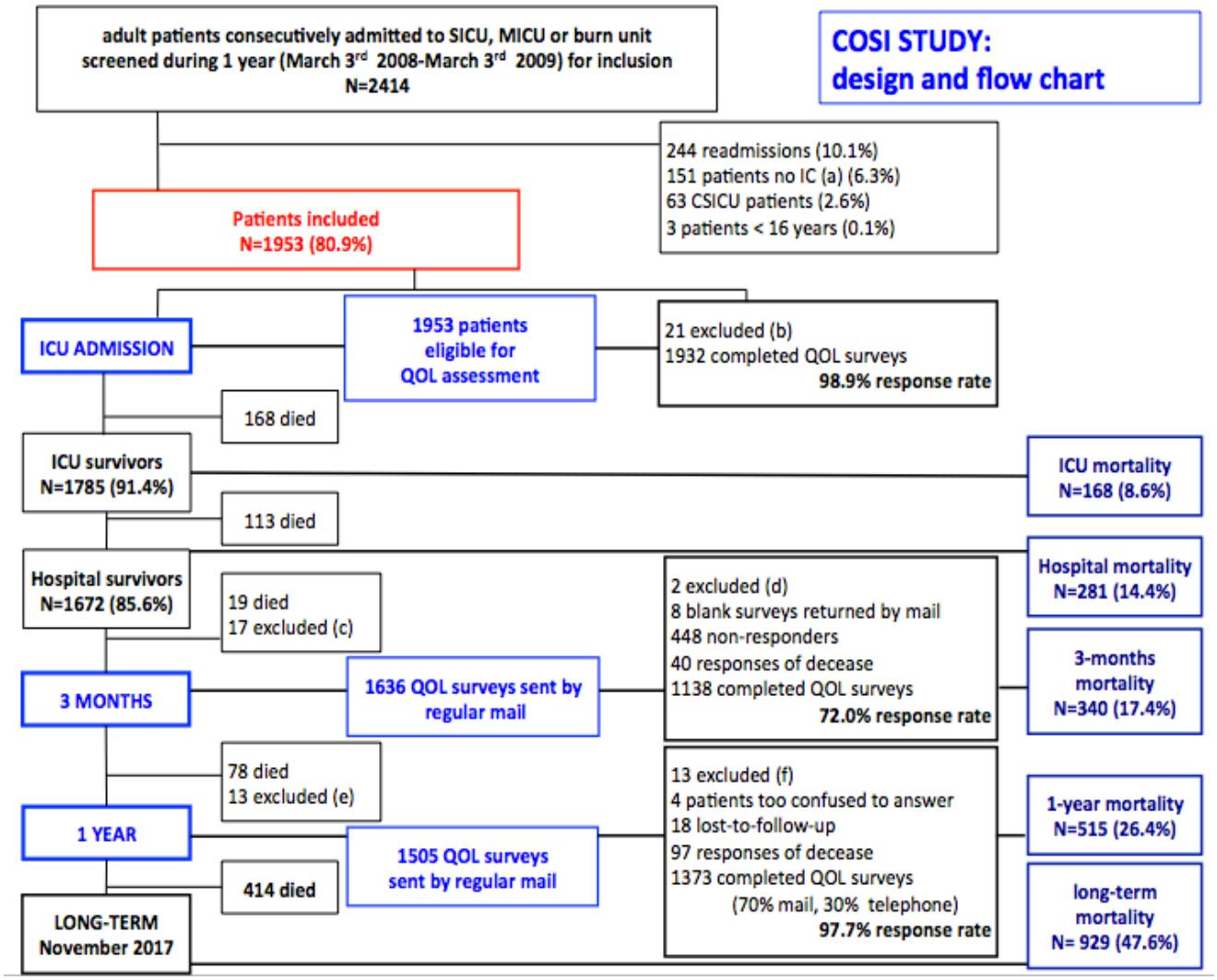
The study was approved by the local ethical committee (Ethisch Comité Ghent University Hospital; project 2007/423 approved 06 December 2007) (B67020072805), and conducted in accordance with the declaration of Helsinki. A signed informed consent was obtained from every included patient or his legal representative.

QOL was assessed using the EQ-5D (and cognitive function assessment) and SF-36 at 3 predefined time points: baseline QOL, 3 months and 1 year after ICU discharge. A computer file with ICU discharge data for each included patient was created in order to respect in an accurate way the time points of second (exactly 3 months after ICU discharge) and third (exactly 1 year after ICU discharge) QOL assessment.

Following ICU admission and study inclusion, a face-to-face interview to assess baseline QOL (defined as QOL 2 weeks before ICU admission) was done as soon as possible. This interview was preferably taken from the patient, or, whenever impossible due to severity of illness, from the proxy. Three months and 1 year after ICU discharge, patients or relatives were sent the EQ-5D and SF-36 surveys by regular mail, after checking their living status and address through the hospital computer system. The envelope contained the two questionnaires, and also a pre-addressed envelope with stamp and a ballpoint pen. At 1 year, questions concerning living situation of the patient, memories of the ICU stay, actual sleep disturbances, and if the patient was willing to be admitted to an ICU department again if needed, were added. If the questionnaires were not returned within one month, patients or relatives were contacted by phone to assess QOL. This was only done at the third time point. If there was no contact by phone, the family practitioner was contacted to assess the living status of the patient.

It is important to notice that we analyzed QOL in survivors over time. Therefore, the population at each follow-up interval represented a different subset of the initial cohort.

3.2 Flow chart of included patients, number of QOL surveys and outcomes in the total cohort



(a)= 151 no informed consent: 97 refusals, 40 language problems, 14 social reasons; (b)= 21 excluded: 11 refusals, 3 living abroad, 7 language problems; (c)= 17 excluded: 3 refusals, 7 living abroad, 7 language problems; (d)= 2 excluded: 1 refusal, 1 mental problem; (e)= 13 excluded: 7 refusals, 3 living abroad, 3 language problems; (f)= 13 excluded: 4 refusals, 1 living abroad, 8 language problems; ICU= intensive care unit; SICU= surgical ICU; MICU= medical ICU; CSICU= cardiac surgery ICU; N= number; QOL= quality of life; IC= informed consent

3.3 Data Collection

Data collected within the first 24 hours of ICU admission included contact information of the patient, proxy, and general practitioner, demographics, hospital days prior to ICU admission, living and work circumstances before ICU admission, functionality as measured by the Katz activities of daily living (ADL) scale [59, 60], hospitalization in the last 6 months, comorbidity as measured by the Charlson comorbidity index [61], main ICU admission reason and diagnosis, admission circumstances (planned-unplanned/during weekend or not), if the patient belonged to 1 or more of the predefined subgroups (sub) (oncological, hematological, liver cirrhosis Child-Pugh B or C, patients developing AKI with need for RRT, patients with a prolonged ICU-LOS (≥8 days) or older patients (≥ 80 years)), APACHE II score [2], Sequential Organ Failure Assessment (SOFA) score [62], Therapeutic Intervention Scoring System-28 score (TISS-28 score) [63], Nine Equivalent of Nursing Manpower Use score (NEMS-score) [64], do-not-resuscitate (DNR) codes, need for invasive mechanical ventilation, vasopressors, RRT, medical imaging (regardless of number and other than chest X-ray or ultrasound examinations), transfusion with blood products, surgery, or tracheotomy. For each included patient, we also collected all ICU and hospital direct costs.

During ICU stay SOFA, TISS-28 and NEMS-scores, DNR-codes, need for invasive mechanical ventilation, vasopressors, RRT, medical imaging (regardless of number and other than chest X-ray or ultrasound examinations), transfusion, surgery, or tracheotomy were collected on a daily base.

ICU-LOS, hospital-LOS, vital status at ICU and hospital discharge, and 1 year following ICU discharge were collected for each patient. Depending on the substudy, we also assessed vital status and QOL at longer terms.

II. Research questions

1. Aim and outline

Drawing strong conclusions from a large case-mix of very heterogeneous medical, surgical, or burned critically ill patients is difficult. Presenting QOL results for ICU patients as a whole may obscure the fact that some types of patient improve whilst others remain stable or deteriorate [49]. A more accurate picture of ICU outcomes might be obtained if the diagnostic category is taken into account, as prior health status, which influences QOL, has been shown to vary across such categories [39, 49, 65]. Assessing QOL in more specific patient groups will therefore result in more refined data. Though, the number of patients in specific diagnostic patient groups will be inherent smaller.

Nevertheless, according to our main study goal, we chose to assess long-term outcomes and QOL within specific patient subgroups of our large COSI study cohort where there are often doubts considering effectiveness of critical care or where the start of specific expensive treatments during ICU stay can be questioned, namely the oncological/hematological patients, the older patients (≥ 80 years), and the patients with need for RRT due to AKI developed during their critical illness.

As more and more critically ill patients – even in these specific and often controversial patient groups - nowadays survive their critical illness; it is for critical care physicians very important to have a better understanding of how critical care affects the long-term health and QOL of its survivors. Better knowledge and insights of long-term outcomes will help physicians to identify who will benefit the most from ICU admission when deciding on allocation therapeutic efforts in the future, and can help in a better and efficient advanced care planning and communication with patient and family.

The focus of our research concentrated therefore around 3 major issues: 1/ reviewing literature concerning long-term QOL, reviewing applied methodology and quality of this published outcome research, 2/ assessing long-term outcomes and QOL in specific critically ill patient where the additional benefit of critical care is frequently questioned, and 3/ developing a prediction model for long-term QOL based upon readily available variables at the first day of ICU admission and so determining the most important predictors for long-term QOL. Five specific research questions addressing these topics were formulated.

2. Specific research questions

2.1. What is already known in the literature concerning long-term outcomes and QOL in critically ill patients? Can we formulate methodological recommendations for further research on this topic?

In this first study, it was our purpose to give a systematic review of the literature, published between January, 1th 1999 and December, 31th 2009, of QOL and its influencing factors, at least one year after discharge from the ICU, and of the methodology used.

A search through EMBASE-PubMed, MEDLINE (OVID), SCI/Web of Science, Cochrane Library, and Google Scholar was done on January 9, 2010 using the medical subject headings (MeSH) or text keywords "quality of life", or "long-term outcome" cross referenced with "intensive care", "critical care", "critically ill patients", "ICU patients", "critical care patients", "ICU stay", or "ICU". Limitations were applied regarding language (only English language), time (articles published within the 10-years interval), age (above 18 years), and humans. Only studies using SF-36, RAND-36, EQ-5D, and NHP were considered. Outcomes articles including exclusively cardiac or thoracic aortic surgery patients, methodological articles, literature reviews, case-reports, editorials, and letters were excluded. Studies with less than 50 patients were also not included.

For each eligible article, information was extracted on authors, journal, year of publication, study design, inclusion period, initial study cohort, baseline variables and outcome, number of eligible patients for long-term QOL assessment, instrument(s) and method(s) used for QOL assessment, response rate, follow-up period, the use of other questionnaires or tests, the final conclusion concerning QOL, and factors determining QOL. Study quality was assessed using four criteria: 1) QOL assessment prior to ICU admission, 2) description of key inclusion or exclusion criteria, 3) description of non-responders and comparison with those remaining in the study, and 4) adjustment for confounders such as age and gender. We hoped with this review to gain and give better insights into long-term QOL, and to make methodological recommendations for further research on this topic.

2.2. What is the long-term outcome and QOL of critically ill patients with a hematological or solid malignancy? What is the evolution of QOL over time in these patients compared to baseline? Can we identify prognostic indicators for the evolution of QOL after ICU discharge?

The prognosis of patients with a solid or hematological malignancy has substantially improved over the past decades due to advances in diagnostics, antineoplastic therapy and supportive care [66]. Additionally, survival of cancer patients developing critical illness [66-68] has increased as well, including those requiring mechanical ventilation [69] or RRT [70, 71]. A diagnosis of cancer should therefore not preclude ICU admission, as it is the severity of the acute illness that will determine short-term mortality, rather than the underlying cancer characteristics [72-74].

In our review study, we demonstrated that major reductions in long-term QOL were seen in critically ill patients with severe acute respiratory distress syndrome, prolonged mechanical ventilation, and severe sepsis, all representing complications that affect cancer patients as much as non-cancer patients [75]. In addition, poor performance following ICU admission in cancer patients may jeopardize long-term outcome by inducing postponements or cancellations of potentially curative chemotherapy. So, to fully appreciate outcomes of critically ill cancer patients, a better knowledge and insights regarding long-term morbidity and QOL after ICU discharge is necessarily.

In order to evaluate long-term outcomes, QOL, and evolution in QOL of critically ill patients with a hematological or solid malignancy, we followed the COSI study design with QOL assessments using EQ-5D and SF-36 at the 3 different time points (baseline, 3 months and after 1 year after ICU discharge), and with additional questions after 1 year. Prognostic indicators for a poor QOL at 3 months and 1 year were formulated. Only patients of the COSI cohort with a solid or hematological malignancy as direct or contributive cause for ICU admission were included. Patients with complete remission for > 5 years were excluded.

2.3. What is the impact of renal replacement therapy (RRT) on long-term outcome and QOL in critically ill patients developing acute kidney injury (AKI) with need for RRT during ICU stay?

Approximately 5-10% of critically ill patients will develop AKI with need for RRT (AKI-RRT) [76]. These patients are amongst the most severely ill patients in the ICU, as may be illustrated by the 50% in-hospital mortality [77-79]. Decisions whether or not to start RRT are not easy to make as the consequence to withhold this therapy will lead in many case to the death of the patient. AKI-RRT patients who survive may develop chronic kidney disease, and experience decreased long-term survival [79-82]. Data regarding long-term QOL in AKI-RRT survivors show that these patients have a decreased QOL compared to the general population but perceive QOL as good [83, 84]. However, these data were retrospective [85-87], evaluated only short-term QOL [83-90], lacked baseline QOL assessment [83-86, 88, 91], or dated back more than a decade [85, 86, 88, 92].

To study the impact of RRT on long-term outcome and QOL, we therefore performed a matched cohort study, according to the STROBE guidelines [93]. Included patients were AKI-RRT patients of the COSI cohort, alive at 1 year after hospital discharge, who were individually matched with 1-year non-AKI-RRT survivors from the same cohort. Equally, AKI-RRT patients alive at time of the study (average 4 years later) were individually matched with 4-year non-AKI-RRT survivors. Matching was based on gender, age (±5 years), APACHE II score (± 5), and admission category. Chronic hemodialysis patients and patients who needed RRT but who did not receive RRT due to therapeutic restrictions were excluded.

2.4. What is the long-term outcome and QOL of critically ill older patients (aged ≥ 80 years)? What is the evolution of QOL over time in these older patients compared to baseline? How do older survivors perceive their long-term QOL? How are their post-hospital trajectories?

Survival to older age has increased, which leads to more hospitalizations and more ICU admissions for older patients [57, 94]. As prognosis of critically ill patients aged 80 or more may be poor, especially in those with severe comorbidity, or a greater illness severity, concerns may rise regarding utility or futility of high-level expensive ICU treatments for these patients [57, 94-98]. To identify which

critically ill older patient would benefit the most from ICU admission, long-term outcomes and QOL are important issues to be taken into account.

However, recent data regarding long-term QOL in critically ill older patients are still limited [95-101]. Studies are either retrospective [95, 102], evaluate only short-term QOL [96, 101, 102], lack baseline QOL evaluation [95, 96, 99], assess QOL after variable follow-up intervals [95], or define older patients as patients aged 65 years or more or even younger [96, 97, 100, 103]. In order to evaluate long-term outcomes, QOL, and evolution in QOL in our critically ill older (≥80 years) patient population, we followed the COSI study design with QOL assessments using EQ-5D and SF-36 at 4 different time points (baseline, 3 months, 1 year and 7 years after ICU discharge), and with additional questions after 1 and 7 years. Only patients of the COSI cohort who were at least 80 years at ICU admission were included.

Older patients often perceive a worsening in long-term QOL but still evaluate their QOL as acceptable [95-97, 101-103]. It suggests that QOL might have another meaning for older patients, with social and mental values being far more important than limited physical functioning and that age itself influences QOL mainly due to increasing number of chronic conditions [96, 104]. We therefore also determined perceived QOL per patient by computing changes between the 3 consecutive time intervals (before ICU admission-3 months; 3 months-1 year; 1 year-7 years). These changes in QOL were considered clinically important if patients reported another level for the different EQ-5D dimensions or for the health transition of the SF-36, or if there was a minimum difference of 7 points in the EQ-VAS or 5 points in the norm-based physical and mental component measures of the SF-36 [105].

Not only long-term outcomes and QOL are important issues to consider when deciding to admit older patients to the ICU, but critical care physicians should consider the whole disease process the older has to endure [106]. Therefore, we also evaluated posthospital trajectories in critically ill older patients who survived to hospital discharge to gain better insights in the further course of the disease and in the recovery phase.

2.5. Can we predict long-term QOL based upon variables readily available at the first day of ICU admission?

The true burden of a critical illness and its long-term consequences on physical, mental and cognitive functioning may be underestimated [107, 108], as well as the possibility to return to former daily life and QOL [109]. It is the important task of critical care physicians to inform critically ill patients and their family in a reliable way about these outcomes. However, for critical care physicians too, long-term functionality and QOL remain difficult to predict [110, 111].

Accurate prediction models can guide physicians in their handling, communication, and decision-making. However, some existing prediction models are not applicable to a broad critically ill patient population [112-117], are rather complex [118, 119], or not accurate enough [120]. Some focused on

long-term mortality [112, 121], or long-term functionality [113], but none of the existing prediction models estimated long-term QOL in general critically ill patients.

Therefore, it was our aim to retrospectively develop an easy to use and accurate prediction model for the mean QOL at 1 year after ICU discharge in general critically ill patients based upon data of the COSI study readily available at the first day of ICU admission (= first 24 hours of ICU stay = D1).

The health states assessed by the first part of the EQ-5D (the 5-digit number) at baseline and at 1 year were converted into the corresponding UI at baseline (UIb) and UI at 1 year after ICU discharge (UI1y) [45]. These were used as surrogate for QOL at that time point. VASb and VAS1y expressed perceived QOL at baseline and 1 year after ICU discharge. UI1y and VAS1y for non-survivors were set at zero to avoid survival bias. QOL assessments 3 months after ICU discharge were not included in the development of the D1-model due to too many missing data at that time point.

For the development of the D1-prediction model, three different multivariate linear regression models, respectively Model I, II, and III, were fitted with UI1y as primary outcome. Model I assessed the bivariate association between UIb and UI1y. Model II ("full" model) included all possible available D1 predictors in the linear regression analysis. Model III ("reduced" model) included only predictors in the linear regression, which were selected by the grouped lasso technique. This technique was applied to identify the optimal number and most important predictors for UI1y in the D1 linear regression model in order to simplify the model, and to cope with the categorical variables [122, 123] as it allows predefined groups of covariates, such as all variables encoding a categorical covariate, to be selected into or out of a model together.

Only complete cases, defined as patients included in the COSI cohort without missing data, were included in the statistical analysis. The model with the best predictive capability for the mean QOL at 1 year after ICU discharge was selected as D1-prediction model.

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Part Two

Systematic Review

And

Original Studies

I. Quality of life after intensive care: A systematic review of the literature

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ABSTRACT

Objectives: 1) To evaluate quality of life (QOL), at least 12-months after discharge from the intensive care unit (ICU), of adult critically ill patients, 2) to evaluate the methodology used to assess long-term QOL, and 3) to give an overview of factors influencing QOL.

Data sources: EMBASE-PubMed, MEDLINE (OVID), SCI/Web of Science, Cochrane Library, Google Scholar, and personal files.

Data extraction: Data extraction was carried out independently and crosschecked by two reviewers using a predefined data extraction form. Eligible studies were published between 1999 and 2009, and assessed QOL ≥ 12-months after ICU discharge by means of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), RAND-36-item Health Survey, EuroQol-5D (EQ-5D), and/or Nottingham Health Profile (NHP) in adult ICU patients.

Data synthesis: 53 articles (10 multicenters) were included, with the majority performed in Europe (68%). The SF-36 was used in 55%, and the EQ-5D, NHP, RAND-36, or a combination, in respectively 21%, 9%, 8% and 8%. A response rate of ≥ 80% was attained in 26 studies (49%). Critically ill patients had a lower QOL than an age-and gender matched population but QOL tended to improve over years. The worst reductions in QOL were seen in severe ARDS, prolonged mechanical ventilation, severe trauma, and severe sepsis. Study quality criteria, defined as baseline QOL assessment, no major exclusion criteria, description of non-responders, and a comparison with a reference population were only met in 4 studies (8%). Results concerning the influence of severity of illness, co-morbidity, pre-admission QOL, age, gender, or acquired complications were conflicting.

Conclusions*:* QOL differed upon diagnostic category, but overall, critically ill patients had a lower QOL than an age-and gender matched population. A minority of studies met the predefined methodological quality criteria. Results concerning influence of the patients' characteristics and illness upon long-term QOL were conflicting.

INTRODUCTION

Since intensive care medicine per definition treats the most critically ill patients, who have an inherent high risk of mortality, it seems logical that for many years, the primary outcome parameter has been survival rate. While this is without any doubt a very important issue, survival or mortality rate have also the advantage of being unambiguous and very easy to measure. Advances in diagnostic and therapeutic options make that more and more patients survive critical illness. While studies investigating survival rates of critically ill patients are widely performed, we also have to question whether critical illness has any impact on an individuals (very) long-term (i.e. ≥12 months after intensive care unit (ICU) discharge) health status and quality of life (QOL). Therefore, next to survival or mortality rate, QOL has to be considered to be of equal importance as outcome parameter.

Although QOL has been accepted to be valuable regarding outcome, it is not routinely included in studies and research on this topic is still in its infancy. This has many reasons. Measuring QOL, with specific questionnaires, is more labour intensive and time consuming and will always be more ambiguous for interpretation than the "death" or "alive" outcome parameters. Optimal follow-up periods for measuring QOL are not defined. Baseline assessment of QOL is difficult but of great value to examine the burden of the critical illness.

Only a few reviews of QOL after intensive care have been published earlier (1-4). There has been no systematic review providing accurate and recent data on the burden of critical illness on a patients' long-term QOL. Nevertheless, a better understanding of how intensive care affects health and well-being of its survivors will help physicians when deciding on allocating therapeutic efforts in the future. Consequently, it is the purpose of this paper to give a systematic review of the literature, published in the past decade, of QOL and influencing factors, at least one year after discharge from the ICU, and of the methodology used. Finally, we hope to give better insights into long-term QOL, and to make methodological recommendations for further research on this topic.

MATERIALS AND METHODS

Data Sources, Search Strategy, Study Selection and Data Extraction

A two-staged systematic review process of existing published original research articles was conducted. First, two authors (SO, DV) independently searched EMBASE-PubMed, MEDLINE (OVID), SCI/Web of Science, Cochrane Library, and Google Scholar on January 9, 2010 using the medical subject headings (MeSH) or text keywords "quality of life", or "long-term outcome" cross referenced with "intensive care", "critical care", "critically ill patients", "ICU patients", "critical care patients", "ICU stay", or "ICU". Limitations were applied regarding; language (English language), time (articles published between January, 1th 1999 and December, 31th 2009), age (above 18 years), and humans. Personal files that were known to the authors and reference lists of relevant articles were hand-searched as well.

Outcomes articles including exclusively cardiac or thoracic aortic surgery patients, methodological articles, literature reviews, case-reports, editorials, and letters were excluded. Studies with less than 50 patients were also not included. If it was unclear whether or not patients were admitted to the ICU, articles were excluded as well (5-7).

In stage two, all abstracts were evaluated independently by two authors (SO, DV) for the following methodological criteria: 1) assessment of QOL by means of at least one of the following instruments: Medical Outcomes Study 36-item Short Form Health Survey (SF-36), RAND-36-item Health Survey, EuroQol-5D (EQ-5D), and/or Nottingham Health Profile (NHP); and 2) follow-up period of ≥ 12-months following discharge from the ICU. Disagreement regarding eligibility was resolved by consensus.

Subsequently, identified articles were downloaded, and screened electronically. For each eligible article, using a predefined categorization system, information was extracted on respectively; authors, journal, year of publication, study design, inclusion period, initial study cohort, baseline variables (age) and outcome (hospital mortality), number of eligible patients for long-term QOL assessment, instrument(s) and method(s) used for QOL assessment, response rate, follow-up period, the use of other questionnaires or tests, the final conclusion concerning QOL, and factors determining QOL. Study quality was assessed using four important criteria, analogous to Dowdy et al. (1): 1) QOL assessment prior to ICU admission, 2) description of key inclusion or exclusion criteria, 3) description of non-responders and comparison with those remaining in the study, and 4) adjustment for confounders such as age and gender. Above mentioned criteria were not used in decisions regarding inclusion or exclusion of eligible studies. Any discrepancies between both reviewers were resolved by discussion.

QOL measurement instruments

SF-36, RAND-36, EQ-5D, and NHP were considered as they are generic instruments commonly used in intensive care research (8); they are well validated and have population norms in the literature (9-16).

The SF-36 questionnaire contains 36 items measuring eight multi-item domains: physical and social functioning, role limitations due to physical or emotional problems, mental health, vitality, bodily pain, and general perception of health (9-13).

Arising from SF-36, the RAND-36 questionnaire was developed. While the count system in the latter differs somewhat compared to SF-36, questions and final results are almost similar (14).

The EQ-5D is a short questionnaire consisting of three parts (15, 17-19). A descriptive system measures health in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has three levels: no problems, moderate, or severe problems, and can therefore be classified into one of 243 (3^5) possible health states. Each of these can be converted into one single summary index, which can be used in health-economy studies. On a visual analogue scale (EQ-VAS), patients can rate their overall health between 0 and 100. Although the EQ-5D is a well-known and

validated instrument to measure QOL in general populations, it has been less well validated in the critically ill population (17-19), and it may provide less information and may be less discriminative than the SF-36 (20).

The NHP consist of a two parts questionnaire (16). The first one is composed of 38 statements related to six domains: physical mobility, pain, sleep, energy, emotional reactions, and social isolation. The second part lists 7 activities of daily life: occupation, house work, social activity, home life, sex life, hobbies and holidays. The NHP has already been used to evaluate QOL in the critically ill population, especially in cardiac surgery patients (21). Nevertheless, internal consistency and sensitivity to change were better for the SF-36 and RAND-36 than for the NHP (22-24).

RESULTS

A total of 53 articles were finally included in the review. The articles were grouped according to diagnostic category. Studies concerning critically ill patients in general were separated based upon follow-up period. Eleven articles concerning acute respiratory distress syndrome (ARDS) (25-35), 3 articles about prolonged mechanical ventilation (36-38), 8 trauma studies (20, 39-45), 6 concerning cardiac arrest (46-51), 6 studies about elderly patients (52-57), 2 pancreatitis studies (58, 59), 3 sepsis studies (60-62), and 4 studies with various topics (63-66) were included. There were 4 studies concerning outcome and QOL in general critically ill patients one year after intensive care (19, 67-69) and 6 with longer follow-up periods (70-75). Table 1 gives an overview of the characteristics of these studies. All the studies were performed in large hospitals. Ten were multicenter studies (32-34, 40, 45, 48, 51, 57, 61, 66). Thirty six were conducted in Europe (19, 20, 26-28, 35, 36, 41, 42, 44-46, 48, 49, 51-56, 59, 61-75), 13 in the USA (25, 29-31, 37-40, 43, 47, 50, 57, 58) and 4 in Canada (32-34, 60). Within Europe, the majority of studies were done in Scandinavian countries (42, 44, 45, 51, 54, 59, 61, 64-67, 72-75), Germany (26-28, 35, 49, 71) and the Netherlands (20, 48, 55, 63).

Inclusion periods varied between less than one year (61, 68, 70, 71) and 10 years or more (26-28, 35, 47, 50). All but 3 studies concerning critically ill patients in general had an inclusion period of one year (19, 67, 69, 72-75). In 3 articles, the inclusion period was not further specified (32, 33, 40) (Table 1).

Table 2 gives an overview of QOL assessment after ICU discharge. The most frequently used QOL-instrument was the SF-36 (55%), followed by the EQ-5D (21%), the NHP (9%), and the RAND-36 (8%). Four studies (8%) used a combination of QOL instruments, either the SF-36 with the EQ-5D (19, 53), the RAND-36 with the EQ-5D (54), or the NHP with the Patrick's Perceived Quality of Life score (PQL), another QOL questionnaire (52).

Follow-up periods for QOL assessment varied between the included studies. Some had a strict follow-up period of one year (29, 30, 37, 40, 41, 56, 67, 68), whereas others had large ranges within their follow-op time (26-28, 35, 43-47, 50, 52, 55, 58-60), and in 1 study, although at least 12 months, the

follow-up period for QOL evaluation was not clearly defined (39). Twelve studies evaluated QOL at very strict time points during the follow-up period (19, 31-34, 38, 51, 57, 66, 72, 74, 75). Median follow-up periods of 5 years or more were found in 8 studies (26-28, 42, 48, 49, 71, 73). Particularly the Scandinavian area seemed to be interested in research on QOL a long period after ICU discharge (42, 54, 59, 64, 65, 72-75).

QOL was assessed at follow-up by a mailed survey in 22 studies (42%) (20, 35, 36, 39, 45, 48, 49, 53, 54, 57, 59, 61, 67, 68, 63-66, 72-75), by phone in 14 (26%) (19, 25, 32, 33, 40, 41, 44, 52, 55, 56, 58, 60, 62, 69), by face-to-face interviews in 12 (23%) (26-31, 34, 43, 46, 47, 50, 51) or by a combination of these methods in 5 studies (9%) (37, 38, 42, 70, 71). To gain the highest response rate possible, many studies sent reminder mails or phoned in absence of any response by mail (20, 35, 39, 42, 45, 49, 53, 54, 57, 59, 65, 67, 68, 72-74). Nevertheless, there were 3 studies (6%) with a response rate below 50% (26, 27, 39), 24 studies (45%) with a response rate between 50-79% (19, 28, 32, 33, 35, 37, 38, 40, 41, 45, 49, 51, 53, 57, 58, 61, 62, 64-66, 69, 73-75), and 26 studies (49%) had a response rate of at least 80% of the eligible patient population for long-term outcome and QOL assessment (20, 25, 29, 30, 31, 34, 36, 42-44, 46-48, 50, 52, 54-56, 59, 60, 63, 67, 68, 70-72).

Four studies (8%) met all of the 4 predefined study quality criteria; assessment of QOL at baseline, no major exclusion criteria within the study population, description of the non-responder group versus the responder group, and comparison with an age-and gender matched normal population (19, 37, 53, 61) (Table 3). By omitting assessment of baseline QOL as quality criterion, the number of studies fulfilling the other 3 quality criteria increased to 21 (40%) (26-28, 32, 35, 36, 39, 40, 42, 45, 47, 49, 57, 59, 62, 64-66, 69, 72, 74). Only 9 studies (17%) measured QOL prior to ICU (19, 37, 38, 44, 52, 53, 61, 68, 70), and in 27 articles (51%) (19, 26-28, 32, 35, 36, 37, 39, 40, 42, 44, 45, 47, 49, 53, 57, 59, 61, 62, 64-66, 69, 70, 72, 74), a description was given of the non-responder group and compared with patients who responded to the QOL survey. All studies defined clearly which patients were in- or excluded.

Table 4 summarizes the major finding concerning long-term QOL per article. Long-term QOL varied between diagnostic categories. ARDS patients, patients after prolonged mechanical ventilation, severe trauma patients, and sepsis survivors showed significant impairments in long-term QOL (25-45, 60-62). While physical aspects improved slowly over the years, mental and emotional impairments were stagnant or declined even further. On the other hand, survivors of cardiac arrest, severe pancreatitis, oesophagectomy, and acute kidney injury had a good QOL which was comparable with or even better than an age-and gender matched population (46-51, 58, 59, 63, 64). In the elderly, QOL was somewhat decreased, especially in the physical domains, but elderly patients generally adapted well to these limitations and perceived their QOL as good (27-32). One year after ICU, critically ill patients in general had a lower QOL, especially in physical domains, than an age-and gender matched population (19, 67-69). However, a slow improvement to pre-morbid QOL levels could be found. The increase in QOL could be

further seen several years after ICU, where QOL was quite comparable with that of the normal population (70-75).

Factors associated with reductions in QOL at least one year after ICU discharge are also displayed in Table 4. In ARDS or patients with prolonged mechanical ventilation, the ARDS and its sequelae influenced QOL by impairments in pulmonary functions, cognitive disorders, weakness, and posttraumatic stress disorders (25-35). In trauma patients, the injury severity, the degree of brain damage, and female gender dominated long-term QOL in a negative way (20, 41, 43, 44). However, in other studies the severity of illness played a less important role (71, 74). In a mixed ICU-patient population, diagnostic category determined QOL (67, 68, 70). There were conflicting results regarding the influence of age on long-term QOL (19, 37, 42, 57, 59, 63, 67, 70, 74). Two studies found that a poor pre-admission QOL played a role in the reduction in QOL a long period after ICU discharge (19, 70).

DISCUSSION

It was the purpose of this review to give an overview of the literature of QOL at least one year after discharge from the intensive care, of the factors that determine QOL, and of the methodology used. Because of differences in study design, patient population, QOL instruments, follow-up time, and response rate, it is impossible to make one overall conclusion. This review has however some important findings.

First, long-term QOL depends largely upon diagnostic category. Patients with severe ARDS, prolonged mechanical ventilation, severe trauma, and severe sepsis appeared to have the worst reductions in QOL, which lasted a long time. While physical aspects improved slowly over the years, mental and emotional impairments were stagnant or declined even further. Trauma patients were usually healthy and young before ICU admission. Their QOL often dropped substantially after the trauma, both on physical and psychosocial dimensions, and delusional memories and the inability to return to work influenced negatively their perceived QOL (20, 41, 45). Survivors of cardiac arrest, elderly, patients with severe pancreatitis, after oesophagectomy, or patients with acute kidney injury had a good QOL or perceived it as even better than before illness. Acceptance of disability is in general higher among older patients, and even better if they have a good socioeconomic status (52). A high QOL despite the severity of illness or persisting symptoms, may be explained by the fact that patients who are confronted with a life-threatening disease are faced with the necessity to accommodate to the disease, which may lower internal standards (63). Critically ill patients in general had a lower QOL than an age-and gender matched population one year after ICU discharge, but a slow improvement in QOL could be seen, and several years after ICU, QOL was quite comparable with that of the normal population.

The second finding was that factors, which could be presumed to result in a poor QOL after ICU, such as age, prolonged mechanical ventilation, or a long ICU or hospital stay, are not per se indicators of

reductions in QOL afterwards (25, 27, 44). Other issues such as cognitive impairments, sleep disturbances, posttraumatic stress disorder, the rehabilitation process, employment status, and cultural and payment differences, can influence QOL in a less tangible way than, for example, physical impairments after major trauma (26, 27, 35, 49, 52, 66).

Third, there were important methodological differences between the included studies. Four of the 53 included studies met all of 4 quality criteria. Only a minority of studies had a uniform follow-up time or measured QOL prior to ICU admission, and response rates to QOL surveys were generally low, which resulted in a limited interpretation of study results.

The ideal assessment of long-term QOL after critical care should use validated QOL instruments in large cohorts without major exclusions, with an extensive but reasonably long and uniform follow-up period, and with comparison with pre-ICU baseline evaluation (61). Future research on long term QOL should focus on that. In this review, only studies which used at least one of 4 generic QOL instruments (SF-36, EQ-5D, RAND-36, NHP) were included. Generic instruments apply for a broad spectrum of populations and are therefore less responsive to changes in specific conditions as compared with specific QOL instruments (9). Although there is still no consensus about which tool should be used to measure QOL in critical care patients, SF-36 and EQ-5D are considered to be valid and reliable instruments for critically ill patients (10). The EQ-5D is validated for European populations (76, 77) but some still consider SF-36 or RAND-36 as the generic instrument of first choice in critically ill patients (19, 60, 67). It can be recommended to use both EQ-5D and SF-36 together (20).

One of the goals of QOL measures is differentiating between people with a better and a worse QOL, and measuring how much QOL has changed over time (9). This change in QOL over time leads to an important and difficult issue in QOL studies. How long is “long” in long-term outcome and when will functional outcome measures and questionnaires no longer give additional information? Follow-up intervals for QOL were very different in the included studies which made it difficult to conclude which time course should be considered as the best to interpret the overall results, and as sufficient to allow regaining the best achievable QOL (71). Not only between studies there were large differences in timing, but also within the studies themselves the follow-up intervals differed a lot, which was correctly considered as a limitation of study results (26, 27, 35, 36, 45-47, 50). A follow-up period of one year is probably too short because physical limitations still tend to dominate over emotional problems (19, 30, 31, 35, 37, 41), and physical problems will not always be recovered (67). One year may also be too short to become accustomed to more restrictions in daily live (72). When follow-up periods extend to more than one year, a tendency towards more emotional problems was found. It is generally accepted that the real burden of critical illness is seen up to 6 months after ICU discharge (32, 64), although it is possible that studies using 6 months as the first time point for data collection missed an earlier fall in QOL (19). Follow-up of 1 or 2 years will probably capture the most and it may be the limit for improvement in most

QOL dimensions as seen after severe trauma (44, 68). Still, mental health will be affected for many years longer (35, 70).

The most important problem of long-term follow-up times is that more patients will be lost to follow-up, which could lead to an important bias in results. Patients who not respond can do so for a lot of different reasons. They can consider QOL questionnaires trivial if they recovered well, they can suffer from posttraumatic stress disorder avoiding seeking memories of their ICU treatment, they can be too ill to have the ability to respond, or they may have died before completing the survey (35, 36, 54). As such, QOL responders may represent a sample of healthier patients (47, 58). Therefore, analyzes of responders versus non-responders concerning severity of illness scores, co-morbidities, mortality, or age should be made (44). To avoid selection bias, every effort has to be made to target the highest response rate possible. In many studies, although time-consuming and labour-intensive, patients, who did not respond to the initial mailed survey or to a mailed reminder, were phoned, which guaranteed however not always a high response rate (35, 39, 73). A lost to follow-up of 20% is considered to be acceptable for QOL studies (19) but only 49% of the studies had a response rate of at least 80% of the eligible patient population for long-term outcome and QOL assessment. As a consequence, the number of patients with a reliable QOL assessment at least 1 year after ICU discharge was low.

When QOL measures are used as discriminative instruments, possible confounders, which could influence QOL, should be eliminated. Therefore, QOL in ICU patients can be compared to an age- and gender- matched general population, which should be considered as the upper limits of what is achievable (75). In most studies, QOL-responders were matched with a representative healthy population. The study findings can also be compared with an appropriate control group eliminating the influence of specific health conditions (25, 62). More important, long-term QOL should also be compared with QOL before ICU admission, to discriminate whether poor long-term QOL is a result of the severity of illness, or due to confounding factors or 'background variables' such as co-morbid disease, poor pre-admission QOL, age, gender, or acquired complications (44). Which factor will influence the most long-term QOL is a very difficult question, and literature is definitively not conclusive about this issue (74). The long-term effect of a certain condition on QOL is cohort-specific and may be the residua of any severe critical illness (34). It will also depend upon the follow-up period, and the tools used, and will probably be a mixture of severity of illness, prior health status, pre-morbid QOL, age, gender, and diagnostic category.

Prior studies of QOL before ICU admission support the hypothesis that patients' premorbid QOL has a large effect on QOL after critical illness (78, 79). It has been proved that pre-ICU QOL is low compared to the general population indicating that ICU patients differ from the average population even before onset of critical illness (10, 44, 80). Poor QOL before critical illness is also correlated with poor outcome (19, 81, 82, 83, 84). Impaired QOL after ICU may thus reflect a poor baseline situation rather than be a function of intensive care (19, 67). Measuring QOL at baseline is difficult and in the majority of

studies (83%) this was not done. One third of these studies considered this as a limitation (20, 25, 31, 36, 42, 43, 54-57, 62, 64, 65, 67). Most patients will not be able to complete questionnaires at time of ICU admission and many studies asked patients or proxies a long period afterwards how QOL was before admission (20, 44, 52, 53, 62). Recall bias can influence results of these QOL surveys. In retrospective studies recall bias can also add some uncertainty to the study findings because QOL assessment is based upon patient's recall of their memories from the ICU stay (45, 46). No baseline assessment of QOL because it would have been assessed retrospectively can be the reason for not measuring QOL prior to ICU admission (56).

Some authors considered that only patients could evaluate their own QOL (56) or considered it as a potential danger for bias if questionnaires were filled in by proxies (67). However, the SF-36 and EQ-5D questionnaire completed by proxies can reliably assess the QOL of the critically ill patient on admission at the ICU (68, 81), although it is difficult to interview proxies when their relatives are critically ill (37). Proxies tend to underestimate the QOL of the patient but differences are usually small (81).

There are some methodological limitations in this review. First, only 4 generic QOL instruments were included, which are, however, commonly used in critically ill patients (8). This allowed us to compare among studies and make more comprehensive conclusions. Second, some studies had a low number of QOL responders and a non-uniform follow-up time which limits the interpretation of study results. The findings of this review are also limited because of infrequent collection of QOL at baseline.

CONCLUSION

Future outcome evaluations should not be limited to "death" or "alive" but should also incorporate QOL, even as this is much more complicated to investigate. Long-term QOL in critically ill patients depends largely upon diagnostic category, with the worst reductions found in patients who survive severe ARDS, sepsis, trauma, and prolonged mechanical ventilation. For critically ill patients in general, a lower QOL compared to an age-and gender matched healthy population was seen. However, evidence for poorer QOL after ICU is misleading when the prior health state of the patient is not taken into account. Baseline QOL assessment is necessary when investigating the influence of the critical illness and should be assessed upon ICU admission to avoid recall bias. Follow-up periods should be kept strictly uniform although there is no consensus regarding the most appropriate follow-up time. Measures to gain the highest response rate to avoid selection bias should be taken. Nevertheless, comparisons between responders and non-responders should always be made.

Table 1. Study characteristics

Reference	Country	Study design	Inclusion period	Patient cohort	Eligible patients for long-term QOL assessment, N(%) *
ARDS					
Davidson, 1999	USA	prospective matched controlled	January 1994-July 1996	102 sepsis or trauma induced ARDS patients	80 (78%)
Schelling, 2000	Germany	follow-up cohort	January 1985-January 1995	192 consecutive ARDS patients	119 (62%)
Rothenhäusler, 2001	Germany	exploratory	January 1985-January 1995	192 consecutive ARDS patients	119 (62%)
Kapfhammer, 2004	Germany	follow-up cohort	January 1985-January 1995	80 long-term ARDS survivors	80 (100%)
Hopkins, 1999	USA	prospective	February 1994-July 1998	106 enrolled out of 274 ARDS patients	67 (63%)
Orme, 2003	USA	prospective, cohort of a RCT	February 1994-December 1999	120 ARDS patients enrolled in HTV vs. LTV study	74 (62%)
Hopkins, 2005	USA	longitudinal prospective, cohort of a RCT	February 1994-December 1999	120 ARDS patients enrolled in HTV vs. LTV study	74 (62%)
Heyland, 2005	Canada	prospective observational multicenter	NA	221 ARDS patients enrolled in a phase III multicenter RCT	103 (47%)
Parker, 2006	Canada	prospective observational multicenter	NA	221 ARDS patients enrolled in a phase III multicenter RCT	103 (47%)
Herridge, 2003	Canada	longitudinal multicenter	May 1998 – May 2001	195 adult ARDS patients	109 (56%)
Deja, 2006	Germany	prospective controlled	1991-2000	263 patients with severe ARDS	129 (49%)
Prolonged mechanical ventilation					
Combes, 2003	France	prospective cohort	January 1995– June 1999	347 consecutive patients receiving mechanical ventilation for ≥ 14 d	99 (29%)
Chelluri, 2004	USA	prospective observational	June 1997– July 1999	817 patients receiving mechanical ventilation for ≥ 48 hrs	359 (44%)
Cox, 2009	USA	prospective observational	April 2006-April 2007	126 consecutive patients receiving mechanical ventilation ≥ 21 d or with a tracheotomy after ≥ 4 d of mechanical ventilation	90 (71%)
Trauma					
Miller, 2000	USA	retrospective	January 1991-December 1997	115 severely injured patients spending ≥ 3 weeks in the ICU	90 (78%)
MacKenzie, 2002	USA	retrospective (hospital stay), prospective (QOL) multicenter	NA	sample of 1587 patients registered in the Pennsylvania Trauma Outcomes Study	1587 (100%)
Dimopoulou, 2004	Greece	prospective cohort	1999-2000	191 consecutive multiple trauma patients requiring mechanical ventilation	117 (61%)
Sluys, 2005	Sweden	retrospective (patient cohort), prospective (QOL)	1996-1997	309 trauma patients	246 (80%)
Vles, 2005	The Netherlands	prospective	January 1996-January 1999	295 severely injured patients (ISS ≥ 16)	196 (66%)
Jackson, 2007	USA	retrospective	2003	97 trauma ICU survivors without	58 (60%)

				ICH	
Ulvik, 2008	Norway	follow-up cohort	1998-2003	325 trauma patients	228 (70%)
Ringdal, 2009	Sweden	exploratory multicenter	September 2001-August 2002	344 adult trauma survivors	344 (100%)
Cardiac arrest					
Saner, 2002	Switzerland	retrospective case-control	1991-1996	439 OOHCA patients (of 1307 resuscitations)	50 (11%)
Bunch, 2003	USA	prospective (cardiac arrest, survival, QOL)	November 1990-January 2001	145 OOHCA patients (of 200 resuscitations)	60 (41%)
Kuilman, 1999	The Netherlands	retrospective multicenter	1988-1994	441 OOHCA patients (of 898 resuscitations)	132 (30%)
Graf, 2008	Germany	prospective cohort	January 1999-December 2000	354 consecutive patients with cardiac arrest	110 (31%)
Mahapatra, 2005	USA	prospective (cardiac arrest, survival, QOL)	November 1990-January 2001	142 OOHCA patients (of 200 resuscitations)	60 (42%)
Lundgren-Nilsson, 2005	Sweden	longitudinal multicenter	1996-1999	51 cardiac arrest survivors	51 (100%)
Elderly					
Montuclard, 2000	France	prospective cohort	January 1993 – August 1998	75 consecutive patients >70 yrs with ICU LOS ≥ 30 d	30 (40%)
Merlani, 2007	Switzerland	retrospective	January 1999-December 2000	141 consecutive patients ≥ 70 yrs with abdominal pathologies	52 (37%)
Kaarlola, 2006	Finland	cross sectional survey	1995 - 2000	882 elderly (≥ 65 yrs) 1827 controls (< 65 yrs)	354 elderly (40%) 1074 controls (59%)
de Rooij, 2008	The Netherlands	retrospective cohort	January 1997-December 2002	578 consecutive patients ≥ 80 yrs	231 (40%)
Garrouste-Orgeas, 2006	France	prospective observational	March 2002-November 2003	180 patients ≥ 80 yrs triaged for ICU admission; 48 ICU admissions	28 (16%) (only 9 ICU patients)
Kleinpell, 2003	USA	longitudinal prospective multicenter	period of 14 months	883 patients ≥ 45 yrs, ICU-LOS ≥ 24 hrs	284 (32 %)
Pancreatitis					
Soran, 2000	USA	retrospective	January 1992-December 1996	52 ICU patients with acute pancreatitis	39 (75%)
Halonen, 2003	Finland	retrospective	January 1989-December 1997	283 consecutive patients with severe acute pancreatitis	174 (61%)
Sepsis					
Heyland, 2000	Canada	cross-sectional survey	1993-1998	78 sepsis patients	30 (38%)
Karlsson, 2009	Finland	prospective observational multicenter	November 2004-February 2005	470 severe sepsis patients	278 (59%)
Korosec, 2006	Slovenia	observational	2003	164 patients (66 sepsis, 98 trauma)	78 patients (48%) (21 sepsis, 57 trauma)
Mixed ICU patients 1 year after ICU					
Pettilä, 2000	Finland	prospective observational	1995	591 consecutive ICU patients	354 (60%)
Badia, 2001	Spain	prospective cohort	October 1994-June 1995	523 consecutive patients (84 T, 239 SS, 57 US, 143 M)	375 (69 T, 198 SS, 23 US, 85 M) (72%)
Cuthbertson, 2005	United Kingdom	prospective cohort	May 2001-April 2002	423 consecutive ICU patients	300 (71%)

Stricker, 2005	Switzerland	prospective observational case-control	September 1998-August 1999	173 patients with ICU-LOS > 7 d vs 1506 with ICU-LOS ≤ 7 d	116 with an ICU-LOS > 7 days (67%)
Long-term QOL					
Garcia Lizana, 2003	Belgium	prospective observational	June 25-September 10, 2000	202 consecutive admitted patients	118 (58%)
Graf, 2005	Germany	prospective cohort	November 1997-February 1998	303 consecutive patients with ICU-LOS > 24 hrs	190 (63%)
Kaarlola, 2003	Finland	prospective observational	1995	591 consecutive patients	169 (29%)
Flaatten, 2001	Norway	retrospective (ICU stay), prospective (survival, QOL)	1987	219 ICU patients	88 (40%)
Kvale, 2003	Norway	prospective cohort	July 1999-August 2000	226 patients with ICU-LOS > 24 hrs discharged alive	226 (100%)
Kvale, 2002	Norway	prospective and retrospective cohort	1987 compared with 1997	219 patients with ICU-LOS ≥ 24 hrs in 1987, 338 in 1997	88 (40%)(1987) 106 (31%)(1997)
Various diseases					
de Boer, 2000	The Netherlands	prospective observational	January 1993-May 1996	100 consecutive patients who underwent a transhiatal oesophagectomy	35 (35%)
Ahlström, 2005	Finland	cross sectional cohort	1998-2002	703 patients receiving RRT for AKI	229 (33%)
Ylipalosaari, 2007	Finland	prospective	May 2002-June 2003	272 hospital survivors with ICU-LOS > 48 hrs	187 (69%)
Orwelius, 2008	Sweden	prospective multicenter cohort	August 2000-November 2003	1625 consecutive adult patients with ICU-LOS > 24 hrs	723 (44%)

QOL= quality of life; N=number; ARDS= acute respiratory distress syndrome; USA= United States of America; RCT= randomised controlled trial; HTV= high tidal volume, LTV= low tidal volume; NA= not available; d=days; hrs= hours; ICU= intensive care unit; ISS= injury severity score; ICH= intracranial hemorrhage; OOHCA= out of hospital cardiac arrest; yrs= years; LOS= length of stay; T= trauma, SS= scheduled surgery; US= unscheduled surgery; M= medical; vs= versus; RRT= renal replacement therapy; AKI= acute kidney injury; * Percentage of initial patient cohort

Table 2. Assessment of quality of life after ICU

Reference	QOL assessment instrument	Method of QOL assessment	Response rate, % (N of QOL responders)	Follow-up period
ARDS				
Davidson, 1999	SF-36	telephone	96% (77)	median 23 months
Schelling, 2000	SF-36	face-to-face	42% (50)	median 5.5 years (range 1-10 years)
Rothenhäusler, 2001	SF-36	face-to-face	39% (46)	median 6 years (range 1-12 years)
Kapfhammer, 2004	SF-36	face-to-face	58% (46)	median 8 years (range 3-13 years)
Hopkins, 1999	SF-36	face-to-face	82% (55)	1 year
Orme, 2003	SF-36	face-to-face	89% (66)	1 year
Hopkins, 2005	SF-36	face-to-face	84% (62)	1 and 2 years
Heyland, 2005	SF-36	telephone	71% (73)	3, 6, 12 months
Parker, 2006	SF-36	telephone	71% (73)	3, 6, 12 months
Herridge, 2003	SF-36	face-to-face	80% (83) 3 months 82% (82) 6 months 86 % (83) at 12 months	3, 6, 12 months
Deja, 2006	SF-36	mail, telephone if no answer	50% (65)	57 ± 32 months
Prolonged mechanical ventilation				
Combes, 2003	NHP	mail	88% (87)	average 3 years
Chelluri, 2004	SF-36	telephone or face-to-face	64% (231) full interview 18% (65) mini-interview	1 year
Cox, 2009	EQ-5D	telephone or face-to-face	78% (70)	3, 12 months
Trauma				
Miller, 2000	RAND-36	mail, telephone if no answer	39% (35)	unclear, mean of several years
MacKenzie, 2002	SF-36	telephone	78% (1230)	1 year (range 10-14 months)
Dimopoulou, 2004	NHP	telephone	74 % (87)	1 year
Sluys, 2005	SF-36	mail or telephone, reminder mail	83% (205)	5 years
Vles, 2005	EQ-5D	mail, telephone if no answer	85% (166)	mean 41 months
Jackson, 2007	SF-36	face-to-face	100% (58)	12-24 months
Ulvik, 2008	EQ-5D	telephone	92% (210)	2-7 years (median 4 years)
Ringdal, 2009	SF-36	mail, one written reminder, then telephone	69% (239)	6-18 months
Cardiac arrest				
Saner, 2002	NHP	face-to-face	100% (50)	mean 31.7 months (range 5-68 months)
Bunch, 2003	SF-36	face-to-face	83% (50)	4.8 ± 3.0 years
Kuilman, 1999	EQ-5D	mail	83% (109)	mean 6.71 years
Graf, 2008	SF-36	mail or telephone if no answer	74% (81)	5 years
Mahapatra, 2005	SF-36	face-to-face	83% (50)	4.8 ± 3.0 years
Lundgren-Nilsson, 2005	NHP	face-to-face	51% (26) at 1 year	14 days, 45 days, 3 months, 1 year
Elderly				
Montuclard, 2000	PQL (1996) NHP (1998)	telephone	93% (28) (first study) 95% (21) (second study)	557 ± 117 days for the first study, second 2 years later
Merlani, 2007	ED-5D, SF-36	mail, telephone if no/incomplete answer	79% (41)	2 years
Kaarlola, 2006	EQ-5D, RAND-36	mail, reminder mail	87% (307) elderly 77% (828) controls	median 3 years for elderly median 4 years for controls

de Rooij, 2008	EQ-5D	telephone	88% (204)	1 to 6 years, median 3.7 years
Garrouste-Orgeas, 2006	NHP	telephone	100% (28)	1 year
Kleinpell, 2003	SF-36	mail, reminder mail, telephone if no answer	70% (199)	1,3, 6, 12 months
Pancreatitis				
Soran, 2000	SF-36	telephone	54% (21)	median 42 months (range 17-69 months)
Halonen, 2003	RAND-36	mail, reminder mail or telephone	83 % (145)	median 61 months (range 19-127 months)
Sepsis				
Heyland, 2000	SF-36	telephone	100% (30) first interview 87% (26) second interview	16.6 ± 10.6 months
Karlsson, 2009	EQ-5D	mail	52% (252) QOL before 58% (156) long-term QOL	median 17 months
Korosec, 2006	EQ-5D	telephone	50% (39)	2 years
Mixed ICU patients 1 year after ICU				
Pettilä, 2000	RAND-36	mail, reminder mail	87 % (307)	1 year
Badia, 2001	EQ-5D	mail, telephone or face-to-face interview if no answer	89 % (334)	1 year
Cuthbertson, 2005	SF-36, also EQ-5D at 12 months	telephone	78% (233) 3 months 67% (201) 6 months 58% (173) 12 months	3, 6, 12 months
Stricker, 2005	SF-36	telephone	65 % (75)	12-18 months
Long-term QOL				
Garcia Lizana, 2003	EQ-5D	mail or telephone	81 % (96)	1,5 years
Graf, 2005	SF-36	mail or telephone	91 % (173)	5 years
Kaarlola, 2003	RAND-36	mail, reminder mail if no response	84 % (298) 1 year 76 % (192) 6 years	1 year and 6 years
Flaatten, 2001	SF-36	mail, reminder mail if no response	58 % (51)	12 years
Kvale, 2003	SF-36	mail, one reminder mail	56% (126) at 6 months 79% (100) after 2 years	6 months and 2 years
Kvale, 2002	SF-36	mail	58 % (51) in 1987 62 % (66) in 1997	3 years and 13 years
Various diseases				
de Boer, 2000	SF-36	mail	100 % (35)	minimum of 2 years
Ahlström, 2005	EQ-5D	mail	67% (153)	median 2.4 years
Ylipalosaari, 2007	EQ-5D	mail, telephone if no response	76% (142)	median 22 months
Orwelius, 2008	SF-36	mail	69% (497) after 12 months	6 and 12 months

ICU= intensive care unit; QOL=quality of life; N= number; ARDS= acute respiratory distress syndrome; SF-36= Short-Form 36; NHP= Nottingham Health Profile; EQ-5D= EuroQol-5D; PQL= Patrick's Perceived Quality of Life

Table 3. Study quality criteria

Reference	QOL prior to ICU	Key inclusion or exclusion criteria	Description of non-responders	Age/gender matched general population to compare QOL
ARDS				
Davidson, 1999	no	ARDS survivors with severe head injuries were excluded.	no	matched with sepsis and trauma patients without ARDS
Schelling, 2000	no	Study population was a follow-up cohort of 80 long-term ARDS survivors and QOL responders in a study 3 years before.	yes	age-and gender-matched control group of normal German subjects
Rothenhäusler, 2001	no	Only long-term ARDS survivors were included.	yes	age-and gender-matched control group
Kapfhammer, 2004	no	Only long-term ARDS survivors were included.	yes	standard values of the SF-36 from volunteers of the West German population
Hopkins, 1999	no	168 ARDS patients were excluded for various reasons.	no	normative population data
Orme, 2003	no	Only long-term ARDS survivors were included.	no	normative population data
Hopkins, 2005	no	Long-term ARDS survivors were included.	no	normative population data
Heyland, 2005	no	Long-term ARDS survivors were included.	yes	age-and gender-matched population derived from literature
Parker, 2006	no	Long-term ARDS survivors were included.	no	no, primary ARDS patients were compared to secondary ARDS patients
Herridge, 2003	no	Only severe ARDS patients were included. Immobile patients, patients with a history of pulmonary resection or with a neurological or psychiatric disease were excluded.	no	the normal Canadian population
Deja, 2006	no	Only severe ARDS patients were included.	yes	age-and gender matched healthy German controls
Prolonged mechanical ventilation				
Combes, 2003	no	Only patients with prolonged mechanical ventilation (≥ 14 d) were included.	yes	community-based age- and gender matched controls
Chelluri, 2004	yes	Patients with prolonged mechanical ventilation (≥ 48 hrs) were included.	yes	samples of the US population
Cox, 2009	yes	Patients with ≥ 21 d mechanical ventilation or with tracheotomy after ≥ 4 d mechanical ventilation were included.	no	UK population norms for persons aged 55-65 years
Trauma				
Miller, 2000	no	Only severely injured patients spending ≥ 3 weeks in the ICU were included.	yes	general US population
MacKenzie, 2002	no	Blunt trauma patients (18-59 yrs), with a hospital stay of ≥ 72 hrs were included. Drownings, electrocutions, burns, and hip or femoral neck fractures were excluded.	yes	age-and gender matched general population
Dimopoulou, 2004	no	Only mechanically ventilated polytrauma patients were included.	no	no
Sluys, 2005	no	Blunt or penetrating trauma patients with an ISS of ≥ 9 were included. Patients with psychiatric disorders or cognitive impairments were excluded.	yes	a Swedish age-and gender-matched reference sample
Vles, 2005	no	Only patients with ISS ≥ 16 were included.	no	Swedish reference

				database, corrected for age and gender
Jackson, 2007	no	Only trauma ICU survivors (ISS > 25) without intracranial hemorrhage were included.	no	the general US population
Ulvik, 2008	yes	Foreign trauma patients were excluded due to difficulties with follow-up.	yes	no
Ringdal, 2009	no	Nonsurvivors, attempted suicide, not resident in Sweden, intellectual impairment, and patients with unknown address were excluded.	yes	age and gender matched reference sample drawn from the Swedish SF-36 norm database.
Cardiac arrest				
Saner, 2002	no	Patients with hypoxic brain damage, drug abusers, in hospital resuscitation, non-German speaking, and < 20 or > 80 yrs were excluded.	no	healthy controls of similar age, gender, and socio-economic status
Bunch, 2003	no	Only patients with an OOHCA with VF were included.	yes	age-and gender-matched norms from a sample of the general US population
Kuilman, 1999	no	Successfully resuscitated patients were included.	no	no
Graf, 2008	no	Patients who received CPR for an IHCA or OOHCA were included.	yes	the healthy German population
Mahapatra, 2005	no	Only patients with an OOHCA with VF were included.	no	age-and gender-matched norms from a sample of the general US population
Lundgren-Nilsson, 2005	no	Only cardiac arrest survivors were included.	no	reference Swedish population
Elderly				
Montuclard, 2000	yes	Consecutive patients > 70 yrs with an ICU LOS ≥ 30 d were included.	no	the general French population of mixed age and 76-yrs old Swedish urban citizens
Merlani, 2007	yes	Patients aged ≥ 70 yrs with abdominal pathologies were included.	yes	age-matched population
Kaarlola, 2006	no	All consecutive patients admitted within the study period were included.	no	controls and an age-and gender-matched Finnish population
de Rooij, 2008	no	Consecutive patients aged ≥ 80 yrs admitted within the study period were included.	no	age-matched British non-ICU general population
Garrouste-Orgeas, 2006	no	In 73% of patients aged ≥ 80 yrs ICU admission was refused.	no	age- and gender-matched general French population
Kleinpell, 2003	no	Patients ≥ 45 yrs with ICU-LOS of ≥ 24 hrs were included.	yes	a general US population
Pancreatitis				
Soran, 2000	no	Only acute pancreatitis patients were included.	no	age-matched normal control group
Halonen, 2003	no	Patients (majority needed ICU admission) with acute pancreatitis were included.	yes	age-and gender-matched Finnish population
Sepsis				
Heyland, 2000	no	Patients with sepsis were included. Patients with disabilities that would preclude a telephone interview were excluded.	no	general US population
Karlsson, 2009	yes	All severe sepsis patients at admission or during ICU stay were included.	yes	age- and gender adjusted Finnish reference population
Korosec, 2006	no	Only sepsis and trauma patients were included.	yes	no
Mixed ICU patients 1 year after ICU				
Pettilä, 2000	no	no major exclusion criteria	no	age-and gender matched

				general Finnish population
Badia, 2001	yes	no major exclusion criteria	no	no
Cuthbertson, 2005	yes	Patients who were not expected to survive ICU were excluded.	yes	age-and gender matched general UK population
Stricker, 2005	no	Surgical and trauma patients with ICU-LOS > 7 d and with ICU-LOS ≤ 7 d were matched. Burn injuries were excluded.	yes	age-and gender matched sample of the German population
Long-term QOL				
Garcia Lizana, 2003	yes	ICU-admissions for uncomplicated elective postoperative surgery were excluded.	yes	no
Graf, 2005	no	Patients with ICU-LOS < 24 hrs were excluded.	no	age-matched group of healthy Germans
Kaarlola, 2003	no	Patients who responded to both questionnaires in 1996 and 2001 were included.	yes	age-and gender matched Finnish population
Flaatten, 2001	no	Heart surgery and burn patients were not included.	no	age-and gender matched general Norwegian population
Kvale, 2003	no	Heart surgery and burn patients were not included.	yes	scores after 6 months compared with scores after 2 years
Kvale, 2002	no	Heart surgery and burn patients were not included.	no	age- and gender matched control groups from the general Norwegian population
Various diseases				
de Boer, 2000	no	Only long-term survivors without tumour recurrence were included.	no	age-matched reference population
Ahlström, 2005	no	Only AKI patients needing RRT were included	yes	age-and gender matched population
Ylipalosaari, 2007	no	Only hospital survivors with ICU-LOS > 48 hrs were included.	yes	no
Orwelius, 2008	no	Only adult patients with ICU-LOS > 24 hrs and alive 6 months after discharge were included.	yes	random sample from the main intake area of the hospitals was used as a reference group

QOL=quality of life; ICU= intensive care unit; ARDS= acute respiratory distress syndrome; SF-36= Short-Form 36; d=days; hrs=hours; US= United States of America; UK= United Kingdom; yrs=years; ISS= injury severity score; OOHCA= out of hospital cardiac arrest; VF= ventricular fibrillation; CPR= cardiopulmonary resuscitation; IHCA= in hospital cardiac arrest; LOS= length of stay; AKI: acute kidney injury; RRT= renal replacement therapy

Table 4. Major findings and factors influencing long-term QOL

Reference	Long-term QOL: Major finding	QOL: Influencing factors
ARDS		
Davidson, 1999	ARDS survivors had a significant reduction in QOL. Sepsis- induced ARDS patients had more severe reductions in QOL than trauma-induced ARDS patients.	ARDS and its sequelae Not: co-morbid disease, severity of trauma or illness, duration of mechanical ventilation or hospital stay
Schelling, 2000	Long-term ARDS survivors have a significant reduced QOL.	multiple pulmonary function impairments
Rothenhäusler, 2001	Long-term QOL was impaired.	cognitive deficits and disability
Kapfhammer, 2004	Long-term ARDS survivors had major impairments in long-term QOL.	posttraumatic stress disorder
Hopkins, 1999	After 1 year, there was improvement for the physical but not for the emotional domains.	cognitive impairments
Orme, 2003	ARDS survivors, treated with high or low tidal volume ventilation, had a reduced QOL, which was related to physical rather than emotional concerns.	pulmonary function impairments
Hopkins, 2005	ARDS survivors had decreased QOL, with physical and emotional domains improving at 1 year, but no additional change or decline at 2 years.	neurocognitive impairments, although these may represent morbidity from critical illness rather than be specific for ARDS
Heyland, 2005	ARDS survivors had a significantly lower QOL than age-and gender-matched controls. After 1 year, there was an improvement in the physical domains, while the mental scores remained unchanged.	pulmonary function impairments, baseline co-morbidities
Parker, 2006	Primary ARDS patients had significantly better QOL scores than patients with secondary ARDS.	primary versus secondary ARDS NOT: ICU LOS, hospital LOS, duration of mechanical ventilation, co-morbidity, lung function
Herridge, 2003	QOL improved over 1 year after ICU discharge but remained lower than these of the control population.	functional disability due to muscle wasting, weakness, fatigue
Deja, 2006	QOL in patients with ARDS was significantly reduced in all dimensions.	posttraumatic stress disorder
Prolonged mechanical ventilation		
Combes, 2003	QOL was impaired but perceived as acceptable, with psychosocial aspects being better than physical performance.	worse QOL seen in ARDS survivors
Chelluri, 2004	QOL was impaired mainly on the physical and social domains but comparable on the mental health and emotional domains.	influence of age and chronic illness predominate the long-term outcome
Cox, 2009	One year after ICU discharge, the majority of patients had a poor QOL.	NA
Trauma		
Miller, 2000	QOL was low, especially in the physical domains.	NA
MacKenzie, 2002	One year after trauma, QOL was low, except for vitality and mental health.	NA
Dimopoulou, 2004	QOL was impaired in physical functioning, working ability, and emotional well-being.	injury severity, degree of brain trauma
Sluys, 2005	Five years after trauma, QOL was low in all dimensions of the SF-36.	age, surgical procedures, ICU-and hospital LOS, in-hospital complications, inadequate information
Vles, 2005	QOL was low and a quarter of those of working age were unable to return to work.	injury severity , female gender
Jackson, 2007	QOL was low.	cognitive impairments
Ulvik, 2008	More than 2 years post-injury, 74% reported impaired QOL, mostly due to pain and discomfort, but only a minority had severe problems.	severity of illness an injury, time since trauma (pain), female gender, degree of brain trauma NOT: age
Ringdal, 2009	Trauma patients scored low on all SF-36 domains.	delusional memories, co-morbidity

Cardiac arrest		
Saner, 2002	Long-term QOL remained fulfilling with only a few changes in the psychosocial profile.	little impact of changes in psychosocial profile
Bunch, 2003	Except from a reduction in vitality, QOL was similar to that of the general population.	NA
Kuilman, 1999	No difference in QOL between patients resuscitated by emergency personnel, physicians, or bystanders.	NA
Graf, 2008	Patients who survive without severe neurological disabilities may expect a good QOL.	NA
Mahapatra, 2005	Long-term survival and QOL are equally favourable in both sexes.	NA
Lundgren-Nilsson, 2005	QOL improved over the year with values comparable to the reference population.	cognitive impairments
Elderly		
Montuclard, 2000	After 1 year, perceived QOL was good, especially emotional and social functioning.	a moderate disability influenced QOL
Merlani, 2007	A high mortality and a decrease in QOL were observed for elderly patients with abdominal pathologies. These patients adapted well to their physical limitations.	NA
Kaarlola, 2006	Aging decreased QOL mostly in the physical domains, but elderly patients had better values for mental health than the younger controls.	acceptance of disability is better with a good social network
de Rooij, 2008	QOL was significantly lower for usual activities. Most patients were willing to receive ICU treatment again if necessary.	NA
Garrouste-Orgeas, 2006	After one year, QOL was poorer than in the general population. One-half of the survivors did not want further ICU admission if necessary.	NA
Kleinpell, 2003	In the middle-aged and elderly patient group, SF-36 scores remained below the general population norms but increased over time.	severity of illness rather than age
Pancreatitis		
Soran, 2000	Long-term QOL is good and comparable with an age-matched control population.	NA
Halonen, 2003	Long-term QOL is good and comparable with an age-matched control population.	working status before acute pancreatitis, age NOT: follow-up time, cause, gender, ICU treatment, ICU-LOS, MOF, operating status
Sepsis		
Heyland, 2000	The QOL of sepsis survivors is lower than that of the general population and comparable to QOL of patients with chronic disease or survivors of acute lung injury.	NA
Karlsson, 2009	QOL in most patients was already lower before the episode of severe sepsis than in the general population, and it was even lower after the critical illness.	NA
Korosec, 2006	SICU-patients with sepsis have a higher mortality than trauma patients. However, QOL after 2 years is reduced to the same level in both groups.	anxiety and depression (trauma)
Mixed ICU patients 1 year after ICU		
Pettilä, 2000	Survivors had a lower QOL than an age-and gender-matched general population. However, patients perceived their QOL as better or similar as before their ICU stay.	MOF, age, diagnostic category
Badia, 2001	Trauma patients experienced a worsening, unscheduled surgery and medical patients a slight deterioration, and scheduled patients a considerable improvement in QOL.	diagnostic category
Cuthbertson, 2005	Physical QOL increased to premorbid levels 1 year after ICU discharge but physical scores remained below the population norms. Mental scores were similar or higher than population norms. Non-survivors had a lower QOL than survivors at all time points.	poor baseline situation NOT: prolonged ICU-LOS, age, surgical or medical admissions
Stricker, 2005	When taking into account severity of illness, QOL 1 year after ICU discharge is comparable between patients with short and long ICU stay. QOL remained lower than in a general population, mostly in	NOT: prolonged ICU-LOS

	physical aspects.	
Long-term QOL		
Garcia Lizana, 2003	38% felt their QOL was worse, 37% felt it to be similar and 25% felt it was better than prior to their ICU admission. Psychology domains were the most frequently affected.	previous QOL, prolonged hospital stay, ICU readmission, diagnostic category, APACHE II score, age, female gender, organ failure
Graf, 2005	After 5 years, most patients lived independently and had a good QOL.	NOT: severity of illness, morbidity, resource consumption, age, gender
Kaarlola, 2003	Six years after ICU discharge, QOL was comparable with that of the general population. QOL revealed worse physical functioning, pain, and general health but improvement in the psychological domains.	NA
Flaatten, 2001	QOL was acceptable but it was still lower than in the general population.	NA
Kvale, 2003	There was an increase in QOL from 6 months to 2 years in a mixed ICU-population.	age minor: severity of illness, ICU-LOS
Kvale, 2002	QOL was still reduced 3 and 13 years after ICU. QOL was more reduced in 1997 patients (3 years follow-up) than in 1987 patients (13 years follow-up).	NA
Various diseases		
de Boer, 2000	Although residual symptoms may persist, patients reported a similar or even better QOL (emotional well-being in particular) than an age-matched reference group.	prolonged hospital stay, age, fatigue, emotional aspects NOT: disease specific symptoms
Ahlström, 2005	The long-term outcome and QOL of patients with AKI were poor but patients perceived their QOL as good.	NA
Ylipalosaari, 2007	QOL was equally reduced in patients with or without ICU-acquired infection.	NOT: ICU-acquired infection
Orwelius, 2008	QOL was reduced due to physical problems, bodily pain, general health, vitality, and mental health.	minor: sleep disturbances

QOL=quality of life; ARDS= acute respiratory distress syndrome; ICU= intensive care unit; LOS= length of stay; NA= not available; SF-36=Short-Form 36; MOF= multiple organ failure; SICU= surgical intensive care unit; APACHE= acute physiology and chronic health evaluation

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II. Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies

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ABSTRACT

Purpose: Data concerning long-term outcomes and quality of life (QOL) in critically ill cancer patients are scarce. The aims of this study were to assess long-term outcomes and QOL in critically ill patients with hematological (HM) or solid malignancies (SM) 3 months and 1 year after intensive care unit (ICU) discharge, to compare these with QOL before ICU admission, and to identify prognostic indicators of long-term QOL.

Methods: During a 1 year prospective observational cohort analysis, consecutive patients with HM or SM admitted to the medical or surgical ICU of a university hospital were screened for inclusion. Cancer data, demographics, co-morbidity, severity of illness, organ failures, and outcomes were collected. QOL before ICU admission, 3 months, and 1 year after ICU discharge was assessed using standardized questionnaires (EuroQoL-5D, Medical Outcomes Study 36-item Short Form Health Survey). Statistical significance was attained at $P<0.05$.

Results: 483 patients (85 HM, 398 SM) (64% men) with a median age of 62 years were included. Mortality rates of HM compared to SM were respectively: hospital (34% vs 13%), 3 months (42% vs 17%), and 1 year (66 % vs 36%) ($P< 0.001$). QOL declined at 3 months, but improved at 1 year although it remained under baseline QOL, particularly in HM. Older age ($P=0.007$), severe comorbidity ($P=0.035$), and HM ($P=0.041$) were independently associated with poorer QOL at 1 year.

Conclusions: Long-term outcomes and QOL were poor, particularly in HM. Long-term expectations should play a larger role during multidisciplinary triage decisions upon referral to the ICU.

INTRODUCTION

The prognosis of patients with a solid or hematological malignancy has substantially improved over the past decades due to advances in diagnostics, antineoplastic therapy and supportive care [1, 2]. In addition, survival of cancer patients developing critical illness [1-7] has increased as well, including those requiring mechanical ventilation [8, 9] or renal replacement therapy (RRT) [10-12]. As recent studies have shown that severity and cause of acute illness rather than the underlying cancer characteristics are predictive for short-term mortality [13-18], a diagnosis of cancer as such should not preclude admission to the intensive care unit (ICU). However, to fully appreciate outcomes of critically ill cancer patients, indices regarding long-term morbidity and quality of life (QOL) after ICU discharge should be taken into account as well.

Major reductions in long-term QOL were seen in cases of severe acute respiratory distress syndrome, prolonged mechanical ventilation, and severe sepsis, representing complications that affect cancer patients as much as non-cancer patients [19]. In addition, poor performance following ICU admission in cancer patients may jeopardize long-term outcome by inducing postponements or cancellations of potentially curative chemotherapy.

Thus far, data about QOL post ICU in cancer patients, though sorely needed to estimate long-term prognosis and to assist physicians in triage decisions, are virtually limited to patients with oesophageal malignancy [20, 21], or to an older report concerning critically ill hematological patients [22]. The aim of the present study was to assess long-term outcomes of critically ill patients with a hematological or solid malignancy, to compare QOL of these patients 3 months and 1 year after ICU discharge with QOL before ICU, and to identify prognostic indicators of the evolution of QOL after discharge.

MATERIALS AND METHODS

Design, Setting, and Patients

The study was a prospective observational cohort analysis performed at the 14-bed medical (MICU) and 22-bed surgical ICU (SICU) of Ghent University Hospital, Belgium. From March 3rd 2008 - March 3rd 2009, all consecutive adult patients (≥ 16 years) with a solid or hematological malignancy as direct or contributive cause for ICU admission were screened for inclusion. Patients with complete remission for > 5 years were excluded, as were patients who underwent cardiac surgery. In case of multiple ICU admissions, only the first was considered. Study patients were part of a larger cohort of ICU patients recruited to study QOL and cost-effectiveness of intensive care [23].

The Ghent University Hospital ICU is run as a “closed” ICU where patients are treated by a team of full-time critical care physicians. Decisions to admit a patient to the ICU, as well as to withdraw or withhold

advanced life support are made by the critical care physician together with the referring physician, consulting the wishes and expectations of the patient and his representatives.

Data Collection and Definitions

Variables collected within the first 24 hours of ICU admission included age, gender, body mass index (BMI), personal, proxy, and family practitioner contact data (address and phone number(s)), living status, activity of daily living (ADL) (no limitations, moderate limitations, chair-bound, bedridden), co-morbidity as measured by the Charlson co-morbidity index (this index was also calculated without adding cancer or hematological disease points in order to limit confounding in the multivariate analysis) [24], hospitalization in the last 6 months before ICU admission, do-not-resuscitate (DNR) codes before ICU admission, cancer status (controlled or remission, uncontrolled or newly diagnosis, uncontrolled or disease progression), weight loss (loss of > 10% of the usual body weight) and/or neutropenia (polynuclear neutrophils < 500/mm^3) at ICU admission, main reason for ICU admission, hospital days before ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE II) score [25], Sequential Organ Failure Assessment (SOFA) score [26], need for invasive mechanical ventilation, use of any vasopressors, and need for RRT. During ICU stay, SOFA scores, need for invasive mechanical ventilation, vasopressors, RRT, and DNR- codes were collected on a daily base. ICU length of stay (LOS), hospital LOS, vital status at ICU and hospital discharges, and vital status 3 months and 1 year following ICU discharges were collected for each patient.

The study was approved by the local ethical committee. A signed informed consent was mandatory for every included patient.

Quality of life

QOL was assessed by means of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQoL-5D (EQ-5D). The SF-36 questionnaire [27, 28] contains 36 items measuring eight multi-item domains: physical- (PF), and social functioning (SF), role limitations due to physical- (RP), or emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP), and general perception of health (GH). Two component scores, a physical (PCS) and a mental (MCS), are calculated summary scores where respectively the physical or the mental domains will account more in the score. We assessed SF-36 as norm-based scores to be able to compare them directly with the general healthy population, with a group-level range of 47-53 considered as average or normal. The validity and reliability of the SF-36 has been confirmed in the critically ill population, and its use is validated in face-to-face interviews, interview by phone or by sending the questionnaire by regular mail [29, 30].

The EQ-5D is a questionnaire, which measures health in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [31]. Each domain has three levels: no problems, moderate problems or severe problems. Therefore, patients can be classified into 1 of 243 (3^5) possible

health states. We converted each health state into a utility index (range -0.1584 to 1.000) indicating the preference of being in a health status. On a visual analogue scale, patients can rate their perceived overall health between 0 and 100. Though the EQ-5D has been less well validated in the critically ill population [32], both the EQ-5D and the SF-36 were considered as suitable for measuring QOL in critical care at the Brussels Roundtable meeting [30].

QOL was assessed at 3 predefined time points: baseline QOL, 3 months and 1 year after ICU discharge. A computer chart with ICU discharge data for each included patient was kept to respect in an accurate way the time points of second (3 months) and third (1 year) QOL assessment. Following ICU admission and study inclusion, a face-to-face interview to assess baseline QOL (defined as QOL 2 weeks before ICU admission) was done as soon as possible. This interview was preferably taken from the patient, or, whenever impossible due to severity of illness, from the proxy. Three months and 1 year after ICU discharge, patients or relatives were sent the EQ-5D and SF-36 surveys by regular mail; at 1 year, questions concerning living situation of the patient, and if the patient was willing to be admitted to an ICU department again if needed, were added. If the questionnaires were not returned within one month, patients or relatives were contacted by phone to assess QOL after 1 year. If there was no contact by phone, the family practitioner was contacted to assess if the patient had died meanwhile.

Statistical analysis

Values are expressed as median (interquartile range) (IQR) for continuous variables and as number (%) for categorical variables when appropriate. QOL before ICU admission and characteristics between both groups (hematological versus solid malignancy) were compared by the Mann-Whitney U test for continuous variables and by the Chi-square test for categorical variables. For long-term analysis of QOL, differences between QOL at baseline (only hospital survivors), at 3 months and at 1 year after ICU discharge were assessed by using Chi-square (EQ-5D) or Friedman test (SF-36).

Linear regression analysis (enter method) was used to assess the multivariate relationship between patient characteristics and the mean utility index, as an indicator for QOL, at 3 months and at 1 year. A significance level of $P<0.2$ in the univariate analysis was specified for including variables in the multivariate model. Stepwise forward and backward elimination regression procedures were used. Variables that remained significant in the final model were considered to be independently associated with QOL 3 months and 1 year after ICU discharge. All statistical analyses were two-tailed and carried out with SPSSv19 (SPSS Inc, Chicago, IL). A two-sided $P<0.05$ was considered significant.

RESULTS

Characteristics and Outcomes of the Study Population

A total of 483 cancer patients fulfilled inclusion criteria (Figure 1). Forty-one (48%) of the hematological malignancies (N=85) were high-grade (25% non-Hodgkin lymphoma, 18% acute myelogenous leukemia, 6% acute lymphoblastic leukemia) and 44 (52%) were low-grade (27% multiple myeloma, 7% chronic lymphocytic leukemia, 5% Hodgkin's disease, 5% low-grade non-Hodgkin lymphoma, 4% myelodysplastic syndrome, 1% chronic myelogenous leukemia, 4% other). Within the solid tumors group (N=398), lower (26%) and higher (25%) gastrointestinal tumors were the most common followed by lung (15%), urogenital (8.5%), brain (8%), head and neck (7%) breast (4%) and other tumors (4%). Almost half of these patients (46%) had metastatic disease.

Patient characteristics, reasons for ICU admission, organ failure and outcomes are shown in Table 1. Patients with hematological malignancies had more co-morbidity, had higher severity of illness at admission and required more organ support than solid tumor patients; survival rates were also significantly lower at all measured time points.

Quality of life

The number of QOL surveys was respectively 478 (admission), 392 (3 months) and 331 (1 year) whereas corresponding response rates were 99.0%, 75.8% and 99.4% respectively. Mortality increased during the study course from 16.4% (admission) to 21.7% (3 months) and to 41.2% at 1 year (Figure 1). Respectively 79%, 86%, and 79% of patients answered the questionnaires themselves at the different time points (Online Resource 1).

QOL before ICU admission was better in patients with solid malignancies, and in hospital survivors compared to hospital nonsurvivors within each malignancy group (data not shown).

EQ-5D assessments three months after ICU discharge showed that patients with hematological and solid malignancies had more disabilities than before ICU admission (Figure 2). QOL improved after 1 year, except for mobility (both malignancy groups) and for anxiety (solid tumors), but remained lower than baseline. Changes in QOL over time were significant in hematological patients for usual activities (P<0.001), and in patients with solid tumors for mobility (P=0.02), self-care (P=0.02), usual activities (P<0.001), and pain (P<0.001). When comparing both groups, patients with hematological malignancies had more problems at 3 months (mobility, P<0.001; self-care, P=0.004) and 1 year (mobility, P=0.004; self-care, P=0.03; usual activities, P=0.002) after ICU discharge, except for usual activities at 3 months.

Evolutions in QOL assessed by the SF-36 are shown in Figure 3. For both groups, QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year, especially the mental domains, but remained under the baseline level. At any moment, QOL was lower in patients with hematological malignancies. Evolution in QOL for patients with solid tumors was significant for all domains (P<0.001 for respectively PCS, PF, RP, BP, VT, SF, MH; P=0.002 for GH; P=0.003 for RE; P=0.006 for MCS) while there were no significant differences in QOL over time for hematological patients, except VT (P=0.03).

Long-term outcomes and utilities, based upon EQ-5D measures, per type of cancer are given in Online Resource 2.

Additional questions after 1 year

Among the one year survivors, patients with hematological malignancies were less likely to live independently without additional help (62% versus 79%; *P*=0.04) and more would refuse ICU readmission again (10% versus 3%; *P*=0.04). 92% of all patients expressed a preference to be readmitted to an ICU department in case of deterioration.

Independent predictors of long-term QOL

Multivariate regression analysis showed that poor QOL 3 months after ICU discharge was independently associated with female gender (*P*<0.001), higher comorbidity scores (*P*=0.001), hematological malignancy (*P*=0.01), older age (*P*=0.03), and a higher mean SOFA score during ICU stay (*P*=0.04) (Online Resource 3). One year after ICU discharge, QOL was still negatively influenced by older age (*P*=0.007), higher comorbidity scores (*P*=0.04), and hematological malignancy (*P*=0.04). These results remained consisted regardless of variables included in the model (data not shown). Being admitted to the ICU for a medical or surgical reason, or cancer status had no influence on long-term QOL.

DISCUSSION

In this prospective study on cancer patients requiring ICU admission, in-hospital and 1-year mortality was 16% and 41%, respectively. QOL measured at 3 months and 1 year after ICU discharge did not return to baseline and was below the average of that of a general healthy western population at all time points.

ICU and hospital mortality rates in our study reflect progress made in critical care of cancer patients, showing feasibility of major surgery backed up by safe postoperative organ support in solid tumor patients, as well as the possibility to reverse acute, life-threatening complications in hematological patients [1-18]. However, short-term mortality may not fully represent the impact of critical illness and the efficacy of critical care. While the 20-30% decline in survival between hospital discharge and 1 year may have been due to tumor progression rather than to additional complications grafted upon post-ICU frailty, it serves to remind that 1-year survival provides a more realistic outcome estimate in these patients.

The measures of utility and QOL may put the gains in survival into a larger perspective. QOL is increasingly considered to represent a major measure of outcome, whilst being poorly studied in this particular patient population. Three months after ICU discharge, QOL was worse on every domain of the SF-36 and more patients reported problems on the different domains of the EQ-5D, particularly in usual activities and pain. After 1 year, QOL improved, especially on the mental domains but still remained under baseline level. The divergence between mental and physical performance probably reflects a gradual

process in which patients adapt to a diminished performance status and come to accept their physical limitations. This is well illustrated by the fact that the vast majority of our patients who were alive after 1 year answered positive to the question whether they would choose to be readmitted to an ICU in case of deterioration.

Evidently, malignancy represents a highly diverse spectrum of disease and cancer patients are heterogeneous in performance status and co-morbidity. As such, outcome should be differentiated among subgroups. We found important differences between solid tumor patients and hematological patients relative to co-morbidity, reason for ICU admission, and severity of illness. These translated into different survival rates and QOL in survivors, with hematological patients having worse on QOL on every moment of the study period, and experiencing no significant improvements beyond 1 year. Some smaller differences could be discerned additionally between different categories of malignancy. Patients with gastro-intestinal tumors had highest survival and highest utility after 1 year, a finding which is in accordance with other studies [21]. In the subgroups with the highest mortality at one year, namely high-grade hematological malignancy and head and neck cancer, a remarkable recovery in QOL was seen within the survivors, however probably due to survivor bias. The best long-term survival was seen in patients with lung cancer, although in contrast, long-term QOL was rather poor.

Prognostication at the individual level in critically ill cancer patients is extremely difficult because many factors related to the underlying cancer, the acute severity of illness, and projections on future anti-cancer treatment have to be taken into account. A good collaboration with open communication regarding these issues is therefore mandatory between all parties with different expertise involved in the ICU triage decision making process [1, 5, 7, 12]. For many years, critical care physicians have been reluctant to admit cancer patients to the ICU [1-3, 5, 12], mainly because of the high mortality at short-term reported in older series but also because of the too optimistic long-term survival expectations of referring physicians [33, 34] and the poor communication regarding these expectations to the patient's and/or the relatives [33, 35, 36]. Future studies should try to focus on the complex dynamic interplay of short-and long-term expectations and evolutions in QOL while taking multidisciplinary triage decisions. Evidently, even the most detailed long-term outcome and QOL data cannot replace clinical evaluation of the individual patient or overrule a patient's personal view, though they certainly assist in taking an informed decision.

The strength of this study lies in the accurate and prospectively collected data. QOL was assessed with validated questionnaires at baseline, which is rarely done in QOL studies but allows for the only reliable evaluation of evolution in QOL over time without recall bias [19]. Very strict time intervals of 3 months and 1 year after ICU discharge to assess QOL again, were respected in all patients. Response rate was very high and only 2 patients were lost-to-follow-up. On the other hand, some limitations should be mentioned. First, single centre data from a university hospital may not reflect general practice, as the

volume of ICU admission has been shown to relate to outcome in these patients [37, 38]. Second, medical decisions leading to ICU referral may have selected for patients with better prospects; indifferent admission of any cancer patient for advanced life support conceivably will result in a worse long-term QOL. Third, there is potentially lack of statistical power to detect differences among the QOL domains in hematological patients. Fourth, although we tried to adjust for important differences between surgical (scheduled surgery 59%, emergency surgery 9%) and medical patients (31%) in the multivariate linear regression, we do not know whether this was sufficient to unweave the complex interplay between underlying malignancy and admission type. Fifth, we did not collect information about oncological status and anticancer therapy after ICU discharge, which could have influenced long-term QOL.

CONCLUSIONS

Our study showed that despite substantial immediate survival of cancer patients following ICU admission, outcome at longer term was more limited, especially with regard to QOL. Long-term expectations of mortality and QOL should be taken into account when deciding whether or not a cancer patient should be considered for referral to the ICU.

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Table 1. Patient characteristics, organ failures and outcomes

	All patients (N=483)	Solid tumor (N=398)	Hematological malignancy (N=85)	P
Characteristics				
age, yrs, (median, IQR)	62 (54-70)	62 (54-69)	60 (48-71)	0.31
male gender, N (%)	310 (64)	261 (84)	49 (58)	0.17
BMI, kg/m^2 (median, IQR)	25 (22-28)	25 (22-27)	25 (22-27)	0.87
hospital days prior to ICU, days (median, IQR)	1 (1-3)	1 (1-1)	2 (0-8)	0.02
Comorbidity				
lives at home before admission, N (%)	478 (99)	393 (99)	85 (100)	0.30
ADL, N (%)				
no limitations	297 (61)	271 (68)	26 (31)	<0.001
moderate limitations	157 (33)	108 (27)	49 (58)	<0.001
chair-bound	13 (3)	8 (2)	5 (6)	0.05
bedridden	16 (3)	11 (3)	5 (6)	0.15
hospitalisation in last 6 months before ICU, N (%)	313 (65)	254 (64)	59 (69)	0.33
Charlson comorbidity index (median, IQR)	4 (2-8)	6 (2-8)	3 (2-4)	<0.001
Charlson recoded (median, IQR)	0 (0-1)	0 (0-1)	1 (0-2)	0.004
Cancer status, N (%)				
controlled/remission	65 (13)	36 (9)	29 (34)	<0.001
uncontrolled, newly diagnosis	247 (51)	221 (56)	26 (31)	<0.001
uncontrolled, recurrence/progression	171 (35)	141 (35)	30 (35)	0.98
neutropenia at ICU admission	32 (7)	3 (1)	29 (34)	<0.001
weight loss	65 (13)	54 (14)	11 (13)	0.88
Type of admission, N (%)				
medical	152 (31)	75 (19)	77 (90)	<0.001
scheduled surgery	287 (59)	283 (71)	4 (5)	<0.001
emergency surgery	44 (9)	40 (10)	4 (5)	0.12
Main reason for ICU admission, N (%)				
postoperative care	331 (69)	324 (81)	7 (8)	<0.001
respiratory failure	63 (13)	25 (6)	38 (45)	<0.001
septic shock	18 (4)	10 (3)	8 (9)	0.002
neurological disorder	12 (2)	7 (2)	5 (6)	0.03
metabolic disorder	11 (2)	9 (2)	2 (2)	0.96
MOF	11 (2)	2 (1)	9 (11)	<0.001
GI hemorrhage	9 (2)	9 (2)	0 (0)	0.16
surveillance	7 (1)	3 (1)	4 (5)	0.006
cardiovascular complications	5 (1)	4 (1)	1 (1)	0.89
renal failure	5 (1)	5 (1)	0 (0)	0.30
other	11 (2)	0 (0)	11 (13)	<0.001
Severity of illness at ICU admission (day 1)				
APACHE II score (median, IQR)	15 (11-20)	13 (11-18)	21 (17-29)	<0.001
SOFA score (median, IQR)	3 (2-5)	3 (2-5)	6 (3-9)	<0.001
Organ failure during ICU stay				
mechanical ventilation, N (%)	144 (30)	114 (29)	30 (35)	0.22
vasopressors, N (%)	103 (21)	71 (8)	32 (38)	<0.001
RRT, N (%)	26 (5)	14 (4)	12 (14)	<0.001
mean SOFA score (median, IQR)	3 (2-5)	3 (2-4)	6 (4-8)	<0.001
Outcomes				
ICU LOS, days (median, IQR)	3 (2-4)	2 (2-4)	4 (2-9)	<0.001
readmissions, N (%)	43 (9)	32 (8)	11 (13)	0.15

ICU mortality, N (%)	38 (8)	20 (5)	18 (21)	<0.001
hospital LOS, days (median, IQR)	15 (10-27)	14 (10-24)	25 (11-49)	0.001
hospital mortality, N (%)	79 (16)	50 (13)	29 (34)	<0.001
DNR decisions, N (%)	53 (11)	28 (7)	25 (29)	<0.001
3 months mortality, N (%)	105 (22)	69 (17)	36 (42)	<0.001
1 year mortality, N (%)	199 (41)	143 (36)	56 (66)	<0.001

N= number; yrs= years; IQR= interquartile range (25%-75%); BMI= body mass index; ICU= intensive care unit; ADL= activity of daily living; Charlson recoded= Charlson co-morbidity index minus points for solid or hematological malignancy; MOF= multiple organ failure; GI= gastro-intestinal; APACHE= Acute Physiology and Chronic Health Evaluation; SOFA= Sequential Organ Failure Assessment; RRT= renal replacement therapy; LOS= length of stay; DNR= do-not-resuscitate

Figure 1. Flow chart of the patient cohort over the 1 year study period, number of surveys, and response rates

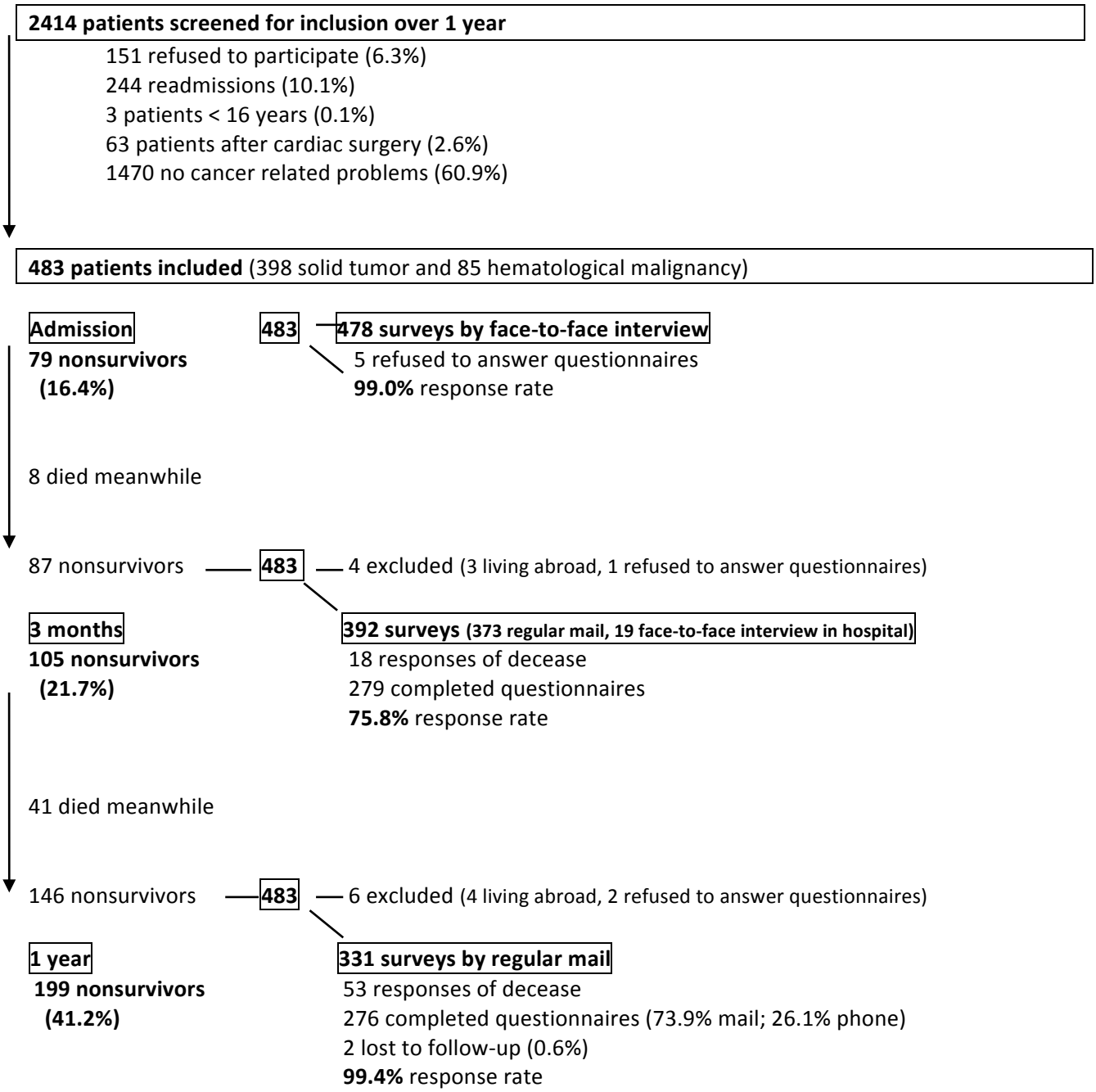
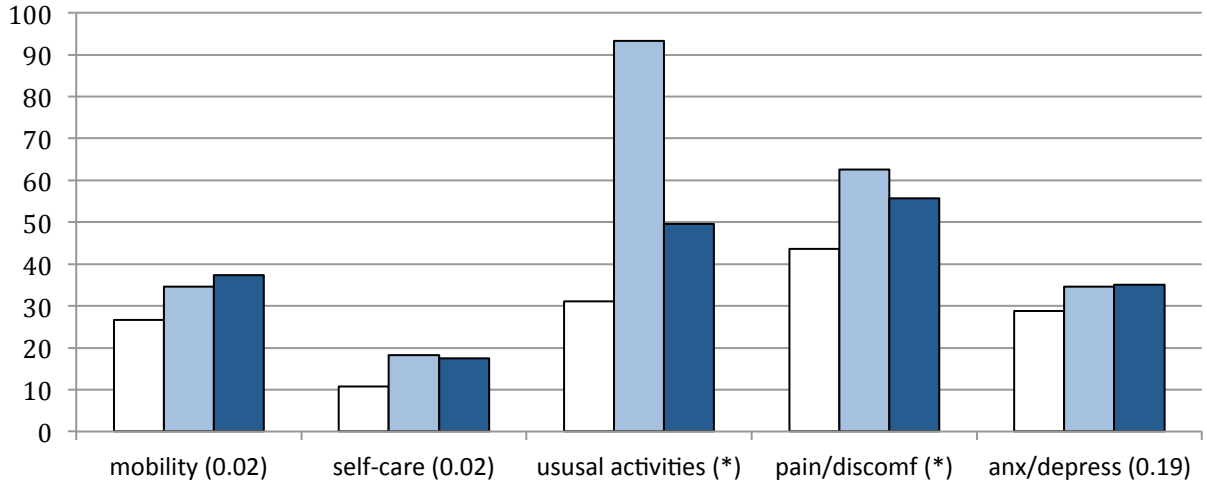
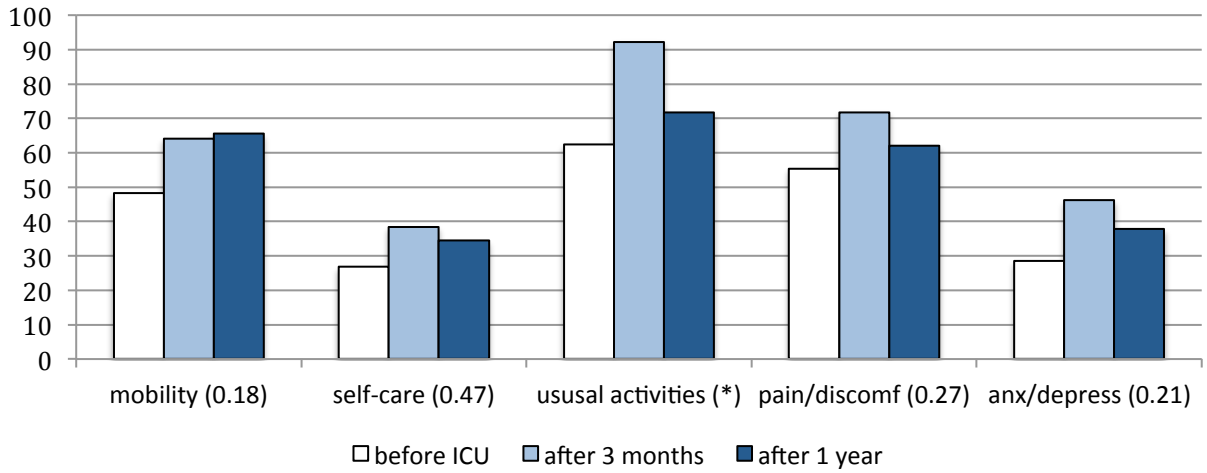


Figure 2. EQ-5D: Percentage of patients with some or extreme problems before ICU (hospital survivors only), 3 months and 1 year after ICU discharge

Solid malignancies



Hematological malignancies

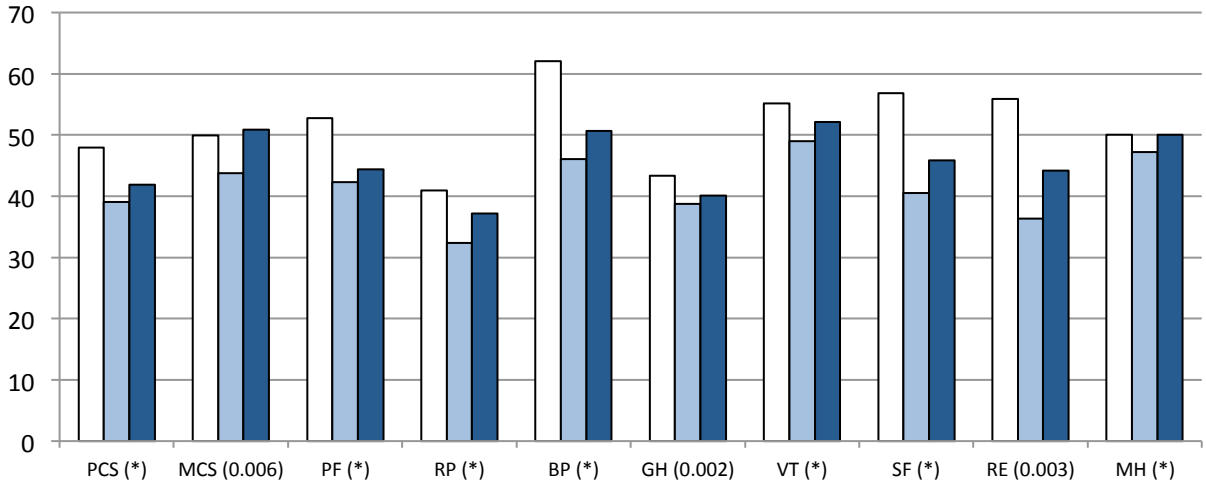


The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension. Chi-square test was used to calculate P-values per domain over the 3 different time points (P<0.05 was considered significant). For each domain, P-values over the different time points are shown between brackets. (*) = P<0.001; ICU=intensive care unit; discomf= discomfort; anx= anxiety; depress= depression

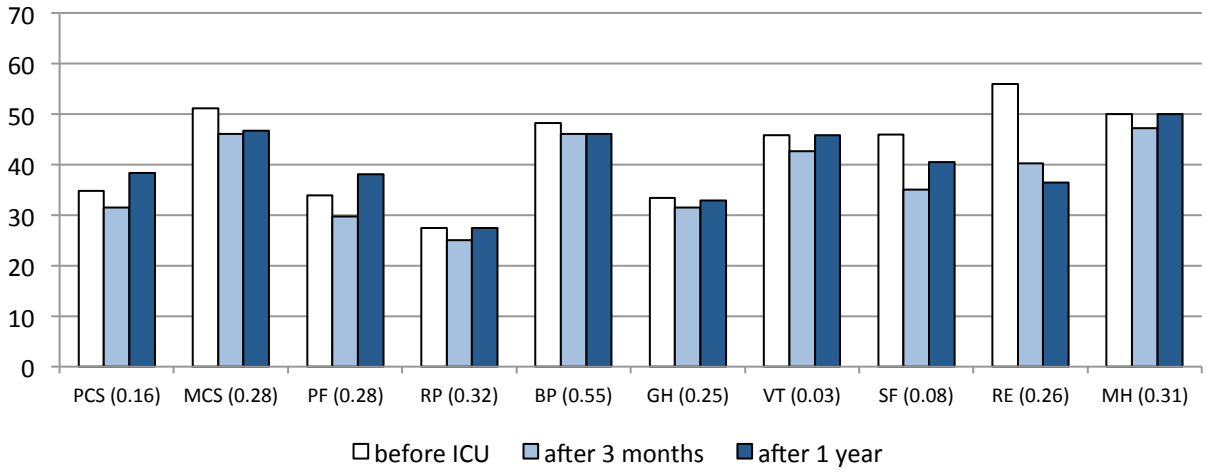
Solid malignancies: Total numbers of patients at the different time points were respectively: 344 (before ICU admission, hospital survivors only); 240 (3 months after ICU discharge); 246 (1 year after ICU discharge)
Hematological malignancies: Total numbers of patients at the different time points were respectively: 56 (before ICU admission, hospital survivors only); 39 (3 months after ICU discharge); 29 (1 year after ICU discharge)

Figure 3. SF-36 before ICU (hospital survivors only), 3 months, and 1 year after ICU discharge: norm-based scores

Solid malignancies



Hematological malignancies



The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based scores (median values) per respective domain. Friedman test was used to calculate P-values per domain over the 3 different time points (P<0.05 was considered significant). For each domain, P-values over the different time points are shown between brackets; (*) = P<0.001; ICU=intensive care unit; PCS= physical component score; MCS= mental component score; PF=physical functioning; RP= role physical; BP= bodily pain; GH= general health; VT= vitality; SF= social functioning; RE= role emotional; MH= mental health

Solid malignancies: Total numbers of patients at the different time points were respectively: 346 (before ICU admission, hospital survivors only); 239 (3 months after ICU discharge); 245 (1 year after ICU discharge).
Hematological malignancies: Total numbers of patients at the different time points were respectively: 56 (before ICU admission, hospital survivors only); 39 (3 months after ICU discharge); 29 (1 year after ICU discharge).

Online resource 1. Persons who completed the QOL questionnaires, N (%)

	All				Solid tumor patients				Hematological patients			
	Base-line *N*=478	3 months after ICU dis-charge *N*=279	1 year after ICU discharge *N*=276	P(*)	Base-line *N*=394	3 months after ICU discharge *N*=240	1 year after ICU discharge *N*=247	*P(*)*	Base-line *N*=84	3 months after ICU discharge *N*=39	1 year after ICU discharge *N*=29	P(*)
Patient	378 (79)	240 (86)	218 (79)	0.04	325 (82)	210 (88)	197 (80)	0.07	53 (63)	30 (77)	21 (72)	0.27
Husband/wife	53 (11)	26 (9)	39 (14)	0.19	37 (9)	19 (8)	33 (13)	0.11	16 (19)	7 (18)	6 (21)	0.96
Son/daughter	32 (7)	9 (3)	10 (4)	0.05	24 (6)	7 (3)	10 (4)	0.16	8 (10)	2 (5)	0 (0)	0.20
Father/mother	6 (1)	0 (0)	2 (1)	0.16	2 (1)	0 (0)	1 (1)	0.56	4 (5)	0 (0)	1 (3)	0.40
Other family, friends	9 (2)	4 (2)	7 (3)	0.64	6 (2)	4 (2)	6 (2)	0.69	3 (4)	0 (0)	1 (3)	0.50

QOL=quality of life; *N*= number; ICU= intensive care unit; *P* (*): *P*-value over the 3 different time points

Online Resource 2. Outcome and utility index (based upon EQ-5D) per type of cancer

Type of cancer	N	Hospital mortality (%)	Mortality 3 months after ICU discharge (%)	Mortality 1 year after ICU discharge (%)	Utility index at baseline (ICU survivors) (*)	Utility index 3 months after ICU discharge (*)	Utility index 1 year after ICU discharge (*)
Lower GI	102	8.8	10.8	31.4	0.76 (0.53-1.00)	0.73 (0.63-1.00)	0.75 (0.65-1.00)
Upper GI	99	12.1	15.2	33.3	0.74 (0.42-1.00)	0.71 (0.57-0.80)	0.73 (0.63-0.95)
Lung	73	9.6	15.1	24.7	0.74 (0.43-1.00)	0.70 (0.56-0.76)	0.71 (0.56-0.76)
Urogenital	34	8.8	26.5	41.2	0.74 (0.37-0.77)	0.73 (0.55-0.77)	0.66 (0.49-0.82)
Brain	31	16.1	22.6	41.9	0.77 (0.76-1.00)	0.69 (0.57-1.00)	0.73 (0.56-1.00)
Head and neck	26	30.8	38.5	65.4	0.77 (0.51-1.00)	0.55 (0.33-0.91)	0.79 (0.60-1.00)
Breast	16	18.8	18.8	37.5	0.66 (0.20-1.00)	0.56 (0.19-0.74)	0.70 (0.63-1.00)
Other solid T	17	17.6	17.6	58.8	0.74 (0.32-0.83)	0.69 (0.52-0.94)	0.69 (0.56-0.77)
High grade HM	41	41.5	46.3	68.3	0.71 (0.29-0.95)	0.66 (0.39-0.74)	0.66 (0.64-0.82)
Low grade HM	44	27.3	38.6	63.6	0.66 (0.29-0.76)	0.33 (0.19-0.68)	0.60 (0.14-0.77)

(*) Utility index is expressed as median (interquartile range); N= number; ICU= intensive care unit; GI= gastro-intestinal; T= tumors; HM= hematological malignancy

Online resource 3. Univariate and multivariate analyses of factors associated with long-term QOL

Factors associated with utility (as indicator for QOL) 3 months after ICU discharge

	Univariate				Multivariate R^2= 0.151	
Variable	**R^2**	**B (SE)**	**95% CI**	**P**	**95% CI**	**P**
age (per year)	0.008	-0.002 (0.001)	-0.004 to 0.001	0.14	-0.005 to 0.000	0.03
female gender	0.026	-0.10 (0.04)	-0.16 to -0.03	0.007	-0.19 to -0.05	<0.001
Charlson recoded	0.043	-0.04 (0.01)	-0.06 to -0.02	0.001	-0.06 to -0.02	0.001
hospital days prior ICU	0.034	-0.01 (0.003)	-0.02 to -0.004	0.002		
cancer status						
controlled disease	-	-	-	reference		
uncontrolled new diagnosis	0.031	0.16 (0.05)	0.05 to 0.26	0.003		
uncontrolled recurr/progr	0.031	0.12 (0.06)	0.009 to 0.23	0.03		
ST vs HM	0.058	-0.20 (0.05)	-0.29 to -0.10	<0.001	-0.23 to -0.03	0.01
surgical/ medical	0.052	-0.16 (0.04)	-0.23 to -0.08	<0.001		
emergency surgery versus other	0.009	-0.11 (0.07)	-0.25 to 0.03	0.11		
APACHE II	0.071	-0.12 (0.003)	-0.017 to -0.007	<0.001		
SOFA day 1	0.031	-0.02 (0.006)	-0.03 to -0.006	0.003		
SOFA mean	0.045	-0.03 (0.008)	-0.04 to -0.01	<0.001	-0.03 to -0.001	0.04

Factors associated with utility (as indicator for QOL) 1 year after ICU discharge

	Univariate				Multivariate R^2= 0.057	
Variable	**R^2**	**B (SE)**	**95% CI**	**P**	**95% CI**	**P**
age (per year)	0.021	-0.003 (0.001)	-0.005 to 0.000	0.02	-0.005 to -0.001	0.007
female gender	0.002	0.026 (0.033)	-0.04 to -0.09	0.43		
Charlson recoded	0.022	-0.03 (0.13)	-0.06 o -0.006	0.02	-0.05 to -0.002	0.04
cancer status						
controlled diseae	-	-	-	reference		
uncontrolled new diagnosis	0.036	0.15 (0.05)	0.05 to 0.25	0.004		
uncontrolled recurr/progr	0.036	0.17 (0.05)	0.06 to 0.27	0.002		
ST vs HM	0.013	-0.09 (0.05)	-0.19 to 0.05	0.06	-0.20 to -0.004	0.04
surgical/ medical	0.011	-0.07 (0.04)	-0.16 o 0.008	0.08		
SOFA mean	0.001	-0.004 (0.008)	-0.02 to 0.01	0.60		

QOL= quality of life; ICU= intensive care unit; R^2= (Pearson correlation coefficient)^2; SE= standard error; CI= confidence interval; Charlson recoded= Charlson co-morbidity index minus points for solid or hematological malignancy; ST= solid tumor; vs= versus; HM= hematological malignancy; recurr= recurrence; progr=progression; APACHE= Acute Physiology and Chronic Health Evaluation; SOFA= Sequential Organ Failure Assessment

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III. Long-term quality of life in critically ill patients with acute kidney injury treated with renal replacement therapy: A matched cohort study

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a common complication in intensive care unit (ICU) patients and associated with increased morbidity and mortality. We compared long-term outcome and quality of life (QOL) in ICU patients with AKI treated with renal replacement therapy (RRT) with matched non AKI-RRT patients.

Methods: During 1 year adult ICU patients consecutively were included in a prospective cohort study. AKI-RRT patients alive at 1 year and 4 years were matched with non AKI-RRT survivors from the same cohort in a 1:2 (1 year) and 1:1 (4 years) ratio on gender, age, APACHE II score, and admission category. QOL was assessed by the EuroQoL-5D and the Short Form-36 survey before ICU admission and at 3 months, 1 and 4 years after ICU discharge.

Results: Of 1953 patients, 121 (6.2%) had AKI-RRT. AKI-RRT hospital survivors (44.6%; N=54) had a 1-year and 4-year survival rate of 87.0% (N=47) and 64.8% (N=35) respectively. Forty-seven 1-year AKI-RRT patients were matched with 94 1-year non AKI-RRT patients. Of 35 4-years survivors 3 refused further cooperation, 3 were lost-to-follow-up, and 1 had no control. Finally, 28 4-years AKI-RRT patients were matched with 28 non AKI-RRT patients. During ICU stay, 1-year and 4-years AKI-RRT patients had more organ dysfunction compared to their respective matches (SOFA scores 7 vs. 5, $P<0.001$; 7 vs. 4, $P<0.001$). Long-term QOL was however comparable between both groups but lower than in the general population. QOL decreased at 3 months, improved after 1 and 4 years but remained under baseline level. Respectively 1 and 4 years after ICU discharge, 19.1% and 28.6% of AKI-RRT survivors remained RRT dependent, and 81.8% and 71% of them were willing to undergo ICU admission again if needed.

Conclusion: In long-term critically ill AKI-RRT survivors, QOL was comparable to matched long-term critically ill non AKI-RRT survivors, but lower than in the general population. The majority of AKI-RRT patients wanted to be readmitted to the ICU when needed, despite a higher severity of illness compared to matched non AKI-RRT patients, and despite the fact that one quarter had persistent dialysis dependency.

INTRODUCTION

Acute kidney injury treated with renal replacement therapy (AKI-RRT) affects approximately 5-10% of intensive care unit (ICU) patients [1]. These patients are amongst the most severely ill patients in the ICU, as may be illustrated by the 50% in-hospital mortality [2-4]. AKI-RRT patients who survive may develop chronic kidney disease, including end stage renal disease, and experience decreased long-term survival [4-8]. Therefore, to fully appreciate outcomes of critically ill AKI-RRT survivors, indices regarding long-term morbidity and quality of life (QOL) should be taken into account as well [9,10].

Major reductions in long-term QOL in critically ill patients are seen in severe acute respiratory distress syndrome, prolonged mechanical ventilation, severe sepsis, and after major trauma, all conditions frequently associated with AKI-RRT [11]. Data regarding QOL in AKI-RRT patients show that these patients have a decreased QOL compared to the general population but perceive QOL as good [12, 13]. However, these studies were either retrospective [14-17], evaluated QOL after a short term [12-15, 17-21], lacked baseline QOL assessment [12-15, 18,22], or dated back more than a decade [14-16, 18,23]. It is also unclear whether impairment in long-term QOL is the consequences of critical illness, AKI-RRT, pre-existing co-morbidities, or a combination of these.

The aim of the present study was to assess long-term outcomes and QOL of critically ill AKI-RRT patients at baseline, and at 3 months, 1 year and 4 years after ICU discharge and to compare QOL with a cohort of matched non AKI-RRT patients [24].

METHODS

Design, Patients, and Setting

The cohort described in this study is a subgroup of a prospective observational cohort. During one year (March 2008- March 2009), all consecutively admitted adult patients at the 14-bed medical (MICU), the 22-bed surgical ICU (SICU), and the 6-bed burn unit of the Ghent University Hospital, Belgium, were screened to study QOL and cost-effectiveness of intensive care [25]. Exclusion criteria were age < 16 y and admission to the ICU after cardiac surgery. In case of multiple ICU admissions, only the first was considered.

In this study, only AKI-RRT patients of the larger cohort were included. Chronic hemodialysis patients were excluded. The attending critical care physician and consulting nephrologist assessed indication for RRT and modality.

To study the impact of RRT on long-term outcome and QOL, we performed a matched cohort study, according to the STROBE guidelines [26]. Included AKI-RRT patients alive at 1 year after hospital discharge were defined as exposed patients and individually matched with 1-year non AKI-RRT survivors (defined as non-exposed patients) from the same cohort. Being a patient in the non AKI-RRT group did not imply normal kidney function; it implied no treatment with RRT. To correct for possible bias, we excluded patients

who needed RRT but who did not receive RRT due to therapeutic restrictions. Equally, AKI-RRT patients alive at time of this study (average 4 years later) were individually matched with 4-years non AKI-RRT survivors. The exposed: non-exposed ratio was aimed at 1:2 to reduce risk of selection bias. When there were more than 2 non-exposed patients for an exposed patient, only the non-exposed patient with the best overall match was selected. If an exposed patient could only be properly matched to 1 non-exposed patient, we accepted matching in a 1:1 ratio for the respective cohort in order to avoid an imbalance of characteristics and to retain the best possible matching. Matching was based on gender, age (±5 years), Acute Physiology and Chronic Health Evaluation (APACHE II) score (± 5), and admission category.

Data Collection and Definitions

Variables collected within the first 24 hours of ICU admission included age, gender, body mass index, personal, proxy, and family practitioner contact data, living situation, activity of daily living, co-morbidity as measured by the Charlson co-morbidity index [27], hospitalization in the last 6 months, main reason for ICU admission, APACHE II score [28], Sequential Organ Failure Assessment (SOFA) score [29], need for mechanical ventilation, use of any vasopressors, and need for RRT. During ICU stay SOFA scores, need for mechanical ventilation, vasopressors, RRT, and do-not-resuscitate codes were collected on a daily base. ICU length of stay (LOS), hospital LOS, vital status at ICU and hospital discharge, and at 3 months, 1 year and 4 years following ICU discharge were collected for each patient.

Values of serum creatinine of AKI-RRT patients were extracted from the STARRT database, which includes all relevant renal and RRT data of ICU patients with AKI–RRT treated in our hospital, and from laboratory data in control patients. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [30]. Renal recovery was defined as independence from RRT.

The study was approved by the local ethical committee (Ethisch Comité Ghent University Hospital; amendment project 2007/423 approved February 19th, 2013) (B67020072805), and conducted in accordance with the declaration of Helsinki. A signed informed consent was obtained from every included patient.

Quality of life

QOL was assessed by means of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2®) and the EuroQoL-5D (EQ-5D). The SF-36 questionnaire contains 36 items measuring 8 health domains: physical- (PF), and social functioning (SF), role limitations due to physical- (RP), or emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP), and general perception of health (GH) [31]. Two component scores, a physical (PCS) and a mental (MCS), are calculated summary scores where respectively the physical domains (PF, RP, BP, GH) or the mental domains (VT, SF, RE, MH) will account more in the score. We assessed SF-36 as norm-based scores to be able to compare them directly with the

general healthy population, with a group-level range of 47-53 considered as average or normal [31]. Group scores less than 47 indicate impaired functioning within that health domain; group scores greater than or equal to 53 should be considered average or above the normative sample.

The 36th item, health transition, provides information about perceived changes in health status. The validity and reliability of the SF-36 has been confirmed in critically ill patients, and its use is validated in face-to-face interviews, interview by phone or by sending the questionnaire by regular mail [32].

The EQ-5D is a generic QOL questionnaire that measures health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [33]. Each dimension has three levels: no problems, moderate problems or severe problems. On a visual analogue scale (VAS), patients can rate their perceived overall health between 0 and 100. The EQ-5D is suitable for measuring QOL in critical care [34, 35].

QOL was assessed at different time points: baseline QOL and at strictly 3 months and 1 year after ICU discharge. QOL was also assessed in August 2013, a median of 4.1 years (3.9 years – 4.3 years) after ICU discharge. Following ICU admission and study inclusion, a face-to-face interview to assess baseline QOL (defined as QOL 2 weeks before ICU admission) was done as soon as possible. This interview was preferably taken from the patient, or when impossible, from the proxy. Three months, 1 year, and 4 years after ICU discharge, patients were sent the EQ-5D and SF-36 surveys by regular mail; at 1 and 4 years, questions concerning living situation, memories, sleep quality, and willingness to be readmitted to an ICU department, were added. If the questionnaires were not returned within one month, patients or relatives were contacted by phone to assess QOL after 1 year and after 4 years. Eventually, the family practitioner was contacted.

Statistical analysis

Data are expressed as median (interquartile range) (IQR) for continuous variables and as number (%) for categorical variables. QOL at the different time points and characteristics between both groups (AKI-RRT versus non AKI-RRT patients) were compared by the Mann-Whitney U test for continuous variables and by the Chi-square test for categorical variables. For long-term analysis of QOL, differences between QOL at baseline (only hospital survivors), at 3 months, at 1 and 4 years after ICU discharge were assessed by Chi-square (EQ-5D) or Friedman test (SF-36). P-values were two-sided and statistical significance was set at 0.05. All statistical analyses were done using IBM SPSS Statistics software version 21.

RESULTS

Characteristics of the study population

During the 1-year study period 1953 patients were included (Figure 1). One hundred forty-seven patients (7.5%) developed AKI with need for RRT. Of these, 121 patients (6.2%) received RRT. ICU

(46.3%), hospital (55.4%), 3 months (57.9%), 1-year (61.1%) and 4-years (71.1%) mortality rates in these patients were high. Twenty-six AKI patients (1.3%) did not receive RRT due to therapeutic restrictions and were excluded for further analysis.

AKI-RRT hospital survivors (44.6%) had a 1-year and 4-years survival rate of 87.0% and 64.8% respectively. Forty-seven 1-year AKI-RRT survivors were individually matched with 94 1-year non AKI-RRT survivors (2 matches for all AKI-RRT patients). Of 35 4-years survivors 3 refused further cooperation, 3 were lost-to-follow-up, and 1 had a double match. In 13 of the 28 included 4-years AKI-RRT survivors only one good match could be withhold, so matching occurred in a 1:1 ratio. Finally, 28 4-years AKI-RRT survivors were individually matched with 28 non AKI-RRT patients. AKI-RRT and non AKI-RRT patients had similar gender, age, APACHE II score, and admission category at 1 year and 4 years (Table 1).

During ICU stay, 1-year and 4-years AKI-RRT patients had higher SOFA scores compared to their respective matches, and more needed mechanical ventilation or vasopressors for a longer time (Table 1).

Renal characteristics and renal outcomes

One year AKI-RRT patients had higher baseline serum creatinine concentrations and lower eGFR compared to their matches. These measurements did not significantly differ between 4-years AKI-RRT and non AKI-RRT patients (Table 1).

Respectively 12 1-year (25.5%) and 10 4-years AKI-RRT patients (35.7%) were RRT dependent at hospital discharge. Nine (19.1%) of the 1-year and 8 (28.6%) of the 4-years AKI-RRT patients remained RRT dependent over time.

Quality of life

An overview of the persons who rated QOL, how QOL was assessed and the number of completed QOL surveys is given in Table 2. Most patients rated their own QOL at the different time points, except at baseline in 1-year AKI-RRT patients.

Significant differences in QOL between AKI-RRT and non AKI-RRT survivors at each different time point were small. Figure 2 and Figure 3 show that the 1-year AKI-RRT versus (vs) 1-year non AKI-RRT patients had comparable baseline QOL. The 1-year AKI-RRT patients were poorer emotionally at 3-months (RE 28.7 vs 38.4; P=0.035), but had a better mental score (MCS 53.3 vs 47.8; P=0.039) and less bodily pain (BP 46.5 vs 41.6; P=0.041) at 1 year (Figure 3). Figure 4 and 5 show that the 4-years AKI-RRT vs 4-years non AKI-RRT patients were emotionally better at baseline (RE 55.9 vs 40.3; P=0.030) (Figure 5), but had more problems with usual activities (81.0% vs 47.8%; P=0.023), pain (71.4% vs 26.1%; P=0.003) and anxiety (61.9% vs 17.4%; P=0.002) at 3 months (Figure 4). QOL after 1 and 4 years showed no differences (Figure 4 and Figure 5).

Comparing QOL within each group between the different time points revealed that QOL particularly decreased after 3 months.

Evolution in QOL over time: 1 year-cohort

All 1-year AKI-RRT patients reported more problems on the EQ-5D after 3 months compared to baseline. After 1 year, they experienced fewer problems but still more than before ICU admission. The EQ-5D showed the same evolution for 1-year non AKI-RRT patients (Additional File 1A/1B).

The SF-36 showed significant evolutions in QOL over time for 1-year AKI-RRT patients in nearly all dimensions. QOL decreased after 3 months, improved after 1 year but without return to the baseline level. QOL also remained under the level of the average population. The same pattern, although less pronounced, was seen in 1-year non AKI-RRT patients (Additional File 2A/2B).

For 1-year AKI-RRT patients median VAS scores ranged from 70 (baseline), to 60 (3 months) and 70 (1 year) (P=0.048). In non AKI-RRT patients the VAS remained the same, respectively 68, 65 and 65 at baseline, 3 months and 1 year after ICU discharge (P=0.917).

Evolution in QOL over time: 4 years-cohort

Changes in QOL over time assessed by the EQ-5D were significant in AKI-RRT patients for mobility (P=0.040), usual activities (P<0.001), and anxiety (P=0.040) (Additional File 1C) and in 4-years non AKI-RRT patients for mobility (P=0.017), and usual activities (P=0.014) with most problems at 3 months after ICU discharge followed by an improvement in QOL after 1 year (Additional File 1D). QOL never returned to baseline level.

The SF-36 showed that in both groups, QOL decreased after 3 months compared to baseline (Additional File 2C/2D). For the 4-years AKI-RRT patients, QOL improved after 1 year, especially in the mental domains. At 4 years, QOL significantly decreased mainly physically but improved or remained the same in the mental components (Additional File 2C). Changes in long-term QOL in the 4-years non AKI-RRT patients were less pronounced (Additional File 2D).

The 4-years AKI-RRT patients showed a decrease in VAS after 3 months (63), and improvements after 1 (70) and 4 years (68) but without regain of the baseline level (70) (P=0.044). The 4-years non AKI-RRT patients had the same evolution but without significance (P=0.327).

Additional file 3 and additional file 4 illustrate more in detail the variability in EQ-5D and SF-36 over time.

Overall, long-term QOL remained under the baseline level for AKI-RRT and non AKI-RRT patients, and under the QOL of the average population.

Additional questions after 1 year and 4 years

One and 4 years after ICU discharge, most survivors lived independently, and only a minority stayed in a special care facility (Table 1). There were no major sleeping problems. One year and 4 years after ICU discharge, AKI-RRT patients had more bad memories than non AKI-RRT patients (17.4% vs 4.3%, P=0.010; 21.4% vs 3.8%, P=0.055). 81.8% of the 1-year AKI-RRT patients preferred to be readmitted to an ICU

department in case of deterioration versus 83.0% of their 1-year matches (P=0.867). This number decreased to 71.4% for the 4-years AKI-RRT patients versus 84.6% for the 4-years non AKI-RRT patients (P=0.244).

DISCUSSION

In this prospective single center matched cohort study concerning long-term outcomes and QOL of AKI-RRT patients, we found high mortality rates and lower QOL levels compared to the general population.

Similar to others, we found high hospital mortality (55%) in this cohort of critically ill AKI-RRT patients, with only moderate increase of mortality at longer follow up (58% at 3 months, 61% at 1 year, 71% at 4 years) [4, 14, 15, 20, 36].

At hospital discharge and at long-term, a quarter of AKI-RRT hospital survivors were RRT dependent. These findings are similar to those reported in literature [37].

Long-term survival data would be meaningless without considering QOL. Remarkably, there was no difference in QOL at different time points between AKI-RRT patients and matched non AKI-RRT patients, although changes in QOL over time were less pronounced in the latter group. QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year, and stayed the same or improved slightly after 4 years, but still remained under baseline level.

The fact that long-term QOL had the same evolution over time in AKI-RRT and non AKI-RRT patients was quite surprising suggesting that the AKI-RRT component during critical illness did not have an important impact on long-term QOL. Others reported very similar findings, however, these studies reported only on QOL after 6 months, and in 1 study not all AKI patients received RRT, and some patients received RRT without AKI [20, 21].

The fact that AKI-RRT patients were more severely ill during their ICU stay compared to matched patients had no influence on QOL over the years. This is in accordance with the findings of Orwelius et al [38]. In a multicenter study they found that 6 months after ICU discharge, perceived QOL in sepsis patients did not differ from ICU survivors with other diagnoses, even though these sepsis patients were more severely ill, and had a longer ICU stay. Another study by Orwelius suggested that long-term QOL was mainly affected by co-morbidity [39]. In our study AKI-RRT and non AKI-RRT patients had a very comparable co-morbidity and medical history, which may explain the comparable long-term QOL between groups in our study.

QOL was perceived as acceptable and both AKI-RRT and non AKI-RRT patients reported low dependence in daily life later on. The number of AKI-RRT and non AKI-RRT patients who agreed to undergo life-sustaining interventions again in case of deterioration remained high. However, QOL was lower

compared to that of the average population in both groups specifically in the more physical domains. This is in accordance with the findings of others [12-16, 20, 21].

Our study has several strengths. First, the matched cohort design demonstrates the real impact of AKI-RRT upon long-term QOL. This has not been evaluated thus far. Second, QOL was assessed with validated questionnaires at baseline, which allows for the only reliable evaluation of QOL over time without recall or selection bias [11, 40]. Third, the additional questions and VAS score allowed evaluation of the patients' perception of the ICU admission and the consequences of severe illness. Finally, most studies report QOL in AKI survivors as a short-term endpoint, while this study provides also data for a longer follow-up period. Strict time intervals of 3 months and 1 year after ICU discharge were respected in all patients. For long-term assessment of QOL, an arbitrary time point was chosen (August 2013) which was between 47-52 months after ICU discharge for all patients. Response rate was very high and only 3 patients were lost-to-follow-up.

Some limitations should also be mentioned. First, single center data from a university hospital may not reflect general practice and may limit external validity of the data. Second, although 1-year and 4-years AKI-RRT patients were matched to non AKI-RRT patients based on 4 criteria, we cannot exclude that matched patients had a different profile compared to AKI-RRT patients. Third, the study cohort is relatively small and may lack of statistical power to detect differences among the QOL domains in our study patients. Fourth, medical decisions leading to ICU referral may have selected for patients with better prospects. Fifth, long-term QOL may also be modified by events happening to the patient after hospital discharge. These were not recorded in the present study.

CONCLUSIONS

We found high mortality rates in AKI-RRT patients. However, in long-term critically ill AKI-RRT survivors, QOL was comparable to matched long-term critically ill survivors without AKI-RRT, but lower than in the general population. The majority of AKI-RRT patients wanted to be readmitted to the ICU when needed, despite a higher severity of illness compared to matched non AKI-RRT patients, and despite the fact that one quarter had persistent dialysis dependency.

KEY MESSAGES

Long-term critically ill AKI-RRT survivors have comparable QOL than matched long-term critically ill survivors without RRT.

QOL in long-term AKI-RRT survivors is lower than in the general population.

AKI-RRT patients are more severely ill during their ICU stay compared to matched non AKI-RRT patients.

The majority of long-term AKI-RRT survivors prefer to be readmitted to the ICU department in case of deterioration.

One quarter of long-term AKI-RRT survivors have persistent dialysis dependency.

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Table 1. Patient characteristics at ICU admission, organ failure during ICU admission, and outcomes

	1-year AKI-RRT patients (N=47)	1-year non AKI-RRT patients (N=94)	P	4-year AKI-RRT patients (N=28)	4-year non AKI-RRT patients (N=28)	P
age, yrs, (median, IQR)	57 (45-69)	57 (48-70)	0.897	54 (45-66)	53 (45-68)	0.718
male gender, N (%)	31 (66.0)	62 (66.0)	0.999	16 (57.1)	16 (57.1)	0.999
BMI, kg/m^2 (median, IQR)	26.2 (22.8-29.7)	25.9 (22.0-29.4)	0.444	27.3 (22.9-31.6)	24.5 (22.9-27.8)	0.092
serum creatinine baseline (mg/dL) (median, IQR)*	1.14 (0.94-1.51)	0.82 (0.66-1.04)	0.001	0.97 (0.80-1.26)	0.78 (0.65-1.11)	0.062
eGFR baseline (mL/min per 1.73 m²) (median, IQR)*	86 (71-100)	100 (83-116)	0.007	99 (85-109)	102 (87-116)	0.629
lives at home before admission, N (%)	45 (95.7)	90 (95.75)	0.999	26 (92.9)	27 (96.4)	0.553
ADL, N (%)						
no limitations	25 (53.2)	47 (50.0)	0.721	18 (63.4)	21 (75.0)	0.383
moderate limitations	19 (40.4)	42 (44.7)	0.631	7 (25.0)	7 (25.0)	0.999
chair-bound	0 (0)	3 (3.2)	0.216	0 (0)	0 (0)	NA
bedridden	3 (6.4)	2 (2.1)	0.198	3 (10.7)	0 (0)	<0.001
hospitalization in last 6 months before ICU, N (%)	20 (42.6)	46 (48.9)	0.474	10 (35.7)	14 (50.0)	0.280
Charlson comorbidity index (median, IQR)	1 (0-3)	2 (0-3)	0.115	0 (0-2)	2 (0-3)	0.110
Type of admission, N (%)						
medical	32 (68.1)	67 (71.3)	0.696	18 (64.3)	18 (64.3)	0.999
scheduled surgery	1 (2.1)	4 (4.3)	0.519	0 (0)	4 (14.3)	0.038
emergency surgery	10 (21.3)	18 (19.1)	0.765	7 (25.0)	3 (10.7)	0.163
trauma	3 (6.4)	4 (4.3)	0.376	2 (7.1)	2 (7.1)	0.999
burns		1 (1)	0.614	1 (3.6)	1 (3.6)	0.999
Severity of illness at ICU admission (first 24 hours)						
APACHE II score (median, IQR)	26 (21-31)	24 (20-30)	0.251	23 (20-28)	22 (18-25)	0.362
SOFA score (median, IQR)	9 (5-11)	7 (5-10)	0.047	7 (4-12)	6 (4-9)	0.139
Mechanical ventilation, N (%)	29 (61.7)	49 (52.1)	0.281	21 (75.0)	13 (46.4)	0.029
Vasopressors, N (%)	21 (44.7)	37 (39.4)	0.545	11 (39.3)	9 (32.1)	0.577
RRT, N (%)	11 (23.4)	0 (0)	<0.001	6 (21.4)	0 (0)	0.010
Organ failure during ICU stay						
Mechanical ventilation, N (%)	39 (83.0)	50 (53.2)	<0.001	24 (85.7)	13 (46.4)	0.002
Length of mechanical ventilation, days (median, IQR)	16 (3-27)	1 (0-3)	<0.001	18 (4-31)	0 (0-7)	<0.001
Vasopressors, N (%)	36 (76.6)	42 (44.7)	<0.001	21 (75.0)	10 (35.7)	0.003
Length of vasopressor therapy, days (median, IQR)	5 (1-8)	0 (0-3)	<0.001	3 (0-10)	0 (0-3)	0.002
RRT, N (%)	47 (100)	0 (0)	<0.001	28 (100.0)	0 (0)	<0.001
Mean SOFA score (median, IQR)	7 (6-9)	5 (4-7)	<0.001	7 (5-10)	4 (4-7)	<0.001
Outcomes						
ICU LOS, days (median, IQR)	22 (11-42)	5 (3-9)	<0.001	24 (13-49)	7 (3-10)	<0.001
Readmissions, N (%)	8 (17.0)	12 (12.8)	0.495	3 (10.7)	4 (14.3)	0.686
Hospital LOS, days (median, IQR)	70 (30-100)	21 (13-44)	<0.001	62 (20-130)	19 (10-46)	0.003
DNR decisions, N (%)	4 (8.5)	3 (3.2)	0.170	2 (7.1)	1 (3.6)	0.312

Long-term mortality, N (%)	12 (25.5)	20 (21.3)	0.570	NA	NA	-
Need for RRT at hospital discharge, N (%)	12 (25.5)	NA	-	10 (35.7)	NA	-
Need for RRT at 3 months, N (%)	9 (19.1)	NA	-	8 (28.6)	NA	-
Need for RRT at 1 year, N (%)	9 (19.1)	NA	-	8 (28.6)	NA	-
Need for RRT at 4 years, N (%)	NA	NA	-	8 (28.6)	NA	-
Living situation after 1 year, N (%)						
	46 answers	93 answers		27 answers	26 answers	
independent without additional help	25 (54.3)	47 (50.5)	0.672	16 (59.3)	14 (53.8)	0.691
independent with some help	12 (26.1)	22 (23.7)	0.754	6 (22.2)	6 (23.1)	0.941
together with relatives (others than spouse)	6 (13.0)	14 (15.1)	0.751	3 (11.1)	4 (15.4)	0.646
special care facility	3 (6.5)	5 (5.4)	0.786	2 (7.4)	1 (3.8)	0.575
other	0 (0)	5 (5.4)	0.109	0 (0)	1 (3.8)	0.304
Living situation after 4 years, N (%)						
	NA	NA		27 answers	26 answers	
independent without additional help	NA	NA	-	18 (66.7)	14 (53.8)	0.340
independent with some help	NA	NA	-	5 (18.5)	6 (23.1)	0.682
together with relatives (others than spouse)	NA	NA	-	2 (7.4)	5 (19.2)	0.204
special care facility	NA	NA	-	2 (7.4)	1 (3.8)	0.575
other	NA	NA	-	0 (0)	0 (0)	0.999

AKI= acute kidney injury; RRT= renal replacement therapy; yrs= years; IQR= interquartile range (25%-75%); N= number; BMI= body mass index; eGFR= estimated glomerular filtration rate; ICU= intensive care unit; ADL= activity of daily living; NA=not applicable; ICU= intensive care unit; APACHE= Acute Physiology and Chronic Health Evaluation; SOFA= Sequential Organ Failure Assessment; LOS= length of stay; DNR= do-not-resuscitate; NA= not applicable

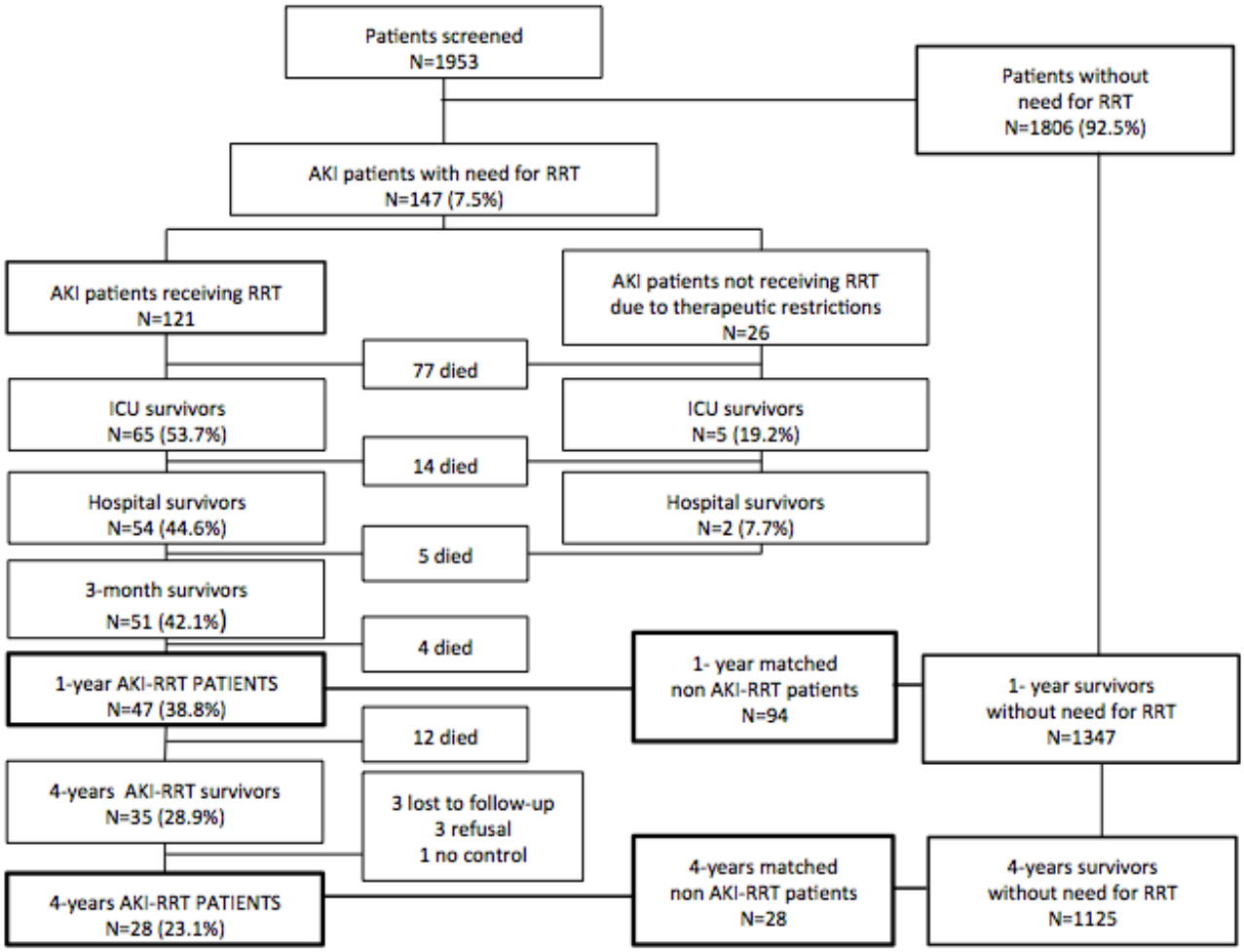
* Serum creatinine at baseline was defined as serum creatinine 6 months before ICU admission. Values were missing in 27 of the 1-year AKI-RRT patients, in 14 of the 94 1-year non AKI-RRT patients, in 21 of the 4-years AKI-RRT patients, and in 4 the 4-years non AKI-RRT patients

Table 2. Persons who rated QOL, assessment of QOL, number of completed QOL surveys

	Baseline			3 Months			1 Year			4 Years		
	AKI-RRT	non-AKI-RRT	*P*	AKI-RRT	non-AKI-RRT	*P*	AKI-RRT	non-AKI-RRT	*P*	AKI-RRT	Non-AKI-RRT	*P*
1-Year survivors	*N* = 47[a]	*N* = 94[a]		*N* = 34[b]	*N* = 71[b]		*N* = 46[c]	*N* = 94[d]				
Patient	14 (29.8)	57 (60.6)	0.001	25 (73.5)	57 (80.3)	0.434	33 (71.7)	65 (69.1)	0.753			
Partner	15 (31.9)	17 (18.1)	0.065	2 (5.9)	7 (9.9)	0.496	7 (15.2)	13 (13.8)	0.826			
Son/daughter	8 (17.0)	9 (9.6)	0.200	3 (8.8)	4 (5.6)	0.540	1 (2.2)	8 (8.5)	0.151			
Other family	4 (8.5)	5 (5.3)	0.465	0 (0)	0 (0)	0.999	1 (2.2)	2 (2.1)	0.986			
Others	6 (12.8)	6 (6.4)	0.200	4 (11.8)	4 (11.8)	0.268	4 (8.7)	6 (6.4)	0.618			
4-Year survivors	*N* = 28[a]	*N* = 27[a]		*N* = 21[b]	*N* = 23[b]		*N* = 27[e]	*N* = 26[f]		*N* = 28[g]	*N* = 28[h]	
Patient	8 (28.6)	18 (66.7)	0.005	17 (81.0)	17 (73.9)	0.578	22 (81.5)	22 (84.6)	0.761	24 (85.7)	21 (77.8)	0.313
Partner	7 (25.0)	4 (14.8)	0.345	1 (4.8)	3 (13.0)	0.340	3 (11.1)	3 (11.5)	0.961	1 (3.6)	2 (7.4)	0.553
Son/daughter	6 (21.4)	2 (7.4)	0.140	2 (9.5)	1 (4.3)	0.496	1 (3.7)	0 (0)	0.322	0 (0)	2 (7.4)	0.150
Other family	3 (10.7)	3 (11.1)	0.962	0 (0)	1 (4.3)	0.334	0 (0)	0 (0)	0.999	0 (0)	2 (7.4)	0.150
Others	4 (14.3)	0 (0)	0.041	1 (4.8)	1 (4.3)	0.947	1 (3.7)	1 (3.4)	0.978	3 (10.7)	1 (3.7)	0.299

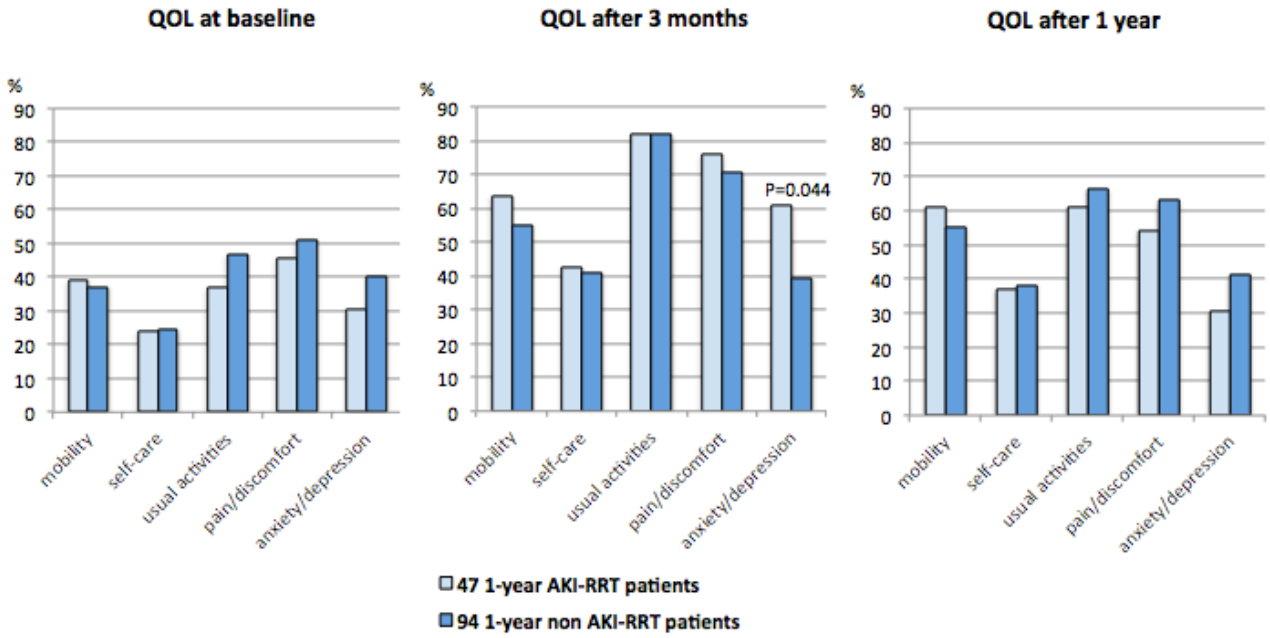
(a) All QOL surveys completed by face-to-face interviews; (b) All QOL surveys completed by regular mail; (c) 46 QOL surveys completed; 32 by regular mail (69.6%) and 14 by phone interview (30.4%); (d) 94 QOL surveys completed; 67 by regular mail (71.3%) and 27 by phone interview (28.7%); (e) 27 QOL surveys completed; 18 by regular mail (66.7%) and 9 by phone interview (33.3%); (f) 26 QOL surveys completed; 19 by regular mail (73.1%) and 7 by phone interview (26.9%); (g) 28 QOL surveys completed; 14 by regular mail (50.0%) and 14 by phone interview (50.0%); (h) 28 QOL surveys completed; 20 by regular mail (71.4%) and 8 by phone interview (28.6%); QOL=quality of life; *N*= number; AKI= acute kidney injury; RRT= renal replacement therapy

Figure 1. Patient cohort



N= number; AKI= acute kidney injury; RRT= renal replacement therapy; ICU= intensive care unit

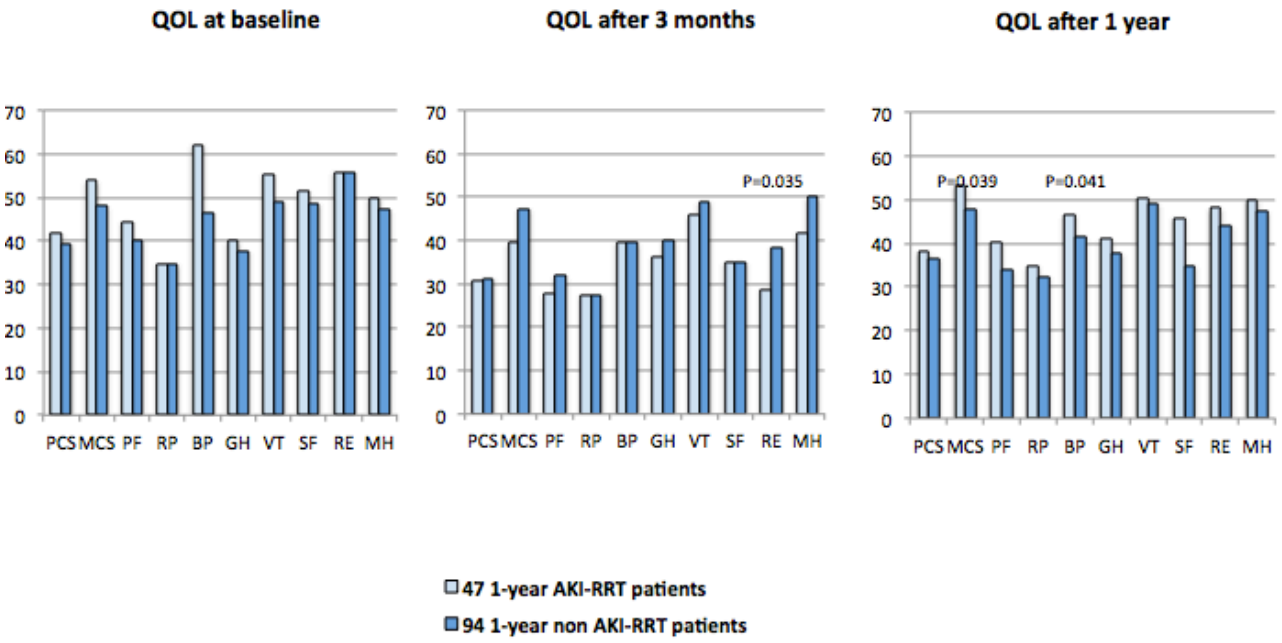
Figure 2. EQ-5D assessments in the 1-year cohort: Percentages of patients with some or severe problems per dimension at the 3 different time points



The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension. Only significant P-values (Chi-Square test) are shown above the respective dimensions.

QOL= quality of life; AKI= acute kidney injury; RRT= renal replacement therapy

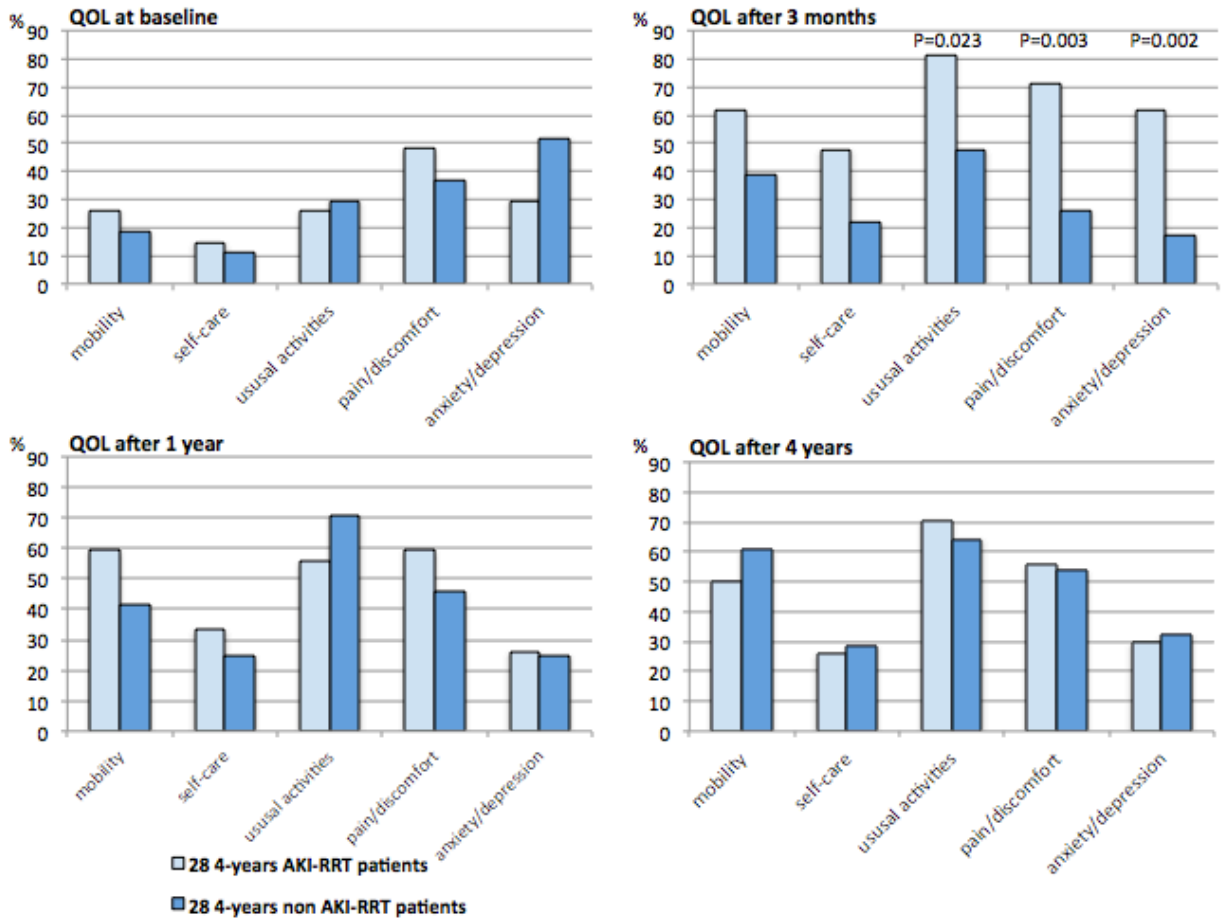
Figure 3. SF-36 assessments in the 1-year cohort: Norm-based median scores per domain at the 3 different time points



The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average. Only significant P-values (Mann-Whitney U analysis) are shown above the respective domains.

QOL= quality of life; AKI= acute kidney injury; RRT= renal replacement therapy PCS= physical component score; MCS= mental component score; PF= physical functioning; RP= role physical; BP = bodily pain; GH= general health; VT= vitality; SF= social functioning; RE= role emotional; MH= mental health

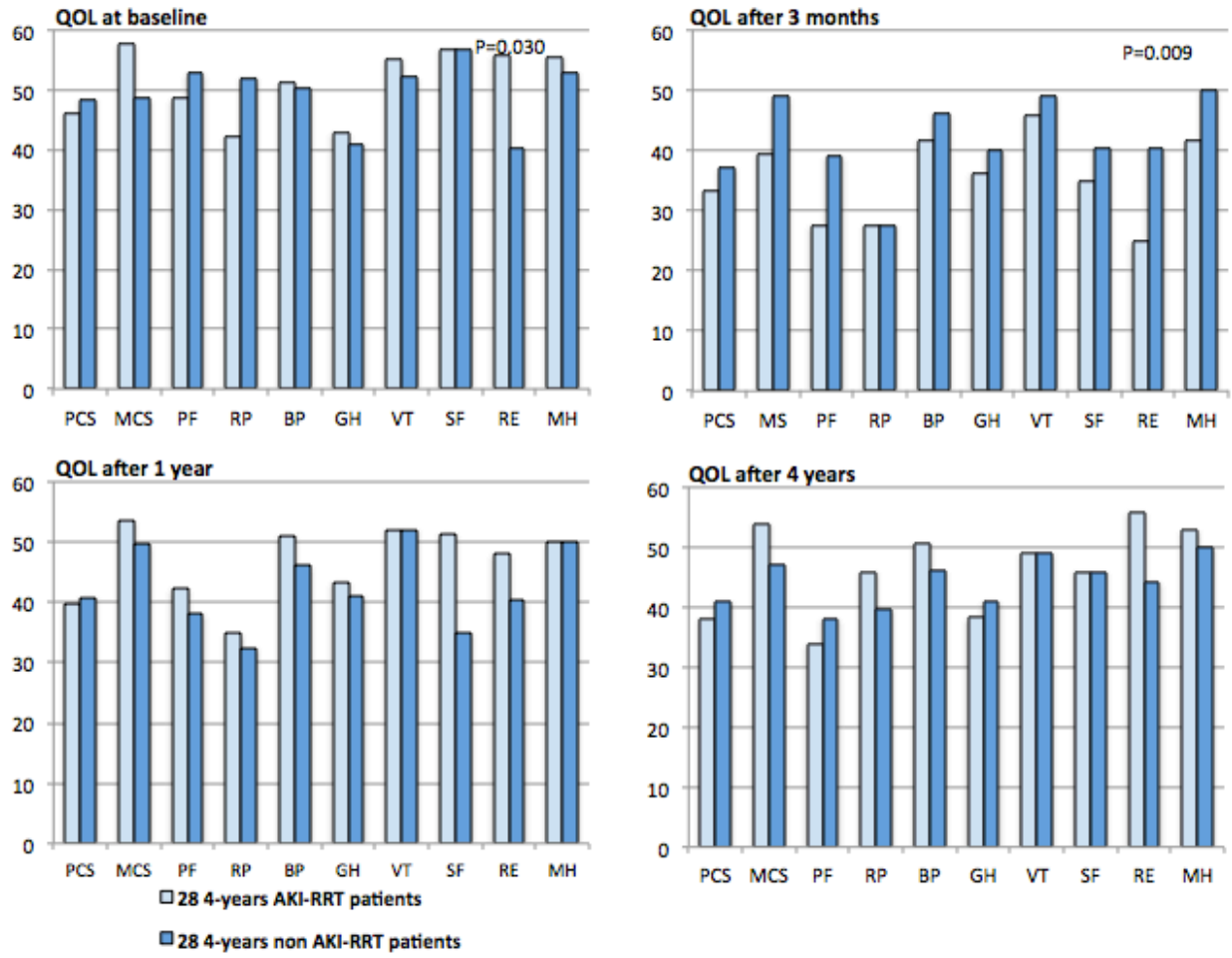
Figure 4. EQ-5D assessments in the 4-years cohort: Percentages of patients with some or severe problems per dimension at the 4 different time points



The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension. Only significant P-values (Chi Square test) are shown above the respective dimensions.

QOL= quality of life; AKI= acute kidney injury; RRT= renal replacement therapy

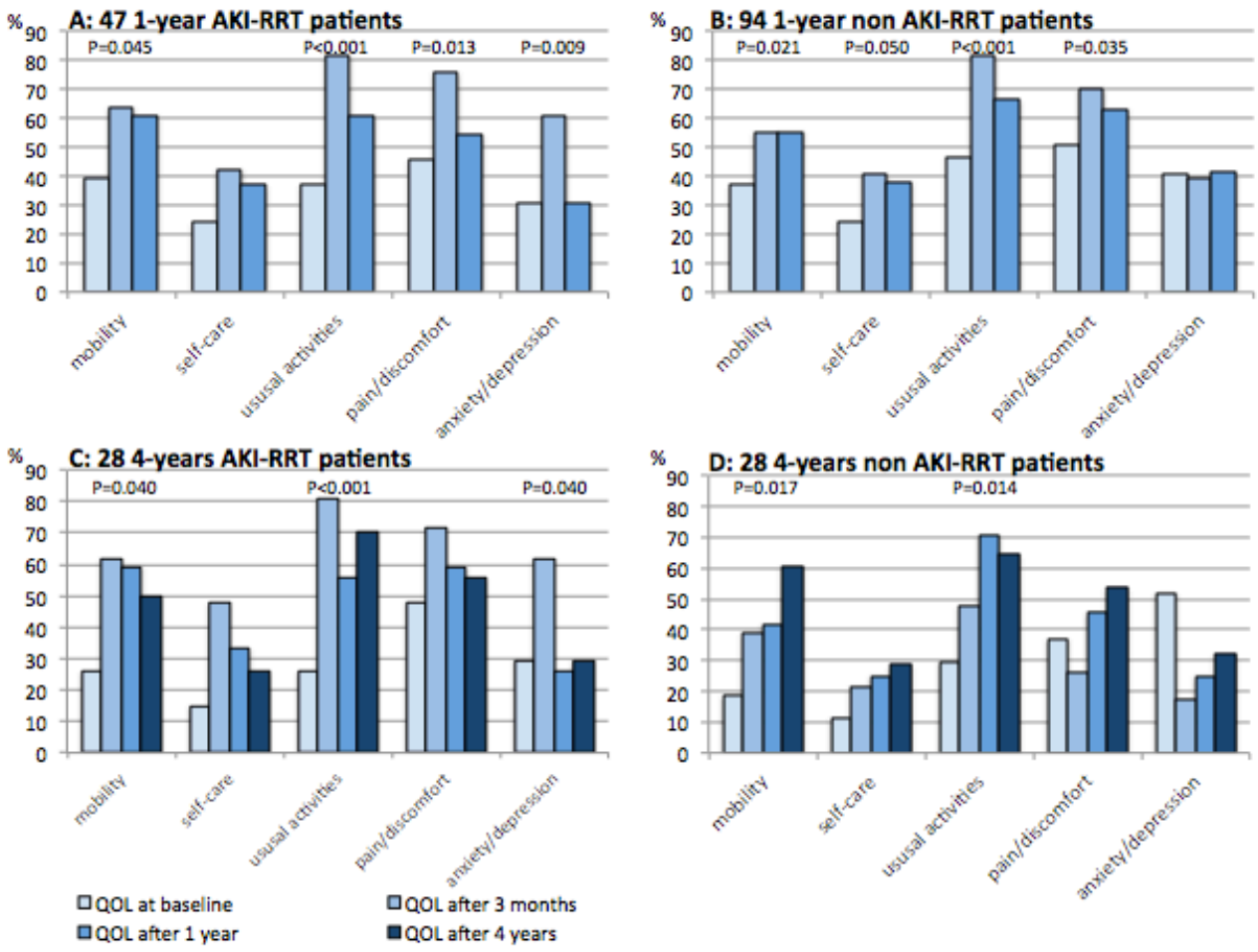
Figure 5. SF-36 assessments in the 4-years cohort: Norm-based median scores per domain at the 4 different time points



The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average. Only significant P-values (Mann-Whitney U analysis) are shown above the respective domains.

QOL= quality of life; AKI= acute kidney injury; RRT= renal replacement therapy PCS= physical component score; MCS= mental component score; PF= physical functioning; RP= role physical; BP = bodily pain; GH= general health; VT= vitality; SF= social functioning; RE= role emotional; MH= mental health

Additional File 1. EQ-5D assessments over time

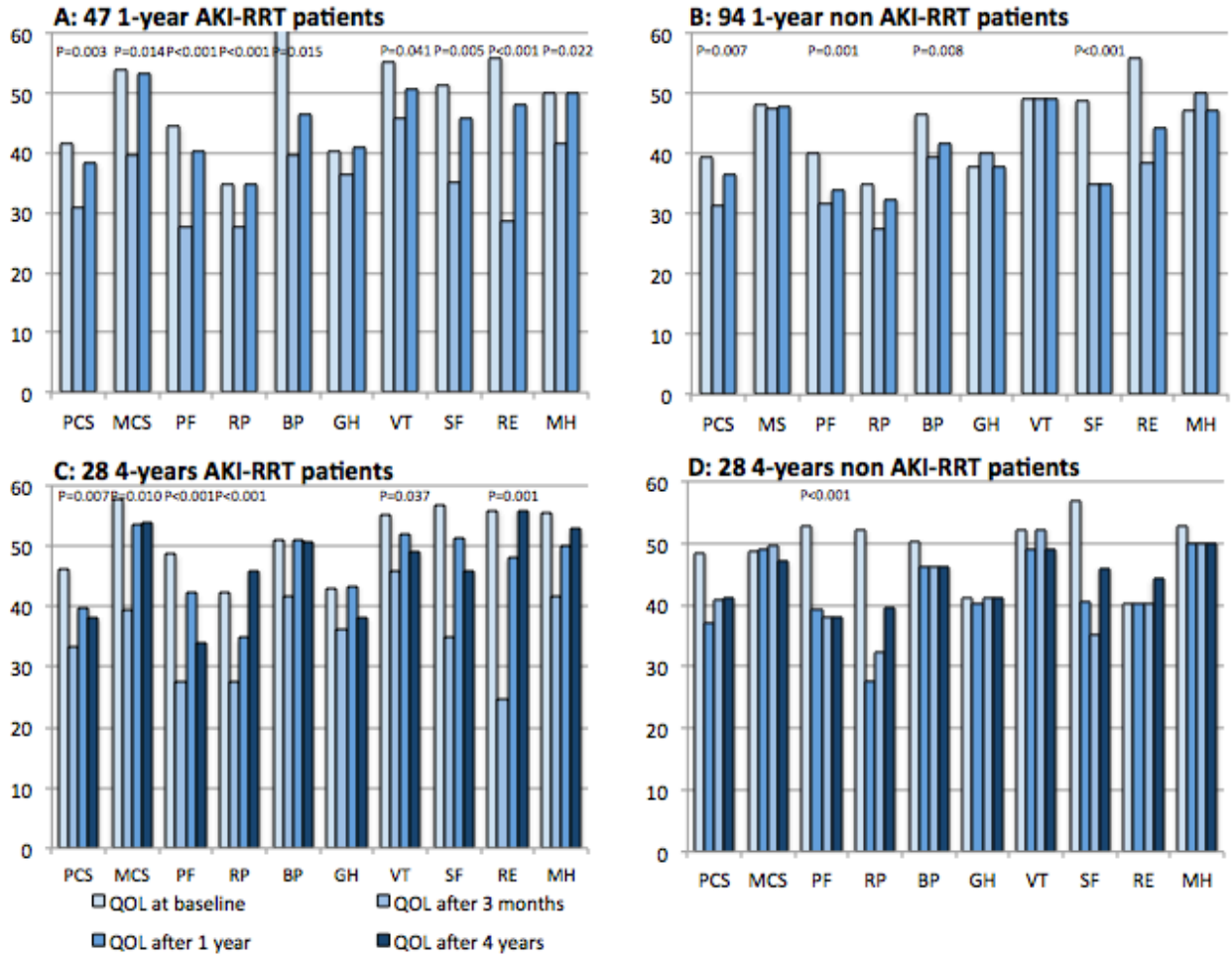


Evolutions in EQ-5D assessments are described through figures in the 1-year cohort (47 AKI-RRT (1A) and 94 non AKI-RRT patients (1B)) and in the 4-years cohort (28 AKI-RRT (1C) patients and 28 non AKI-RRT patients (1D)). Percentages of patients with some or severe problems in the different dimensions of the EQ-5D are given over the different time points: baseline, 3 months and 1 year (1-year cohort) and baseline, 3 months, 1 year and 4 years (4-years cohort).

The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with some or severe problems in a respective dimension. Only significant P-values (Chi Square test) are shown above the respective dimensions.

QOL= quality of life; AKI= acute kidney injury; RRT= renal replacement therapy

Additional File 2. SF-36 assessments over time



Evolutions in SF-36 assessments are described through figures in the 1-year cohort (47 AKI-RRT (2A) and 94 non AKI-RRT patients (2B)) and in the 4-years cohort (28 AKI-RRT (2C) patients and 28 non AKI-RRT patients (2D)). Norm-based median scores in the different domains of the SF-36 are given over the different time points: baseline, 3 months and 1 year (1-year cohort) and baseline, 3 months, 1 year and 4 years (4-years cohort).

The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average. Only significant P-values (Friedman test) are shown above the respective domains.

QOL= quality of life; AKI= acute kidney injury; RRT= renal replacement therapy PCS= physical component score; MCS= mental component score; PF= physical functioning; RP= role physical; BP = bodily pain; GH= general health; VT= vitality; SF= social functioning; RE= role emotional; MH= mental health

Additional File 3. Variability in EQ-5D

47 1-year AKI-RRT patients

	Baseline	3 months	1 year	P
% (95% CI)				
Mobility	39.1 (26.4-53.5)	63.6 (46.6-77.8)	60.9 (46.5-73.6)	0.045
Self-care	23.9 (13.9-37.9)	42.4 (27.2-59.2)	37.0 (24.5-51.4)	0.190
Ususal activities	37.0 (24.5-51.4)	81.8 (65.6-91.4)	60.9 (46.5-73.6)	<0.001
Pain/discomfort	45.7 (32.2-59.8)	75.8 (59.0-87.2)	54.3 (40.2-67.8)	0.013
Anxiety/depression	30.4 (19.1-44.8)	60.6 (43.7-75.3)	30.4 (19.1-44.8)	0.009

94 1-year non AKI-RRT patients

	Baseline	3 months	1 year	P
% (95% CI)				
Mobility	37.2 (28.1-47.3)	54.9 (43.4-66.0)	55.4 (45.3-65.2)	0.021
Self-care	24.5 (16.9-34.0)	40.8 (30.2-52.5)	38.0 (28.8-48.3)	0.050
Ususal activities	46.8 (37.0-56.8)	81.7 (71.2-89.0)	66.3 (56.2-75.1)	<0.001
Pain/discomfort	51.1 (41.1-60.9)	70.4 (59.0-79.8)	63.0 (52.8-72.2)	0.035
Anxiety/depression	40.4 (31.1-50.5)	39.4 (28.9-51.1)	41.3 (31.8-51.5)	0.971

28 4-years AKI-RRT patients

	Baseline	3 months	1 year	4 years	P
% (95% CI)					
Mobility	25.9 (13.2-44.7)	61.9 (40.9-79.2)	59.3 (40.7-75.5)	50.0 (32.6-67.4)	0.040
Self-care	14.8 (5.9-32.5)	47.6 (28.3-67.6)	33.3 (18.6-52.2)	25.9 (13.2-44.7)	0.090
Ususal activities	25.9 (13.2-44.7)	81.0 (60.0-92.3)	55.6 (37.3-72.4)	70.4 (51.5-84.1)	<0.001
Pain/discomfort	48.1 (30.7-66.0)	71.4 (50.0-86.2)	59.3 (40.7-75.5)	55.6 (37.3-72.4)	0.439
Anxiety/depression	29.6 (15.9-48.5)	61.9 (40.9-79.2)	25.9 (13.2-44.7)	29.6 (15.9-48.5)	0.040

28 4-years non AKI-RRT patients

	Baseline	3 months	1 year	4 years	P
% (95% CI)					
Mobility	18.5 (8.2-36.7)	39.1 (22.2-59.2)	41.7 (24.5-61.2)	60.7 (42.4-76.4)	0.017
Self-care	11.1 (3.9-28.1)	21.7 (9.7-41.9)	25.0 (12.0-44.9)	28.6 (15.3-47.1)	0.436
Ususal activities	29.6 (15.9-48.5)	47.8 (29.2-67.0)	70.8 (50.8-85.1)	64.3 (45.8-79.3)	0.014
Pain/discomfort	37.0 (21.5-55.8)	26.1 (12.5-46.5)	45.8 (27.9-64.9)	53.6 (35.8-70.5)	0.227
Anxiety/depression	51.9 (34.0-69.3)	17.4 (7.0-37.1)	25.0 (12.0-44.9)	32.1 (17.9-50.7)	0.054

Percentages and 95% confidence intervals of patients with some or severe problems on the respective dimensions of the EQ-5D over time are given. AKI= acute kidney injury; RRT= renal replacement therapy; CI=confidence interval

(*) The confidence interval was calculated according to DG Altman, D Machin,TN Bryant, M Gardner (2000).
Statistics with confidence: Confidence intervals and statistical guidelines. BMJ Books

Additional File 4. Variability in SF-36

47 1-year AKI-RRT patients

	Baseline	3 months	1 year	P
Median (IQR)				
PCS	41.7 (28.5-54.2)	30.7 (25.1-40.4)	38.3 (27.7-47.4)	0.003
MCS	53.8 (38.9-61.6)	39.5 (29.3-47.2)	53.3 (39.2-58.6)	0.014
Physical functioning	44.4 (29.1-53.4)	27.6 (19.2-39.1)	40.2 (26.5-46.5)	<0.001
Role physical	34.8 (22.6-56.9)	27.5 (17.7-29.9)	34.8 (25.0-45.8)	<0.001
Bodily pain	62.1 (37.2-62.1)	39.7 (29.2-50.9)	46.5 (37.2-62.1)	0.015
General health	40.1 (30.5-48.2)	36.3 (31.1-41.0)	41.0 (30.5-50.6)	0.078
Vitality	55.2 (42.7-61.5)	45.8 (39.6-50.5)	50.5 (41.9-59.1)	0.041
Social functioning	51.4 (35.0-56.8)	35.0 (24.1-40.5)	45.9 (29.6-56.8)	0.005
Role emotional	55.9 (40.3-55.9)	28.7 (20.9-38.4)	48.1 (32.6-55.9)	<0.001
Mental health	50.0 (33.1-61.3)	41.6 (30.3-50.0)	50.0 (40.2-58.4)	0.022

94 1-year non AKI-RRT patients

	Baseline	3 months	1 year	P
Median (IQR)				
PCS	39.4 (29.1-49.6)	31.3 (26.3-43.2)	36.6 (26.0-46.4)	0.007
MCS	48.0 (37.5-55.7)	47.3 (31.6-54.9)	47.8 (34.8-54.0)	0.759
Physical functioning	40.2 (23.4-53.4)	31.8 (21.3-44.4)	33.9 (22.3-48.6)	0.001
Role physical	34.8 (22.6-56.9)	27.5 (17.7-37.3)	32.4 (23.2-42.2)	0.059
Bodily pain	46.5 (33.3-62.1)	39.5 (29.2-50.5)	41.6 (29.2-55.4)	0.008
General health	37.7 (30.5-50.6)	40.1 (31.1-45.8)	37.7 (30.5-45.8)	0.871
Vitality	49.0 (36.5-58.3)	49.0 (39.6-55.2)	49.0 (36.5-58.3)	0.896
Social functioning	48.7 (35.0-56.8)	35.0 (24.1-45.9)	35.0 (24.1-51.4)	<0.001
Role emotional	55.9 (31.6-55.9)	38.4 (20.9-55.9)	44.2 (24.8-55.9)	0.410
Mental health	47.2 (33.1-58.4)	50.0 (34.5-55.7)	47.2 (34.5-55.6)	0.562

28 4-years AKI-RRT patients

	Baseline	3 months	1 year	4 years	P
Median (IQR)					
PCS	46.1 (38.7-53.7)	33.2 (26.0-40.4)	39.8 (31.6-46.7)	38.1 (31.6-47.1)	0.007
MCS	57.6 (42.8-62.3)	39.5 (29.3-47.1)	53.5 (40.9-61.6)	53.9 (42.4-60.3)	0.010
Physical functioning	48.6 (36.5-57.0)	27.6 (18.1-43.4)	42.3 (29.7-48.6)	33.9 (29.7-40.2)	<0.001
Role physical	42.2 (27.5-56.9)	27.5 (17.7-31.8)	34.8 (27.5-47.1)	45.9 (27.5-56.9)	<0.001
Bodily pain	51.1 (38.2-62.1)	41.8 (30.1-50.9)	51.1 (41.8-62.1)	50.7 (34.4-62.1)	0.178
General health	42.9 (30.3-47.9)	36.3 (32.9-42.9)	43.4 (36.3-50.6)	38.2 (32.9-48.0)	0.093
Vitality	55.2 (43.5-64.6)	45.8 (42.7-50.5)	52.1 (45.8-61.5)	49.0 (45.8-58.3)	0.037
Social functioning	56.8 (40.5-56.8)	35.0 (26.9-40.5)	51.4 (35.0-56.8)	45.9 (35.0-56.8)	0.101
Role emotional	55.9 (50.0-55.9)	24.8 (9.2-38.4)	48.1 (32.6-55.9)	55.9 (20.9-55.9)	0.001
Mental health	55.6 (33.1-64.1)	41.6 (33.1-51.4)	50.0 (41.6-61.3)	52.8 (41.6-58.5)	0.188

28 4-years non AKI-RRT patients

	Baseline	3 months	1 year	4 years	P
Median (IQR)					
PCS	48.4 (36.3-57.0)	37.1 (26.1-45.5)	40.8 (27.9-46.5)	41.0 (32.1-52.6)	0.358
MCS	48.6 (34.3-57.6)	48.9 (37.2-54.8)	49.7 (40.6-54.7)	47.0 (37.4-55.5)	0.913
Physical functioning	52.8 (40.2-54.9)	39.1 (19.2-44.4)	38.1 (22.3-48.6)	38.1 (25.5-48.6)	<0.001
Role physical	52.0 (17.7-56.9)	27.5 (25.0-39.7)	32.4 (25.0-39.7)	39.7 (25.0-47.1)	0.158
Bodily pain	50.3 (41.2-62.1)	46.1 (37.2-55.4)	46.1 (36.1-62.1)	46.1 (37.2-62.1)	0.489
General health	41.0 (35.3-55.3)	40.1 (29.8-49.4)	41.0 (35.3-48.8)	41.0 (34.7-53.5)	0.577
Vitality	52.1 (42.7-58.3)	49.0 (39.6-58.3)	52.1 (39.6-58.3)	49.0 (42.7-55.2)	0.403
Social functioning	56.8 (35.0-56.8)	40.5 (24.1-51.4)	35.0 (22.8-52.8)	45.9 (24.1-56.8)	0.058
Role emotional	40.3 (20.9-55.9)	40.3 (28.7-55.9)	40.3 (24.8-55.9)	44.2 (24.8-55.9)	0.071
Mental health	52.8 (35.9-58.4)	50.0 (37.3-58.5)	50.0 (37.3-58.5)	50.0 (41.6-52.8)	0.962

Median norm-based scores with interquartile ranges on the different domains of the SF-36 over time are given.
AKI= acute kidney injury; RRT= renal replacement therapy; IQR= interquartile range (25%-75%); PCS= physical component score; MCS= mental component score

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IV. Critically Ill Octogenarians and Nonagenarians: Evaluation of Long-Term Outcomes, Post-Hospital Trajectories and Quality of Life One Year and Seven Years after ICU Discharge

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ABSTRACT

Background: To investigate long-term outcomes, post-hospital trajectories, and quality of life (QOL) in patients ≥ 80 years admitted to the intensive care unit (ICU) of a tertiary care hospital.

Methods: A 1-year prospective observational cohort analysis was performed. All consecutive patients ≥ 80 years admitted to the ICU were screened for inclusion. Demographics, comorbidity, organ failures, and outcomes were analyzed. QOL before admission, 3 months, 1 year, and 7 years after ICU discharge was assessed using EuroQoL-5D (EQ-5D) and Medical Outcomes Study 36-item Short Form Health Survey (SF-36) questionnaires. Statistical significance was attained at $P<0.05$.

Results: 131 patients with a median age of 83 years (IQR 81-85), a Charlson comorbidity index of 2 (IQR 0-4), a SOFA score of 4 (3-8) upon ICU admission and an APACHE II score of 20 (IQR 15-24) were included. ICU, hospital, 3 months, 1-year, and 7-years mortality rates were 17%, 29%, 39%, 50%, and 84% respectively. QOL decreased significantly over time. Most elderly considered QOL as acceptable and perceived only a worsening in physical functioning and self-care at long-term. Of the 1-year and 7-years survivors, 21% and 39% ($P=0.122$) lived in nursing homes, and 81% and 72% ($P=0.423$) preferred to be readmitted to an ICU department if necessarily.

Conclusions: Most critically ill long-term elderly survivors lived at home, perceived their QOL as acceptable, and wanted to be readmitted to the ICU if necessarily. In older patients, age alone is a poor indicator of the possible value to be gained from an ICU admission.

INTRODUCTION

Survival to older age has increased, which leads to more hospitalizations and more intensive care unit (ICU) admissions for older patients.[1-3] Concerns may rise regarding utility or futility of high-level expensive ICU treatments for these patients. Prognosis of critically ill patients aged 80 or more may be poor, especially in those admitted from a chronic care facility, or with severe comorbidity, or a greater illness severity.[1-6]

To identify who would benefit from ICU treatment, long-term quality of life (QOL) should be taken into account as well.[7] Major reductions in long-term QOL in critically ill patients were seen in severe acute respiratory distress syndrome, prolonged mechanical ventilation, and severe sepsis, representing complications that affect elderly patients as much as younger patients.[8]

Recent data regarding long-term QOL in critically ill elderly patients are increasing but still limited.[4, 5-7, 9-17] They show that elderly have a comparable or slightly decreased QOL compared to the general population but perceive QOL as good.[4, 5, 6, 11, 12, 15, 16] However, these studies were either based on a retrospective cohort,[4, 12, 15] evaluated QOL after a short term,[5, 11, 15] lacked baseline QOL assessment,[4, 5, 9, 10, 12-14, 16] assessed QOL after variable follow-up intervals,[4, 12, 13] included only elderly with an ICU stay of 24 hours or more,[9-11, 17] or defined elderly as patients aged 65 years or more [5, 6, 16, 17] or even younger.[10] Most studies identified independent predicting factors for outcome [5, 13] but lacked any information about the post-hospital courses of survivors.

The aim of the present study was to evaluate long-term outcomes of elderly patients aged 80 years or more admitted to the ICU, to assess post-hospital trajectories, and to compare baseline QOL of these patients with QOL 3 months, 1 year and 7 years after ICU discharge.

MATERIALS AND METHODS

Design, setting, and patients

The study was a prospective observational cohort analysis performed at the 14-bed medical (MICU), 22-bed surgical ICU (SICU), and 6-bed burn unit of the Ghent University Hospital in Belgium. From March 3rd 2008 - March 3rd 2009, all consecutive patients ≥ 80 years were screened for inclusion. Study patients consisted of a predefined subgroup of a larger observational cohort study concerning QOL in an ICU population.[18] In case of readmission or multiple ICU admissions, only the first was considered. Elderly patients admitted at the cardiac surgical unit after cardiac surgery were not included.

The Ghent University Hospital ICUs are closed ICUs where patients are treated by full-time critical care physicians. Decisions concerning admission, withdrawing or withholding advanced life support are made by the critical care physician together with the referring physician, consulting the wishes and expectations of the patient and representatives.

The study was approved by the Ethics Committee of the Ghent University Hospital (project 2007/423; amendment 0095/2015) and conducted in accordance with the Helsinki declaration. A signed informed consent was obtained from every included patient or his legal representative.

Data Collection and Definitions

Data collected within the first 24 hours of ICU admission included demographics, contact information of the patient, proxy, and general practitioner, hospital days prior to ICU admission, living circumstances before ICU admission, functionality according to activity of daily living (ADL),[19] hospitalization in the last 6 months, comorbidity as measured by the Charlson comorbidity index,[20] main reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE II) score,[21] Sequential Organ Failure Assessment (SOFA) score,[22] need for invasive mechanical ventilation, use of any vasopressors, or need for renal replacement therapy (RRT). During ICU stay, SOFA scores need for invasive mechanical ventilation, vasopressors, RRT, tracheotomy, and do-not-resuscitate (DNR) codes were collected on a daily base. ICU length of stay (LOS), hospital LOS, vital status at ICU and hospital discharge, and at 3 months, 1 year and 7 years following ICU discharge were collected for each patient.

Quality of life

QOL was assessed by means of the Medical Outcomes Study 36-item Short Form Health Survey version 2 (SF-36v2®)[23] and the EuroQoL-5D (EQ-5D).[24] Both questionnaires were validated and found suitable for measuring QOL in the critically ill population.[25, 26] An extensive explanation of these surveys can be found in previous publications of our group.[27, 28]

Quality of life: evolution over time

QOL was assessed at 4 different time points: baseline QOL and strictly at 3 months and 1 year after ICU discharge. QOL was also assessed between 18-24 February 2015, a median of 6.6 years (interquartile range (IQR) 6.0 years – 6.8 years) - rounded to 7 years - after ICU discharge. Following ICU admission and study inclusion, a face-to-face interview to assess baseline QOL (defined as QOL 2 weeks before ICU admission) was done as soon as possible. This interview was preferably taken from the patient, or if deemed impossible, from the proxy. Three months, 1 year, and 7 years after ICU discharge, patients were sent the EQ-5D and SF-36 surveys by regular mail; at 1 and 7 years, questions concerning living situation, memories, sleep quality, and willingness to be readmitted to an ICU department, were added. After 7 years, patients were also questioned about their social network, medical follow-up, financial situation, and happiness. If the questionnaires were not returned within one month, patients or relatives were contacted by phone to assess QOL after 1 year and after 7 years. Eventually, the general practitioner was contacted concerning vital status of the patient.

Quality of life: changes per patient per time interval

Changes in QOL per patient between the 3 consecutive time intervals (before ICU admission-3 months; 3 months-1 year; 1 year-7 years) were assessed for each dimension of the EQ-5D and each domain of the SF-36. These changes could only be assessed if the patient answered the QOL survey on both the start and end of the respective time interval. Changes in QOL were considered clinically important if patients reported another level for the different EQ-5D dimensions or for the health transition (HT) of the SF-36, or if there was a minimum difference of 7 points in the EQ-visual analogue scale (VAS) or 5 points in the norm-based physical (PCS) and mental (MCS) component scores of the SF-36. Otherwise, QOL was considered the same between the different time intervals.[29]

Post-hospital trajectories

Post-hospital trajectories were assessed for each surviving patient by the electronic patient record, which is kept in the hospital computer system. Within this system, the patient's records and consultations in other hospitals can also be assessed so a complete trajectory of the patient after the initial hospital admission can be made.

Statistical analysis

Values are expressed as median (IQR) for continuous variables and as number (%) for categorical variables. QOL before ICU admission and characteristics between hospital survivors and non-survivors were compared by the Mann-Whitney U test for continuous variables and by Chi-square test for categorical variables. Chi-square (EQ-5D) or Friedman test (SF-36) assessed differences between QOL at baseline (only hospital survivors), at 3 months, at 1 year and 7 years after ICU discharge. All statistical analyses were done using IBM SPSS Statistics software version 22. A two-sided $P<0.05$ was considered significant.

RESULTS

Characteristics and Outcomes of the Study Population

Patient characteristics, organ failures and outcomes are shown in Tables I and II. 131 patients (60% males) with median age of 83 years (IQR 81-85) and Charlson comorbidity index of 2 (IQR 0-4) were included. ICU admission reasons were medical (55%), emergency surgery (23%), elective surgery (12%), trauma (9%), and burns (1%). APACHE II and SOFA scores upon ICU admission were 20 (IQR 15-24) and 4 (3-8) respectively. Hospital non-survivors had higher severity of illness at admission and required more organ support than hospital survivors although there were no differences in comorbidity, baseline functionality, or ICU admission reason. Therapeutic limitations were set in 34 patients (26%) after 2 days (IQR 1-5) at the ICU. ICU, hospital, 3 months, 1-year and 7-years mortality rates were 17%, 29%, 39%, 50%, and 84% respectively.

Quality of life: evolution over time

The number of QOL surveys at each time point, response rate, and patients dying during the study course are shown in Figure 1. Most patients answered the questionnaires themselves, respectively 60% before ICU, 60% at 3 months and 57% 1 year (P=0.94) after ICU discharge. After 7 years, QOL surveys were completed by next of kin (44%), by the patient themself (28%), or by other family (28%). Median age at QOL evaluation after 7 years was 89 years (IQR 88-90 years).

There were no differences in QOL before ICU admission between hospital survivors and non-survivors (data not shown).

EQ-5D assessments over time showed that the number of patients with disabilities increased almost at each of the consecutive time points, which was significant for mobility (P=0.018), self-care (P=0.011), usual activities (P=0.007), and anxiety/depression (P=0.035) (Figure 2.I).

SF-36 measurements demonstrated that QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year, especially mentally, but worsened again after 7 years (Figure 2.II). This was significant for physical functioning (P=0.001), general health (P=0.009), and social functioning (P=0.001). Long-term QOL remained under baseline level and under QOL of the general population.

VAS in elderly did not significantly change over time (respectively 70, 60, 65, and 63 at baseline, 3 months, 1 year, and 7 years after ICU discharge (P=0.464)).

Quality of life: Perception of changes per patient per time interval

For all EQ-5D dimensions, most patients perceived no change in QOL per time interval (Figure 3). After 7 years, significant more elderly experienced a worsening in mobility (P=0.025), self-care (P=0.044), and VAS (P=0.030).

Perception of changes in PCS, MCS, and HT are shown in Figure 4. After 3 months, the majority of patients perceived deterioration in PCS, MCS, and HT, which changed into a perception of no change or even better after 1 year and again a perception of worsening in most patients after 7 years.

Post-hospital trajectories and additional questions after 1 and 7 years

Post-hospital trajectories (Table III) showed no big differences between survivors and non-survivors per respective time interval. In the first 3 months after hospital discharge, more non-survivors were discharged to other hospitals (30.8% vs 5.0%; P=0.002) and more had therapeutic limitations (53.8% vs 11.3%; P<0.001), which increased further in the year after hospital discharge (64.3% vs 9.2%; P<0.001). Few patients had a living will, which was drawn up belatedly. The number of new hospital admissions was similar between survivors and non-survivors per time interval.

Among the 1-year and 7-years survivors respectively, 37% and 11% (P=0.036) lived independently at home, 26% and 28% (P=0.867) had additional home help, 13% and 22% (P=0.330) lived with relatives, and 21% and 39% (P=0.122) lived in a special care facility. The majority of patients had good (48% and 28%; P=0.134) or no memories (38% and 67%; P=0.031) of their ICU stay. Increased sleeping disturbances were

rare (11% and 17%; P=0.528). 81% and 72% (P=0.423) of the long-term survivors expressed a preference to be readmitted to an ICU department in case of deterioration.

All but 1 of the 7-years survivors reported a very good familial and social network, a good paramedical and medical follow-up, experienced no financial problems, and were happy to be still alive despite their advanced age.

DISCUSSION

The ICU (17%), hospital (29%) and long-term (50% at 1 year, 84% at 7 years) mortality rates found in our study can be compared to other studies[1, 4, 5, 6, 9, 15, 16, 30, 31] although mortality rates may be difficult to compare because of differences in patient selection, in the applied definition of elderly patients, differences in pre-ICU triage decisions, and in timeline.[3, 9, 32] A high number of therapeutic limitations (26%) were set shortly after ICU admission.

Objectively seen, the long-term QOL in elderly in our study was low compared to a general population, particularly in self-care, usual activities and the physical domains, with an increasing number of patients experiencing more problems over time. It seems however within normal evolutionary expectations that the more physical components of QOL will deteriorate with advanced age, even whether or not elderly have been admitted to an ICU department before.[3] More important is to assess their perceptions and changes in QOL.

Elderly perceived some worsening in QOL at long-term but still evaluated their QOL as acceptable. This is in accordance with QOL and ADL measurements found in other studies.[4-6, 11-17] It suggests that QOL might have another meaning for older patients, with social and mental values being far more important than limited physical functioning and that age itself influences QOL mainly due to increasing number of chronic conditions.[5, 13, 14, 31] Therefore, QOL can be helpful in decision-making concerning ICU admission of elderly patients but its role may be limited at the same time. QOL interpretation in elderly is therefore difficult and intensivists should not use their own frame of values and references in making judgments.

The elderly in our study also expressed preferences for a longer life, even with reduced QOL, probably due to changes in individual's expectations, values, and steady acceptance of disability, especially when they had a good social network.[3, 7, 11, 15, 16] This may explain why 1 and 7 years after ICU discharge, 81% and 72% of the elderly patients in our study wanted ICU admission again if needed, which is in accordance with percentages found in literature.[6, 14, 15] These numbers may seem surprising as physicians often incorrectly assume that elderly patients do not want life-extending care.[12]

Still, it remains essential to identify these elderly patients who are most likely to benefit from critical care, not only to prevent suffering from unnecessary treatments but also to optimise the use of resources.[33, 34] Reaching this balance is difficult and would be easier with reliable prognostication, which

unfortunately has been proven to remain challenging at the moment. Neither triage scores, nor high quality prognostic models can currently be considered as sufficiently valid to be applicable in clinical practice in the elderly.[35, 36] Decisions based upon chronological age and comorbidities may also not be appropriate, as these may not capture sufficiently all characteristics of elderly patients.[37] Recent literature highlights the importance of knowledge of frailty and baseline functionality in prognostication and appropriate decision-making for elderly critically ill patients as patients who are less frail are more likely to survive and regain good physical functioning.[3, 6, 9, 10, 31, 33, 38] Biological age and frailty also proved to be more important in determining outcomes in elderly compared to severity of illness scores.[38]

Intensive care should therefore only be indicated when the critical condition has the potential to be reversible, when benefits outweigh burdens and when the outcome is acceptable for the patient.[39] Helpful guidelines for decision-making concerning ICU admission or refusal are published in the SIAARTI recommendations.[40]

Importantly, in deciding to admit elderly to the ICU, intensivists should consider the whole health process rather than focusing on the ICU period alone.[37] Therefore, we also evaluated post-hospital trajectories in elderly hospital survivors. Overall, there were no big differences after hospital discharge between survivors and non-survivors per respective time interval. The majority of the 1- and 7-years survivors lived at home - with or without additional help - which is an important patient-centered outcome.[3] A good familial, paramedical and medical network without financial problems added to perceive QOL as acceptable. Over time, more patients had therapeutic limitations but few had a living will, which was drawn up belatedly. Factors associated with admission in nursing homes were mainly cognitive impairments and high dependency in daily activities.

To the best of our knowledge, this is the first study that evaluated long-term outcomes and QOL with validated questionnaires in patients aged 80 years or more at baseline, and 3 months, 1 year and almost 7 years after ICU discharge. Response rates were high and only one patient was lost to-follow-up. Consequently, the impact of an ICU admission upon long-term physical, mental and cognitive functioning in the elderly could be assessed, which is rarely possible.[7, 17] We hope our study provides better insights in the long-term QOL and trajectories of elderly ICU survivors and can help in better decision-making and advance care planning in this growing patient cohort.

However, some limitations have to be mentioned. First, this was a single center study performed in a large university hospital. Study results might not be applicable to other centers. Second, the inclusion period of 12 months was short and consequently, although all eligible patients were included, the total number of study patients was low and may lack statistical power to detect differences in QOL. Still, we believe that our study gives a good overview of the long-term outcomes in critically ill patients aged 80 or more. Third, most patients did not respond to the QOL surveys themselves for long-term QOL assessments

after 7 years. Although QOL may be preferentially evaluated from the patient, we believe that for some elderly patients proxies may provide the most reliable information. Fourth, we do not have data on medical decision-making leading to ICU referral. Consequently, the included patients, of whom only a minority chair-bound or bedridden at baseline, might already represent a selection of fitter elderly patients with a possible inherent better prognosis and QOL. This limitation is hardly avoidable and can also be found in other studies on this topic.[2, 4, 5, 11, 12] Fifth, evaluations of long-term QOL always imply survival bias as QOL can only be assessed in survivors.[3] We acknowledge that long-term QOL may also be modified by events happening to the patient after hospital discharge. Sixth, we did not assess degree of frailty during follow-up, as we did not have data of baseline frailty. Nevertheless, we can rely upon very detailed data from our QOL surveys and additional questions.

CONCLUSION

Most critically ill long-term elderly survivors lived at home, perceived only decline in mobility and self-care, considered their QOL as acceptable, and wanted to be readmitted to the ICU if necessarily. In older patients, knowledge of baseline condition is more important than age in estimating the possible value of an ICU admission.

KEY MESSAGES

The majority of critically ill long-term elderly survivors perceives only changes in mobility and self-care over time and evaluates QOL as acceptable.

The majority of critically ill long-term elderly survivors prefer to be readmitted to an ICU department in case of deterioration.

Intensive care for very elderly people should only be indicated when the critical condition has the potential to be reversible, when benefits outweigh burdens and when the outcome is acceptable for the patient.

Age alone is a poor indicator of the value to be gained from an ICU admission in critically ill elderly patients.

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Table 1. Patient characteristics and comorbidities

	All patients (N=131)	**Hospital survivors (N=93)**	**Hospital non-survivors (N=38)**	**P**
age, yrs (median, IQR)	83 (81-85)	83 (81-85)	83 (81-86)	0.70
age between 80-84 years, N (%)	91 (69.5)	66 (71.0)	25 (65.8)	0.56
age between 85-89 years, N (%)	32 (24.4)	23 (24.7)	9 (23.7)	0.90
age between 90-94 years, N (%)	8 (6.1)	4 (4.3)	4 (10.5)	0.18
male gender, N (%)	78 (59.5)	57 (61.3)	21 (55.3)	0.52
BMI, kg/m^2 (median, IQR)	25.3 (22.6-27.4)	25.2 (23.1-27.3)	25.4 (21.2-27.7)	0.97
hospital days prior to ICU (median, IQR)	1 (0-3)	1 (0-3)	0 (0-4)	0.80
hospitalization in last 6 months, N (%)	45 (34.3)	28 (30.1)	17 (44.7)	0.11
living status before admission, N (%)				
at home	122 (93.1)	86 (92.5)	36 (94.7)	0.64
chronic care facility	8 (6.1)	6 (6.5)	2 (5.3)	0.80
other	1 (0.8)	1 (1.1)	0 (0)	0.52
ADL, N (%)				
no limitations	52 (39.7)	39 (41.9)	13 (34.2)	0.41
moderate limitations	67 (51.1)	45 (48.4)	22 (57.9)	0.32
chair-bound	10 (7.6)	7 (7.5)	3 (7.9)	0.94
bedridden	2 (1.0)	2 (2.2)	0 (0)	0.36
Charlson comorbidity index (median, IQR)	2 (0-4)	1 (0-3)	2 (1-3)	0.93
specific comorbidity, N (%)				
cardiovascular	79 (60.3)	56 (60.2)	23 (60.5)	0.97
neurological	34 (26.0)	24 (25.8)	10 (26.3)	0.95
solid tumor	34 (26.0)	25 (26.9)	9 (23.7)	0.70
respiratory	31 (23.7)	21 (22.6)	10 (26.3)	0.65
gastrointestinal	21 (16.0)	14 (15.1)	7 (18.4)	0.63
renal	19 (14.5)	16 (17.2)	3 (7.9)	0.17
Immunocompromised	7 (5.3)	5 (5.4)	2 (5.3)	0.97
metastatic cancer	7 (5.3)	4 (4.3)	3 (7.9)	0.41
hematological cancer	6 (4.6)	5 (5.4)	1 (2.6)	0.50

N= number; yrs= years; IQR= interquartile range (25%-75%); BMI= body mass index; ICU= intensive care unit; ADL= activity of daily living

Table 2. ICU admission reasons, organ failures and outcomes

	All patients (N=131)	**Hospital survivors (N=93)**	**Hospital non-survivors (N=38)**	**P**
Main reason for ICU admission, *N* (%)				
Medical	72 (55.0)	52 (55.9)	20 (52.6)	0.73
Emergency surgery	30 (22.9)	18 (19.4)	12 (31.6)	0.13
Scheduled surgery	15 (11.5)	12 (12.9)	3 (7.9)	0.41
Trauma	12 (9.2)	10 (10.8)	2 (5.2)	0.32
Burns	2 (1.5)	1 (1.1)	1 (2.6)	0.51
Severity of illness at ICU admission (first 24 hours)				
APACHE II score (median, IQR)	20 (15-24)	18 (14-23)	24 (19-29)	<0.001
SOFA score (median, IQR)	4 (3-8)	4 (2-6)	8 (4-10)	<0.001
mechanical ventilation, N (%)	46 (35.1)	24 (25.8)	22 (57.9)	<0.001
vasopressors, N (%)	35 (26.7)	18 (19.4)	17 (44.7)	0.002
RRT, N (%)	5 (3.8)	3 (3.2)	2 (5.3)	0.58
Organ failure during ICU stay				
mean SOFA score (median, IQR)	4 (3-6)	5 (3-7)	7 (4-11)	<0.001
mechanical ventilation, N (%)	56 (42.7)	29 (31.2)	27 (71.1)	<0.001
vasopressors, N (%)	43 (32.8)	23 (24.7)	20 (52.6)	0.002
RRT, N (%)	7 (5.3)	3 (3.2)	4 (10.5)	0.09
Outcomes				
ICU readmissions, N (%)	10 (7.6)	4 (4.3)	6 (15.8)	0.02
ICU LOS, days (median, IQR)	3 (2-5)	3 (2-5)	3 (2-5)	0.33
hospital LOS, days (median, IQR)	17 (9-38)	22 (11-47)	10 (3-21)	<0.001
DNR decisions, N (%)	34 (25.9)	11 (11.8)	23 (60.5)	<0.001
ICU mortality, N (%)	22 (16.8)	0 (0)	22 (57.9)	<0.001
hospital mortality, N (%)	38 (29.0)	0 (0)	38 (100)	<0.001
3-months mortality, N (%)	51 (38.9)	13 (14.0)	NA	-
1-year mortality, N (%)	65 (49.6)	27 (29.7)	NA	-
7-years mortality, N (%)	110 (84.0)	82 (77.4)	NA	-

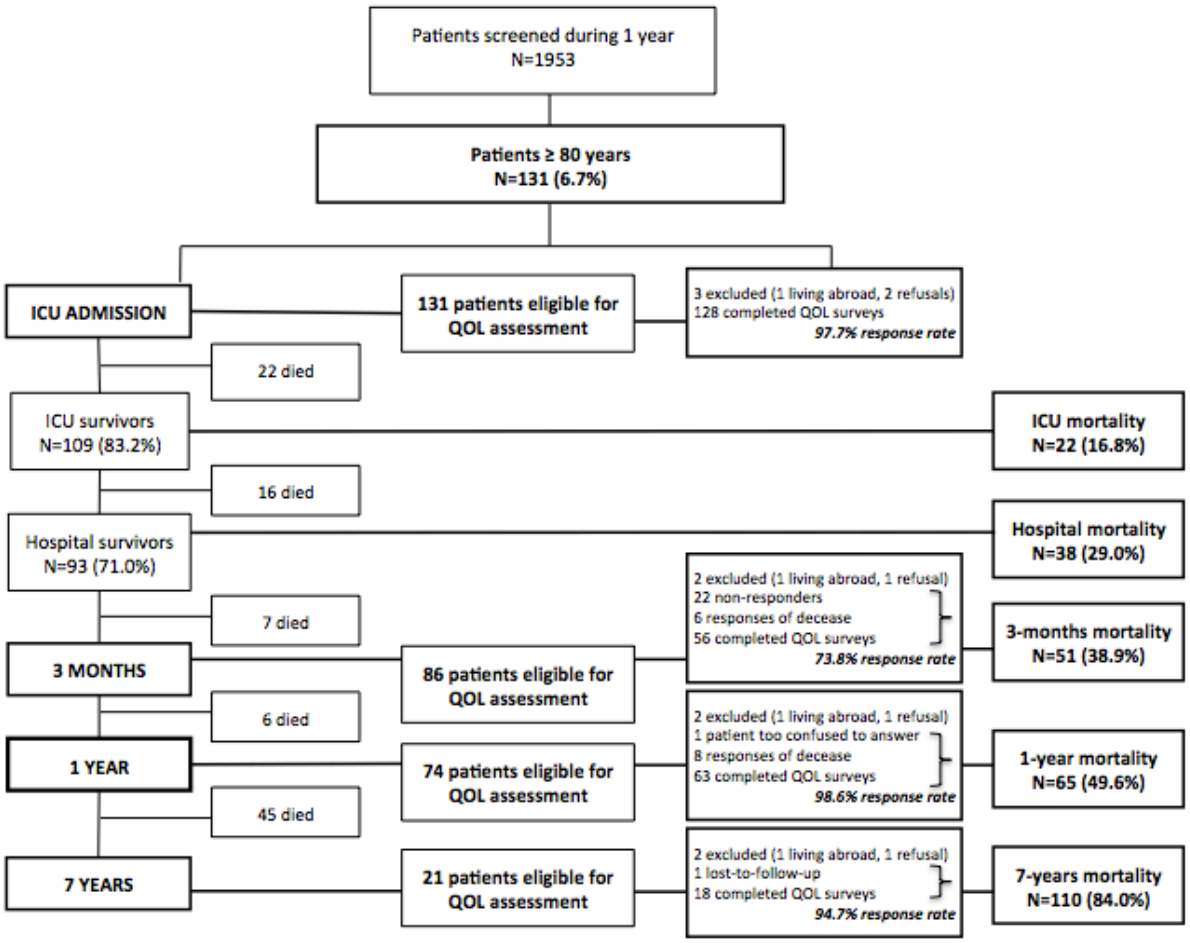
N= number; ICU= intensive care unit; IQR= interquartile range (25%-75%); APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA= Sequential Organ Failure Assessment; RRT= renal replacement therapy; LOS= length of stay; DNR= do-not-resuscitate; NA= not applicable

Table 3. Trajectories per time interval

	hospital discharge to 3 months		P	3 months to 1 year after hospital discharge		P*	1 year to 7 years after hospital discharge		P**
	survivors N=80	3 months non-survivors N=13		survivors N=65	1-year non-survivors N=14 1 living abroad		survivors N=20	7-years non-survivors N=45	
discharge location from the initial hospital admission, N (%)									
home	57 (71.3)	8 (61.5)	0.479	44 (67.7)	12 (85.7)	0.178	13 (65.0)	31 (68.9)	0.757
other hospital	4 (5.0)	4 (30.8)	0.002	3 (4.6)	1 (7.1)	0.696	7 (35.0)	3 (6.7)	0.003
special care facility	19 (23.8)	1 (7.7)	0.191	18 (27.7)	1 (7.1)	0.103	0 (0)	11 (24.4)	0.015
patients with therapeutic limitations, N (%)									
	9 (11.3)	7 (53.8)	<0.001	6 (9.2)	9 (64.3)	<0.001	5 (25.0)	21 (46.7)	0.100
new hospital admission, N (%)									
none	52 (65.0)	5 (38.5)	0.068	39 (60.0)	7 (50.0)	0.491	4 (20.0)	17 (37.8)	0.157
1	20 (25.0)	6 (46.2)	0.115	17 (26.2)	4 (28.6)	0.854	6 (30.0)	9 (20.0)	0.377
2	4 (5.0)	1 (7.8)	0.690	5 (7.7)	1 (7.1)	0.944	1 (5.0)	8 (17.8)	0.169
> 2	4 (5.0)	1 (7.8)	0.690	4 (6.2)	2 (14.3)	0.298	9 (45.0)	11 (24.4)	0.097
patients with last will, N (%)									
	0 (0)	0 (0)	NA	0 (0)	4 (28.6)	<0.001	0 (0)	5 (11.1)	0.121
ICU admission to death, days (median, IQR)									
	NA	43 (29-78)	-	NA	248 (150-327)	-	NA	1196 (689-1737)	-
hospital discharge to death, days (median, IQR)									
	NA	20 (8-40)	-	NA	196 (110-319)	-	NA	1130 (646-1712)	-
places where patients died, N (%)									
tertiary hospital, ICU	NA	1 (7.8)	-	NA	0 (0)	-	NA	1 (2.2)	-
tertiary hospital, ward	NA	3 (23.1)	-	NA	4 (28.6)	-	NA	6 (13.3)	-
other hospital	NA	4 (30.8)	-	NA	2 (14.3)	-	NA	4 (8.9)	-
at home	NA	4 (30.8)	-	NA	3 (21.4)	-	NA	9 (20.0)	-
special care facility	NA	1 (7.8)	-	NA	1 (7.1)	-	NA	17 (37.8)	-
unknown	NA	0 (0)	-	NA	4 (28.6)		NA	8 (17.8)	-

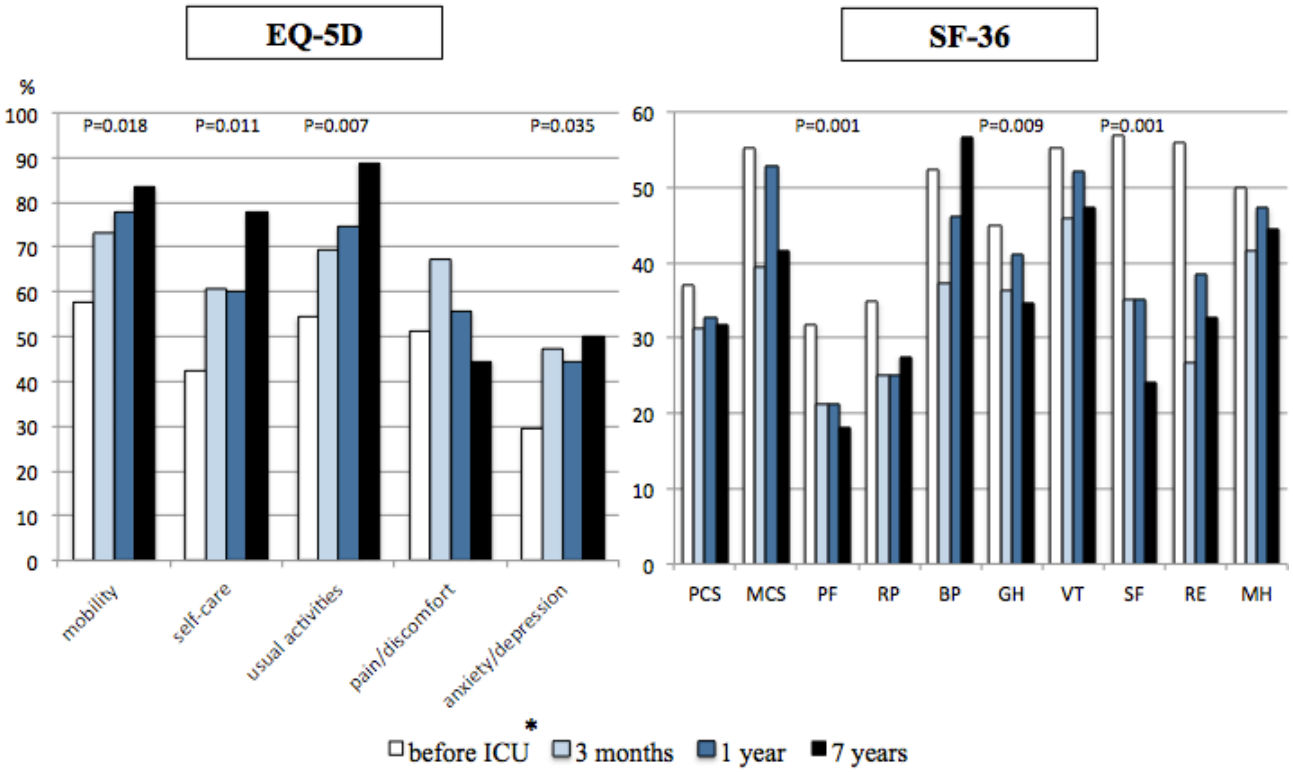
N=number; IQR= interquartile range; ICU= intensive care unit; NA= not applicable; P= level of significance between survivors and non-survivors in the after hospital discharge-3 months after ICU discharge time range; P*= level of significance between survivors and non-survivors in the 3 months-1 year after ICU discharge time range; P**= level of significance between survivors and non-survivors in the 1 year-7 years after ICU discharge time range

Figure 1. Patient cohort



N= number; ICU= intensive care unit; QOL= quality of life

Figure 2. QOL assessments over time

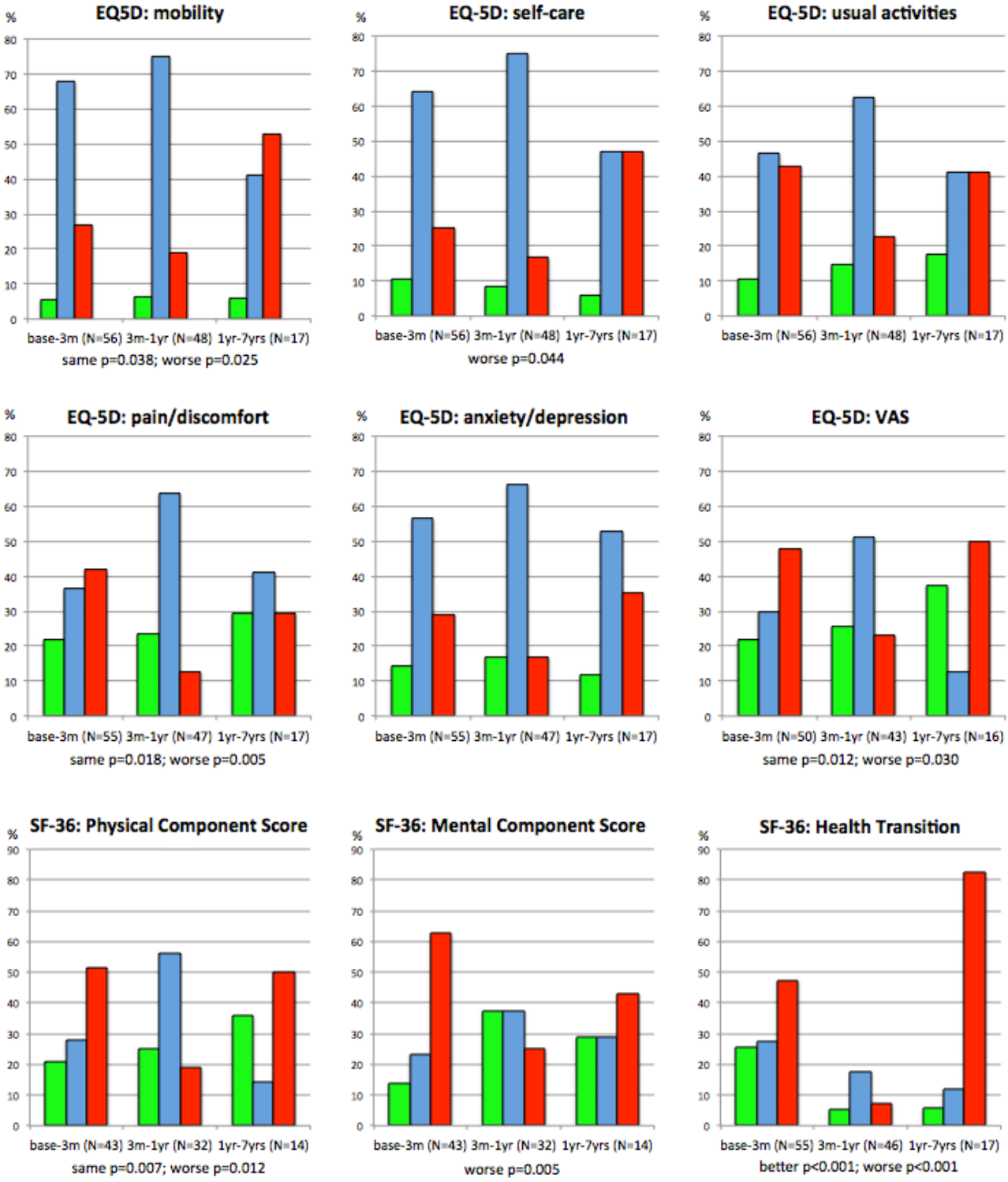


EQ-5D assessments over time: Percentage of patients with moderate or severe problems per dimension at the 4 different time points. The X-axis represents the different dimensions of the EQ-5D. The Y-axis represents the percentages (%) of patients with moderate or severe problems in a respective dimension. Significant P-values (P<0.05) (Chi-Square test) are shown above the respective dimensions.

SF-36 assessments over time: Norm-based median scores per domain at the 4 different time points. The X-axis represents the different domains of the SF-36. The Y-axis represents the norm-based median scores in a respective domain of the SF-36. A norm-based median score between 47-53 in a group of patients is considered as normal or average. Norm-based median scores below 47 indicate impaired functioning or below average; norm-based median scores above 53 indicate better functioning or above average; the higher the score, the better the condition. Significant P-values (P<0.05) (Mann-Whitney U analysis) are shown above the respective domains.

PCS= physical component score; MCS= mental component score; PF= physical functioning; RP= role physical; BP = bodily pain; GH= general health; VT= vitality; SF= social functioning; RE= role emotional; MH= mental health; ICU= intensive care unit; *= hospital survivors only

Figure 3. Perceptions of changes in QOL per patient per time interval



The X-axis represents the different time intervals with the number of patients who responded on both start and end of the respective time interval. The Y-axis represents the percentages (%) of patients who perceived the change in QOL as the same (blue), worse (red), or better (green) per respective time interval and per respective dimension (EQ-5D) or domain (SF-36). Only significant p-levels of differences in percentage of patients who perceive the change as the same, worse or better over time are shown.
QOL= quality of life; N= number; VAS= visual analogue scale; base-3m= change in QOL per patient between QOL before ICU admission and 3 months after ICU discharge; 3m-1yr= change in QOL per patient between 3 months and 1 year after ICU discharge; 1yr-7yrs= change in QOL per patient between 1 year and 7 years after ICU discharge

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V. Development of a prediction model for long-term quality of life in critically ill patients

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ABSTRACT

Purpose: We developed a prediction model for quality of life (QOL) 1 year after intensive care unit (ICU) discharge based upon data available at the first ICU day to improve decision-making.

Methods: The database of a 1-year prospective study concerning long-term outcome and QOL (assessed by EuroQol-5D) in critically ill adult patients consecutively admitted to the ICU of a university hospital was used. Cases with missing data were excluded. Utility indices at baseline (UIb) and at 1 year (UI1y) were surrogates for QOL. For 1-year non-survivors UI1y was set at zero. The grouped lasso technique selected the most important variables in the prediction model. R^2 and adjusted R^2 were calculated.

Results: 1831 of 1953 cases (93.8%) were complete. UI1y depended significantly on: UIb (*P*<0.001); solid tumor (*P*<0.001); age (*P*<0.001); activity of daily living (*P*<0.001); imaging (*P*<0.001); APACHE II-score (*P*=0.001); ≥80 years (*P*=0.001); mechanical ventilation (*P*=0.006); hematological patient (*P*=0.007); SOFA-score (*P*=0.008); tracheotomy (*P*=0.018); admission diagnosis (surgical *P*<0.001 (versus medical); and comorbidity (*P*=0.049). Only baseline health status and surgical patients were positively associated with UI1y. R^2 was 0.3875 and adjusted R^2 0.3807.

Conclusion: Although only 40% of variability in long-term QOL could be explained, this prediction model can be helpful in decision-making.

INTRODUCTION

Uncertainty about outcomes in critically ill patients admitted to the intensive care unit (ICU) is heavy to bear for patients and family. In general, patients and family only associate outcome with survival and often, unrealistic expectations at long-term are hoped for [1]. The true burden of disease and its long-term consequences on physical, mental and cognitive functioning may be underestimated [2, 3], as well as the possibility to return to former daily life and overall quality of life (QOL) [4].

It is the important task of critical care physicians to inform patients and family in a reliable way about these outcomes. However, for critical care physicians too, uncertainty concerning long-term functionality and QOL is difficult to handle [5]. Major reductions in long-term QOL were seen in cases of severe acute respiratory distress syndrome, prolonged mechanical ventilation, trauma, and severe sepsis [6]. Still, long-term QOL remains difficult to predict for the individual patient and patients and families frequently are not well briefed about expected long-term survival and functionality despite explicit wishes to have this information [7].

Accurate prediction models can guide physicians in their handling, communication, and decision-making. Prediction models in critical care do exist but their role in decision-making is however limited [8]. Severity of illness and organ failure scores mainly focus on estimation of short- term mortality risk [9-15]. Some prediction models may focus on very specific patient populations or problems and are not generalizable to a broad patient application in critical care [7, 16-22]. Some models are rather complex [10, 23], not accurate enough [24], or ignore that better future treatments may improve prognosis [19]. Although some prediction models focused on long-term mortality [7, 25], short-term [24] and long-term functional outcome [16], none of the models estimated long-term QOL in general critically ill patients.

Therefore, it was our aim to develop an easy to use and accurate prediction model for the mean QOL at 1 year after ICU discharge in general critically ill patients based upon data readily available at the first ICU day (D1) (D1= first 24 hours of ICU admission).

MATERIALS AND METHODS

Design and setting

The D1-prediction model was retrospectively developed based upon data of a 1-year prospective cohort study. This study focused on long-term outcome and QOL in critically ill adult (≥ 16 years) patients consecutively admitted to the 22-bed surgical ICU, the 14-bed medical ICU, and the 6-bed burn unit of the Ghent University Hospital, a tertiary care facility in Belgium [26]. In case of multiple ICU admissions, only the first was considered. Patients admitted to the 10-bed cardiac surgical unit after cardiac surgery were not included in the study cohort.

The Ghent University Hospital ICU is a closed ICU where patients are treated by a team of full-time critical care physicians, nurses and physiotherapists.

The original observational study was approved by the local ethical committee (Ethisch Comité Ghent University Hospital; project 2007/423 approved 06 December 2007) (B67020072805), and conducted in accordance with the declaration of Helsinki. A signed informed consent was obtained from every included patient or his legal representative.

Data Collection and Definitions

Data collected within the first 24 hours of ICU admission included contact information of the patient, proxy, and general practitioner, demographics, hospital days prior to ICU admission, living and work circumstances before ICU admission, functionality as measured by the Katz activities of daily living (ADL) scale [27], hospitalization in the last 6 months, comorbidity as measured by the Charlson comorbidity index [28], main ICU admission diagnosis (surgical, medical, burns, or trauma), admission circumstances (planned-unplanned/during weekend or not), if the patient belonged to 1 or more of the predefined subgroups (sub) (oncological, hematological, liver cirrhosis Child-Pugh B or C, or elderly (≥ 80 years) patient), Acute Physiology and Chronic Health Evaluation (APACHE II) score [9], Sequential Organ Failure Assessment (SOFA) score [13], Therapeutic Intervention Scoring System-28 score (TISS-28 score) [29], Nine Equivalent of Nursing Manpower Use score (NEMS-score) [30], do-not-resuscitate (DNR) codes, need for invasive mechanical ventilation, vasopressors, renal replacement therapy (RRT), medical imaging (regardless of number or type), transfusion with blood products, surgery, or tracheotomy.

During ICU stay SOFA, TISS-28 and NEMS-scores, DNR-codes, need for invasive mechanical ventilation, vasopressors, RRT, medical imaging, transfusion, surgery, or tracheotomy were collected on a daily base. ICU length of stay (LOS), hospital LOS, vital status at ICU and hospital discharge, and 1 year following ICU discharge were collected for each patient.

Quality of life assessments

QOL was assessed by means of the EuroQoL-5D (EQ-5D) [31]. This questionnaire is validated and found suitable for measuring QOL in the critically ill population [32]. It measures health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, moderate problems or severe problems. Therefore, patients can be classified into 1 of 243 (3^5) possible health states.

We converted each health state into the corresponding utility index (UI), indicating the preference of being in a health status [33]. UI can range from -0.1584 (severe problems on all dimensions) to 1.000 (no problems on all dimensions). UI=0.0000 equals dead. In 17 of the 243 possible health states the corresponding UI goes below zero, indicating a health state assumed to be worse than dead. The patient

will then have severe problems in at least 3 or 4 or in all 5 dimensions, mainly in the pain/discomfort and anxiety/depression dimensions.

Another part of the EQ-5D is the visual analogue scale (VAS), where patients can rate their perceived overall health between 0 and 100.

QOL was assessed at baseline (defined as QOL 2 weeks before ICU admission) and at strictly 1 year after ICU discharge. Following ICU admission and study inclusion, a face-to-face interview to assess baseline QOL was done as soon as possible. This interview was preferably taken from the patient, or if deemed impossible, from the proxy. One year after ICU discharge, patients were sent the EQ-5D by regular mail. Patients or relatives were contacted by phone to assess the 1-year QOL if the questionnaire was not returned within one month. Eventually, the general practitioner was contacted concerning survival status of the patient.

UI at baseline (UIb) and UI at 1 year after ICU discharge (UI1y) were used as surrogate for QOL at that time point. VASb and VAS1y expressed perceived QOL at baseline and 1 year after ICU discharge. UI1y and VAS1y for non-survivors were set at zero to avoid survival bias.

Statistical analysis

For the development of the D1-prediction model, three different multivariate linear regression models, respectively Model I, II, and III, were fitted with UI1y as primary outcome. Model I assessed the bivariate association between UIb and UI1y. Model II ("full" model) included all possible available D1 predictors in the linear regression analysis. Model III ("reduced" model) included only predictors in the linear regression, which were selected by the grouped lasso technique.

Lasso (least absolute shrinkage and selection operator) is a regression analysis method that performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the statistical model it produces. The grouped lasso technique allows predefined groups of covariates, such as all variables encoding a categorical covariate, to be selected into or out of a model together. This technique was applied to identify the optimal number and most important predictors for UI1y in the D1 linear regression model in order to simplify the model, and to cope with the categorical variables [34, 35].

Only complete cases (=patients without missing data) were included in the statistical analysis. The number of included cases varied relative to the considered model.

For each respective model, the R^2 (= proportion of explained variance), adjusted R^2 (= proportion of explained variance, taking into account the number of variables), and the root of the cross-validated prediction error were calculated. By using (10-fold) cross-validation, the root of the cross-validated prediction error gives an honest reflection of the predictive capability of the considered model by splitting

the data into a training set and test set 10 times enabling prediction of the test data based on solely the training data.

The F-test compared the fit of the reduced Model III with the full Model II. Descriptive statistics were done with IBM SPSS Statistics software version 23. Linear regression analysis for the development of the D1-model was done with the R 3.2.2 software package [36]. The grouped lasso technique was executed using the "grpreg" routine available in the "grpreg" package [37].

RESULTS

A total of 1953 patients (847 surgical, 895 medical, 48 burn, 163 trauma) were included in the original observational study. Respectively 1867 (95.6%), 1809 (92.6%), and 1831 (93.8%) of the 1953 cases were complete and included for development of respectively models I, II, and III. Demographics, admission characteristics, organ failures and outcomes for all cases and for the subsets of complete cases per model are described in Table 1. Results were very similar between the different models, which is a strong indication that there were no systematic differences in the subsets of included cases per model. Missingness of variables is described in Table 2.

Development of the D1-prediction model was based upon all 32 variables (10 continuous, 16 binary, 6 categorical) readily available at D1 of ICU admission (Table 3).

For each respective model the R^2, adjusted R^2, and the root of the cross-validated prediction error were calculated (Table 4).

Model I revealed a positive association between UIb and UI1y. UIb could explain 20% of variability in UI1y (Table 4).

Model II ("full" model) held all possible 32 D1-predictors (Table 3). The multivariate linear regression analysis (data not shown) revealed the following significant D1-predictors (significance level 0.10) for UI1y (in order of decreasing importance): UIb, main ICU diagnosis, sub oncological, ADL, age, APACHE II, D1.medical imaging, sub elderly, sub hematological, D1.surgery, origin of ICU admission, D1.SOFA, D1.MV, D1.tracheotomy, origin of hospital admission and Charlson co-morbidity index. UIb was positively associated with UI1y. The model could explain 40% of the variability in UI1y (Table 4). Variable selection was difficult because of the many correlations between the different covariates (data not shown).

The grouped lasso technique revealed 17 possible D1-predictors to be included in Model III ("reduced" model) (Figure 1). We excluded one D1-predictor (D1.NEMS) because of lack of significance (coefficient estimate 0.00006, standard error= 0.0018, p=0.973) and finally, 16 selected D1-predictors were included in Model III. Multivariate regression analysis is shown in Table 5. Finally, D1-prediction of mean UI1y based upon Model III can be obtained by:

Mean UI1y= 0.56 + 0.0009*VASb + 0.3017*UIb – 0.1190*sub oncological – 0.1077*sub hematological – 0.1035*sub elderly - 0.0023*age – 0.0931*ADL2 – 0.1794*ADL3 – 0.1186*ADL4 – 0.0067*Charlson – 0.0047*APACHE II + 0.1102*main ICU diagnosis2 + 0.0346*main ICU diagnosis3 – 0.0151*main ICU diagnosis4 – 0.0092*D1.SOFA – 0.0728*D1.DNR – 0.0530*D1.mechanical ventilation – 0.0329*D1.vasopressors – 0.0689*D1.medical imaging– 0.1238*D1.tracheotomy.

Only UIb, VASb, and surgical or burn patients (versus medical patients) were positively associated with UI1y.

Explanation of variability in UI1y and cross-validated prediction error of Model III were comparable or even better than these of Model II (Table 4). By using cross-validation, the latter provides an honest reflection of the uncertainty for making new predictions using the corresponding model. The F-test revealed no significant better fit for the full Model II compared to the reduced Model III (p=0.432).

DISCUSSION

We fitted 3 different linear regression models to develop an easy to use and accurate prediction model for the mean QOL at 1 year after ICU discharge in general critically ill patients based upon data readily available at the first ICU day. Model I, which positively related UIb and UI1y could only explain 20% of the variability in UI1y. Both models II, which held all 32 possible D1-predictors, and III, with a reduced amount of the most important and powerful D1-predictors, explained 40% of variability in mean UI1y. As this latter D1-prediction model was less complex, had a better performance and fit, and could easily be implemented in an electronic patient data file, we preferred this "reduced" D1-prediction model for prediction of UI1y.

For centuries, humans have tried to predict the future. In medicine, the data rich environment of critical care has led the way in outcome prediction because of its usefulness in improving decision-making under uncertainty, especially when the stakes are so high. However, ICU risk predicting systems lack patient-centeredness and often fail to predict long-term mortality and long-term functional outcomes [38]. Even until recent, estimation of long-term QOL was considered too challenging to be reliably used in medical decision-making as QOL was thought to be too personal and too subjective [39].

A prediction model for long-term QOL based upon readily available data in an early stage of ICU admission could therefore help critical care physicians to identify those patients who will return to their baseline functionality, or those who will need a long revalidation. It could also help to inform patients and families in a reliable way, to triage patients for ICU admission, to guide in treatment decisions, and it could eventually help to transform future healthcare by making better prospects of recovery and better allocation of resources [40, 41].

Still, prediction models have not gained much acceptance in clinical practice, mainly because of

complex algorithms that hamper implementation in daily practice, and because of concerns of being wrong [24]. Our reduced D1-prediction model could explain 40% of variability of UI1y. This is acceptable but nevertheless, a higher accuracy would be better. Still, model III, as it is based upon readily available data within the first 24 hours of ICU admission, and as it is easy to use within an electronic patient data file, could be considered as a helpful tool for a more systematic approach of integration of all D1-variables of the individual critically ill patient.

Although it is not defined to what level model predictions could be helpful and beyond the scope of our study, it certainly might facilitate decisions, which otherwise should have been taken based upon subjective evaluation alone [42]. The D1-prediction model will never replace clinician's judgments, but rather inform and reinforce these judgments, as recommendations for further care highly correlate with physician's estimations of a good long-term QOL [7, 8, 16, 43]. Further research should focus on refining of this QOL prediction model.

Within our QOL prediction model, we were able to identify 16 D1-variables that had great impact on long-term outcome. Baseline QOL and functionality appeared to be strong positive predictors for long-term QOL. This is in accordance with the findings of Veerbeeck [24] and Heyland [16] who respectively demonstrated that a good baseline neurological status in stroke patients and good baseline functionality in elderly patients had a great impact on long-term ADL and functionality.

We also found that the predicted UI1y for surgical patients was significantly higher versus medical patients ($p<0.001$). This was in contrast to burn patient ($p=0.484$) or trauma (0.618) patients, for whom we could not demonstrate any significant difference in UI1y versus medical patients.

The study has several strengths. First, to the best of our knowledge, this is the first simple D1-prediction model which has an acceptable accuracy and which focus on long-term QOL in general critically ill patients. Second, it is original and deals with a very important issue nowadays in critical care. It might have several consequences on resources allocation and anticipates a clear discussion with patients and family members regarding prognosis and preparation for outcomes. Third, the prediction model was developed upon prospectively accurately collected data. Fourth, there was no selection bias in the database, because of the consecutive and prospective enrollment of patients and the high long-term follow-up rate for mortality and QOL. Fifth, the D1-model is not too complex and can aid in decision-making early in ICU stay. Sixth, the database held data concerning baseline condition and QOL, which is of importance in outcome studies and in developing objective prediction models, but still is exceptionally assessed [6]. The high impact of UIb on UI1y illustrates the requirement of knowledge of baseline condition to make any prediction on outcome at long-term. Seventh, we used a grouped lasso technique, which is an objective selection and shrinkage estimation method for linear regression models [34, 35]. We preferred this technique above the widely used stepwise selection method – where prediction accuracy only

improves when covariates have a strong relationship with the outcome - to select the optimal number and most important predictors for UI1y in the D1 linear regression model in order to simplify the model, and to cope with the categorical variables.

Our study also has some limitations. First, the D1-model was developed based upon a single-center dataset. Second, the model was not externally validated, nor was it validated into clinical practice. Implementation studies are needed to investigate the added value of our model in decision-making compared to clinical expertise alone [24]. Third, the model could only explain 40% of variability of UI1y. This could be considered as not accurately enough. However, at this moment, it should be seen as a unique help in informing patients and families, in decision-making and in advanced care planning.

CONCLUSION

We developed an easy to use prediction model for the mean QOL at 1 year after ICU discharge in general critically ill patients based upon data readily available at the first ICU day. Although only 40% of the variability in long-term QOL could be explained, this prediction model can be a helpful tool in decision-making, in good and informative communication towards patients and families, in resource allocation, and in advanced care planning. Further research should now focus on prospective and multicenter validation and refining of this QOL prediction model.

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Table 1. Demographics, ICU admission, D1 characteristics, and outcomes*

	1953 cases	Model I	Model II	Model III
Complete cases included, N (%)	1953 (100%)	1867 (95.6%)	1809 (92.6)	1831 (93.8)
Baseline Characteristics				
Male gender, N (%)	1211 (62.0)	1152 (61.7)	1120 (61.9)	1133 (61.9)
Age (years)	57.2 ± 16.8	57.6 ± 16.7	57.5 ± 16.6	57.5 ± 16.7
BMI (kg/m^2)	25.6 ± 5.4	25.6 ± 5.3	25.6 ± 5.3	25.6 ± 5.3
Charlson co-morbidity index	2.5 ± 2.7	2.5 ± 2.7	2.5 ± 2.7	2.5 ± 2.7
Previous hospitalization in past 6 months, N (%)	843 (43.2)	813 (43.5)	784 (43.3)	794 (43.4)
Living at home before ICU admission, N (%)	1891 (96.8)	1808 (96.8)	1754 (97.0)	1773 (96.8)
ADL at baseline, N (%)				
No limitations	1162 (59.5)	1099 (58.9)	1080 (59.7)	1089 (59.7)
Moderate limitations	625 (32.0)	609 (32.6)	576 (31.8)	587 (32.1)
Chair bound	96 (4.9)	94 (5.0)	91 (5.0)	92 (5.0)
Bedridden	70 (3.6)	65 (3.5)	62 (3.4)	63 (3.4)
UIb	0.62 ± 0.33 (a)	0.62 ± 0.33	0.63 ± 0.33	0.62 ± 0.33
VASb	65.6 ± 20.0 (b)	65.7 ± 19.9	65.8 ± 19.9	65.7 ± 19.9
ICU admission characteristics				
ICU admission during weekend, N (%)	564 (28.9)	535 (28.7)	512 (28.3)	522 (28.5)
ICU admission unplanned, N(%)	1430 (73.2)	1364 (73.1)	1318 (72.9)	1333 (72.8)
Hospital days prior ICU admission (days)	3.1 ± 14.0	2.9 ± 11.7	2.7 ± 9.8	2.7 ± 9.8
ICU-D1 characteristics				
APACHE II	16.9 ± 8.2 (c)	17.0 ± 8.2	16.9 ± 8.1	16.9 ± 8.1
SOFA score	4.6 ± 3.8	4.6 ± 3.8	4.6 ± 3.7	4.6 ± 3.8
Need for mechanical ventilation, N (%)	606 (31.0)	572 (30.6)	557 (30.8)	564 (30.8)
Need for vasopressor therapy, N (%)	390 (20.0)	371 (19.9)	361 (20.0)	364 (19.9)
Need for RRT, N (%)	43 (2.2)	43 (2.3)	39 (2.2)	40 (2.2)
Need for tracheotomy, N (%)	35 (1.8)	35 (1.9)	34 (1.9)	35 (1.9)
Outcomes				
ICU-LOS (days)	6.5 ± 10.5	6.5 ± 10.3	6.5 ± 10.4	6.5 ±10.3
ICU mortality, N (%)	168 (8.6)	160 (8.6)	151 (8.3)	152 (8.3)
Hospital-LOS (days)	29.3 ± 42.4	29.0 ± 40.7	28.7 ± 40.4	28.6 ± 40.3
Hospital mortality, (%)	285 (14.6)	275 (14.7)	259 (14.3)	262 (14.3)
UI1y*	0.46 ± 0.38 (d)	0.46 ± 0.38	0.47 ± 0.38	0.46 ± 0.38
1-year mortality, N (%)	515 (26.4)	504 (27.0)	477 (26.4)	483 (26.4)

D1= first 24 hours of ICU admission; ±= mean and standard deviation; ICU=intensive care unit; N=number; BMI=body mass index; ADL=activities of daily living; UIb=utility index at baseline; VASb= visual analogue scale at baseline; APACHE II= Acute Physiology and Chronic Health Evaluation score; SOFA= sequential organ failure assessment; RRT= renal replacement therapy; LOS= length of stay; UI1y=utility index at 1 year after ICU discharge; *= based upon 1953 cases in database unless indicated otherwise; (a)= 28/1953 missing data (1.43%); (b)= 39/1953 missing data (2.00%); (c)= 5/1953 missing data (0.26%); (d)= 72/1953 missing data (3.7%), *UI1y for non-survivors=0

Table 2. Description of missingness

Variable	Number missing (N) (total 1953 cases)	Proportion missing (%)
Number of cases with at least 1 variable missing	144	7.37
UI1y	72	3.69
VASb	39	2.00
UIb	28	1.43
Sub oncological	20	1.02
Sub hematological	1	0.05
BMI	27	1.38
APACHE II	5	0.26
Baseline job	24	1.23
D1.TISS-28 score	1	0.05
D1.NEMS-score	1	0.05
D1.medical imaging	1	0.05
D1.transfusion	1	0.05

N= number; UI1y= utility index at 1 year after ICU discharge; VASb= visual analogue scale at baseline; UIb= utility index at baseline; sub= predefined subgroup of a specific patient population; BMI= body mass index; APACHE II= Acute Physiology and Chronic Health Evaluation score; D1= describes variable at D1 (D1= first 24 hours of ICU admission); TISS-28 score= Therapeutic Intervention Scoring System 28-score; NEMS-score= Nine Equivalent of Nursing Manpower Use score

Table 3. All 32 possible D1-variables to predict UI1y

Variable	Description
10 continuous variables	UIb, VASb, age, BMI, Charlson co-morbidity index, hospital days prior ICU admission, APACHE II, D1.SOFA, D1. TISS-28, D1.NEMS
16 binary variables (only 1 dummy possible for each binary variable in the D1-model: 0/1*)	sub oncological, sub hematological, sub cirrhosis, sub elderly (≥80 years), gender, previous hospitalization in the past 6 months, admission during weekend, admission unplanned, D1.DNR, D1.MV, D1.VP, D1.RRT, D1.surgery, D1.medical imaging, D1.tracheotomy, D1.transfusion
6 categorical variables (more than 1 dummy for each categorical variable in the D1-model)	living situation at baseline (reference= 1/at home with 2 dummies: 2/special care facility; 3/other); ADL (reference= 1/no limitations with 3 dummies: 2/moderate limitations, 3/chair bound, 4/bedridden); origin of hospital admission (reference= 1/home with 5 dummies: 2/emergency department, 3/other hospital, 4/psychiatric institution, 5/special care facility, 6/other); origin of ICU admission (reference= 1/emergency department with 8 dummies: 2/hospital ward, 3/high-care unit, 4/coronary care unit, 5/operation theatre, 6/catheterization room, 7/recovery room, 8/other hospital, 9/other); baseline work (reference= 1/student with 5 dummies: 2/at work, 3/unemployed, 4/housekeeping, 5/invalidity, 6/retired); main ICU diagnosis (reference= 1/medical with 3 dummies: 2/surgical, 3/burns, 4/trauma)

D1= first 24 hours of ICU admission; UI1y= utility index at 1 year after ICU discharge; UIb= utility index at baseline; VASb= visual analogue scale at baseline; BMI= body mass index; APACHE II= Acute Physiology and Chronic Health Evaluation score; D1.= describes variable at D1; SOFA= Sequential Organ Failure Assessment (SOFA) score; TISS-28= Therapeutic Intervention Scoring System 28 score; NEMS-score= Nine Equivalent of Nursing Manpower Use score; sub= predefined subgroup of a specific patient population; DNR= do-not-resuscitate score; MV= mechanical ventilation; VP= vasopressors; RRT= renal replacement therapy; ADL= activities of daily living; ICU= intensive care unit; *0/1 = either the variable is present (1) or not (0)

Table 4. Fitting of the 3 different D1-prediction models to predict UI1y

Model	Description	Number of D1-variables Included (N)	Number of complete cases included (of 1953 cases) (N) (%)*	R^2	Adjusted R^2	Root of cross-validated prediction error
I	Bivariate association between UIb-UI1y	1	1867 (95.6%)	0.2050	0.2050	NA
II	Full model	32	1809 (92.6%)	0.3980	0.3800	0.3068
III	Reduced model	16	1831 (93.8%)	0.3875	0.3807	0.3026

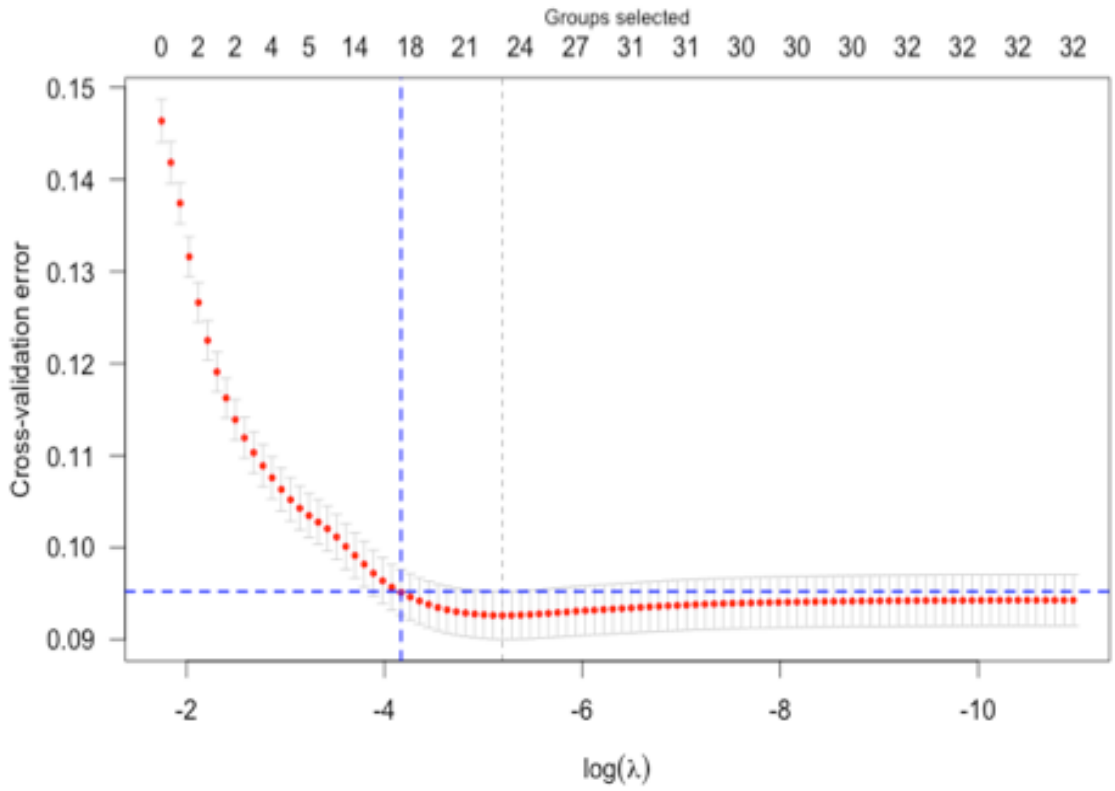
D1= first 24 hours of ICU admission; UI1y= utility index at 1 year after ICU discharge; R^2= proportion of explained variance; adjusted R^2= proportion of explained variance, taking into account the number of variables; N= number; UIb= utility index at baseline; NA= not applicable; *=cases with partial information (=missing of at least 1 variable in at least 1 case) were excluded for the development of the respective model

Table 5. Model III: Multivariate regression analysis

D1 variables	Estimate	SE	t-value	p-value	95% CI
VASb	0.0009	0.0004	1.956	0.051	-0.000 to 0.002
UIb	0.3017	0.0325	9.277	< 0.001	0.238 to 0.365
Sub oncological	-0.1190	0.0232	-5.120	< 0.001	-0.165 to -0.073
Sub hematological	-0.1077	0.0402	-2.679	0.007	-0.187 to -0.029
Sub elderly (≥80 yrs)	-0.1035	0.0318	-3.259	0.001	-0.166 to -0.041
Age	-0.0023	0.0005	-4.330	< 0.001	-0.003 to -0.001
ADL,					
Reference = no limitations	-0.0931	0.0198	-4.712	< 0.001	-0.132 to -0.054
moderate limitations	-0.1794	0.0384	-4.675	< 0.001	-0.255 to -0.104
chair bound	-0.1186	0.0456	-2.601	0.009	-0.021 to -0.029
bedridden					
Charlson co-morbidity index	-0.0067	0.0034	-1.969	0.049	-0.013 to -0.000
APACHE II	-0.0047	0.0014	-3.289	0.001	-0.007 to -0.002
Main ICU diagnosis,					
Reference = medical					
surgical	0.1102	0.0172	6.423	< 0.001	0.076 to 0.144
burns	0.0346	0.0495	0.700	0.484	-0.063 to 0.132
trauma	-0.0151	0.0302	-0.499	0.618	-0.074 to 0.044
D1.SOFA	-0.0092	0.0035	-2.656	0.008	-0.016 to -0.002
D1.DNR	-0.0728	0.0480	-1.517	0.129	-0.167 to 0.021
D1.mechanical ventilation	-0.0530	0.0192	-2.761	0.006	-0.091 to -0.015
D1.vasopressors	-0.0329	0.0258	-1.273	0.203	-0.084 to 0.018
D1.medical imaging	-0.0689	0.0191	-3.603	< 0.001	-0.106 to -0.031
D1.tracheotomy	-0.1238	0.0525	-2.360	0.018	-0.227 to -0.021

D1= first 24 hours of ICU admission; SE= standard error; CI= confidence interval; VASb= visual analogue scale at baseline; UIb= utility index at baseline; sub= predefined subgroup of a specific patient population; ADL= activities of daily living; APACHE II= Acute Physiology and Chronic Health Evaluation score; ICU= intensive care unit; D1= describes variable at D1; SOFA= Sequential Organ Failure Assessment (SOFA) score; DNR= do-not-resuscitate score

Figure 1. Grouped lasso technique to select D1-variables in Model III



Description:
X-axis (above): all 32 D1-variables; X-axis (under): logarithm of penalty parameter λ
Y-axis: cross-validated prediction error (red dots) with error-bar (± standard error of the cross-validated prediction error)

Cross-section of X-axes and Y-axis (light grey dotted line) revealed that the lowest value of the cross-validated prediction error was reached when 24 of all 32 D1-variables were selected in the prediction model. Subsequently, the one-standard-error rule was applied in order to select the λ-value where the corresponding cross-validated prediction error is within 1 standard error of the optimal (lowest) cross-validated prediction error. This was done to avoid too many D1-variables in the prediction model. Cross-section of X-axes and Y-axis (blue dotted line) after applying of the one-standard-error rule revealed that the optimal number of D1-variables in the prediction model was 17 out of all 32 D1-variables.

D1= first 24 hours of ICU admission; log= logarithm; λ= penalty parameter

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Part Three

Overview of the Thesis

I. Concise overview of the study results

1. Inclusions

In our review study, we included a total of 53 articles. There were 4 studies concerning outcome and QOL in general critically ill patients one year after intensive care and 6 with longer follow-up periods. The other articles were grouped according to diagnostic category: acute respiratory distress syndrome (ARDS) (N=11), prolonged mechanical ventilation (N=3), trauma (8), cardiac arrest (N=6), older patients (N=6), pancreatitis (N=2), sepsis (N=3), and studies with various topics (N=4). Huge variations were found in used QOL instruments, in timing and method for long-term QOL assessments, and in final response rate. Only 4 of all the 53 included studies (8%) met all of the 4 predefined study quality criteria; assessment of QOL at baseline, no major exclusion criteria, description of the non-responder group versus the responder group, and comparison with an age-and gender matched normal population. All studies defined clearly which patients were in- or excluded but only 9 studies (17%) measured QOL prior to ICU.

In our second study, 483 cancer patients (398 oncological and 85 hematological patients) were included. Patients with hematological malignancies had significant higher co-morbidities, significant higher severity of illness at admission, required significant more organ support during ICU stay and had significant longer ICU and hospital stays although their disease status was significant more under control or in remission compared to solid tumor patients.

In our third study, we found that 147 patients (7.5%) in the total COSI cohort developed AKI with need for RRT. Of these, 26 AKI patients (1.3%) did not receive RRT due to therapeutic restrictions and were excluded for further analysis; the other 121 patients (6.2%) received RRT. Forty-seven 1-year AKI-RRT survivors were individually matched with 94 1-year non-AKI-RRT survivors, and 28 4-year AKI-RRT survivors were individually matched with 28 non-AKI-RRT patients. During ICU stay, 1-year and 4-year AKI-RRT patients were more severely ill compared to their respective matches.

In our fourth study concerning patients aged 80 or more, we included 131 patients (60% males) with median age of 83 years (IQR 81-85) and Charlson comorbidity index of 2 (IQR 0-4). Reasons for ICU admission were mainly medical (55%) or postoperative after emergency surgery (23%). Fewer older patients were admitted after elective surgery (12%), trauma (9%), or burns (1%) Therapeutic limitations were set in 34 patients (26%) after 2 days (IQR 1-5) at the ICU.

In our fifth study, the COSI database was used for development of a prediction model for the mean QOL at 1 year after ICU discharge in general critically ill patients based upon data readily available at the first ICU day. Respectively 1867 (95.6%), 1809 (92.6%), and 1831 (93.8%) of the 1953 cases were complete and included for development of respectively models I, II, and III. We fitted these 3 different linear regression models and compared their performance towards prediction accuracy and usability. We preferred the reduced Model III, which held only 16 of the most important and powerful D1-variables, for

prediction of UI1y.

2. Mortality

We measured mortality at baseline (ICU and hospital mortality), and at 3 months and 1 year after ICU discharge. In the COSI cohort, in the AKI-RRT patients, and in the patients aged ≥80 years, we also assessed mortality at longer-term, respectively at about 9 years (*), 4 years (**) and 7 years (***) after ICU discharge. High mortality rates were found in all the critically ill patients we studied.

Cohort / Mortality	All COSI patients	Oncological patients	Hematological patients	AKI-RRT patients	Older patients
	N=1953	N=398	N=85	N=121	N=131
ICU (%)	9	5	21	46	17
hospital (%)	14	13	34	55	29
3 months (%)	17	17	42	58	39
1 year (%)	26	36	66	61	50
long-term (%)	48 (*)	-	-	71 (**)	84 (***)

3. Quality of life

In our review article, we found that one year after ICU, critically ill patients in general had a lower QOL, especially in physical domains, than an age-and gender matched population. However, a slow improvement to pre-morbid QOL levels could be found. Particularly ARDS patients, patients after prolonged mechanical ventilation, severe trauma patients, and sepsis survivors showed significant impairments in long-term QOL. While physical aspects improved slowly over the years, mental and emotional impairments were stagnant or declined even further. In older patients, QOL was somewhat decreased, especially in the physical domains, but these patients generally adapted well to these limitations and perceived their QOL as good.

In our second study, QOL assessments showed that for both oncological and hematological patient groups long-term QOL was lower than that of a general population. QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year, especially the mental domains, but remained under the baseline level. At any moment, QOL was especially lower in patients with hematological malignancies.

Among the one-year survivors, patients with hematological malignancies were also less likely to live independently without additional help and more would refuse ICU readmission again.

In our third study, we found that differences in QOL between AKI-RRT and their non-AKI-RRT matches at each different time point were very small. Evolution in QOL over time for the 1-year and 4-year AKI-RRT patients showed that most problems in QOL were seen at 3 months after ICU discharge, particularly in the AKI-RRT group. QOL improved after 1 year, especially in the mental domains, but without return to the baseline level. At 4 years, QOL significantly decreased mainly physically but improved or remained the same in the mental components. The same pattern, although less pronounced, was seen in the 1-year and 4-year non-AKI-RRT patients. Overall, long-term QOL remained under the baseline level for AKI-RRT and non-AKI-RRT patients, and under the QOL of the average population specifically in the more physical domains. QOL was however perceived as acceptable. Both AKI-RRT and non-AKI-RRT patients reported low dependence in daily life later on. The majority of AKI-RRT patients wanted to be readmitted to the ICU when needed, despite the fact that one quarter had persistent dialysis dependency.

In our fourth study, we saw that the number of older patients with problems in mobility, self-care, usual activities, and anxiety/depression significantly increased at each of the consecutive time points. QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year, especially mentally, but worsened again after 7 years. Long-term QOL remained under baseline level and under QOL of the general population. Perceived deterioration in QOL was seen after 3 months, which however changed into a perception of no change or even better after 1 year and again a perception of worsening in most patients after 7 years, mainly in the dimensions of mobility and self-care. All but 1 of the 7-years survivors reported a very good familial and social network, a good paramedical and medical follow-up, experienced no financial problems, and were happy to be still alive despite their advanced age. Among the 1-year and 7-years survivors respectively, 37% and 11% lived independently at home, 26% and 28% had additional home help, 13% and 22% lived with relatives, and 21% and 39% lived in a special care facility. The majority of the long-term older survivors expressed a preference to be readmitted to an ICU department in case of deterioration.

4. Factors with impact on long-term quality of life

Although it was not the main target through our research, we also tried to determine factors with impact on long-term QOL. In our review article, results concerning influence of the patients' characteristics and illness upon long-term QOL were conflicting. It was difficult to withhold certain factors impacting on long-term QOL due to different study designs, methodologies, patient populations, applied QOL instruments, follow-up periods, and response rates through the included articles. We found that in ARDS patients or patients with prolonged mechanical ventilation, the ARDS and its sequelae influenced QOL by

impairments in pulmonary functions, cognitive disorders, weakness, and posttraumatic stress disorders. In trauma patients, the injury severity, the degree of brain damage, and female gender dominated long-term QOL in a negative way. However, in other studies the severity of illness played a less important role. Medical or non-scheduled surgical patients, older age, and a poor pre-admission QOL had also a negative impact on long-term QOL.

In our study concerning oncological and hematological patients, we specifically searched for factors with impact on QOL. Being admitted to the ICU for a medical or surgical reason, or cancer status had no influence on long-term QOL. Multivariate regression analysis showed however that poor QOL 3 months after ICU discharge was independently associated with female gender (p<0.001), higher comorbidity (p=0.001), hematological malignancy (p=0.010), older age (p=0.030), and a higher mean SOFA score during ICU stay (p=0.040). QOL 1 year after ICU discharge was still negatively influenced by older age (p=0.007), higher comorbidity (p=0.035), and hematological malignancy (p=0.041).

These factors also played an important role in our D1-prediction model for mean QOL at 1 year. Baseline QOL and baseline VAS appeared to be strongly positively related with long-term QOL. Variables negatively related with mean QOL at 1 year were an oncological or hematological disease, older age, limitations in ADL, higher APACHE II score, organ failure with need for mechanical ventilation or vasopressors, and a high comorbidity. We also found that the predicted UI1y for surgical patients was significantly higher versus medical patients, which was in contrast to burn or trauma patients, for whom we could not demonstrate any significant difference in UI1y versus medical patients.

II. General discussion

The focus of our research concentrated around 3 major issues resulting in a systematic review and 4 original studies: 1/ reviewing literature concerning long-term QOL, reviewing applied methodology and quality of this published outcome research, 2/ assessing long-term outcomes and QOL in specific critically ill patient populations (oncological-hematological, AKI-RRT and older patients (≥ 80 years)), and 3/ developing a prediction model for long-term QOL based upon readily available variables at the first day of ICU admission and so determining the most important predictors for long-term QOL.

At first, we evaluated what was already known concerning long-term QOL in critically ill patients. We found huge variations in applied methodology resulting in a rather poor overall quality of outcome research, which hampered the ability to compare results or draw strong conclusions out of this research. This problem was already underlined some decades ago [1, 2]. Recently, many professional and scientific organizations have prioritized outcome research on survivors of critical illness after hospital discharge and peer-reviewed publications reporting on these patient outcomes grew from 3 in 1970 up to nearly 500 just now [3]. However, there is still no consensus on the most important outcomes, measurement instruments for assessments, and timing of these assessments [4].

So, within critical care medicine thus far, there has been little critical evaluation of outcome measures used in clinical outcome research. This partly reflects the large number of measures that have been used in critical care research in the past and partly the poor quality of this research. Our recommendation, therefore, is that the research community should agree on a limited list of measures from which to select for any given project and a common time point for follow-up. This would at least enable a considerable body of experience and knowledge to be built up around a few measures [4, 5]. It would also allow investigators to make comparisons between studies, facilitate overviews of published results and enable physicians to draw conclusions out of the growing number of studies in this field [3, 4, 6].

Lately, more attention has been paid to this problem and there are some projects within international societies focusing on the need for standardized definitions of appropriate and valid outcome measures, standardized timing of outcome assessments, minimizing loss to follow-up, and appropriate statistical methods [6].

As QOL is a patient-centered and subjective outcome parameter by itself, we believe that the use of validated tools to assess QOL is an absolute “must”. In critical care outcomes research mainly generic QOL measures are being used. In our review article, we chose to include only studies assessing QOL by SF-36, RAND-36, EQ-5D, and NHP because these are generic instruments commonly used in critical care research; they are validated and have population norms in the literature. Although these questionnaires

have a well-known validity, reliability, and are responsive to changes in health [5], they have substantial gaps in their coverage of the survivors' QOL [7]. For example the EQ-5D and SF-36v2®, which are the most commonly used QOL measures, and which we used throughout our research, do not assess memory, concentration, the ability to complete tasks, multi-tasking, problem solving, or decision-making [8, 9]. The dimension of "usual activities" of the EQ-5D is very broad defined and might eventually include cognitive problems although this might not be clearly interpreted by patients. However, cognitive functions together with physical and mental functions are the three main players in determining long-term outcomes [10].

As we considered evaluation and evolution of cognition in the critically ill patient to be very important, we added an extra 6th dimension "cognition" to the first part of the EQ-5D, which has, equal to the EQ-5D, 3 levels of problems. This sixth dimension is however not incorporated into calculation of UI. This "EQ-6D" is in fact an extended form of the EQ-5D and was developed within the scope of the Dutch Disability Weights Study, which was carried out to obtain disease-specific preference weights for many diseases [11]. The expert group of the study proposed to extend the EQ-5D with a cognitive dimension to capture cognitive dysfunction. The EQ-6D construct validity was examined with good results [12]. The EQ-6D is however far less well known and consequently, its use is rather limited. The EQ-6D is particularly used in the Netherlands for outcome research in a Dutch patient population [12-16]. During analyzing of our study results, we therefore preferred the use of EQ-5D and SF-36v2®, which are both commonly used and very well-known standardized QOL questionnaires in outcome research. We considered the extra question regarding cognition as a bonus to gain more complete information about the health status of the patient.

Both questionnaires also do not address sexual functioning, social support, family and marital functioning, place of residence, living situation, finances, problems to return to work, sleep quality, health distress, and many other issues such as changes in appearance, problems with clothing due to weight loss, relationship to others, etc. All these physical and psychophysiological symptoms could heavily impact on QOL [7]. To overcome somewhat these shortcomings, we added in our research 4 additional short questions at long-term (regarding living situation, memories of the ICU stay, sleep quality and preferences to be readmitted to an ICU), in an attempt to overcome partly and easily these gaps. We are unaware of measures to specifically assess cognitive function except for the Informant Questionnaire on Cognitive Decline (IQCODE). This questionnaire has to be answered by the next of kin and assesses actual cognitive functioning of the older patient compared with cognition 10 years ago. It is a very frequently used and validated questionnaire in geriatrics but in the general critically ill setting it has not been used before [17].

It is difficult to select the most appropriate survey(s), both in number and in content. All have shortcomings and it is important to select depending on the research question, the research population, and timing of the survey. The advantage of the EQ-5D is that it is a very short survey, which has nevertheless the possibility to gain a lot of information. However, due to its shortness, it is less

discriminative than the SF-36v2®, which is very well validated in critically ill patients, and may be considered as the first choice for QOL assessment in this patient group. Therefore, we believe that the combination of SF-36v2® with EQ-5D yields the most to assess baseline QOL and QOL shortly after ICU discharge: a lot of discriminative QOL information combined with a preference-based QOL measure with the possibility of an index value to be used in health economics studies.

Timing of QOL assessments will also influence the choice and number of measures. At baseline, too many questionnaires will tire the critically ill patient or the family, and will increase the probability for incomplete surveys and decrease the probability for further participation in the study. At longer-term, after a period of some recovery, it will be easier for most patients to complete questionnaires. These issues must be balanced to ensure that sufficient and meaningful data are collected at appropriate time points, without overburdening patients, family or researchers. A clear explanation of why, when, and how QOL assessments will be made and what will happen to the data patients provide, will help in keeping study participants motivated.

Patients are often unable to make a clear distinction between normal disease-specific processes and consequences of being in a critical care department [7]. Therefore, to have a more complete picture of outcomes and QOL at long-term, when the critical illness has been past for a while, we can now recommend adding additional validated questionnaires to the generic QOL questionnaires such as the Post-traumatic Stress Syndrome 14-questions inventory (PTSS-14), the Hospital Anxiety and Depression Scale (HADS), and the Montreal Cognitive Assessment test (MoCA). The PTSS-14 is a 14-item screening tool that has been validated in ICU patients [18, 19] and has a high sensitivity (86%) and specificity (97%) for diagnosis of post-traumatic stress disorder (PTSD). The PTSS-14 is short (5 to 10 minutes to complete), can be easily used in an outpatient setting or over the telephone and does not overtire patients. The HADS is a reliable and valid instrument for detecting the presence and for measuring severity of depression and anxiety in the setting of a hospital medical outpatient clinic, in psychiatric cases, in primary care patients and in the general population [20, 21]. The MoCA test is a validated one-page 30-point test, which can be administered in approximately 10 minutes. It assesses several cognitive domains such as short-term memory, visual-spatial abilities, executive functions, attention, concentration and working memory, language, fluency and orientation to time and place [22].

When combining all these measures, it should be possible to assess a more complete picture of the physical, mental and cognitive functioning of the critically ill survivor and to make a better advanced care plan.

Where QOL is a subjective outcome parameter, which can be difficult, time-consuming and labor-intensive to assess, death is, on the contrary, an easy to determine and unequivocal endpoint. There are several points in time at which to measure it: ICU, or hospital mortality, time until death, or death at a fixed

time point. We measured mortality at baseline (ICU and hospital mortality), and at 3 months and 1 year after ICU discharge. In the older and AKI-RRT group, we also assessed mortality at longer-term. We found high mortality rates in all groups of critically ill patients we studied, especially in the first 3 months since ICU admission, with only moderate increase of mortality at longer follow up. These mortality rates are however comparable with the numbers found in literature [23-31]. Practice patterns such as admission policy before ICU, therapeutic restrictions during ICU, discharge policy and destination, and case-mix of patients may have impact on the interpretation of these mortality rates. As a tertiary care facility, the chance of receiving complex and high-risk patients transferred from other hospitals is high, which can attribute to the high mortality rates. Although there is an actual trend for a significant decrease in short-and long-term mortality, it is also known that ICU survivors have an ongoing increased risk of mortality much beyond ICU discharge, when compared to a matched general population [32-35]. In general, ICU patients reach a life expectancy similar to that of the general population 2 years after ICU admission [34, 35].

The measures of long-term QOL may put surviving a critical illness into a larger perspective. When making a global conclusion concerning long-term QOL, we found that critically ill patients had a lower long-term QOL than a general population, but a slow improvement in QOL could be seen, although it remained under baseline level. Several years after ICU, QOL was quite comparable with that of the normal population. In our review study, we found that patients with severe ARDS, prolonged mechanical ventilation, severe trauma, and severe sepsis appeared to have the worst reductions in QOL, which lasted also for a long time. The impact of diagnostic category upon long-term QOL was also partly reflected in our prediction model. We saw that the predicted long-term QOL for surgical patients was significantly higher compared to medical patients.

Being a hematological, oncological, AKI-RRT, or older patient certainly impacted on outcome. Evidently, cancer patients, AKI-RRT patients or older patients admitted to the ICU represented not only a highly diverse spectrum of diseases but also patients with a very heterogeneous performance status and co-morbidity at baseline. As such, outcomes should be differentiated among these subgroups.

We found important differences between solid tumor patients and hematological patients relative to co-morbidity, reason for ICU admission, and severity of illness. These translated into a different long-term QOL in survivors, with hematological patients having a worse QOL on every moment of the study period, and experiencing no significant improvements beyond 1 year. Recent outcome studies in the critically ill cancer patient still focus on mortality [24, 36, 37]. Other QOL studies in the group of critically ill cancer patients, beyond ours, are very scarce which is rather bizarre given the growing number of these patients being admitted to the ICU combined with increasing short-term survival rates although overall mortality remains high [23, 24, 37-39]. QOL assessments seem therefore of particular interest to differentiate if the dying process is being prolonged or if we can guarantee a quality and meaningful life at

longer-term [40, 41]. Azoulay et al. found in a huge study concerning outcomes in critically ill hematological patients that QOL, assessed by SF-36 surveys, was not significantly different from age-and gender matched cancer patients not admitted to the ICU. Only a minority of patients perceived alterations in QOL 3 months after ICU discharge. In this study however, only short-term QOL was assessed without baseline evaluation and with a response rate of only 69% [37]. Another recent study found quite the same [38]. This suggests that the critical illness does not impact that much on long-term QOL and consequently, should not be a reason not to transfer these patients to the ICU [23]. Very recently, the study by Normilio-Silva et al. confirmed our data [39]. They demonstrated in a mixed critically ill cancer population - with predominantly oncological patients - that QOL in patients with a good baseline status decreased directly after ICU admission, and then gradually increased but never returned to baseline level. However, patients with a poor baseline condition and QOL steadily improved over 18 months reaching a moderate QOL.

We also compared QOL of AKI-RRT patients with that of matched non-AKI-RRT patients, and found very similar measurements in both groups. This implied that the RRT component during critical illness did not have an important impact on long-term QOL. QOL was however lower than in the general population.

In contrast to the extensive literature on epidemiology and RRT modalities, there is still a paucity of literature on QOL and long-term outcome in critically ill patients who survive an episode of AKI-RRT [42-44]. However, these patients are some of the most severely ill patients in the ICU were prognosis, survival estimation, and starting or withholding RRT is frequently a matter of difficult clinical decision-making, taking also into account the high costs of RRT [45, 46]. Recently, some studies concerning QOL were published, but only a minority reported on long-term QOL [25, 27, 47-51]. Consistent with outcome research in general, interpretation of study results was challenging due to heterogeneity of study design, QOL assessment tools, case-mix of patients, RRT modalities and duration of follow-up. Nevertheless, overall QOL data in these studies were very similar to ours with a QOL of AKI or AKI-RRT survivors that was comparable with QOL of matched non-AKI or non-AKI-RRT patients but lower than in the general population. QOL was seldom assessed at baseline but often already impaired at that moment, consistent to our findings [25, 48, 49].

A recent study showed that although development of AKI was not an independent risk factor for increased 3-year mortality in 30-day AKI-survivors, an episode of AKI-RRT might portend long-term risks such as evolution to chronic kidney disease (CKD), accelerated progression to end-stage kidney disease (ESKD), chronic RRT dependency or major cardiovascular events, which all may impact heavily on long-term outcome and QOL [43, 44, 52]. We found that 19% of the 1-year AKI-RRT and 29% of the 4-year AKI-RRT survivors remained RRT dependent, which is an adverse outcome strongly associated with an ongoing increased risk of death [42]. Rates of RRT dependency after an episode of AKI-RRT differ among populations and can vary between 0%-40% [53]. Patient-related factors such as age and comorbidity may be risk factors

for non-recovery of kidney function, but also the severity of the AKI and of the acute illness [53, 54]. The impact of RRT modality on renal recovery at long-term remains controversial and was not one of our study endpoints [53]. Whether there is a role for robust pathways to monitor and screen AKI-RRT survivors to improve these long-term outcomes has not been formally studied although potential follow-up schemes do exist [43, 53, 55].

Determining patients who should benefit the most from ICU admission becomes more and more complicated and this is particularly the fact in patients aged 80 years or older. The long-term QOL in the critically ill older patients in our study was low compared to a general population, particularly in self-care, usual activities and the physical domains, with an increasing number of patients experiencing more problems over time. This is in accordance with data found in other recent studies concerning long-term QOL in the (very) old patient [56-60]. These older patients however recognized little changes in QOL over time except for mobility and self-care at long-term. We found, similar as what is described in literature, that older patients adapted well to their advanced age and perceived their overall QOL as acceptable [58-64]. It suggests that QOL might have another meaning for old patients, with social and mental values being far more important than limited physical functioning and that age itself influences QOL mainly due to increasing number of chronic conditions [28, 59, 62, 64, 65].

A difference has indeed to be made between QOL measurements and perception of QOL as experienced by the patient himself, assessed by the VAS. Oncological patients had a better perception of their QOL compared to hematological patients, but for both groups QOL was still acceptable. AKI-RRT patients perceived QOL as good and both AKI-RRT and non-AKI-RRT patients reported low dependence in daily life later on, which was also found in other studies [51]. This perception of a fair QOL was also well illustrated by the fact that the vast majority of all our included patients who were alive after 1 year or even longer answered positive to the question whether they would choose to be readmitted to an ICU in case of deterioration. A good perception of QOL despite persisting symptoms may be explained by the fact that patients who are confronted with a life-threatening disease are faced with the necessity to accommodate to the disease, which may lower internal standards. The divergence between mental and physical performance probably reflects this gradual process in which patients adapt to a diminished performance status and come to accept their physical limitations. Acceptance of disability is in general higher among older patients, and even better if they have a good socioeconomic status [66]. Indeed, the older patients in our study expressed preferences for a longer life, even with reduced QOL, especially when they had a good social network.

We not only differentiated between patients with a better and a worse QOL, but also measured how QOL changed over time within a certain patient group. Generally, QOL decreased 3 months after ICU discharge compared to baseline, improved after 1 year or longer, especially the mental domains, but

remained under the baseline level. This change in QOL over time leads to an important and difficult issue in QOL studies. How long is "long" in long-term outcome and when will outcome measures and questionnaires no longer give additional information? In all our included patients, mainly the physical components deteriorated over time. While physical aspects improved slowly over the years, mental and emotional impairments were rather stagnant. Our follow-up period of one year was probably too short because physical limitations still tended to dominate over emotional problems and physical problems were not always recovered. One year may also be too short to become accustomed to more restrictions in daily live [38, 67]. The absence of any correlation between the physical and mental problems through our research is remarkable. This may however be explained by the fact that ICU survivors can accommodate to the critical illness and its consequences leading to acceptance and adjustments to the disease [68]. Although we do not doubt these observations, it should be underlined that mental or cognitive problems bear a higher risk to be remained unrecognized.

The most important problem of long-term follow-up times is that more patients will be lost to follow-up, which could lead to an important bias in results. Patients who not respond can do so for a lot of different reasons. They can consider QOL questionnaires trivial if they recovered well, they can suffer from posttraumatic stress disorder avoiding seeking memories of their ICU treatment, they can be too ill to have the ability to respond, or they may have died before completing the survey [69-71]. As such, QOL responders may represent a sample of healthier patients. Selection bias may also be induced before ICU admission. Patients who are referred to the ICU might already represent a selection of fitter patients with a possible inherent better prognosis and QOL. This was probably seen in our study concerning long-term outcome in older patients of whom only a minority was chair-bound or bedridden at baseline. We also cannot rule this out in the study evaluating oncological and hematological patients. This limitation is hardly avoidable and can also be found in other studies concerning older or cancer patients [28, 41, 61-63, 72].

Anyway, to avoid selection bias in long-term QOL data, every effort has to be made to target the highest possible response rate. Otherwise, analyses of responders versus non-responders concerning severity of illness scores, co-morbidities, mortality, or age should be made [73]. A lost to follow-up of 20% is considered to be acceptable for QOL studies [74], but more than half of the studies in our review article did not attain to this. To assess QOL 1 year after ICU discharge in the COSI study, and also at longer term in the AKI-RRT and elderly study, we phoned all patients who did not respond to the initial mailed survey after one month, although it was time-consuming and labour-intensive. This finally resulted in a very high response rate (97.7%) and a very low number of patients - only 18 out of 1953 patients in the total COSI cohort –, which were lost to follow-up. Because of the consecutive and prospective enrollment of patients in the COSI study and the high long-term follow-up rate for mortality and QOL, we tried to reduce any form of selection bias to an absolute minimum.

Besides the risk of selection bias, survival bias remains a problem in outcome research. Correction for patients, who died during the observational period, was not necessarily in our study concerning the impact of RRT on long-term outcome since we only included long-term survivors in the analysis. In the studies regarding cancer and older patients, it is likely that only the "best" or the "fittest" patients survived long-term. We cannot change this fact. As QOL at long-term can only be measured in survivors, in whom you may assume that overall QOL will be better that in nonsurvivors, QOL at long-term may be overestimated. To correct for patients who died during the total observational period, QOL may be indicated as "zero" for the nonsurvivors in the study cohort, which however will underestimate the observed QOL of the survivors in the cohort. When developing the D1-prediction model we gave QOL at 1 year a "zero" input for 1-year nonsurvivors. This allowed for comparisons between the same patient cohort at baseline and at 1 year after ICU discharge and avoided that long-term prediction of QOL only would be developed upon data of survivors.

Although survivors of critical illness share the common experience of coming extremely close to death as they survive a life- threatening illness, they can differ from one another in many ways such as their health status before the illness, the specific event or disease triggering the illness, their reactions to the illness, and their capacity to recover. Another problem in interpretation and comparison of long-term outcome in critically ill patients is that the period of critical illness is only a small part of the whole illness episode and therefore, the whole process of illness and care should in fact be scrutinized: ICU admission policy, level of care during the ICU stay, end-of-life (EOL) decision, ICU discharge policy, further hospital stay, and post-hospital aftercare. Possible confounders, which could influence QOL, should be eliminated.

Therefore, QOL in ICU patients can be compared to an age- and gender- matched general population, which should be considered as the upper limits of what is achievable. In all our original studies, we therefore used the norm-based scores of the SF-36v2®, which allowed for direct comparisons with a general healthy population. More important, long-term QOL should also be compared with QOL before ICU admission, to discriminate whether poor long-term QOL is a result of the severity of illness, or due to confounding factors such as co-morbid disease, poor pre-admission QOL, age, gender, or acquired complications.

Our research was observational, so looking for causes or explanations for long-term QOL is difficult. However, we tried to determine the most important predictors, besides diagnostic category, for long-term QOL. Although baseline QOL can be viewed as a an important predictor of long-term QOL, only 17% of the included studies in our review article measured QOL prior to ICU. In more recent outcome research, measurement of baseline QOL is still rarely done [25, 39, 48, 49, 58, 75]. Prior studies of QOL before ICU admission support the hypothesis that patients' premorbid QOL has a large effect on QOL after critical illness [39, 76]. It has been proved that pre-ICU QOL is low compared to the general population indicating

that ICU patients differ from the average population even before onset of critical illness [73]. Poor QOL before critical illness is also correlated with poor outcome [74, 76-78]. Impaired QOL after ICU may thus reflect a poor baseline situation rather than be a function of intensive care [74, 76]. We found a very high impact of baseline QOL on long-term QOL in our D1-prediction model. This illustrates the requirement of knowledge of baseline condition to make any prediction on outcome at long-term.

In our review article, it was difficult to withhold certain factors impacting on long-term QOL due to different study designs, methodologies, patient populations, applied QOL instruments, follow-up periods, and response rates through the included articles. We however found that factors, which could be presumed to result in a poor QOL after ICU, such as a long ICU or hospital stay, are not per se indicators of reductions in QOL afterwards [73]. Other issues such as cognitive impairments, sleep disturbances, posttraumatic stress disorder, the rehabilitation process, employment status, and cultural and payment differences, can influence QOL in a less tangible way than, for example, physical impairments after major trauma [69, 79, 80]. We matched AKI-RRT survivors with non-AKI-RRT survivors, to evaluate the effect of RTT on long-term QOL. The factor "RRT" seemed surprisingly not to have a very big impact on long-term-QOL. However, long-term QOL was impaired, mainly driven by poor physical functioning. The great comorbid burden in these survivors combined with an already impaired baseline QOL may also contribute to the final long-term QOL. In our study concerning oncological and hematological patients, we specifically searched for factors with impact on QOL. Multivariate regression analysis showed that poor QOL 3 months after ICU discharge was independently associated with female gender, higher comorbidity, hematological malignancy, older age, and more organ failure during ICU stay. One year after ICU discharge, older age, higher comorbidity, and hematological malignancy still negatively influenced QOL.

These factors also played an important role in our D1-prediction model for mean QOL at 1 year. Within this prediction model, we were able to identify 16 D1-variables that had great impact on long-term outcome. As already mentioned, baseline QOL appeared to be strong positive predictor for long-term QOL. This underlines the importance of knowledge of this baseline condition. It is also is in accordance with the findings of Veerbeeck [81] and Heyland [82] who respectively demonstrated that a good baseline status in stroke patients and in older patients had a great impact on long-term functionality. Normilio-Silva also confirmed that baseline QOL and functionality were the variables that best discriminated QOL at 18 months [39]. Variables in our D1-prediction model that had a negative influence on QOL at 1 year were older age, limitations in functionality, a higher comorbidity, a more severe critical illness, a medical reason as ICU main diagnosis and more organ failure.

This is similar to what is found in literature and In general, we may conclude that the most important determinants of long-term QOL are baseline QOL, co-morbidity, age, functionality, and social interplays [76-78, 83-85]. In a large multicenter longitudinal study evaluating long-term QOL, Orwelius et al

found that comorbidity was a very important factor that influenced long-term QOL [83]. In another multicenter study, they also found that ICU-related factors or the severity of the critical illness had little effect on the reported long-term QOL [86]. They saw that 6 months after ICU discharge, perceived QOL in sepsis patients did not differ from ICU survivors with other diagnoses, even though these sepsis patients were more severely ill, and had a longer ICU stay. Indeed, our AKI-RRT and their matched non-AKI-RRT patients had a very comparable co-morbidity and medical history, which may explain the fact that the RRT component during ICU stay had no effect on long-term QOL, which was very similar between both groups in our study. AKI-RRT patients were also more severely ill during their ICU stay compared to matched patients but this had no influence on QOL over the years. This is however not in accordance with our findings in cancer patients, where hematological patients had a higher severity of illness during ICU stay and a lower long-term QOL compared to oncological patients.

In our D1-prediction model, we found that comorbidity certainly impacted on long-term QOL but to a lesser extent than baseline QOL, age, functionality, and severity of illness or organ failure. In a study by Luna et al. the presence of comorbidities was associated with poorer outcome in patients with a community-acquired pneumonia [87]. However, when there was no or only one comorbidity, the fact itself of being 80 years or older increased mortality. Although we clearly demonstrated the impact of age on long-term outcome in older patients, in cancer patients and in our D1-prediction model, age remains a difficult parameter to handle in outcome research. Using QOL instruments that are not specific to a particular age group enables comparisons to be made with other age groups, i.e. younger or middle-aged groups. However, the questionnaire items of QOL instruments tend to be phrased predominantly in relation to physical function and thus may inadvertently discriminate against older persons, whose physical function is likely to be not as good as that of younger people. Particular issues in the assessment of QOL in older patient populations include the persistent finding of a poor relationship between QOL and disability/disease severity, and the importance of valid proxy ratings for those unable to make decisions or communicate for themselves. It is important, therefore, that assessment of QOL incorporates issues of importance to individual older people by broadening the scope of the measurement instruments, thus representing more validly the QOL status of older patient groups. Therefore, QOL measurements can be helpful in decision-making concerning ICU admission of older patients but its role may be limited at the same time. Biological age as comorbid burden is therefore more important than chronological age in outcome research. Biological age does not necessarily parallel chronological age and it is more difficult to estimate [31]. This concept of “frailty” as marker of biological age and predictor of outcome is relatively new in critical care medicine. It reflects a decline in reserve and function in a wide range of physiological systems and accordingly, may represent a more robust predictor of vulnerability and recoverability than chronological age alone.

The Clinical Frailty Score (CFS) will give a more complete picture of the general health status of the (older) critically ill patient [56, 88, 89]. Although we did not measure the CFS in our studies, recent literature highlights the importance of knowledge of this CFS in prognostication and appropriate decision-making for older critically ill patients as patients who are less frail are more likely to survive and regain good physical functioning [28, 31, 56, 57, 65, 89-91]. Although frailty is frequently associated with advanced age, not all older patients are frail. Younger patients can also be frail as the accumulation of health impairments driving the development of frailty may occur during the total adult lifespan [92, 93]. In any age group, this CFS is therefore a good parameter to outweigh the balance between the burden of ICU management and the goal to restore an acceptable QOL that is meaningful based on life expectancy [94, 95]. We therefore recommend assessing CFS for any critical ill patient at ICU admission.

The overall functionality or performance status of a critically ill patient, which is somewhat in line with the CFS, is rather easy to determine. We measured it through the ADL with 4 different categories (no limitations, moderate limitations, chair bound or bedridden) and found it to be one of the important D1-variables for prediction of long-term QOL, although only a minority of our included patients was chair-bound or bedridden at baseline. Poor functionality often reflects irreversible factors such as older age or severe comorbidities and strong associations between functionality and QOL were found [39]. Recently, its key role in outcome in critically ill patients was also demonstrated in another study [84]. They found that poor functionality was associated with higher mortality, irrespective of other markers of chronic health status such as age or comorbidity, and concluded that assessment of functionality was necessarily to capture a more complete picture of a patient's health status.

Another important variable with impact on long-term outcome and QOL, although difficult to measure, is the role of social interplays and integration. We saw in our review article that patients with a good familial surrounding had a better long-term QOL. This was confirmed in a controlled multicenter prospective explorative study where the level of social integration, measured by the AVSI (Availability of Social Integration) instrument, significantly affected long-term QOL in former ICU patients, even to a larger extent than age [85]. Although we did not measure social relationships with a validated instrument, we also demonstrated in our elderly study that a good familial, paramedical and medical network, and no financial problems added to perceive QOL as acceptable.

As already highlighted, all these important determinants of long-term QOL - baseline QOL, co-morbidity, age, and functionality, as demonstrated in literature and in our studies - were also captured in our D1-prediction model, with the exception of the variable "social integration" because we did not had a quantitative measurement of it. Severity of illness and the level of organ failure at the first day of ICU admission appeared to have also an important impact on long-term QOL. This illustrates the complex interplay of pre-ICU health state, and acute and persisting illness in determining long-term QOL [96].

Although only 40% of the variability in long-term QOL could be explained, this prediction model can be a helpful tool to guide critical care physicians in decision-making, communication, resource allocation, and advanced care planning. Although it is not defined to what level model predictions could be helpful and beyond the scope of our study, it certainly might facilitate decisions, which otherwise would have been taken based upon subjective evaluation alone. Decision-making can be difficult particularly in the specific patient subgroups we studied, namely critically ill cancer patients, AKI-RRT patients and older patients, where there are often doubts considering effectiveness of critical care or where the start of specific expensive treatments during ICU stay can be questioned.

Specific prediction models for critically ill older patients do exist but they focused on mortality [97, 98] or functionality [82] in this specific patient group. One study specifically studied the predictive value of early development of AKI on survival and long-term QOL [99]. Our prediction model is unique in its form because it has the advantage that it can be applied in any critically ill patient but meanwhile also has a patient-centered outcome approach as it predicts mean long-term QOL of the individual patient instead of short-term mortality estimated by the classical severity of illness scores [100].
Therefore we may state that it responds to the criteria of modern and patient-centered outcome prediction research [101].

Still, our D1-prediction model will never replace clinician's judgments, but rather inform and reinforce these judgments, as recommendations for further care highly correlate with physician's estimations of a good long-term QOL [102]. A recent study demonstrated that prognoses made by critical care physicians at ICU discharge incorrectly predicted long-term survival and QOL in one-third of ICU survivors. Inaccurate prognoses were generally the result of overoptimistic expectations of outcome [103]. The need for an objective prediction tool to aid decision-making in the complex environment of a critical care department seems therefore obvious.

III. Conclusions of the thesis

Our study results might help in gaining better knowledge about long-term QOL and in the design of future studies on long-term QOL. While the focus in critical care medicine is still on "survival", we believe that long-term QOL must become as important in outcome target. With more and more studies now focusing on long-term QOL, it will certainly influence our decision-making process, although to which extend will be quite hard to measure. Despite the fact that the interest and the number of studies reporting on post-discharge outcomes of ICU survivors has now increased substantially, the ability to compare results or draw strong conclusions remains impeded by the use of many different outcome measurements and various timings of assessments.

Nevertheless, we now know that the burden of critical illness in ICU survivors is a substantial and an under recognized problem. In the years after ICU discharge, critically ill survivors present excess mortality and prolonged physical, mental and cognitive morbidity with different degrees of severity. Consequently, the overall well-being of the individual patient at long-term must be taken into account when taking decisions during the ICU stay. Critical care physicians should not only use their own frame of ideals and standards to make these decisions but respect the patient's preferences and values. Consequently, the degree and duration of advanced life-supporting measures should be in balance with the expected long-term survival and QOL in the critically ill patient.

With the growing and better knowledge of these problems that ICU survivors and their relatives may experience after ICU discharge, it has become clear that awareness of these consequences are crucial if we want to improve long-term outcomes and QOL. As we now have the tools to recognize and understand these sequelae, it enables the introduction of better preventive measures and more structured and established post-hospital interventions. Although the benefit of ICU follow-up consultations or specific rehabilitation programs needs to be proven yet, it is of importance that both prevention and intervention measures should be patient-tailored to guarantee the best possible results. This leads us to the next chapter: future perspectives in outcome research.

IV. Future perspectives

1. Research level: **an ongoing better knowledge of long-term outcomes and QOL**

Commitment of critical care physicians towards critically ill patients should not end at ICU discharge but instead prolongs much beyond. The focus of further research seems therefore rather straightforward.

1.1 Further research based upon the COSI cohort

Many critically ill patient populations are of interest for outcome research. Long-term outcomes and QOL in COSI patients with a prolonged ICU-LOS (at least 8 days) have been assessed and data need to be further analyzed. These patients are especially at risk to develop major dysfunctions on the physical, mental and cognitive level. Their prolonged ICU-stay can be explained by several reasons: the complexity and severity of their acute critical illness, combined with a long time period needed to recover and to be able to be discharged to a general hospital ward for further rehabilitation. Their prolonged ICU-stay is also part of the decision to not withdraw or not withhold therapy and to give these patients a chance to survive without medical obstinacy or futility. This implies a good baseline condition in these patients, which however will make the final long-term outcome in many cases confronting. Preventive and interventional measures for good recovery are important in these patients.

Our D1-prediction model should be externally validated and should finally be evaluated in a clinical prospective impact study comparing predictions made by the D1-model and real life long-term outcome data [104]. A user-friendly electronic format could eventually be implemented bedside for convenient data processing and transmission [101, 105].

We also developed a longitudinal prediction model taking into account the factor “time” (data not published yet). It is a more complex model than the D1-model but with the refined possibility of long-term QOL prediction per consecutive day of the ICU stay. Although time had a weak effect on prediction of long-term QOL, taking into account the “time” variable increased the predictive power of the model as it considerate the day-to-day evolution - improvement or deterioration – of the individual patient during ICU treatment. This longitudinal model also should be externally validated in the future.

1.2 Global research

An ongoing better knowledge and broader picture of long-term outcomes and QOL in critically ill patients remains important. Better methodology, a more uniform outcome research with more uniform, standardized and validated QOL instruments, with a reasonable long and uniform follow-up period (long enough to have any idea about the long-term QOL but with a low number of patients lost to follow up), with assessment of baseline (pre-ICU) QOL (to compare with long-term QOL) and with a focus on very specified critically ill patient groups to gain the best and most information are however needed [3, 6]. The

critically care society recently has paid more attention to this and recently some articles concerning this were published [23, 31, 43, 106]. Future studies should try to focus on the complex dynamic interplay of short-and long-term expectations and evolutions in QOL while taking multidisciplinary decisions. Evidently, even the most detailed long-term outcome and QOL data cannot replace clinical evaluation of the individual patient or overrule a patient's personal view, though they certainly assist in taking an informed decision. Future research in QOL should ideally incorporate the perspective of the individual in order to enable valid conclusions to be derived based on content that is relevant to the individual being assessed, thus informing management decisions, policy and practice more meaningfully [107].

2. ICU and hospital level: improving outcomes by preventive measures

2.1. Triage upon ICU admission

Through our research and through the recently expanding current literature, we now have a better understanding of long-term outcomes and QOL in critically ill patients. Long-term QOL is impaired compared to baseline and lower than QOL in the general population. It is therefore essential to identify these patients who are most likely to benefit from critical care, not only to prevent suffering from unnecessary treatments but also to optimise the use of resources. Reaching this balance is difficult and would be easier with reliable prognostication, which unfortunately has been proven to remain challenging at the moment. The classical ICU scoring systems frequently take age and comorbidity into account but they are not adapted to the specific characteristics of the individual patient and they are not designed for triage [30, 31]. Routine knowledge and implementation of bedside QOL instruments, such as the EQ-5D with immediate and automatic calculation of UI - to acknowledge baseline situation - will already give some information concerning outcome and future long-term QOL, in combination with comorbidity, functionality, age, social environment, and frailty assessment. It should become an automatism to assess all these factors before or at ICU admission, next to medical history, use of medication, and a clinical examination, to estimate patients' prognoses at longer-term. Even small changes in QOL may be of importance to patients and QOL data should therefore be used to inform patients.

Additionally, when deciding to refer or admit a patient to the ICU, prognostications at the individual level in critically ill patients should consider the whole health process rather than focusing on the ICU period alone. This remains however extremely difficult because many factors related to the underlying disease, the acute severity of illness, and projections on future treatment have to be taken into account.

An equally important part of a well-considered ICU admission policy is knowledge of the patient's wishes, preferences and thoughts before or at ICU admission. This is what personalized medicine differentiates from precision medicine. It takes into account the patient's personality, preferences, values, goals, health beliefs, social networks, financial resources, and life circumstances – "the personomics" of the

patient [108]. It has been demonstrated, particularly in the older population, that physicians frequently do not seek or are unaware of patient's preferences regarding ICU admission or level of ICU treatment, although their decisions and actions during ICU stay are frequently based upon a patient's wishes and may even change when knowing these choices [109-112]. Good insights of a patient's wishes may not only assist clinicians in providing better and more patient-centered care, it may finally help to transform healthcare [113]. Survival per se should not be our only aim, rather survival with a good QOL, or al least a QOL that matches a patient's preference [114].

2.2 Clinical patient-centered outcome prediction tool

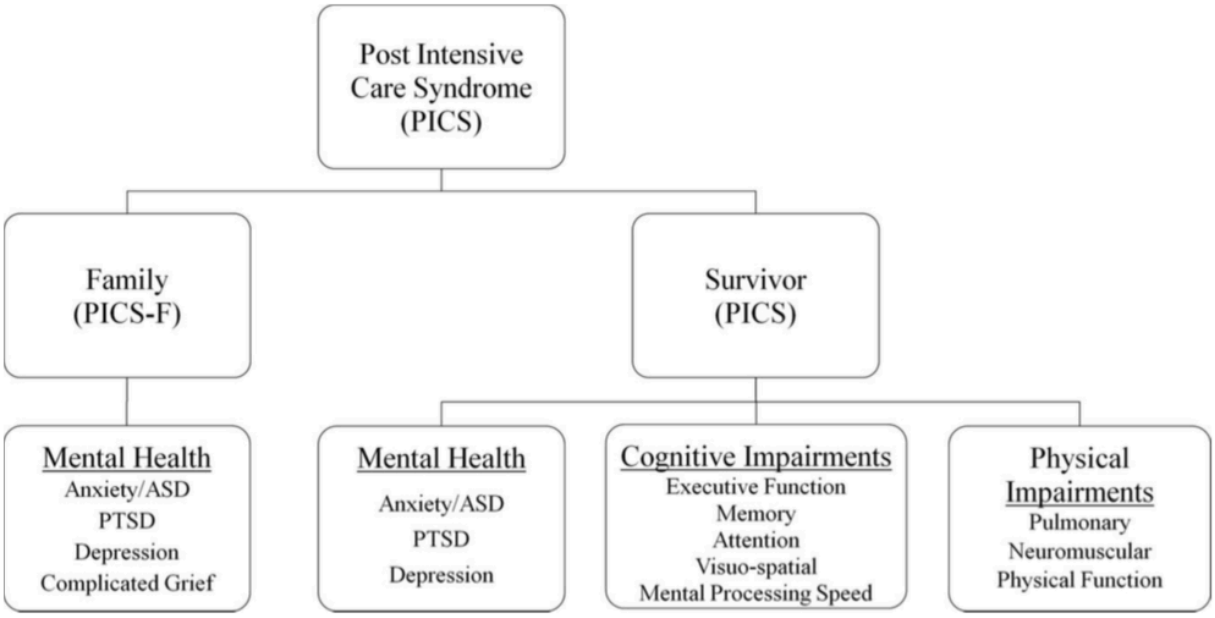
When referring a patient to the ICU, QOL is frequently of secondary importance when medical outcomes – particular survival – can be significantly affected by critical care treatment. Clinicians often do not have sufficient confidence in QOL data to incorporate them in clinical decision-making, because of lack of knowledge, experience and understanding of the measurements and scores. However, estimation of the benefits of an ICU admission should be considered not only in terms of survival but also taking into account the restoration of an acceptable QOL. A prediction model for long-term QOL based upon readily available data could therefore help critical care physicians to triage patients for ICU admission, to identify those patients who will return to their baseline functionality, or those who will need a long revalidation. It could also help to inform patients and families in a reliable way, to guide in treatment decisions, and it could eventually help to transform future healthcare by making better prospects of recovery and better allocation of resources. Although it is not defined to what level prediction models could be helpful, they certainly might facilitate decisions, which otherwise should have been taken based upon subjective evaluation alone. Our developed D1-prediction model will therefore rather inform and reinforce clinical judgments, as recommendations for further care highly correlate with physician's estimations of a good long-term QOL [102, 115]. As highlighted earlier, further research should focus on prospective external multicenter validation of our D1-prediction model and our longitudinal prediction model for long-term QOL.

2.3 Strategies to decrease long-term consequences of critical illness

2.3.1 Increasing awareness of PICS and PICS-F

As shown in literature and in our studies, many critically ill patients will suffer from long-term consequences of their acute illness on the physical, mental and or cognitive level. "Post-Intensive Care Syndrome" (PICS) was agreed as the recommended term to describe these new or worsening physical, mental or cognitive problems arising after a critical illness and persisting beyond acute care hospitalization. The term could be applied to either a survivor or family member (PICS-F) [10, 116, 117]. Although the

critical care community is becoming increasingly aware of PICS or PICS-F, patients, families, and the post-hospital care community need more information. This is important since awareness can decrease fear of the unknown, decrease feelings of being unique, alone, abandoned, or of something else being terribly wrong with them, and alert them meanwhile to the possible need for follow-up assessments and prevent unrealistic expectations and frustrations [118]. A clear information brochure dedicated to PICS should be available on the ICU and should be provided to patients and/or families ad risk for PICS or PICS-F.



From: Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012; 40:502-509

In order to increase awareness of PICS, the American Society of Critical Care Medicine (SCCM) established a Wikipedia section, videos on YouTube with patients and families describing their experiences, and a "PICS" pamphlet on their website. Dedicated websites with specific information on the ICU environment and on post-ICU and post-hospital care may be a source of feedback, information, comfort, less stress, and continued follow-up for patients, families, outpatient clinicians or general practitioners [119]. Although such websites already exist in other countries (www.fcic.nl; www.aftertheicu.org; www.intensiva.it; www.opeenicliggen.nl), it would be an opportunity for our ICU department and our hospital to develop a similar website but with the additional unique possibility of a personal login to receive - as a patient or as a family member - very specific patient- or family-centered information tailored upon the critical illness and health state of the individual patient. It would also be an opportunity to receive, as critical care physician, data from the patient or family concerning physical, mental and cognitive functioning for further research and to give advise upon the most appropriate aftercare for that moment.

2.3.2 Implementation of the ABCDEFGH bundle

Patient risks for PICS include immobility, duration of sedation and mechanical ventilation, length of ICU stay, delirium, sepsis, ARDS, hypoglycemia, and hypoxia [118]. An important preventive measure to reduce the prevalence of these risk factors is the implementation of the multifaceted "ABCDEFGH" care bundle, which stands for Airway and Awakening management, spontaneous Breathing trials, Coordination of Care and Communication, Delirium assessment and treatment, Early mobilization, Family involvement, Good handoff communication, and Handout material for PICS and PICS-F [118]. Each component of this bundle addresses a specific practice in the ICU independently associated with improved patient-centered outcomes. The effectiveness and safety of the bundle was demonstrated in a before-and-after study [120], and the bundle also facilitated the implementation of the Pain-Agitation-Delirium guidelines of the SCCM [121]. Higher bundle compliance was associated with improved survival, and less delirium and sedation after adjustment for age, severity of illness and presence of mechanical ventilation [121].

Although its promising results, a worldwide survey showed that only 57% of all respondents had implemented this bundle with high variations across implementation of the individual components. Use of sedation and pain scales scored the best, moderate adherence scores were seen for awakening trials, spontaneous breathing trails, and early mobilization. Low adherence was found in delirium assessment, and a minority reported their unit to be 24/7 open for family, or to have a dedicated psychologist to support families [122].

This reflects a compelling need for greater use and implementation of the ABCDEFGH care bundle to reduce or prevent PICS in the future. Only a decade ago, the majority of ICUs - including ours - were closed to family members – with exception of 2 very short visit moments a day - practicing heavy sedation and ventilation, and patient immobilization. Now, the ABCDEFGH care bundle reflects a shift away from this approach to a "less is more" culture in the ICU with less sedated or awake patients, who are breathing spontaneously as quick and as much as possible and who are mobilized early and more actively, to reduce the deconditioning and dysfunction so often seen in ICU survivors [123]. The attention lies also in a more multidisciplinary approach with an important role for physiotherapists and psychologists. This culture shift needs time to expand and to become standard of care, which is normal for every change in practice. In our ICU, the implementation of the bundle goes further, and compared to some years ago, progression has certainly been made on all different components.

However, family involvement in rounds or in care is still rarely done. An open ICU visitation policy is uncommon, also in our ICU, where pure architecturally it is almost impossible for families to stay 24/7. Although we are now more flexible regarding visiting hours and visiting possibilities, there is need to improve or change our interactions with family members in the future [124].

2.3.3 Attention for the environment of care

More attention should be paid to provide a more healing and compassionate environment that can decrease anxiety and delirium and promote sleep in critically ill patients. It is therefore important to attend to room temperature and lighting, decrease noise and false alarms, to make sure the patient can use their glasses or hearing aids if necessary, and promote feasibility of family presence and family participation in care. Future ICU departments and future hospitals should be designed and should be built taking this into account.

2.3.4 Implementation of ICU step-down units: "The Intensive Care Recovery Center" (IRC)

Most ICU patients, once their acute medical problems are resolved, will be discharged to the general ward. However, many of these patients will still be very weak and the step from the intensive care unit and intensive monitoring at the ICU to the general ward will be (too) big. Premature discharge from the ICU is associated with higher risk of death [125]. The complexity and magnitude of the physical, mental and cognitive rehabilitation in combination with further recovery from elaborate organ-related problems may exceed the capacity of the ward where the nurse to patient ratio is far below that of the ICU.

Earlier discharge from the ICU for patients needing more care than could be provided on general wards may be facilitated by **a** specifically designed ICU step down-unit. Patients expressed a preference to name this ICU-step down unit the "Intensive Care Recovery Centre" (IRC), combining both the aspects of an ongoing need for care and need for recovery. The IRC should be a department, only dedicated for former ICU patients and parallel to the intensive care unit, that has the potential for intensive physical rehabilitation, which should be done by critical care physiotherapists and specific rehabilitation specialists in close collaboration with critical care physicians. Mental and cognitive recovery should be equally treated with intensive training and care of psychologists and occupational therapists. The IRC should also have no family visiting restrictions and facilitate presence and aid of close family members.

We prefer a parallel model of such an IRC because we see many advantages: excellent treatment continuity in the transfer from ICU to IRC with no or very little loss of information, a very short transfer distance between ICU and IRC, simplified patient allocation, a common use of intensive care technical devices (if needed), a common administration, and high flexibility in the exchange of medical and paramedical personnel between ICU and IRC. An integration model – where IRC patients stay at the ICU department – has as most important disadvantage that IRC-patients are obligated to rehabilitate in the turbulent environment of an ICU, which is not designed for that purpose, and where it will be less feasible for family to have the possibility to be present 24/7. An independent model (stand alone unit) could be useful as a specialized treatment unit for specific patients, such as a coronary care or a stroke unit, but not as recovery unit for such a heterogeneous and weak patient group as former complex ICU patients [126].

Defining which patients should be transferred from the ICU to the IRC can only be done in a very general way, as conditions will be very patient-specific. Overall, these patients should have an ongoing need of care and monitoring but at another level and in another way than ICU patients. This also will be reflected in a, compared to the ICU, lower nurse-to-patient ratio (and lower costs), from 1:2 to 1:3 or 1:4 depending on complexity of the patients and time of the day. IRC-patients will no longer need invasive mechanical ventilation or vasopressors but they will need intensive revalidation, before discharge to the general ward can be considered. A dedicated team of critical care physicians, critical care nurses, physiotherapists, occupational therapists, psychologists and rehabilitation physicians should have the leading of this IRC. Defining the need for the number of beds in such an IRC is difficult, as there is no reliable information of an upper limit for bed numbers in such a step-down unit. We propose for our hospital, as tertiary care center, at least 10 to 12 beds; larger units will be more difficult to manage [126].

3. Post-hospital level: improving outcomes by intervention measures

3.1 Post-discharge follow-up programs

An intervention measure to treat patients with PICS is the implementation of an ICU follow-up clinic. Post-hospital follow-up clinics or consultations will give us a better understanding of specific problems in physical, mental or cognitive functioning. The information gained through these consultations can be used to improve critical care itself and can be itself a quality service for patients and their relatives [4]. Still, these follow-up consultations are yet not commonplace in critical care. Traditionally seen, critical care is not a medical subspecialty that has a well-established patient follow-up program and follow-up consultations are not common. Ultimately, many critically ill patients will get their medical follow-up by an organ specialist or by their general practitioner. Both may have a limited knowledge of what happened during ICU stay and therefore, both may have difficulties to have good insights into the post-ICU related problems of the patient. The critical care physician together with an ICU psychologist, a rehabilitation specialist, and dedicated ICU nurse may be in a better position to understand the consequences that patients suffer from after having survived their critical illness. They also may better understand which interventions may improve outcome. Continuity of care through the continuum of care is therefore a challenge.

Consequently, ICU-aftercare needs a better and more structured organization. In the UK, around 30% of ICU departments run a follow-up clinic [127]. Although it seems as though post-discharge rehabilitation with specific programs and follow-up clinics would be a logical way to address PICS, until now, ICU follow-up clinics or randomized controlled trials concerning specialized rehabilitation programs versus standard care, still not have proven their benefit [118, 128-131]. The effect of ICU-follow-up

consultations improved when the ICU diary, kept by relatives and/or members of the ICU team, was discussed [132].

At the moment, there are no gold standards for post-ICU follow-up programs but a pragmatic model in the Scandinavian countries and clear recommendations in the Netherlands have been formulated [133, 134]. Nevertheless, a recent electronic survey of ICU-aftercare in Denmark demonstrated an abundant heterogeneity of criteria and interventions [135]. So, many questions still arise. Who will fund this follow-up? Which patients should be targets for ICU-follow-up clinics, the sickest of the sick or just any ICU survivor? It is common to think of ARDS patients, sepsis patients, patients with prolonged mechanical ventilation, or patients with a prolonged ICU stay. What kind of post-ICU intervention do these patients need? They will certainly need physical, functional and cognitive rehabilitation but they will also need education, information and care coordination for transition to primary care in the future. What should be offered: a rehabilitation package, post-hospital visits and dialogue, or smartphones apps with advices for self-rehabilitation? Where? What is the best timing? At this moment, the optimal time to start with these follow-up consultations after ICU-discharge, the best time interval between visits or the best place for these follow-up visits are still unknown.

Although there is no proven benefit of ICU-follow-up consultations at the moment, intuitively we might assume that they may be important for both patients and relatives. It might be possible that we cannot measure the possible positive effects of post-ICU follow-up through easy measurable biomedical tests. Walsh et al. found a higher patient satisfaction with many aspects of recovery in the intervention group where patients received more physical and nutritional rehabilitation and more information compared to the standard group [131]. Overall, where extended ICU follow-up existed, patients reported great satisfaction with the service [127, 136].

As long-term outcomes and QOL can be very different from patient to patient, so must be any kind of revalidation too. Patients with PICS are a very heterogeneous group of former critically ill patients who will rehabilitate in a different way and where one patient will respond better to a certain therapy than the other. So an individually based rehabilitation program should therefore possibly be preferred above the "one size fits all" approach, which will make the whole discussion concerning post-ICU follow-up interventions even more difficult.

Trying to implement post-ICU follow-up consultations without evidence and with many barriers is hard. Common barriers for implementation of post-ICU follow-up are low evidence, no concept of proof, no funding, no staff, no place, too complicated, no clinical benefit, no quick fix, and not scalable. However, based upon a small pilot study we performed regarding feasibility of establishing post-ICU follow-up consultations 3 months after ICU discharge (unpublished data), I strongly belief it could help some patients, although it might indeed be strongly individually based. Our study sample was small, but all the 43 patients

we saw appreciated these follow-up consultations. Most patients were accompanied by a close relative, either a husband or wife, or one of their children. During the consultation, the former ICU-patients had to complete the EQ-5D, the HADS, the PTSS-14, and the MoCA tests in a face-to-face interview [8, 18-22]. Next to these assessments, we also asked about their living circumstances, return to work plans, weight loss and gain, perceived changes in taste, problems with talking, swallowing, eating or sleeping, sexual problems, driving a car possibilities, financial problems, healthcare utilization, current use of medication, and appreciation of the follow-up consultation. All patients and their family were happy to come back and to tell their story about their experiences while being on the ICU and post-ICU and post-hospital. They felt respected and appreciated the follow-up initiative a lot. We have to acknowledge that we only saw a selection of "the best" post-ICU patients as the ones who still needed more care and inpatient recovery were admitted to special care facilities and were unable to attend the consultation 3 months after ICU discharge.

So further research is absolute needed to provide a clear "pro or con" based evidence for post-ICU follow-up consultations. In my opinion, these post-ICU follow-up consultations should become an integrated part in the general strategy of patient well-being and recovery. For patients for whom it may be less convenient to visit the post-ICU follow-up clinic due to long travel distance or transportation problems, a telephone follow-up or a dedicated, individualized and well-developed website could be of help, as highlighted earlier. Such a website could also be informative and of help for many others, such as general practitioners, physiotherapists, revalidation physicians, etc.

3.2 Peer support

At this moment, our ICU-psychologists started a new initiative where ICU-survivors can meet ICU physicians, physiotherapists, psychologists, and other former ICU-patients in the very informal environment of a pub and talk about their experiences during and after ICU. These "drop-in" meetings started in November 2017 and future meetings in 2018 have been planned. As survivors and their caregivers have first-hand experience of the challenges that survivors face, they are well suited to educate and prepare peer survivors for certain aspects of the recovery process [137]. They can also be an inspiration for professional caregivers in their understanding and improving of the rehabilitation after ICU.

Bigger events and groups for specific former ICU-patients such as Transplantoux, for patients who received a solid organ transplant, already have proven their success [138].

4. Health-economics level: resource allocation

The costs of intensive care are high and consume a large fraction of available resources for health care. A significant amount of resources in the ICU are devoted to patients with a poor prognosis, and many

of them will ultimately die or survive with a poor QOL. Given this, there is an increasing pressure to examine, evaluate and justify utilization of critical care resources. Further research and insights into patient preferences and long-term outcomes combined with cost-effectiveness and cost-utility studies are necessarily to improve allocation of scarce resources [139].

Cost-utility studies analyze costs per quality adjusted life years (QALYs) and allow for comparisons between certain therapies. QALYs are measures that combine duration and quality of life, thus capturing both the effects of therapy or interventions and consequences of a disease. They are calculated based upon the patient's estimated survival time while weighing each life year by a QOL index value, for example the UI of the EQ-5D. A better understanding of long-term QOL will also lead to a better estimation of QALYs, but still, decisions to optimize resource allocation will remain difficult in critically ill patients.

So how will the future of healthcare expenditure in critical care medicine look alike? Governments will make further choices to minimize expensive care based upon quality improvement programs. Techniques and treatments will focus on reducing the need for inpatient hospital care and promote outpatient treatment, eventually leading to hospitals with relatively more ICU beds [140]. This does not imply that intelligent allocation of resources in critical care medicine will no longer be necessary. On the contrary, the crucial question will still be how to select these patients who will benefit the most from ICU treatment to aim for a cost-effective use of ICU beds. Prevention of high costs for patients with a limited life expectation and poor long-term outcomes will be the main tool for optimizing the use of scarce resources. A better knowledge of long-term outcomes, more transparency and insights into costs and benefits of certain medical treatments, combined with a good well thought out admission policy, and well-considered EOL-decisions, in respect with the individual patient's values and preferences, might improve cost-efficiency in the future.

V. Summary

Our research concentrated around 3 major issues: 1/ reviewing literature and applied methodology concerning long-term QOL and outcomes research, 2/ assessing long-term outcomes and QOL in specific critically ill patient populations where there are often doubts concerning effectiveness of critical care, or where the start of specific treatments during ICU stay can be questioned (namely the oncological-hematological, AKI-RRT and older (≥80 years) patients), and 3/ developing a prediction model for long-term QOL based upon readily available variables at the first day of ICU admission and so determining the most important predictors for long-term QOL.

In our review article, we found that at least one year after ICU, critically ill patients had a lower QOL than an age-and gender matched general population. It was difficult to withhold certain factors with impact on long-term QOL due to huge variations in methodology and study design, patient populations, applied QOL instruments, follow-up periods, and response rates through the included articles. Recently, more attention has been paid to this problem and international societies now focus on the need for more standardization in outcomes research.

It is difficult to select the most appropriate QOL survey(s), both in number, in content and in timing. As QOL is a patient-centered and subjective outcome parameter by itself, we believe that the use of validated tools to assess QOL is an absolute must. Through our research, we chose to assess QOL by the EQ-5D and SF-36 because these are generic instruments commonly used in critical care; they have a well-known validity, reliability, and are responsive to changes in health. As they do not assess memory, concentration, the ability to complete tasks, problem solving, or decision-making, we added a sixth dimension “cognition” to the EQ-5D.

We assessed baseline mortality rates (ICU and hospital mortality) and baseline QOL (defined as QOL 2 weeks before ICU admission), and at 3 months and 1 year after ICU discharge. In the study concerning AKI-RRT and older patients, we also assessed living status and QOL at respectively 4 years and at 7 years after ICU discharge. We found high mortality rates in all groups of critically ill patients we studied, especially in the first 3 months since ICU admission, with only moderate increase of mortality at longer follow-up. These mortality rates were however comparable with the numbers found in literature.

The measures of long-term QOL put surviving a critical illness into a larger perspective. We found that the critically ill patients in our research had a lower long-term QOL, mainly in the physical dimensions, than a general population, but a slow improvement in QOL over time could be seen, although it remained under baseline level. In our review study, we found that patients with severe ARDS, prolonged mechanical ventilation, severe trauma, and severe sepsis appeared to have the worst reductions in QOL, which lasted a long time. The impact of diagnostic category upon long-term QOL was also reflected in our prediction model; with surgical patients having a significantly better predicted long-term QOL than medical patients.

Evidently, the included cancer, AKI-RRT and older patients represented not only a highly diverse spectrum of diseases but also patients with a very heterogeneous performance status and co-morbidity. As such, outcomes should be differentiated among subgroups.

We found important differences between solid tumor patients and hematological patients with hematological patients having a worse QOL on every moment of the study period, and experiencing no significant improvements beyond 1 year. Differences in QOL between AKI-RRT and their non-AKI-RRT matches at each different time point were very small. This implied that the RRT component during critical illness did not have an important impact on long-term QOL. Overall, long-term QOL remained under the baseline level for AKI-RRT and non-AKI-RRT patients, and under the QOL of the average population, specifically in the more physical domains. Determining patients who should benefit the most from ICU admission becomes more and more complicated, and this is particularly the fact in patients aged 80 years or older. The long-term QOL in the critically ill older patients in our study was low compared to a general population, particularly in self-care, usual activities and the physical domains, with an increasing number of patients experiencing more problems over time. These older patients however recognized little changes in QOL over time except for mobility and self-care. Older patients adapted well to their advanced age and perceived their overall QOL as acceptable. It suggests that QOL might have another meaning for older patients, with social and mental values being far more important than limited physical functioning.

A difference has to be made between QOL measurements and perception of QOL as experienced by the patient himself, assessed by the VAS**.** Oncological patients had a better perception of their QOL compared to hematological patients, but for both groups QOL was still acceptable. AKI-RRT patients perceived QOL as good and both AKI-RRT and non-AKI-RRT patients reported low dependence in daily life later on. This perception of a fair QOL was also illustrated by the fact that the vast majority of all our included patients who were alive after 1 year or even longer wanted to be readmitted to an ICU in case of deterioration.

Our research was observational, so looking for causes or explanations for long-term QOL is difficult. However, we developed a prediction model for long-term QOL and hence, tried to determine the most important variables for predicting this outcome. We found a very strong positive relation of baseline QOL with long-term QOL in our D1-prediction model. This illustrates the requirement of knowledge of baseline condition to make any prediction on outcome at long-term. Variables negatively related with mean QOL at 1 year were an oncological or hematological disease, older age, limitations in functionality, a higher severity of illness, organ failure with need for mechanical ventilation or vasopressors, and a high comorbidity. Although only 40% of the variability in long-term QOL could be explained by our prediction model, it might certainly facilitate decisions, which otherwise should have been taken based upon subjective evaluation alone.

Based upon literature and based upon our research, we may conclude that the most important determinants of long-term QOL are baseline QOL, co-morbidity, age, functionality, and social interplays. Although we clearly demonstrated the impact of age on long-term outcome in older patients, in cancer patients and in our D1-prediction model, age remains a difficult parameter to handle in outcome research. In fact, biological age as comorbid burden is more important than chronological age. The concept of "frailty" as marker of biological age reflects a decline in reserve and function and accordingly, may represent a more robust predictor of vulnerability and recoverability than chronological age alone. Although frailty is frequently associated with advanced age, younger patients can also be frail. In any age group, assessing frailty is therefore a good parameter to outweigh the balance between the burden of ICU management and the goal to restore an acceptable QOL that is meaningful based on life expectancy.

Through our research and through the recently expanding current literature, we now have a better understanding of long-term outcomes and QOL in critically ill patients. There is no doubt that critical illness affects long-term outcomes in the physical, mental, and cognitive dimensions, a syndrome which was recently defined as "PICS". Implementation of the ABCDEFGH bundle during ICU stay could be the first step to prevent patients from developing PICS. This bundle implies a shift in culture at the ICU, with less sedated patients, who are breathing spontaneously as quick and as much as possible and who are mobilized early and more actively. The attention will lie in a more multidisciplinary approach with an important role for physiotherapists, psychologists, and more family involvement. This culture shift needs time to expand and to become standard of care.

Although the critical care community is now becoming increasingly aware of PICS, patients, families, and the post-hospital care community need more information. This is important since awareness can decrease fear of the unknown, and alert them meanwhile to the possible need for follow-up assessments and prevent unrealistic expectations and frustrations. Dedicated websites or apps with specific information on the ICU environment and on post-ICU and post-hospital care may be a source of feedback, information, comfort, and continued follow-up for patients, families, outpatient clinicians or general practitioners. It would also be an opportunity to receive, as critical care physician, data from the patient or family concerning post-hospital physical, mental and cognitive functioning for further research and to give advise upon the most appropriate aftercare for that moment.

ICU step-down units to facilitate the step towards the general ward and post-ICU follow-up consultations may be future initiatives to further improve long-term outcomes, QOL and cost-effective care in critically patients.

VI. Samenvatting

Het onderzoek in deze doctoraatsthesis concentreerde zich op 3 belangrijke domeinen: 1/ het bestuderen van de literatuur aangaande levenskwaliteit (QOL) op lange termijn en van de toegepaste methodologie, 2/ het analyseren van lange-termijn gevolgen en QOL bij die kritiek zieke patiënten waar er vaak twijfels zijn over de effectiviteit van Intensieve zorg (IZ), of waar de start van bepaalde behandelingen tijdens de IZ-opname in vraag wordt gesteld (met name de oncologische-hematologische, de AKI-RRT, en de oudere (≥80 jaar) patiënten), en 3/ het ontwikkelen van een predictiemodel voor QOL op lange termijn, gebaseerd op gegevens die beschikbaar zijn op de eerste dag van IZ-opname.

In ons overzichtsartikel vonden we dat, minstens 1 jaar na ontslag van IZ, kritiek zieke patiënten een verminderde QOL hadden ten opzichte van een algemene populatie met vergelijkbaar geslacht en leeftijd. Het was moeilijk om bepaalde factoren te weerhouden die een impact hadden op lange termijn QOL door grote variaties in methodologie en studie design, patiëntenpopulaties, gebruikte meetinstrumenten voor QOL, opvolgperiodes, en responspercentage binnen de geïncludeerde artikels. Recent is er meer aandacht voor dit probleem en internationale verenigingen concentreren zich op de nood voor betere standaardisatie binnen outcome onderzoek.

Het is moeilijk om de meest geschikte vragenlijsten te selecteren voor het meten van QOL, zowel naar inhoud als naar timing. Gezien QOL een patiënt-gerichte en subjectieve parameter is op zich, vinden we dat het gebruik van gevalideerde vragenlijsten om QOL na te gaan, een echte “must” is. Binnen ons onderzoek kozen wij voor de EQ-5D en de SF-36 vragenlijsten omdat het algemene vragenlijsten zijn die vaak gebruikt worden binnen kritiek zieke patiënten. Ze hebben een goed gekende validiteit en betrouwbaarheid en zijn gevoelig voor veranderingen in de gezondheidstoestand van de patiënt. Deze vragenlijsten evalueren echter niet het geheugen, concentratievermogen, of mogelijkheden om opdrachten uit te voeren, problemen op te lossen, of om beslissingen te nemen. Daarom voegden we zelf een 6e vraag over cognitie aan de EQ-5D toe.

In ons onderzoek werd basis-mortaliteit (mortaliteitspercentage op IZ en in het ziekenhuis) en basis-QOL (gedefinieerd als QOL 2 weken voor IZ-opname) nagegaan, alsook 3 maanden en 1 jaar na ontslag van IZ. In de studies aangaande AKI-RRT patiënten en oudere patiënten werden mortaliteit en QOL ook nagegaan na respectievelijk 4 en 7 jaar na ontslag van de IZ-afdeling. We vonden hoge mortaltiteitspercentages in alle groepen van IZ-patiënten binnen onze studies, voornamelijk in de eerste 3 maanden sinds IZ-opname, met enkel een matige toename op langere termijn. Deze mortaliteitscijfers zijn vergelijkbaar met diegene die beschreven worden in de literatuur.

QOL op lange termijn plaatst het overleven van een kritieke ziekte in een ander perspectief. De kritiek zieke patiënten binnen ons onderzoek hadden een lagere QOL op lange termijn, voornamelijk op

fysiek vlak, in vergelijking met de algemene bevolking. Een trage verbetering van QOL kon worden waargenomen, maar deze bleef wel onder het niveau van de basis-QOL. In ons overzichtsartikel zagen we dat voornamelijk patiënten met een ernstig ARDS, langdurige mechanische ventilatie, na een zwaar trauma of na ernstige sepsis de meest uitgesproken vermindering hadden in QOL. Deze daling in QOL hield lang aan. De impact van een bepaalde diagnose op lange-termijn QOL werd ook teruggevonden in ons predictiemodel waar chirurgische patiënten een significant betere voorspelde lange-termijn QOL hadden dan medische patiënten. Het is dan ook logisch dat onze geïncludeerde kanker-, AKI-RRT, en oudere patiënten niet enkel een zeer divers spectrum van zieke patiënten vertegenwoordigden, maar ook patiënten waren met een verschillende functionaliteit en comorbiditeit bij aanvang van de IZ-opname. Bijgevolg moet outcome gedifferentieerd worden tussen deze verschillende patiëntengroepen.

Er waren belangrijke verschillen tussen oncologische en hematologische patiënten, waarbij de hematologische patiënten op elk ogenblik van de studie een slechtere QOL hadden dan de oncologische patiënten, en waarbij er geen significante verbeteringen waren binnen het jaar. De verschillen tussen AKI-RRT en niet AKI-RRT patiënten waren op elk gemeten tijdstip erg klein. Dit zou kunnen betekenen dat de factor “dialyse” weinig impact had op lange-termijn QOL. In het algemeen was de lange-termijn QOL voor AKI-RRT én niet AKI-RRT patiënten onder het basisniveau van QOL en lager dan de QOL van de algemene bevolking, voornamelijk op fysiek vlak. Bepalen welke patiënten het meest voordeel halen uit een IZ-opname is erg complex, en dat is voor zeker zo voor de groep van oudere patiënten. De lange-termijn QOL in deze groep van patiënten was laag in vergelijking met een algemene populatie. Voornamelijk op fysiek vlak, zelf-zorg en dagdagelijkse activiteiten werden er meer en meer problemen waargenomen over het verloop van tijd. Toch ervaarden oudere patiënten, behalve in mobiliteit en zelf-zorg, weinig verandering in QOL. Oudere patiënten pasten zich in het algemeen vrij goed aan aan hun gevorderde leeftijd en vonden hun QOL aanvaardbaar. Dit suggereert dat QOL voor oudere patiënten een andere betekenis heeft, waarbij een goede sociale omgeving en een goede mentale functionaliteit van veel groter belang zijn dan een verminderde mobiliteit of zelf-zorg.

Daarom is het belangrijk een verschil te maken tussen de gemeten QOL en de QOL zoals die ervaren wordt door patiënten. Deze perceptie van QOL kan worden nagegaan via de VAS. Oncologische patiënten hadden een beter perceptie van hun QOL dan hematologische patiënten maar voor beide groepen was de lange-termijn QOL aanvaardbaar. Ook voor AKI-RRT en niet AKI-RRT patiënten was de lange-termijn QOL erg aanvaardbaar en beide patiëntengroepen hadden van een vrij onafhankelijk leven op lange termijn. Deze perceptie van accepteerbare QOL op lange termijn werd ook bevestigd door het feit dat de grote meerderheid van al onze geIncludeerde studiepatiënten opnieuw wensten opgenomen te worden op een IZ-afdeling indien dit nodig zou zijn.

Ons onderzoek was observationeel dus oorzaken of verklaringen vinden voor lange-termijn QOL was moeilijk. Desondanks konden we door het ontwikkelen van een predictiemodel voor QOL op lange termijn wel enkele factoren selecteren die belangrijk bleken voor lange-termijn QOL. We vonden binnen ons D1-predictiemodel een zeer sterke positieve relatie tussen basis-QOL en lange-termijn QOL. Dit illustreert het belang van het kennen van deze basisconditie om enige inschatting te kunnen maken op langere termijn. Variabelen die negatief gerelateerd waren aan lange-termijn-QOL waren de aanwezigheid van een oncologische of hematologische aandoening, oudere leeftijd, verminderde functionaliteit, een grotere ernst van ziek-zijn, orgaanfalen met nood aan mechanische ventilatie en/of vasopressoren, en een grotere comorbiditeit. Ondanks het feit dat we slechts 40% van de variabiliteit in lange-termijn QOL konden verklaren door ons predicitiemodel, zal dit model ons toch kunnen helpen met het nemen van bepaalde beslissingen die anders louter op subjectieve basis zouden genomen zijn.

Gebaseerd op ons predictiemodel en op de literatuur, kunnen we besluiten dat basis-QOL, comorbiditetit, leeftijd, functionaliteit en sociaal milieu de meest belangrijke factoren zijn die invloed zullen hebben op lange-termijn QOL. Ondanks het feit dat we de invloed van leeftijd op lange-termijn QOL duidelijk konden aantonen bij ouderen, bij kankerpatiënten en in ons predictiemodel, blijft leeftijd een moeilijke parameter in outcome onderzoek. Eigenlijk is biologische leeftijd van groter belang dan kalenderleeftijd. Het concept van “frail-zijn” als merker van deze biologische leeftijd kenmerkt een vermindering in fysiologische reserve en functie en zal een betere voorspellende waarde hebben voor kwetsbaarheid en mate van revalideerbaarheid dan kalenderleeftijd alleen. Deze mate van frail-zijn wordt vaak geassocieerd met hogere leeftijd maar ook jongeren kunnen evengoed frail zijn. Daarom zal, in welke leeftijdsgroep dan ook, het bepalen van dit frail-zijn een goede parameter zijn om de impact van het kritiek ziek-zijn af te wegen ten opzichte van mogelijkheden tot herstel naar een aanvaardbare QOL.

Door ons onderzoek en door de recent toegenomen literatuur hebben we nu een beter inzicht in lange-termijn outcome en QOL in kritiek zieke patiënten. Er is geen twijfel meer dat dit kritiek ziek-zijn de lange-termijn outcome zal beïnvloeden op fysiek, mentaal en cognitief vlak; een syndroom dat recent “PICS” werd genoemd. Het implementeren van de “ABCDEFGH” zorgbundel kan een eerste stap zijn ter preventie van PICS bij patiënten opgenomen op IZ. Deze bundel veronderstelt wel een zekere cultuursverandering op IZ, waarbij patiënten minder én minder lang gesedeerd zullen zijn, meer en sneller spontaan zullen ademen en meer en actiever zullen gemobiliseerd worden. Er zal meer aandacht zijn voor een multidisciplinaire samenwerking waarbij kinesisten, psychologen en familieleden een belangrijke rol zullen spelen. Sowieso zal het tijd vergen vooraleer deze zorgbundel als algemene norm wordt erkend.

Ondanks het feit dat binnen de IZ-wereld er meer en meer erkenning en herkenning is van PICS, is het noodzakelijk om patiënten, familieleden, en post-hospitaal zorgverleners hierover goed te informeren. Deze informatie is belangrijk om angst voor het onbekende te voorkomen, om inzicht te geven in de nood

voor verder opvolging en om onrealistische verwachtingen en frustaties te beperken. Speciaal ontworpen websites en/of apps met goede informatie over IZ, de post-IZ periode en de post-hospitaal zorgverlening kunnen een bron zijn van feedback, uitleg, comfort, and continue opvolging van patiënten, familieleden, poliklinieken of huisartsen. Het zou tevens een opportuniteit zijn om als IZ-arts vervolg-data op fysiek, mentaal en cognitief vlak van de patient of familie te krijgen; data die belangrijk kunnen zijn voor verder onderzoek en die omgekeerd ook een zeer gerichte en persoonlijke nazorg naar de patient en familie mogelijk maken.

Step-down eenheden na een IZ-opname, om de overgang naar de algemene afdeling makkelijker te maken, en post-IZ opvolg consultaties kunnen initiatieven zijn in de toekomst die een verdere verbetering van lange-termijn outcome, QOL en een kosten-effectieve zorg in kritiek zieke patiënten mogelijk kunnen maken.

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Addendum

I. List of abbreviations

• ABCDEFGH bundle	Airway and awakening management, spontaneous breathing trials, coordination of care and communication, delirium assessment and treatment, early mobilization, family involvement, good handoff communication, and handout material for PICS and PICS-F
• ADL	activities of daily living
• AKI	acute kidney injury
• APACHE II	Acute Physiology and Chronic Health Evaluation II
• CFS	Clinical Frailty Score
• CKD	chronic kidney disease
• COSI	Costs and Outcome Study in the ICU
• D1	day 1 = first 24 hours of ICU admission
• DNR	do-not-resuscitate
• EOL	end-of-life
• EQ-5D	EuroQol-5Dimensions
• ESICM	European Society of Intensive Care Medicine
• ESKD	end-stage kidney disease
• HADS	Hospital Anxiety and Depression Scale
• HRQOL	health-related quality of life
• ICU	intensive care unit
• ICU-AW	intensive care unit-acquired weakness
• IRC	intensive care recovery center
• IZ	Intensieve Zorg
• LOS	length of stay
• MoCA	Montreal Cognitive Assessment test
• MOS	Medical Outcomes Study
• NEMS	Nine Equivalent of Nursing Manpower Use score
• NHP	Nottingham Health Profile
• PICS	post-intensive care syndrome
• PICS-F	post-intensive care syndrome-family
• PTSD	post-traumatic stress disorder
• PTSS-14	Post-traumatic Stress Syndrome 14-questions inventory
• QOL	quality of life

- QWB Quality of Well-Being
- RAND-36 RAND-36-item Health Survey
- RRT renal replacement therapy
- SCCM Society of Critical Care Medicine
- SF-36 Medical Outcomes Study 36-item Short Form Health Survey
- SIP Sickness Impact Profile
- SOFA Sequential Organ Failure Assessment
- TISS-28 Therapeutic Intervention Scoring System-28
- UI utility index
- UIb utility index at baseline (=2 weeks before ICU admission)
- UI1y utility index 1 year after ICU discharge
- VAS visual analogue scale
- VASb visual analogue scale at baseline (=2 weeks before ICU admission)
- VAS1y visual analogue scale 1 year after ICU discharge

II. Concise Curriculum Vitae

PERSONALIA

Name: OEYEN Sandra Germaine Raymonda

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DEGREES AND EDUCATION

Institution and location	Degree	Year	Field of study
Koninklijk Atheneum Malle, Malle, Belgium	Diploma of secondary school	1982-1988	Latijn-Wetenschappen
Ghent University, Ghent, Belgium	MD, with great distinction	1988-1995	Medicine
Ghent University, Ghent, Belgium	Certificate	1997	Advanced Anesthesiology
Ghent University, Ghent, Belgium	Anesthesiologist	1995-2000	Anesthesiology
Ghent University, Ghent, Belgium	Critical care physician	2000-2001	Critical Care Medicine
Ghent University, Ghent, Belgium	Certificate	2000	Emergency Medicine

POSTGRADUATE COURSES

Institution and location	Course	Year	Field of study
Society of Medical Decision Making, Atlanta, USA	Causal inference and causal diagrams in medical decision making	2004	Statistics
Hospital Erasme, Brussels, Belgium	Cardiovascular and respiratory physiology	2004	Critical care
Society of Medical Decision Making, Boston, USA	Changing physician behaviour	2006	Evidence based medicine
Vlerick School Gent-Leuven	Financial management in hospitals	2007	Economics
Ghent University, Ghent, Belgium	Statistics	2007	Statistics
Ghent University, Ghent, Belgium	Statistical analysis with PASW18	2010	Statistics
Ghent University, Ghent, Belgium	Multivariate analysis and logistic regression	2012	Statistics
Medical evaluation technology assessment, Ghent, Belgium	Economic evaluations in health science	2014	Health-economics
Ghent University, Ghent, Belgium	Train the trainer	2016	Management

EXPERIENCE IN CLINICAL TRIALS

- Experience as sub-investigator in several multicenter and internationals trials (phase II-IV) in the field of sepsis, ARDS and infectiology
- Principal investigator of the LIPOS™ study (GSK) (severe sepsis trial) 2005-2006
- Principal investigator of the ACCESS study (severe sepsis trial) 2009 - 2010
- Principal investigator of the Oasis study (severe sepsis trial) 2011-2012
- Country Coordinator for Belgium for the Eloise study (2013), endorsed by ESICM (principal investigator Maurizia Capuzzo)
- Country Coordinator for Belgium for the VIP1 study (2016), endorsed by ESICM (principal investigator Hans Flaatten)
- Country Coordinator for Belgium for the VIP2 study (2018), endorsed by ESICM (principal investigator Hans Flaatten)

PROFESSIONAL MEMBERSHIP

- European Society of Intensive Care Medicine

EDUCATIONAL TASKS

- Teaching pathophysiology in the 3rd year Medicine 2002 - 2011
- "Hemodynamic monitoring and shock in the ICU"; Continuing education of physician and nursing staff
- "Long-term outcomes"; Continuing education of physician and nursing staff
- " Vasopressors in the ICU"; Teaching in the 7th year Medicine: 2007-ongoing
- " Long-term outcomes"; Teaching in the 7th year Medicine: 2007-ongoing
- "Outcomes, quality of life, scoring systems"; Teaching in the Interuniversity postgraduate course critical care medicine: 2013-ongoing
- Reviewer function in different critical care journals: Critical Care Medicine, Intensive Care Medicine, Critical Care, Journal of Critical Care, British Medical Journal

A1 PUBLICATIONS

- **Adherence to and efficacy and safety of an insulin protocol in the critically ill: A prospective observational study.**
  Oeyen SG, Hoste EA, Roosens CD, Decruyenaere JM, Blot SI.
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- **Long-term outcome after acute kidney injury in critically ill patients.**
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- **Daily cost of antimicrobial therapy in patients with intensive care unit-acquired, laboratory-confirmed bloodstream infection.**
  Vandijck DM, Depaemelaere M, Labeau SO, Depuydt PO, Annemans L, Buyle FM, Oeyen S, Colpaert KE, Peleman RP, Blot SI, Decruyenaere JM.
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- **Hyperglycemia upon Onset of ICU-acquired Bloodstream Infection is Associated with Adverse Outcome in a Mixed ICU Population.**
  Vandijck DM, Oeyen S, Buyle FM, Claus BO, Blot SI, Decruyenaere JM.
  Anaesth Intensive Care 2008; 36: 25-29.

- **A 50-year old man with severe hypercalcemia: a case report.**
  K Van den Hauwe, SG Oeyen, BF Scrijvers, JM Decruyenaere, WA Buylaert.
  Acta Clin Belg 2009; 64: 442-446

- **Quality of life after intensive care: A systematic review of the literature.**
  Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM.
  Crit Care Med 2010; 38: 2386-2400

- **Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: a single center study.**
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  Poster presentation at the 38th International Symposium on Intensive Care and Emergency Medicine (March 2018, Brussels); the abstract will be published in a Supplemental edition of Critical Care 2018

III. Additional publications related to the subject of the thesis

Long-term outcome and health-related quality of life in difficult-to-wean patients with or without ventilator dependency at ICU discharge: a retrospective cohort study.
Published as Depuydt P, Oeyen S, De Smet S, De Raedt S, Benoit D, Decruyenaere J, Derom E. Long-term outcome and health-related quality of life in difficult-to-wean patients with or without ventilator dependency at ICU discharge: a retrospective cohort study. BMC Pulm Med 2016; 27:133

The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years).
Published as Flaatten H, De Lange DW, Morandi A, Andersen FH, Artigas A, Bertolini G, Boumendil A, Cecconi M, Christensen S, Faraldi L, Fjølner J, Jung C, Marsh B, Moreno R, Oeyen S, Öhman CA, Pinto BB, Soliman IW, Szczeklik W, Valentin A, Watson X, Zaferidis T, Guidet B; VIP1 study group. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). Intensive Care Med 2017; 43: 1820-1828

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It’s not about the destination,

it is about the ride.