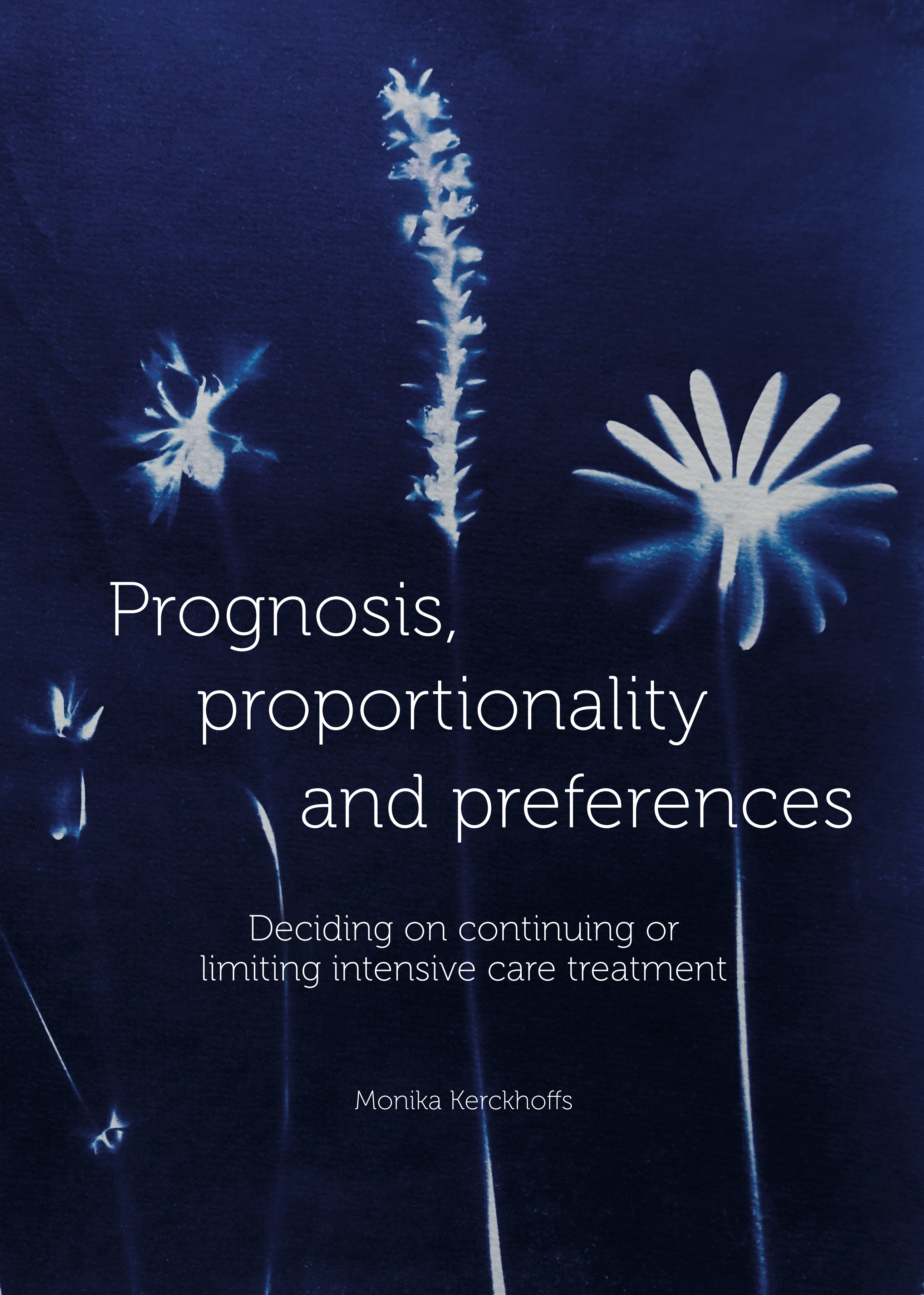


Prognosis, proportionality and preferences

Deciding on continuing or limiting intensive care treatment

Monika Kerckhoffs

Prognosis, proportionality and preferences

Deciding on continuing or limiting intensive care treatment

Monika Kerckhoffs

Artwork cyanotype, cover design & design lay-out: Esther Beekman (www.estherontwerpt.nl)
Printed by: GVO drukkers B.V., Ede

ISBN: 978-94-6332-665-0

Prognosis, proportionality and preferences

Deciding on continuing or limiting intensive care treatment

Prognose, proportionaliteit en patiëntvoorkeuren

Beslissen over het voortzetten of beperken van de intensive care behandeling

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 30 september 2020 des middags te 2.30 uur

door

Monika Cecilia Kerckhoffs

geboren op 17 oktober 1978
te Schiedam

Promotoren: Prof. dr. D. van Dijk
Prof. dr. J.J.M. van Delden

Table of content

Part one Long-term outcome of Intensive Care treatment

Part two Decision-making on Intensive Care treatment

1

General introduction

Each year around 80.000 patients are treated in a Dutch Intensive Care Unit (ICU) [1]. These ICU patients are a heterogeneous group. They vary in severity of illness, age, frailty and co-morbidities, and may be admitted unplanned or after elective surgery. Although most patients survive, mortality during and after the ICU remains significant [2]. Besides the burden caused by the ICU treatment itself, more than one third of ICU survivors suffer from the sequelae of critical illness. These comprise of impairments in physical, cognitive and/or mental health, often referred to as the Post Intensive Care Syndrome (PICS), and lead to increased hospital resource use and decreased quality of life [3-6].

Since ICU treatment can be burdensome and the outcome may be disappointing, the benefit and harm of an ICU treatment should be assessed repeatedly [7]. Prognosis, proportionality and patient preferences should be aligned in order to provide proportional and goal-concordant care. This means that the ICU treatment must have the potential to realize patient-specific goals concerning survival, functional-outcomes and participation in society [8-10].
In approximately 10% of all ICU patients the decision to forgo life sustaining treatment is made [11]. In the majority of patients who die in an ICU, a decision to withhold or withdraw life-sustaining therapy preceded death [12-15]. Previous studies, however, reported high variability in the proportion of ICU patients dying after some sort of limitation in life sustaining therapy [13]. These variations were observed between countries, within countries and even between physicians within the same ICU [15, 16].

Avoiding decision-making about limiting life support carries the risk of unjustified continuation of unlimited ICU treatment, potentially resulting in unwanted or disproportionate ICU treatment [17-21]. To prevent unjustified ICU treatments, ICU physicians are repeatedly challenged to evaluate the fit between prognosis and patient preferences. This should be done within a process of careful and shared decision-making, in which clinicians and patients or their surrogate decision-makers make rational, evidence based and individualized health care decisions [7]. For each individual ICU patient, the relevant information concerning prognosis, proportionality and patient preferences has to be integrated in a decision-making process.

The prognosis of the individual ICU patient, is nevertheless difficult to determine. Although there is growing evidence that long-term outcomes are mostly influenced by patient characteristics, like frailty, co-morbidities and healthcare utilization, a clear understanding of the impact of the different predicting factors on consecutive days

during the ICU admission is currently lacking [22-25]. In addition, the predictive value of the duration of the ICU admission itself, is not undisputed [26-29].
Besides the uncertainty concerning (long-term) mortality, the effect of physical, cognitive and mental impairments on quality of life for ICU survivors is also undefined. Research that involved former ICU patients to define relevant outcomes, revealed that there is no validated questionnaire that covers all symptoms that impact wellbeing nor all relevant aspects of a good outcome [22, 30, 31]. Understanding how ICU survivors evaluate their lives in the period after discharge, could support informed decision-making on the proportionality of ICU treatment.

In the assessment of proportionality, the expected long-term outcome of an ICU admission is balanced against the cost of the treatment (duration, suffering etc.) in relation with the individual patient's preferences concerning outcome. This process of patients and professional caregivers discussing future goals-of-care is called advance care planning (ACP) [32, 33]. Although ACP typically describes decision-making on the appropriateness of life-saving treatments before the actual threat of such event, aligning ICU treatments with preferences concerning future outcome can also be considered ACP as far as it discusses goals of care and future decisions.

How to modify the process of future care planning and subsequent decision-making to the context of the ICU is not clear. Important differences apply to the highly complex environment of the ICU and to the inability of the patient to participate. In incapacitated patients, preferences often have to be deduced from previous expressions in order to align ICU treatment with individual goals. If formal advance directives lack, surrogate decision-makers carry the responsibility to verbalise patient's preferences, which is both stressful as well as prone to error [34]. How both ICU caregivers as well as (surrogate) decision-makers can be encouraged to participate in shared decision-making to enhance goal-concordant ICU care is not clear yet.

There is broad consensus that in the process of evaluating ICU care, current health status and expected mortality and morbidity, should be integrated with preferences expressed before ICU admission [35]. In addition, a shared decision-making process is well defined [7]. At the same time, there is limited evidence on the required steps of the decision making process on continuing or limiting ICU treatment and how each step contributes to a proportionate process and optimal decision [36].

These insights led to the following research questions concerning outcome of ICU patients and decision-making;

- What is the longterm outcome of ICU patients? Is it possible to predict outcome during the ICU admission? And how do ICU survivors evaluate their outcome?
- Which strategies and elements are useful in decision-making in the ICU?

OUTLINE OF THIS THESIS

When making decisions regarding life-sustaining treatments in the ICU, prognosis is an important factor. Since most patients place emphasis on long-term outcomes when defining treatment goals, it is important to acknowledge long-term prognosis in order to make goal-concordant treatment decisions [10, 37]. Therefore, the first part of this thesis focusses on long-term outcomes of ICU patients.

In **chapter two**, the current knowledge on long-term outcome of ICU patients is reviewed. Data from the Dutch National ICU Evaluation (NICE) are combined with a review of the literature to describe long-term mortality as well as the prevalence and pathophysiology of persistent physical, cognitive and mental impairments after ICU treatment.

Chapter three describes how antecedent patient factors, like age and co-morbidities, compare to acute admission characteristics, like diagnosis and severity of illness, in regard to the prediction of one-year mortality in the Dutch ICU population during consecutive days in the ICU. In addition, the association between of length of ICU stay itself and one-year mortality is studied. All three models are additionally tested on their ability to predict hospital mortality.

The **fourth chapter** describes how ICU survivors perceive their outcome in terms of acceptance of their health status one year after ICU discharge. This self perceived outcome is related to the patient reported outcomes measures that evaluated health related quality of life together with physical, cognitive and mental impairments after ICU treatment. In addition, self-perceived quality of life is compared to a quality of life questionnaire in order to find a cut-off value reflecting an unacceptable outcome of ICU treatments.

The second part of this thesis is dedicated to the process of decision-making on continuing or forgoing life-sustaining ICU treatments in patients treated in the ICU.

The **fifth chapter** is a comprehensive review of the literature on decision-making strategies. It describes the decision-making strategies that have been studied in the past together with outcome-measures that have been used in these studies. This review aims to identify the components of effective decision-making processes, together with feasible outcome measures that can be used to evaluate the decision-making process.

The **sixth chapter** describes an international Delphi consensus study in which physicians, nurses, patients and surrogate decision-makers co-created a decision-making framework aimed to support and improve the decision-making process on continuing versus forgoing life-sustaining ICU treatments in patients admitted to the ICU.

In the **seventh chapter** the effect of a weekly time-out meeting as part of the decision-making framework is evaluated in a before-after study. In a weekly multi-disciplinary time-out meeting, current health, pre-morbid functioning, perceived suffering and patient preferences are addressed before decisions to continue or forgo ICU treatments are made. The effect of the intervention is evaluated in terms of days in the ICU for patients who died within 90 days of admission.

In **chapter eight** the use of decision-making framework in the ICU is discussed in further detail. We argue why a framework that combines standardized and individualized decision-making on life-sustaining ICU treatments could help to prevent unwanted or non-beneficial ICU treatments. In addition, we explore the main concerns of the decision-making framework, like the complexity of prognostication, interpretation of preferences and physician- and culture-related factors. Finally, we suggest how the decision-making process on life-sustaining ICU treatments for ICU patients can be enhanced in the future. We advocate the development of an ICU decision-aid as an ACP intervention for ICU patients and surrogate decision-makers.

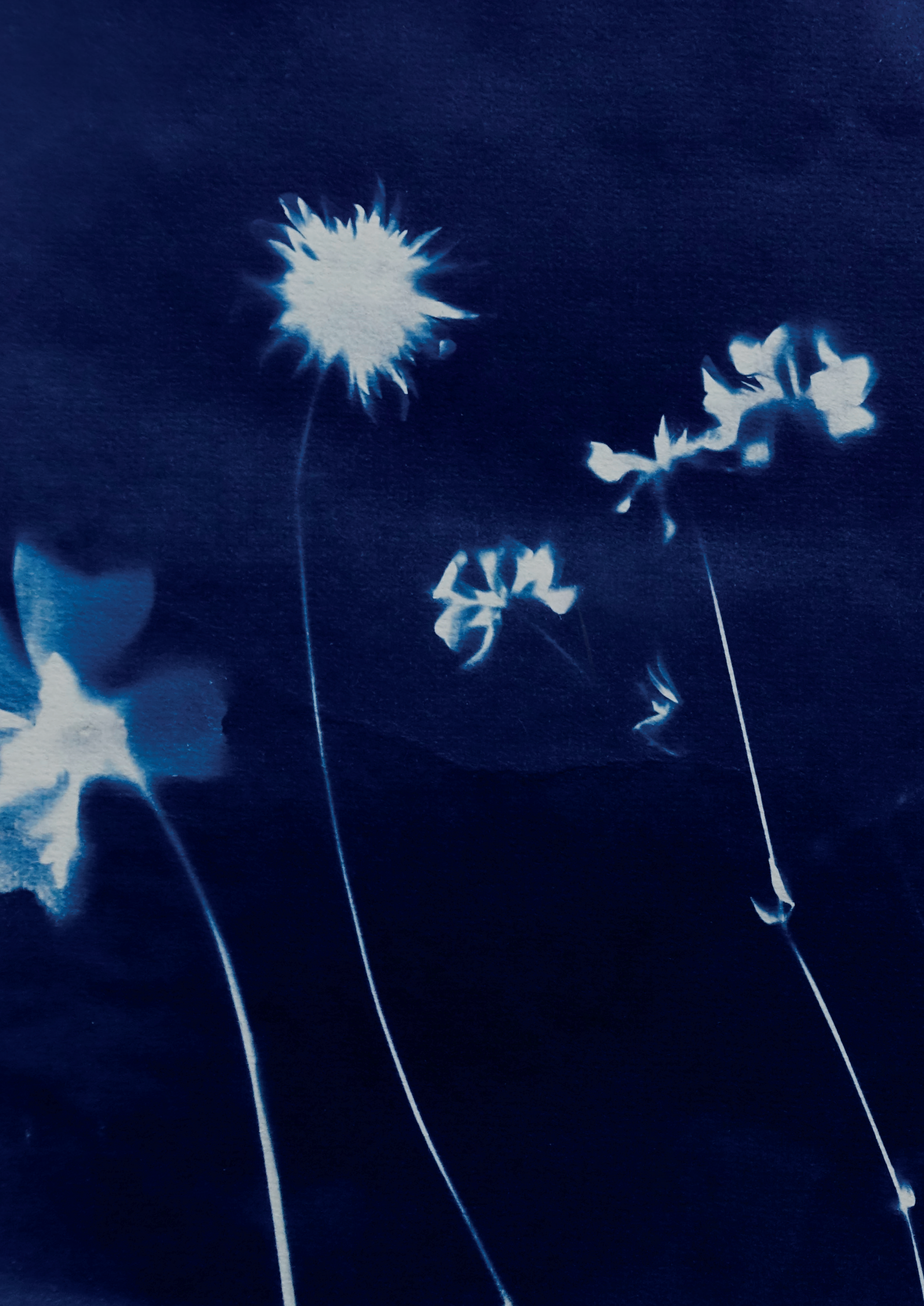
REFERENCES

1. http://www.stichting-nice.nl/doc/jaarboek-2018-web.pdf.
2. Brinkman S, de Jonge E, Abu-Hanna A, et al (2013) Mortality after hospital discharge in ICU patients. Crit Care Med 41:1229–1236. doi: 10.1097/CCM.0b013e31827ca4e1
3. Soliman IW, de Lange DW, Peelen LM, et al (2015) Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care 30:181–186. doi: 10.1016/j.jcrc.2014.09.009
4. Hofhuis JGM, van Stel HF, Schrijvers AJP, et al (2015) ICU survivors show no decline in health-related quality of life after 5 years. Intensive Care Med 41:495–504. doi: 10.1007/s00134-015-3669-5
5. Herridge MS, Tansey CM, Matté A, et al (2011) Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med 364:1293–1304. doi: 10.1056/NEJMoa1011802
6. Needham DM, Davidson J, Cohen H, et al (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 40:502–509. doi: 10.1097/CCM.0b013e318232da75
7. Kon AA, Davidson JE, Morrison W, et al (2016) Shared Decision-Making in Intensive Care Units. Executive Summary of the American College of Critical Care Medicine and American Thoracic Society Policy Statement. Am J Resp Crit Care Med193:1334–1336. doi: 10.1164/rccm.201602-0269ED
8. Sanders JJ, Curtis JR, Tulsky JA (2018) Achieving Goal-Concordant Care: A Conceptual Model and Approach to Measuring Serious Illness Communication and Its Impact. J Palliat Med 21:S17–S27. doi: 10.1089/jpm.2017.0459
9. Turnbull AE, Hartog CS (2017) Goal-concordant care in the ICU: a conceptual framework for future research. Intensive Care Med 43:1847–1849. doi: 10.1007/s00134-017-4873-2
10. Dinglas VD, Chessare CM, Davis WE, et al (2018) Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. Thorax 73:7–12. doi: 10.1136/thoraxjnl-2017-210234
11. Azoulay E, Metnitz B, Sprung CL, et al (2009) End-of-life practices in 282 intensive care units: data from the SAPS 3 database. Intensive Care Med 35:623–630. doi: 10.1007/s00134-008-1310-6
12. Sprung CL, Cohen SL, Sjokvist P, et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. doi: 10.1001/jama.290.6.790
13. Prendergast TJ, Claessens MT, Luce JM (1998) A national survey of end-of-life care for critically ill patients. Am J Resp Crit Care Med 158:1163–1167. doi: 10.1164/ajrccm.158.4.9801108
14. Higginson IJ, Koffman J, Hopkins P, et al (2013) Development and evaluation of the feasibility and effects on staff, patients, and families of a new tool, the Psychosocial Assessment and Communication Evaluation (PACE), to improve communication and palliative care in intensive care and during clinical uncertainty. BMC Med 11:213. doi: 10.1186/1741-7015-11-213
15. Mark NM, Rayner SG, Lee NJ, Curtis JR (2015) Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. Intensive Care Med 41:1572–1585. doi: 10.1007/s00134-015-3810-5
16. Barnato AE, Tate JA, Rodriguez KL, et al (2012) Norms of decision making in the ICU: a case study of two academic medical centers at the extremes of end-of-life treatment intensity. Intensive Care Med 38:1886–1896. doi: 10.1007/s00134-012-2661-6
17. Benoit DD, Jensen HI, Malmgren J, et al (2018) Outcome in patients perceived as receiving excessive care across different ethical climates: a prospective study in 68 intensive care units in Europe and the USA. Intensive Care Med 44:1039–1049. doi: 10.1007/s00134-018-5231-8
18. Piers RD, Azoulay E, Ricou B, et al (2014) Inappropriate care in European ICUs: confronting views from nurses and junior and senior physicians. Chest 146:267–275. doi: 10.1378/chest.14-0256

19. Piers RD, Azoulay E, Ricou B, et al (2011) Perceptions of appropriateness of care among European and Israeli intensive care unit nurses and physicians. JAMA 306:2694–2703. doi: 10.1001/jama.2011.1888
20. Huynh TN, Kleerup EC, Wiley JF, et al (2013) The frequency and cost of treatment perceived to be futile in critical care. JAMA Intern Med 173:1887–1894. doi: 10.1001/jamainternmed.2013.10261
21. Quenot J-P, Large A, Meunier-Beillard N, et al (2019) What are the characteristics that lead physicians to perceive an ICU stay as non-beneficial for the patient? PLoS ONE 14:e0222039. doi: 10.1371/journal.pone.0222039
22. Griffith DM, Salisbury LG, Lee RJ, et al (2018) Determinants of Health-Related Quality of Life After ICU: Importance of Patient Demographics, Previous Comorbidity, and Severity of Illness. Crit Care Med 46:594–601. doi: 10.1097/CCM.0000000000002952
23. Szakmany T, Walters AM, Pugh R, et al (2019) Risk Factors for 1-Year Mortality and Hospital Utilization Patterns in Critical Care Survivors: A Retrospective, Observational, Population-Based Data Linkage Study. Crit Care Med 47:15–22. doi: 10.1097/CCM.0000000000003424
24. Lone NI, Gillies MA, Haddow C, et al (2016) Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. Am J Resp Crit Care Med 194:198–208. doi: 10.1164/rccm.201511-2234OC
25. Bagshaw M, Majumdar SR, Rolfson DB, et al (2016) A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care 20:175. doi: 10.1186/s13054-016-1338-x
26. Moitra VK, Guerra C, Linde-Zwirble WT, Wunsch H (2016) Relationship Between ICU Length of Stay and Long-Term Mortality for Elderly ICU Survivors*. Crit Care Med 44:655. doi: 10.1097/CCM.0000000000001480
27. Williams TA, Ho KM, Dobb GJ, et al (2010) Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. Br J Anaesth 104:459–464. doi: 10.1093/bja/aeq025
28. Laupland KB, Kirkpatrick AW, Kortbeek JB, Zuege DJ (2006) Long-term mortality outcome associated with prolonged admission to the ICU. Chest 129:954–959. doi: 10.1378/chest.129.4.954
29. Marshall DC, Hatch RA, Gerry S, et al (2020) Conditional Survival With Increasing Duration of ICU Admission: An Observational Study of Three Intensive Care Databases. Crit Care Med 48:91–97. doi: 10.1097/CCM.0000000000004082
30. Lim WC, Black N, Lamping D, et al (2016) Conceptualizing and measuring health-related quality of life in critical care. J Crit Care 31:183–193. doi: 10.1016/j.jcrc.2015.10.020
31. König C, Matt B, Kortgen A, et al (2018) What matters most to sepsis survivors: a qualitative analysis to identify specific health-related quality of life domains. Qual Life Res 193:259–11. doi: 10.1007/s11136-018-2028-8
32. Rietjens JAC, Sudore RL, Connolly M, et al (2017) Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. Lancet Oncol 18:e543–e551. doi: 10.1016/S1470-2045(17)30582-X
33. Sudore RL, Lum HD, You JJ, et al (2017) Defining Advance Care Planning for Adults: A Consensus Definition From a Multidisciplinary Delphi Panel. J Pain Symptom Manage 53:821–832.e1. doi: 10.1016/j.jpainsymman.2016.12.331
34. Miller JJ, Morris P, Files DC, et al (2016) Decision conflict and regret among surrogate decision makers in the medical intensive care unit. J Crit Care 32:79–84. doi: 10.1016/j.jcrc.2015.11.023
35. Sprung CL, Truog RD, Curtis JR, et al (2014) Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. In: Am. J. Respir. Crit. Care Med. American Thoracic Society, pp 855–866

36. Scheunemann LP, Cunningham TV, Arnold RM, et al (2015) How clinicians discuss critically ill patients' preferences and values with surrogates: an empirical analysis. Crit Care Med 43:757–764. doi: 10.1097/CCM.0000000000000772
37. Turnbull AE, Sepulveda KA, Dinglas VD, et al (2017) Core Domains for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. Crit Care Med 45:1001–1010. doi: 10.1097/CCM.0000000000002435

1



Part one

Long-term outcome of Intensive Care treatment

2

Long-term outcome of Intensive Care Unit treatment

MC Kerckhoffs, IW Soliman, AE Wolters, L Kok, M van der Schaaf,
D van Dijk

Published in; Netherlands Journal of Medicine 2016

ABSTRACT

Patients admitted to an intensive care unit (ICU) comprise of a heterogeneous population with substantial differences in admission diagnosis, length of stay and co-morbidity. Therefore, very often the prognosis for each patient differs. In the Netherlands, over 20% of the more than 80,000 patients treated in ICU annually will die within a year of admission. Some of those who survive and are discharged from ICU, experience persistent physical, mental and cognitive health problems post-discharge; this is called the post-intensive care syndrome (PICS). One year following discharge, circa 50% of patients continue to report physical symptoms, including muscle weakness and walking difficulties. Approximately one in five patients discharged from the ICU will develop symptoms akin to post-traumatic stress disorder, and one third will experience depressive symptoms for some time. It remains unclear to what extent the ICU admission itself may potentially contribute to the decline in performance status and quality of life.

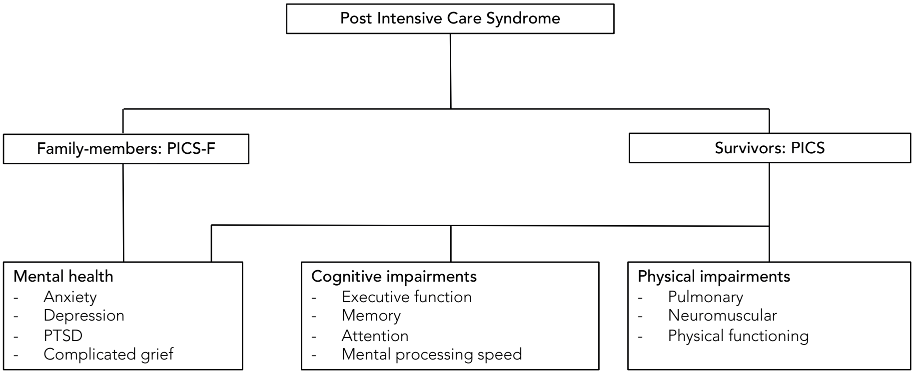
SUMMARY

- Intensive Care Unit (ICU) patients comprise a heterogenous group with large differences in reason of admission, duration of treatment and comorbidity. The prognosis of these patients therefore differs enormously.
- Of the approximate 80.000 patients who are treated in the ICU in the Netherlands yearly, more than 20% die within one year.
- After discharge from the hospital, a proportion of ICU patients retain physical, cognitive or mental symptoms, called the Post Intensive Care Syndrome (PICS).
- After one year, around 50% of the patients still have physical complaints such as muscle weakness and problems with walking.
- About one in five former ICU patients develop symptoms that fit with a Post-Traumatic Stress Disorder (PTSD) and one in three develop features of a depression over time.
- The contribution of ICU admission to the limitations of functioning and quality of life observed after ICU treatment is unclear.

CASE

Patient A is a 75-year-old man, who is admitted to the Intensive Care Unit (ICU) due to pneumosepsis. He is known to have hypertension, diabetes mellitus type 2 and a chronic renal insufficiency (glomerular filtration rate 40 ml/min). The patient is intubated and ventilated. In addition, renal replacement therapy is necessary and he has a hyperactive delirium with hallucinations for a week. Three weeks after admission, the patient is still dependent on ventilation and renal replacement therapy. In a conversation with the family, the wife of the patient expresses her concern about the future. Will her husband survive this? She also asks what his quality of life will be. Her husband has always said he does not want to live in a nursing home.
What can you tell his wife about the prognosis and long-term outcome?

Every year more than 80.000 patients are treated in Intensive Care Units (ICU) in the Netherlands. This is a heterogeneous patient group with large differences in reason of admission, age and co-morbidity. About 80% of the patients are admitted to the ICU for a short term (1-3 days) and 10% of the patients are treated in the ICU for longer than a week. [1]
Admission to the ICU is accompanied by mortality and morbidity. Around 9% of all patients die during the ICU stay itself and another 4% die on a hospital ward or Medium Care in the hospital after discharge from ICU. After one year, 75-80% of the patients who have been treated in ICU, are still alive. [1-3]
A proportion of the patients who survive ICU treatment, retain restrictions in daily functioning. Since 2012, the term Post Intensive Care Syndrome (PICS) has been used to describe this. [4] PICS stands for a number of physical, mental and cognitive symptoms, which appear frequently in patients who have been treated in ICU after discharge from the hospital. In addition, mental complaints of their relatives or next of kin are included (PICS-F) (see Figure 1).
In this article, we provide an overview of the possible consequences of a treatment in the ICU.



Based on Needham, Crit Care 2012

Figure 1. The Post Intensive Care Syndrome describes three domains of complaints; physical disabilities, cognitive disabilities and mental health.

Survival

Patients who have been treated in ICU have a higher risk of dying than persons in a control group (age- and sex-matched), who have not been treated in the ICU. Thirteen percent of patients die within the hospital (in ICU or on the ward). Subsequently, a further 8-10% die in the first year after discharge, the risk of dying being the highest in the first three months after discharge. [1-3] In addition, various follow-up studies show that the mortality of former ICU patients remains increased for years in comparison with their reference population. [2]
However, the differences between the subgroups are large. Logically, the outcome is strongly influenced by the reason of admission and seriousness of the illness. A patient who has had elective cardiac surgery has a better prognosis than a patient who has had a subarachnoid hemorrhage. [2] Also, the duration of hospitalization influences mortality. In the first 10 days of ICU treatment, mortality increases with each extra day of admission in the ICU. Many other factors also influence prognosis, such as age, pre-existing functioning, acute renal insufficiency and seriousness of illness at admission.[5]

Physical functioning

A large proportion of ICU patients have cardiopulmonary disturbances and complaints of the musculoskeletal system after discharge. These express themselves as decreased tolerance to exercise, less muscle power and a decreased mobility of the joints. One year after discharge, about half of the patients, who have been treated in ICU for more than two days, still have physical restrictions in their daily functioning. [6]

Muscle weakness that has been acquired in ICU (ICU acquired weakness; ICUAW) is an umbrella term that describes newly developed weakness of the limbs and respiratory muscles, which appear in ICU patients. ICU-AW can be an expression of critical illness polyneuropathy, critical illness polymyopathy or both. [7] The incidence is estimated to be around 50% of ICU patients with sepsis, multiple organ failure or prolonged ventilation. [8] At the time of discharge from the hospital, a quarter to one third of the patients still have muscle weakness. [7] The muscle weakness concerns both limb and respiratory muscles leading to a delayed revalidation after discharge.

Pathophysiologically, complex functional and structural changes of the nerve (axonal degeneration) and muscle (atrophy) are found in patients with an ICU-AW. Risk factors are for example sepsis, hyperglycemias and immobilization. [7]

Post-traumatic stress disorder and depression

An ICU treatment is experienced by many patients as stressful because of episodes of dyspnea and pain, feelings of powerlessness and the threat of death or serious harm. Former ICU patients therefore run an increased risk of the development of mental complaints or psychiatric disturbances such as a posttraumatic stress disorder (PTSD) and depression. [9,10] About one in five former ICU patients have complaints that match PTSD and one in three patients have complaints of depression in the first three months after discharge. [9-11] Although symptoms of PTSD and depression occur most frequently in the first months after discharge, these psychiatric disturbances are still being reported years after ICU admission. [9,12] A recent meta-analysis showed that pre-existing psychiatric disturbances, the use of benzodiazepines during ICU stay and having early memory of anxious moments in ICU increase the development of PTSD. [11]

Also, immediate family members of an ICU patient retain feelings of fear and depression in the sense of PICS (PICS-F). Various factors increase the risk of PICS in next of kin. These are both patient bound factors (lesser age, more seriously ill), characteristics of the next of kin (female sex, lesser age, pre-existing mental complaints) as well as health care related factors (less confidence in the physician). [13]

Pathophysiologically, an imbalance between the degree of stress and the stress response of the hypothalamic-pituitary-adrenal (HPA) axis is hypothesized. In PTSD an overall dampened HPA response is observed, while with depression an overall hyperreactivity is described. [14] Individual differences in the functionality and sensitivity of the HPA axis can (partly) explain the variation in occurrence of PTSD and depression after ICU admission.

Cognitive disturbances after an ICU treatment

After ICU treatment, there is a risk of cognitive disturbances such as memory loss, disturbances of attention and concentration and limitations of goal-oriented functioning. The extent of the risk varies in the literature between 4 and 62% because of the heterogeneity of study populations, but more especially by differences in the neuropsychological test used, definitions of cognitive disturbance and the duration of follow-up. [16]

Two investigations, based upon large-scale population studies, had access to neuropsychological measurements of cognitive functioning before ICU admission. [17-18] Both studies demonstrated that after ICU admission, patients had a higher chance of cognitive decline than a reference population. [17-18] However, the speed of normal, gradual cognitive decline did not change after ICU admission, so that it was concluded that ICU admission results in an abrupt loss of cognitive functioning. [17]

Risk factors for cognitive disturbances after ICU treatment include amongst others delirium, serious illness, hyper- or hypoglycemia, hypoxemia and hypotension. [16,19] The pathophysiology is unknown, but probably multifactorial. Cytokines, which are released during inflammation and sepsis possibly initiate a neuro-inflammatory response, which leads to neuronal damage and cognitive decline. [16,18] There are indications that in the short-term, delirium and in the long-term, cognitive disturbances are manifestations of the same insult. [20]

Quality of life

In the past years, much research has been done on the quality of life after ICU treatment. A recent Dutch study has compared ICU patients with a group of people not treated in ICU and found a lower quality of life 36 months after discharge. [3] Another study with a five-year follow-up after discharge found comparable results. [21] Lower scores were found specifically in the domains of physical functioning and vitality. In addition, only half of the former ICU patients appeared to have returned to work. [6,21]

For which patients the quality of life will be limited more seriously or for a longer time, is difficult to predict. Subgroups of older patients, patients with chronic renal insufficiency and patients with pre-existing physical or mental disorders have the lowest measured quality of life after ICU treatment. [3,22] Also, in recent studies the degree of frailty at admission seems to be associated with quality of life after discharge. [23] A measurement of the quality of life before the ICU admission is usually lacking. Therefore, it cannot be distinguished whether this low quality of life results from the underlying disorder, a natural decrease of the quality of life with age, or from ICU treatment. [21,24]

Interventions

With the growing awareness that many patients retain physical, cognitive or mental complaints after ICU treatment, various interventions which might be able to reduce these complaints have been studied. [25] Restraint with sedation, physiotherapy and keeping a diary do reduce the risk of PICS. [12,25]

An increasing number of hospitals perform a follow-up of their patients in an ICU aftercare outpatient clinic. Here, patients and their next of kin talk about their ICU stay, receive explanation about complaints and symptoms, which fit to PICS and often receive a tour of the ICU. Where necessary, patients are referred to rehabilitation specialists or mental health care. The degree to which this follow-up and referral of patients to the appropriate care has effects on the physical and mental recovery of the patient, is not yet clear.

Considerations

The more than 80.000 patients, who are treated in Dutch ICUs each year, form a heterogeneous group. The outcome of a patient with a planned, short admission, is generally good. For the patient with increased comorbidity, and who has to be treated for a longer time in the ICU, the outcome is uncertain. A proportion of the patients who are treated in ICU have characteristics of PICS after their discharge from the hospital, irrespective of their underlying illness. The duration of ICU stay, rather than the reason for ICU admission, is herewith a determinant of PICS. Research that has been done in the last decades, has increased the knowledge about the long-term outcome, but does not allow us as yet to predict a decrease in functioning for an individual patient. In the first place, the pre-existing functioning of patients who have been treated in ICU, has not been recorded in measure and number in most studies. Because of this, it is difficult to precisely determine the extent of the decline in physical, mental and cognitive functioning and the quality of life in comparison with the months before admission. In addition, the exact contribution of ICU stay to the possible decline is still unclear. Further, the underlying illness or the hospital stay probably contribute to the differences in functioning between ICU patients and the reference population.

Finally, there is no uniformity with respect to definitions. The numbers of patients described with a decline in cognitive functioning, PTSD or depression after ICU treatment differ strongly because of the use of different neuropsychological tests and definitions.

The growing knowledge of mortality of ICU treatment and PICS will play a stronger role in the care of ICU patients in the years to come. This holds true for the decision to admit a patient to ICU, the decision to continue or stop a treatment as well as in

discussions with patients and their next of kin. For additional information about the impact of ICU treatment, patients and their next of kin can be referred to the website of the foundation Family and patient Centered Intensive Care (FCIC, http://fcic.nl)
In the UMC Utrecht, in the last five years, we have asked all former ICU patients about their functioning and quality of life one year after discharge. In addition, we have gathered information about their pre-existing functioning in order to be able to register changes. In the future we hope this knowledge will increase the possibility of being able to inform an ICU patient and their next of kin about the chances of survival, limitations in functioning and quality of life.

Finally, we return to the question of the wife of patient A about his chance of survival and quality of life. It can be discussed with the family that 80% of all ICU patients are still alive after one year, but that 20-50% of these patients have residual effects. Considering the history and the course of the illness with amongst others a delirium, the patient has a high chance of (some) limits to his physical, mental and cognitive functioning. Additionally, recovery of his renal function is still uncertain. The measure of "good recovery" is however subjective and dependent upon individual values and expectations, but also of coping mechanisms and the social support system. For that reason, it has to be evaluated in each discussion whether an expected outcome is acceptable for the patient. Wishes expressed by the patient also have to be taken into account when deciding whether or not to continue the treatment.

REFERENCES

1. Stichting NICE: http://www.stichting-nice.nl/doc/jaarboek-2014-web.pdf, accessed September 25th 2015
2. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. Crit. Care Med. 2013;41:1229–36.
3. Soliman IW, de Lange DW, Peelen LM, Cremer OL, Slooter AJC, Pasma W, et al. Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care 2015;30:181–6.
4. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit. Crit. Care Med. 2012;40:502–9.
5. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman M, Webb SAR. Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. Br. J. Anaesth. 2010;104:459–64.
6. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med 2009;41:360–6.
7. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care 2015;19:274.
8. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med 2007;33:1876–91.
9. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatICU stress disorder in survivors of ICU treatment: a systematic review. Intensive Care Med 2007;33:1506–18.
10. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med 2014;2:369–79.
11. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic Stress Disorder in Critical Illness Survivors: A Metaanalysis*. Crit. Care Med. 2015;43:1121–9.
12. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, Shanholtz C, Dennison-Himmelfarb CR, Pronovost PJ, et al. Cooccurrence of and remission from general anxiety, depression, and posttraumatICU stress disorder symptoms after acute lung injury: a 2-year longitudinal study. Crit. Care Med. 2015;43:642–53.
13. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: Postintensive care syndrome–family. Crit. Care Med. 2012;40:618–24.
14. Spijker AT, van Rossum EFC. Glucocorticoid sensitivity in mood disorders. Neuroendocrinology 2012;95:179–86.
15. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-Term Cognitive Impairment after Critical Illness. N Engl J Med 2013;369:1306–16.
16. Wolters AE, Slooter AJC, van der Kooi AW, van Dijk D. Cognitive impairment after intensive care unit admission: a systematic review. Intensive Care Med 2013;39:376–86.
17. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJPA, Carson SS, Curtis JR, et al. Association Between Acute Care and Critical Illness Hospitalization and Cognitive Function in Older Adults. JAMA 2010;303:763–70.
18. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. JAMA 2010;304:1787–94.
19. van den Boogaard M, Schoonhoven L, Evers A, van der Hoeven JG, Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health related quality of life and cognitive functioning. Crit. Care Med. 2012;40:112-8

20. van Gool WA, van de Beek D, Eikelenboom P. SystemICU infection and delirium: when cytokines and acetylcholine collide. Lancet 2010;375:773–5.
21. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med 2011;364:1293–304.
22. Orwelius L, Nordlund A, Nordlund P, Simonsson E, Bäckman C, Samuelsson A, et al. Pre-existing disease: the most important factor for health related quality of life long-term after critical illness: a prospective, longitudinal, multicentre trial. Crit Care 2010;14:R67.
23. Bagshaw SM, Stelfox HT, Johnson JA, McDermid RC, Rolfson DB, Tsuyuki RT et al. Long-term association between frailty and health-related quality of life among survivors of critical illness: a prospective multicenter cohort study. Crit. Care Med. 2015;43:973-82
24. Hofhuis JGM, van Stel HF, Schrijvers AJP, Rommes JH, Spronk PE. ICU survivors show no decline in health-related quality of life after 5 years. Intensive Care Med 2015;41:495–504.
25. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit. Care Med. 2014;42:1263–71.

3

The performance of acute versus antecedent patient characteristics for one-year mortality prediction during intensive care unit admission; a national cohort study

MC Kerckhoffs, S Brinkman, NF de Keizer, IW Soliman,
DW de Lange, JJM van Delden, D van Dijk

Published in; Critical Care 2020

ABSTRACT

Background Multiple factors contribute to mortality after ICU, but it is unclear how the predictive value of these factors change during ICU admission. We aimed to compare the changing performance over time of the acute illness component, antecedent patient characteristics and ICU length of stay (LOS) in predicting one-year mortality.

Methods In this retrospective observational cohort study, the discriminative value of four generalized mixed-effects models were compared for one-year and hospital mortality. Among patients with increasing ICU LOS, the models included a) acute illness factors and antecedent patient characteristics combined, b) acute component only, c) antecedent patient characteristics only and d) ICU LOS. For each analysis, discrimination was measured by area under the receiver operating characteristics curve (AUC), calculated using the bootstrap method. Statistical significance between the models was assessed using the DeLong method (p-value <0.05).

Results In 400.248 ICU patients observed, hospital mortality was 11.8% and one-year mortality 21.8%. At ICU admission, the combined model predicted one-year mortality with an AUC of 0.84 (95% CI 0.84-0.84). When analyzed separately, the acute component progressively lost predictive power. From an ICU admission of at least three days, antecedent characteristics significantly exceeded the predictive value of the acute component for one-year mortality, AUC 0.68 (95% CI 0.68-.0.69) versus 0.67 (95% CI 0.67-0.68) p-value < 0.001). For hospital mortality, antecedent characteristics outperformed the acute component from a LOS of at least seven days, comprising 7,8% of patients and accounting for 52,4% of all bed-days. ICU LOS predicted one-year mortality with an AUC of 0.52 (CI 95% 0.51-0.53) and hospital mortality with an AUC of 0.54 (CI 0.53-0.55) for patients with a LOS of at least seven days.

Conclusions Comparing the predictive value of factors influencing one-year mortality for patients with increasing ICU LOS, antecedent patient characteristics are more predictive than the acute component for patients with a ICU LOS of at least three days. For hospital mortality, antecedent patient characteristics outperform the acute component for patients with an ICU LOS of at least seven days. After the first week of ICU admission, LOS itself is not predictive of hospital nor one-year mortality.

BACKGROUND

Each year, millions of people receive Intensive Care Unit (ICU) treatment. Most patients are admitted to the ICU for only a few days. Some patients however, survive their initial acute illness but go on to experience persistent organ failure necessitating a prolonged stay in the ICU [1-4].

Prolonged treatment in the ICU may lead to increased suffering and high health care consumption [5,6]. Moreover, it is known that patients with persistent critical illness have an increased hospital- and one year mortality, with the highest mortality observed in the first months after discharge [3,7-14].
Most prediction models used in the ICU predict hospital mortality [15-18]. Since most patients place emphasis on long-term outcomes when defining treatment goals, it is important to acknowledge long-term prognosis in order to make goal-concordant treatment decisions [10,19].

Multiple factors contribute to the risk of mortality after ICU, for example type of critical illness, physiologic derangement at admission, higher age and frailty [11,20-22]. Therefor current prediction models use both acute illness variables and antecedent patient characteristics. However, it is unclear how each of these factors contribute to prognosis during the course of an ICU admission.

Recent studies described that for hospital mortality, the predictive value of antecedent patient characteristics (e.g. co-morbidities, demographics), and acute characteristics (admission diagnosis and first day physiological derangements) change during ICU admission [3,4]. After approximately ten days in the ICU, antecedent patient characteristics start to outperform acute characteristics for the prediction of hospital mortality [3,4]. There is growing evidence that also one-year mortality and morbidity is mostly influenced by factors present before ICU admission, like frailty, co-morbidities and healthcare utilization [8,22-24]. The predictive value of length of ICU stay (LOS) for long-term outcome, is not undisputed with studies showing heterogeneous results [15,25-27].

This study aimed to compare the predictive value of acute characteristics on the one hand and antecedent patient characteristics on the other, for hospital mortality and one-year mortality among patients with increasing ICU LOS. We hypothesized that the predictive value of the acute component would decrease as ICU LOS increases, while antecedent patient characteristics would have a more constant effect over time. In addition, we aimed to quantify the predictive value of ICU LOS itself for hospital mortality and one-year mortality.

METHODS

Aim

The aim of this study was to compare the predictive value for hospital and one-year mortality of a) acute admission characteristics and antecedent patient characteristics combined (regarded as current practice), with b) acute component only, c) antecedent patient characteristics only and d) ICU length of stay itself, among patients with increasing ICU LOS.

Study design, setting and data sources

This study was a retrospective observational cohort study, comprising all ICU patients included in the Dutch National Intensive Care Evaluation (NICE) registry between 1-1-2013 and 1-1-2018. The NICE registry routinely collects data of all Dutch ICU patients until hospital discharge, to monitor quality of ICUs by benchmarking [28].

Patient records in the NICE registry contain demographic, physiological and diagnostic data of all consecutive ICU patients, including the Acute Physiology and Chronic Health Evaluation (APACHE) score, chronic co-morbidity, reason for ICU admission and date of death when during hospital admission [29]. Date of death after hospital discharge was derived for each patient by linking patient data to a national administrative database of health insurance companies (Vektis, https://www.vektis.nl). Readmissions within the same hospitalization were only included for their first ICU admission. After discharge from the hospital, a re-admission to the ICU was included as a new admission. Patients with a missing length of ICU admission were excluded. Missing data on other included covariates was imputed by the median value of comparable groups of patients.

Variables

The primary outcome measure was one-year mortality. Secondary outcome measure was hospital mortality. We evaluated four groups of variables to predict one-year mortality:

(a) acute component and antecedent characteristics combined (see b. and c.)

(b) acute component: diagnosis at ICU admission and acute (first 24 hours) physiology [i.e. APACHE III Acute Physiology Score, APACHE IV reason for ICU admission categorized in 10 groups (cardiovascular, gastro-intestinal, genitourinary, hematological, metabolic, musculoskeletal, neurologic, respiratory, transplant, trauma), type of admission (medical, elective surgical, urgent surgical), lead time (calendar days, continuous variable) and source of ICU admission categorized in four groups (emergency room, operation room, general ward, other)] [17].

(c) antecedent patient characteristics: demographics and chronic health components [i.e. gender, age, cirrhosis, neoplasm, hematological malignancy, immunocompromised, diabetes mellitus, chronic respiratory insufficiency and renal insufficiency].

(d) length of ICU stay divided into 24 hour-periods.

Bias

Since data from all Dutch ICU patients are both in the NICE registry, as well as registered by Vektis, the risk of selection, information and attrition bias is negligible.

Statistical methods

Four different generalized mixed-effects models were developed. In all models, we corrected for the fact that patients in the same hospital are more similar than patients from different hospitals by including 'hospital of admission' as random intercept. All continuous covariates were included as splines. The secondary outcome, hospital mortality, was assessed using the same mixed-effects models.

To assess the predictive performance of the model during ICU admission, the discrimination, expressed as the area under the receiver operating characteristics curve (AUC) of each model was assessed for all patients with a length of ICU stay (LOS) of 0 days or longer, patients with a LOS of 1 day or longer through patients with a LOS of 30 days or longer separately. These patient groups are not mutually exclusive, meaning that patients with a LOS of four days are also in the group of patients with a LOS of one, two and three days. The AUC and 95% confidence interval (CI) were calculated using the bootstrap method [30]. In this method, the AUC of each generalized mixed-effects model was assessed in 500 bootstrap samples for each LOS patient group. Significant difference between the three models was tested using the DeLong method, with a p-value of < 0.05 defined as being significantly different [31]. All statistical analyses were performed using R (Statistical Environment Package), version 3.6.0.

RESULTS

Between 01-01-2013 and 01-01-2018, 407.851 admissions were registered in the NICE registry. After exclusion of patients with missing length of stay (n=7603, 1.9%), 400.248 admissions were included (table 1). There were 656 (0.2%) records with missing age and 3510 records (0.9%) with missing lead time. Missing age was imputed with the median age of patients of the same gender, missing lead time was imputed with the median value of patients with the same source of ICU admission. The reason for ICU admittance was medical in 48.5%, elective surgical in 38.9% and 12.7% urgent surgical. Patient were more often male (59.5%) and 40.3% were mechanically ventilated at admission. Detailed characteristics like co-morbidities are reported in additional file 1. Table E1.

Of all 400.248 patients, 21.7% had a LOS of > 2 days, 7.8% of > 7 days, and 1.1% of patients were admitted for more than 28 days. ICU, hospital, and one-year mortality for all patients treated in the ICU were 8.0%, 11.5%, and 21.7% respectively. For patients with an ICU stay of > seven days, these values were 19.6%, 26.8%, and 40.3% respectively.

From all patients who died within the first year after ICU admission, 63.0% died after ICU discharge and in 46.8% after hospital discharge. Increasing length of ICU admission was associated with one-year mortality during the first week. For patients with a LOS of > 7 days, one-year mortality remained constant around 40%, also with increasing LOS (figure 1, additional figure E1).

Primary outcome; one-year mortality

In figure 2. the predictive value of acute and antecedent characteristics separately and combined, and of LOS for one-year mortality among patients with increasing LOS is illustrated. The model combining the acute component with antecedent characteristics had an AUC of 0.84 (95% CI 0.84-0.84) at admission. The AUC decreased over time to an AUC of 0.74 (95% CI 0.74-0.74) for patients with a LOS of at least three days and an AUC of 0.70 (95% CI 0.69-0.70) for patients with a LOS of at least seven days. The acute component showed an AUC of 0.80 (95% CI 0.79-0.80) at admission, progressively decreasing for patients with a longer LOS to an AUC of 0.67 (95% CI 0.67-0.68) for patients with a LOS of at least three days and 0.62 (95% CI 0.61-0.63) for patients with a LOS of at least seven days. The predictive value of the model using only antecedent patient characteristics, showed an AUC of 0.74 (CI 95% 0.73-0.74) at admission. The value declined and stabilized at an AUC of 0.68 (CI 95% 0.68-0.69) for a LOS of at least

Length of ICU stay	>=0 days		>= 2 days		>= 7 days		>= 14 days		>= 21 days		>= 28 days	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Total	400.248	*100*	86.948	*21.7*	31.140	*7.8*	13.520	*3.4*	7.397	*1.8*	4.476	*1.1*
Male	238.306	*59.5*	52.521	*60.4*	19.308	*62*	8.566	*63.4*	4.786	*64.7*	2.938	*65.6*
Age*	66 (55-75)		67 (57-75)		66 (56-74)		66 (55-74)		66 (55-73)		66 (55-73)	
APACHE III score*	52 (37-71)		72 (55-93)		79 (61-99)		81 (63-101)		82 (64-102)		82 (63-102)	
Reason admission												
- Medical	193.925	*48.5*	59.019	*67.9*	21.712	*69.7*	9.310	*68.9*	5.052	*68.3*	2.982	*66.6*
- Urgent surgery	50.634	*12.7*	14.446	*16.6*	6.126	*19.7*	2.808	*20.8*	1.560	*21.1*	973	*21.7*
- Elective surgery	155.689	*38.9*	13.483	*15.5*	3.302	*10.6*	1.402	*10.4*	785	*10.6*	521	*11.6*
Mech. Vent. at admission	161.419	*40.3*	48.917	*56.3*	19.576	*62.9*	8.757	*64.8*	4.862	*65.7*	2.971	*66.4*
Mech. Vent. in first 24 hours	185.067	*46.2*	60.750	*69.9*	25.103	*80.6*	11.343	*83.9*	6.293	*85.1*	3.823	*85.4*
ICU mortality	32.152	*8.0*	13.132	*15.1*	6.112	*19.6*	2.750	*20.3*	1.390	*18.8*	795	*17.8*
Hospital mortality	46.186	*11.5*	18.709	*21.5*	8.357	*26.8*	3.694	*27.3*	1.866	*25.2*	1.076	*24.0*
Mortality 7 days after ICU admission	32.902	*8.2*	7.723	*8.9*	0	*0*	0	*0*	0	*0*	0	*0*
Mortality 28 days after ICU admission	50.981	*12.7*	18.832	*21.7*	7.337	*23.6*	2.432	*18.0*	655	*8.9*	0	*0*
Mortality 90 days after ICU admission	63.889	*16.0*	24.134	*27.8*	10.332	*33.2*	4.431	*32.8*	2.202	*29.8*	1.209	*27.0*
Mortality 180 days after ICU admission	73.152	*18.3*	26.805	*30.8*	11.411	*36.6*	5.008	*37.0*	2.591	*35.0*	1.510	*33.7*
Mortality 365 days after ICU admission	86.857	*21.7*	30.293	*34.8*	12.564	*40.3*	5.514	*40.8*	2.920	*39.5*	1.725	*38.5*

Table 1. Demographic characteristics of ICU patients admitted between 01-01-2013 and 01-01-2018. Mech. Vent. mechanical ventilation; ICU Intensive Care Unit;

* for Age/APACHE III score the median and interquartile ranges are reported

(online via https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03017-y/figures/1)

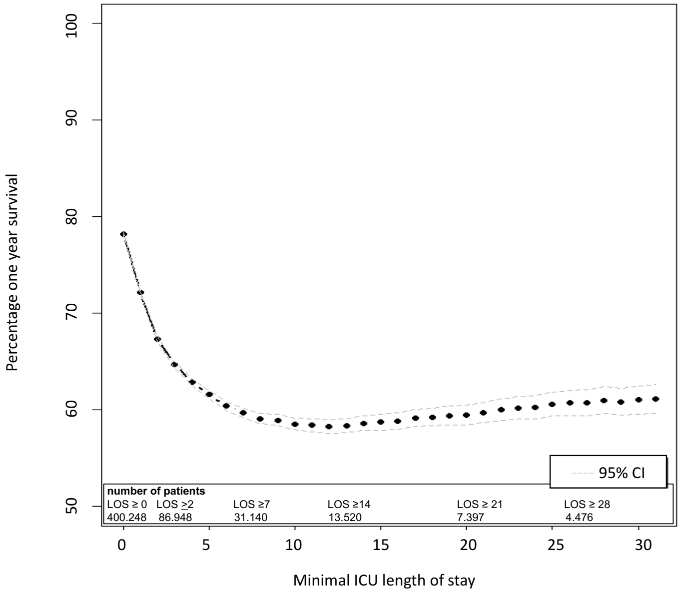


Figure 1. One year survival in relation to ICU length of stay.

Dotted line illustrates percentage of patients that survived to one year in relation to the minimal ICU length of stay. Dashed lines indicates 95% confidence intervals. For different minimal durations of admission, the number of patients are shown in the bottom of the table. *ICU* Intensive Care Unit; *LOS* Length of stay in the Intensive Care Unit.

three days and 0.68 (CI 95% 0.67-0.68) when LOS was at least seven days. Length of ICU stay had an AUC of 0.66 (CI 95% 0.66-0.66) at admission, decreasing to an AUC of 0.56 (CI 95% 0.55-0.56) for patients with a LOS of at least three days and 0.52 (CI 95% 0.51-0.53) for at least seven days.

Separating and comparing the acute component with the antecedent patient characteristics, showed that for patients with a LOS of at least three days, the predictive value of antecedent characteristics on one-year mortality significantly exceeded the acute component with an AUC of 0.68 (95% CI 0.68-0.69) versus AUC 0.67 (95% CI 0.67-0.68), p-value < 0.001. From an ICU length of stay of eleven days or more, the predictive ability of the combined model and the antecedent patient characteristics are equal (AUC 0.68 (95% CI 0.67-0.69) versus AUC 0.67 (95% CI 0.67-0.68), p-value 0.17).

Secondary outcome; hospital mortality

Figure 3 shows the predictive value of antecedent and acute factors separately or combined, and of LOS for hospital mortality among patients with increasing LOS. The model combining the acute component with antecedent patient characteristics had an AUC of 0.89 (95% CI 0.89-0.90) at admission, compared to an AUC of 0.88 (95%

CI 0.87-0.88) for the acute component and 0.71 (95% CI 0.71-0.72) for the antecedent patient characteristics.

The model using ICU length of stay to predict hospital mortality started with an AUC of 0.63 (CI 95% 0.63-0.64) the first day after admission, decreasing to 0.54 (95% CI 0.53-0.55) for a LOS of at least seven days.

Separating and comparing the acute component with the antecedent patient characteristics, showed that for patients with a LOS of at least seven days, the predictive value of the model using antecedent patient characteristics significantly exceeded the predictive ability of the acute component (AUC 0.66 (95% CI 0.65-0.66) versus 0.64 (95% CI 0.63-0.65), p-value < 0.001) for hospital mortality. This concerns 7,8% of all ICU patients, accounting for 52,4% of all bed-days and 18,1% of the total hospital mortality. For patients admitted for at least ten days in the ICU, there is no significant difference between the predictive value of only the antecedent patient characteristics compared to the combined model (AUC of both models is 0.66, p-value=0.20) implying no impact of the acute component on hospital mortality.

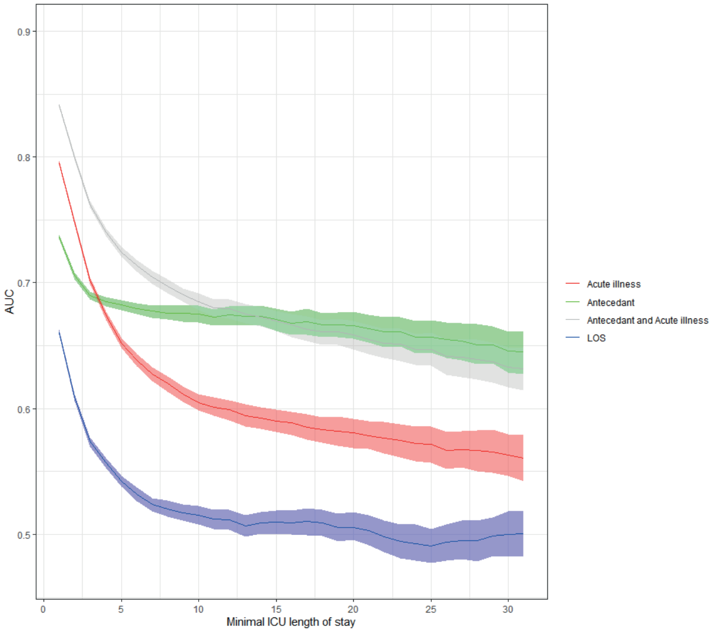


Figure 2. Predictive value of four different mixed models on one-year mortality expressed by the AUC over time.

Red; acute illness characteristics (diagnosis at ICU admission, acute physiology, type of admission, lead time, source of ICU admission). Green; antecedent characteristics (demographics, chronic health condition). Grey; combined model with acute illness characteristics and antecedent characteristics. Blue; duration of ICU stay in days. *AUC* Area Under the receiver operating Characteristics curve, *LOS* Length of stay *ICU* Intensive Care Unit

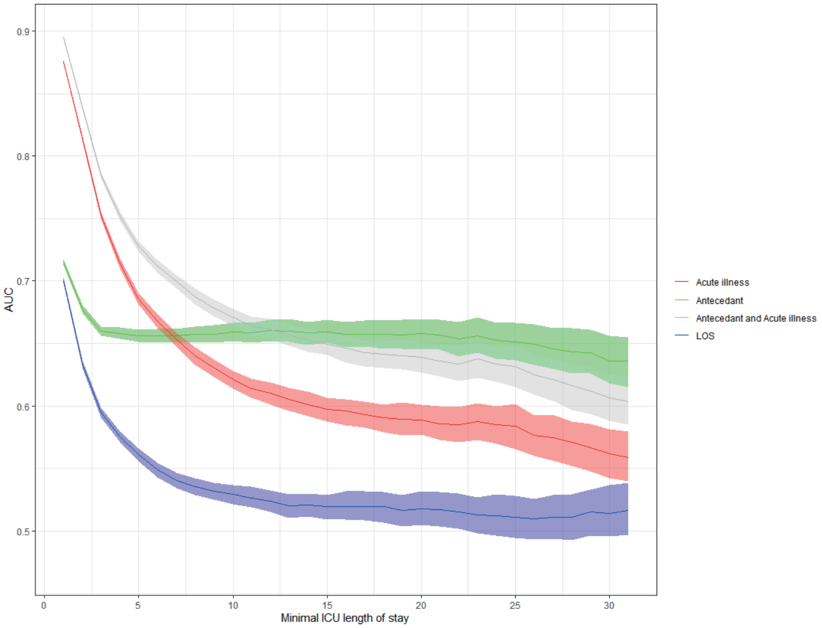


Figure 3. Predictive value of four different mixed models on hospital mortality expressed by the AUC over time.

Red; acute illness characteristics (diagnosis at ICU admission, acute physiology, type of admission, lead time, source of ICU admission). Green; antecedent characteristics (demographics, chronic health condition). Grey; combined model with acute illness characteristics and antecedent characteristics. Blue; duration of ICU stay in days.
AUC Area Under the receiver operating Characteristics curve, *LOS* Length of stay *ICU* Intensive Care Unit

DISCUSSION

In this national cohort study with over 400.000 ICU patients, we explored the predictive value for one-year mortality of acute illness characteristics, antecedent patient characteristics and length of stay in the ICU. We found that for patients with a LOS of at least three days, antecedent patient characteristics outperformed the acute component in predicting one-year mortality. After the first week of ICU admission, length of ICU itself had no predictive value for long-term outcome.

Timing

The moment when antecedent characteristics outperform acute illness characteristics in predicting hospital mortality, has been described as the onset of persistent critical illness [3,4]. In our large cohort, we found this moment at day seven, which is comparable to earlier studies. However, for the prediction of one-year mortality this moment was much earlier, namely after three days of admission. This difference in timing is likely to reflect the more pronounced effect of antecedent patient characteristics than of acute illness characteristics on survival beyond hospital discharge. Previous research has reported that acute illness influences short time survival, while mortality beyond 3 months was determined by age, co-morbidities and frailty [8,13,26,32,33]. Comparable findings have been reported for resource use after hospital discharge and persistent physical symptoms, which are largely determined by factors present before ICU admission and seldom from ICU disease severity [23,24].

In our study, antecedent patient characteristics showed a relatively constant predictive value for mortality after surviving the first days of ICU admission. Both for hospital mortality as well as for one-year mortality, the models based on antecedent patient characteristics had a stable AUC over time. This effect has also been described for frailty, which affects short- and long-term mortality in a comparable manner [34,35].

We found that beyond the first week, prolonged LOS cannot be used to predict mortality. Although the risk of one year mortality doubled in the first week in ICU (from 20% to 40%), the AUC curves were low and additional days in ICU after a LOS of nine days, did not contribute to the risk of mortality. Our Dutch data corresponds with that of a large Australian cohort, describing that treatment days beyond day 10 are unrelated to outcome in unselected ICU patients [26]. Although contra-intuitive, these findings stress that a prolonged ICU LOS should not immediately lead to pessimism regarding survival.

Use in clinical practice

This study aimed to give insight in the specific contribution of the acute component and antecedent patient characteristics on one-year mortality prediction during ICU admission. In current practice both factors are combined when making outcome estimates. We showed that antecedent characteristics outperform the acute illness characteristics for patients with a LOS of at least three days. Moreover, the impact of admission diagnosis and severity, either high or low, diminished for both hospital mortality and one-year mortality from a LOS of at least 10-11 days. However, all components showed relatively low AUC curves and should not be interpreted as prediction models. Since we currently lack reliable models able to predict survival beyond hospital discharge, acknowledging the change in importance over time of antecedent patient characteristics versus admission diagnosis and physiologic derangements, is important. Our findings should be regarded as a strong argument to gather background information on patients early during ICU treatment. Especially in patients with a delayed recovery from their primary illness, pre-morbid health might be crucial in their chances of survival.

The strengths of our study include the use of a very large sample of unselected ICU patients, with the number of missing values of 0.9%, minimizing the risk of bias. This is also reflected by the small confidence intervals. However, there are also some limitations to be mentioned. Firstly, we expect that our findings regarding the predictive value of antecedent characteristics compared to acute critical illness are generalizable. However, due to differences in discharge and admission policy among countries, the moment when antecedent patient characteristics have better predictive value than acute illness characteristics, might differ with respect to settings. In addition, we were not informed about the discharge locations. A small number of patients might be discharged to a hospice with death anticipated. Secondly, the co-variates of the models, may have affected the predictive value. For example, only the co-morbidities available in the NICE registry were used as antecedent patient characteristics. Although this is a pragmatic approach, it resembles the available information in daily practice, additional background information like frailty and functional dependency is likely to influence the predictive value. Furthermore, the elements of our acute illness model demonstrated limited predictive value for one-year mortality, which could possibly be enhanced by improving the model by adding elements like vasopressor use or mechanical ventilation and thus affecting our results. Thirdly, we only have information about the mortality of ICU patients and not about functional capacity, cognitive or mental disabilities following (prolonged) ICU treatment. Prolonged LOS could have adverse effects, not captured by mortality as a single outcome construct. Fourthly, mortality can be the result of treatment limitations, which introduced a risk of bias.

Future research could focus on combining the antecedent patient model with dynamic information during the ICU treatment, such as the development and severity of organ failure during admission. Such a dynamic model might be able to enhance the identification of patients who are (un)likely to have long-term survival.

CONCLUSIONS

Models for prediction of ICU outcomes are typically based on a combination of antecedent patient characteristics with admission diagnosis and disease severity. Comparing the predictive value of these factors for one-year mortality among patients with increasing ICU LOS, antecedent patient characteristics are more predictive than the acute component for patients with a ICU LOS of three days or more. For hospital mortality, antecedent patient characteristics outperform the acute component for patients with a LOS of at least seven days in the ICU. After the first week of ICU admission, LOS itself is not predictive of hospital or one-year mortality.

REFERENCES

1. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, et al. The epidemiology of chronic critical Illness in the United States. Crit. Care Med.; 2015;43:282–7.
2. Yearbook NICE registry 2016 [Internet]. Available from: https://www.stichting-nice.nl/doc/jaarboek-2016-web.pdf accessed July 2019
3. Iwashyna TJ, Hodgson CL, Pilcher D, Bailey M, van Lint A, Chavan S, et al. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. Lancet Respir Med. 2016;4:566–73.
4. Bagshaw SM, Stelfox HT, Iwashyna TJ, Bellomo R, Zuege D, Wang X. Timing of onset of persistent critical illness: a multi-centre retrospective cohort study. Intensive Care Med.; 2018;182:446–11.
5. Wintermann G-B, Weidner K, Strauß B, Rosendahl J, Petrowski K. Predictors of posttraumatic stress and quality of life in family members of chronically critically ill patients after intensive care. Ann Intensive Care; 2016;6:69.
6. Cameron JI, Chu LM, Matté A, Tomlinson G, Chan L, Thomas C, et al. One-Year Outcomes in Caregivers of Critically Ill Patients. NEJM; 2016;374:1831–41.
7. Hill AD, Fowler RA, Pinto R, Herridge MS, Cuthbertson BH, Scales DC. Long-term outcomes and healthcare utilization following critical illness – a population-based study. Crit Care; 2016;20:76.
8. Szakmany T, Walters AM, Pugh R, Battle C, Berridge DM, Lyons RA. Risk Factors for 1-Year Mortality and Hospital Utilization Patterns in Critical Care Survivors: A Retrospective, Observational, Population-Based Data Linkage Study. Crit. Care Med. 2019;47:15–22.
9. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA; 2010;303:849–56.
10. Dinglas VD, Chessare CM, Davis WE, Parker A, Friedman LA, Colantuoni E, et al. Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. Thorax;2018;73:7–12.
11. Williams TA, Dobb GJ, Finn JC, Knuiman MW, Geelhoed E, Lee KY, et al. Determinants of long-term survival after intensive care. Crit. Care Med. 2008;36:1523–30.
12. Reardon PM, Fernando SM, Van Katwyk S, Thavorn K, Kobewka D, Tanuseputro P, et al. Characteristics, Outcomes, and Cost Patterns of High-Cost Patients in the Intensive Care Unit. Crit Care Res Pract; 2018;2018:5452683–7.
13. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. Crit. Care Med. 2013;41:1229–36.
14. Keenan SP, Dodek P, Chan K, Hogg RS, Craib KJP, Anis AH, et al. Intensive care unit admission has minimal impact on long-term mortality. Crit. Care Med. 2002;30:501–7.
15. Marshall DC, Hatch RA, Gerry S, Young JD, Watkinson P. Conditional Survival With Increasing Duration of ICU Admission: An Observational Study of Three Intensive Care Databases. Crit. Care Med. 2020;48:91–7.
16. Krinsley JS, Wasser T, Kang G, Bagshaw SM. Pre-admission functional status impacts the performance of the APACHE IV model of mortality prediction in critically ill patients. Crit Care; 2017;21:110–9.
17. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. Crit. Care Med. 2006;34:1297–310.
18. Ball IM, Bagshaw SM, Burns KEA, Cook DJ, Day AG, Dodek PM, et al. A clinical prediction tool for hospital mortality in critically ill elderly patients. J Crit Care. 2016;35:206–12.
19. Turnbull AE, Sepulveda KA, Dinglas VD, Chessare CM, Bingham CO, Needham DM. Core Domains for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. Crit. Care Med; 2017;45:1001–10.

20. Brummel NE, Bell SP, Girard TD, Pandharipande PP, Jackson JC, Morandi A, et al. Frailty and Subsequent Disability and Mortality Among Patients With Critical Illness. Am J Resp Crit Care Med; 2017;196-64-72.
21. Heyland DK, Stelfox HT, Garland A, Cook D, Dodek P, Kutsogiannis J, et al. Predicting Performance Status 1 Year After Critical Illness in Patients 80 Years or Older: Development of a Multivariable Clinical Prediction Model. Crit. Care Med. 2016;44:1718–26.
22. Bagshaw M, Majumdar SR, Rolfson DB, Ibrahim Q, McDermid RC, Stelfox HT. A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care; 2016;20:175.
23. Griffith DM, Salisbury LG, Lee RJ, Lone N, Merriweather JL, Walsh TS, et al. Determinants of Health-Related Quality of Life After ICU: Importance of Patient Demographics, Previous Comorbidity, and Severity of Illness. Crit. Care Med; 2018;46:594–601.
24. Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH, et al. Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. Am J Resp Crit Care Med; 2016;194:198–208.
25. Moitra VK, Guerra C, Linde-Zwirble WT, Wunsch H. Relationship Between ICU Length of Stay and Long-Term Mortality for Elderly ICU Survivors*. Crit. Care Med. 2016;44:655.
26. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman M, Webb SAR. Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. Br. J. Anaesth; 2010;104:459–64.
27. Laupland KB, Kirkpatrick AW, Kortbeek JB, Zuege DJ. Long-term mortality outcome associated with prolonged admission to the ICU. Chest. 2006;129:954–9.
28. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol. 2015;44:1850–1850h.
29. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit. Care Med. 1981;9:591–7.
30. Efron B. Estimating the Error Rate of a Prediction Rule: Improvement on Cross-Validation. J Am Stat Ass; 1983;78:316–31.
31. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–45.
32. Garland A, Olafson K, Ramsey CD, Yogendran M, Fransoo R. Distinct determinants of long-term and short-term survival in critical illness. Intensive Care Med. 2014;40:1097–105.
33. Brummel NE, Bell SP, Girard TD, Pandharipande PP, Jackson JC, Morandi A, et al. Frailty and Subsequent Disability and Mortality among Patients with Critical Illness. Am J Resp Crit Care Med; 2017;196:64–72.
34. Muscedere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med; 2017;43:1105–22.
35. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ. 2014;186:E95–102.

ADDITIONAL FILE 1

Characteristics	LOS>=0 N	LOS>=0 %	LOS>2 N	LOS>2 %	LOS>7 N	LOS>7 %	LOS>14 N	LOS>14 %	LOS>21 N	LOS>21 %	LOS>28 N	LOS>28 %
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
Number of patients	400248		86948	21,7	31140	7,8	13520	3,4	7397	1,8	4476	1,1
Male	238306	59.5	52521	60.4	19308	62	8566	63.4	4786	64.7	2938	65.6
medical	193925	48.5	59019	67.9	21712	69.7	9310	68.9	5052	68.3	2982	66.6
urgent surgery	50634	12.7	14446	16.6	6126	19.7	2808	20.8	1560	21.1	973	21.7
elective surgery	155689	38.9	13483	15.5	3302	10.6	1402	10.4	785	10.6	521	11.6
cardiovascular	166117	41.5	34927	40.2	11422	36.7	4903	36.3	2771	37.5	1731	38.7
gastro-intestinal	53628	13.4	10372	11.9	3498	11.2	1511	11.2	834	11.3	514	11.5
genitourinary	15049	3.8	1902	2.2	453	1.5	164	1.2	82	1.1	48	1.1
hematological	1903	0.5	581	0.7	231	0.7	106	0.8	54	0.7	26	0.6
metabolic	7757	1.9	984	1.1	178	0.6	58	0.4	32	0.4	19	0.4
musculoskeletal	9013	2.3	837	1	267	0.9	119	0.9	62	0.8	38	0.8
neurologic	49142	12.3	8207	9.4	3313	10.6	1458	10.8	724	9.8	407	9.1
respiratory	69423	17.3	24237	27.9	9704	31.2	4198	31.1	2277	30.8	1361	30.4
transplant	1565	0.4	494	0.6	184	0.6	91	0.7	58	0.8	42	0.9
trauma	18622	4.7	4001	4.6	1746	5.6	847	6.3	464	6.3	265	5.9
immunological insuf.	30305	7.6	9819	11.3	3996	12.8	1850	13.7	1060	14.3	648	14.5
chr. cardiovasc. insuf.	19819	5	5090	5.9	1700	5.5	715	5.3	371	5	236	5.3
chr. renal insuf.	22248	5.6	6779	7.8	2377	7.6	1037	7.7	569	7.7	325	7.3
cirrhosis	5050	1.3	1560	1.8	576	1.8	224	1.7	116	1.6	56	1.3
COPD	52778	13.2	15733	18.1	5485	17.6	2226	16.5	1181	16	701	15.7
hematological malignancy	6301	1.6	2475	2.8	1105	3.5	515	3.8	284	3.8	155	3.5
metastatic cancer	17306	4.3	3330	3.8	1013	3.3	402	3	203	2.7	117	2.6
respiratory insuf.	17601	4.4	6938	8	2714	8.7	1206	8.9	650	8.8	406	9.1
mech. ventil at admission	161419	40.3	48917	56.3	19576	62.9	8757	64.8	4862	65.7	2971	66.4
mech. ventil in first 24 hours of admission	185067	46.2	60750	69.9	25103	80.6	11343	83.9	6293	85.1	3823	85.4
ICU mortality	32152	8	13132	15.1	6112	19.6	2750	20.3	1390	18.8	795	17.8
hospital mortality	46186	11.5	18709	21.5	8357	26.8	3694	27.3	1866	25.2	1076	24
mortality 7 days after ICU admission	32902	8.2	7723	8.9	0	0	0	0	0	0	0	0
mortality 28 days after ICU admission	50981	12.7	18832	21.7	7337	23.6	2432	18	655	8.9	0	0
mortality 90 days after ICU admission	63889	16	24134	27.8	10332	33.2	4431	32.8	2202	29.8	1209	27
mortality 180 days after ICU admission	73152	18.3	26805	30.8	11411	36.6	5008	37	2591	35	1510	33.7
mortality 365 days after ICU admission	86857	21.7	30293	34.8	12564	40.3	5514	40.8	2920	39.5	1725	38.5

Table E1. Detailed demographic characteristics.

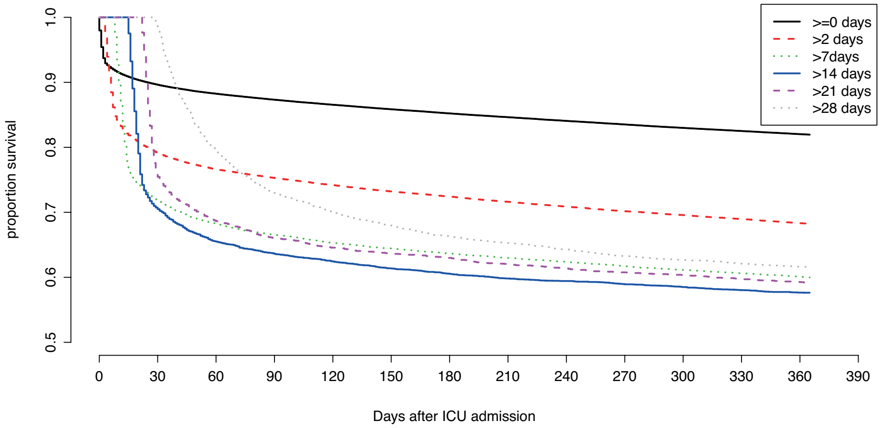


Figure E1. Percentage survival over time for groups with different ICU lengths of stay.

ICU intensive care unit

4

Determinants of self-reported unacceptable outcome of intensive care treatment one year after discharge

MC Kerckhoffs, FFL Kosasi, IW Soliman, JJM van Delden,
OL Cremer, DW de Lange, AJC Slooter, J Kesecioglu,
D van Dijk

Published in; Intensive Care Medicine 2019

ABSTRACT

Purpose Survivors of critical illness often suffer from reduced Health-Related Quality of Life (HRQoL) due to long-term physical, cognitive and mental health problems, also known as post-intensive care syndrome (PICS). Some Intensive Care Unit (ICU) survivors even consider their state of health unacceptable. The aim of this study was to investigate the determinants of self-reported unacceptable outcome of ICU treatment.

Methods Patients who were admitted to the ICU ≥48 hours and survived the first year after discharge, completed validated questionnaires on overall HRQoL and the components of PICS and stated whether they considered their current state of health an acceptable outcome of ICU treatment. The effect of overall HRQoL and components of PICS on unacceptable outcome were studied using multiple logistic regression analysis.

Results Of 1453 patients, 67 (5%) reported their health state an unacceptable outcome of ICU treatment. These patients had a lower score on overall HRQoL (EQ-5D-index value of 0.57 versus 0.81; $p < 0.001$), but we could not determine a cut-off value of the EQ-5D-index value that reliably identified unacceptable outcome. In the multivariate analysis, only the hospital anxiety and depression scale was significantly associated with an unacceptable outcome (OR 2.06, 99% CI 1.18-3.61).

Conclusion Although there is a strong association between low overall HRQoL and self-reported unacceptable outcome of ICU treatment, patients with low overall HRQoL may still consider their outcome acceptable. The mental component of PICS, but not the physical and cognitive component, is strongly associated with self-reported unacceptable outcome.

INTRODUCTION

The primary aim of Intensive Care Medicine used to be saving lives. However, Intensive Care Unit (ICU) survival may come at a price: many patients suffer from post-intensive care syndrome (PICS) comprising of ICU related limitations in physical, cognitive and mental functioning [1]. With the recognition of these sequelae of ICU treatment, the focus in outcome research shifted more and more from hospital survival towards long-term survival, health-related quality of life (HRQoL) and functional outcomes [2-8].
Functional outcomes are usually measured with standardized and validated questionnaires, filled in by the patient without interpretation by a clinician [9]. These so-called 'patient-reported outcome measures' (PROMs) exist for overall HRQoL as well as for the components of PICS and there is broad consensus to use these in long-term outcome studies [10]. Although both patients and researchers agree on the importance of measuring these outcomes, evidence that supports the measurement quality of the various PROMs in ICU survivors specifically, is limited [11]. Research that involved patients to define relevant outcomes, revealed that there is no PROM that covers all relevant aspects of a good outcome [12, 13]. In addition, not all symptoms that impact wellbeing are included in currently used PROMs [14].

Some patients state that they do not want to survive critical illness if it results in a poor quality of life, but it appears very difficult to uniformly define poor outcome. There is hardly evidence that helps to classify overall HRQoL values into acceptable or unacceptable outcome and researchers arbitrary define poor outcome when conducting long-term outcome studies in ICU patients [15]. In addition, for ICU survivors reporting a lower quality of life, it is not fully known how the various components of PICS contribute to a lower quality of life or an unacceptable outcome.

The aim of this study was to investigate the effect of overall HRQoL and of the components of PICS on the risk of a self-reported unacceptable outcome of ICU treatment.

METHODS

Study design and setting

This cohort study was conducted in the ICU of the University Medical Center Utrecht, the Netherlands. This is a tertiary, adult, mixed ICU with 2200 admissions per annum. All consecutive patients admitted to the ICU between 2010 (start of prospective data collection) and 2016 were eligible.

Participants

Patients who had been admitted to the ICU for at least 48 hours and who were still alive one year after ICU discharge were eligible. If case of re-admission, data from the first admission was used. Patients were excluded when under 16 years of age, without a known address, not traceable through the municipal registry or when they opted out for participation in scientific studies. The institutional review board of the University Medical Center Utrecht approved the study and waived the need for informed consent (UMC Utrecht IRB 10/006). One year after ICU discharge the Dutch municipal population register was consulted to identify and exclude deceased patients. A survey was subsequently sent by mail to all surviving patients.

Variables

Baseline characteristics are reported in Table 1.

The survey contained PROMs to evaluate overall HRQoL, physical, cognitive and mental functioning (Table 2). These are the possible determinants of an unacceptable outcome.

(1) Overall HRQoL measured by the EuroQol-5 Dimension (EQ-5D-3L)[16,17].
(2) Physical functioning measured by the Barthel Index [18].
(3) Cognitive functioning measured by the Cognitive Failures Questionnaire (CFQ) [19].
(4) Depressive symptoms measured by the Hospital Anxiety and Depression Scale (HADS) [20].
(5) Post-traumatic stress disorder symptoms measured by the Impact of Event Scale (IES) [21].

The outcome measure of this study was disagreement with the statement “I consider my current condition an acceptable outcome of the ICU treatment”. This was measured by including a question in the survey asking a response (agree/neutral/disagree) to this statement.

	Determinant	PROM	Measures	Scale	Interpretation
1	Overall HRQoL [16,17]	EuroQoL EQ-5D (EQ-5D-3L) index value	Five dimensions: mobility, self-care, usual activities, pain/ discomfort and mood	-0.3 to 1.0	Higher index values reflect a better overall HRQoL
2	Physical functioning [18]	Barthel Index	Degree of functional ability and dependency concerning activities of daily living	0- 20	Higher scores reflect more functional independence
3	Cognitive functioning [19]	Cognitive Failures Questionnaire (CFQ)	Cognitive functions in four categories evaluated with 25 items	0- 100	Higher scores reflect more cognitive failures
4	Depressive symptoms [20]	Hospital Anxiety and Depression Scale (HADS)	Anxiety and depression levels. Seven questions concern anxiety and seven questions concern depression	0-42 (two subscales 0-21)	Higher scores reflect more symptoms of anxiety and/or depression
5	Post-traumatic stress disorder symptoms [21]	Impact of Event Scale (IES)	Intrusion and avoidance on subscales, evaluated with fifteen items	0-75	Higher scores reflect more posttraumatic stress symptoms

Table 2. Possible determinants of unacceptable outcome

PROM; patient reported outcome measure

Data sources

Baseline characteristics were collected by consulting the electronic patient record, the remaining by the surveys. The participants were asked to fill in the survey themselves or to explicit received assistance. Data were entered in an electronic database by independent research assistants.

Bias

To reduce bias, patients received several reminders by mail and telephone. Multivariate analyses were applied to correct for known confounders.

Study size

The inclusion of five determinants in the multivariate logistic regression model required at least fifty cases (patients with unacceptable outcome) in the study. Recruitment stopped after 5,5 years when 67 cases and a total number of 1453 patients were included.

Statistical methods

Patients were divided into three groups according to their response to the acceptable outcome statement; 1) acceptable; patients responding with 'agree', 2) neutral; patients responding with 'neutral', 3) unacceptable; patients responding with 'disagree'. A baseline table was constructed comparing the three groups. Differences between the groups were studied using the appropriate tests (Chi square test or Fisher's exact test for categorical data, one-way ANOVA for continuous data).

In order to analyze the association between the various PROMs and self-reported unacceptable outcome of ICU treatment, multiple logistic regression was performed. Since the undesirable outcome was unacceptable outcome, the other two groups were merged. To assess the effect of merging these groups, we performed a sensitivity analysis in which we combined the 'neutral' respondents with the patients who reported an unacceptable outcome. In addition, we performed a multinomial regression analysis to assess the differences between the three groups.

The strength of the association between the PROMs and self-reported unacceptable outcome was analyzed using the odds ratios from multiple logistic regression models. Since each PROM is measured with a different questionnaire and uses different scales, the questionnaire scores were standardized by converting them into z-scores for the multivariate analyses. The HRQoL and Barthel score were first inverted, so that higher z-scores implied worse outcomes for every PROM.

To correct for differences between the patient groups, we performed three multivariate logistic regression analyses. In the first logistic regression analysis, the effect of the various PROMs on acceptable outcome of ICU treatment was calculated with correction for demographic characteristics such as age, gender and place of residence.

In the second, a correction for demographic and ICU characteristics was applied. ICU characteristics were type of admission, length of stay, comorbidities, APACHE score, highest SOFA score and use of continuous venovenous hemofiltration (CVVH). The APACHE score, SOFA score and use of CVVH were chosen as indicators for severity of illness. Comorbidities were classified in three groups: no comorbidity, one comorbidity and two or more comorbidities.

Lastly, a third logistic regression analysis was performed to calculate the individual effect of each PROM by adjusting for the other PROMs in addition to the demographic characteristics and ICU characteristics. Because overall HRQoL, as measured in the EQ-5D, includes all the components of PICS, overall HRQoL was left out of the final analysis.

Since we calculated 19 different p-values for the comparison of the study outcomes, the significance level was modified using the Bonferroni correction to <.003 (0.05/19). The odds ratios (ORs) obtained with the logistic regression analyses are presented with 99 percent confidence intervals (99% CI).

As post-hoc analysis, the EQ-5D index values were analyzed to define a cutoff point in EQ-5D index values that indicates a self-reported unacceptable outcome of ICU treatment. A box plot and ROC curve were constructed to compare the distribution of EQ-5D index values in the two groups.

We also performed a post-hoc logistic regression analysis to assess the association between each EQ-5D domain (mobility, self-care, usual activities, pain, mood) and unacceptable outcome of ICU treatment.

RESULTS

Participants

A flowchart of the study population enrolment is presented in Figure 1. During the 6-year study period 2294 patients were admitted for at least 48 hours and survived at least one year. The survey was returned by 1632 patients (71%). Complete responders (n=1453, 89%) were defined as patients who answered the question about acceptable outcome and all the questions of the EQ-5D. Within the complete responders, 1073 patients (74%) agreed with the statement that their current condition is an acceptable outcome of ICU treatment, 313 (22%) responded neutral and 67 patients (5%) disagreed with the statement. Characteristics of the participants are presented in Table 1. Gender, place of residence and highest SOFA score differed significantly across the three groups.

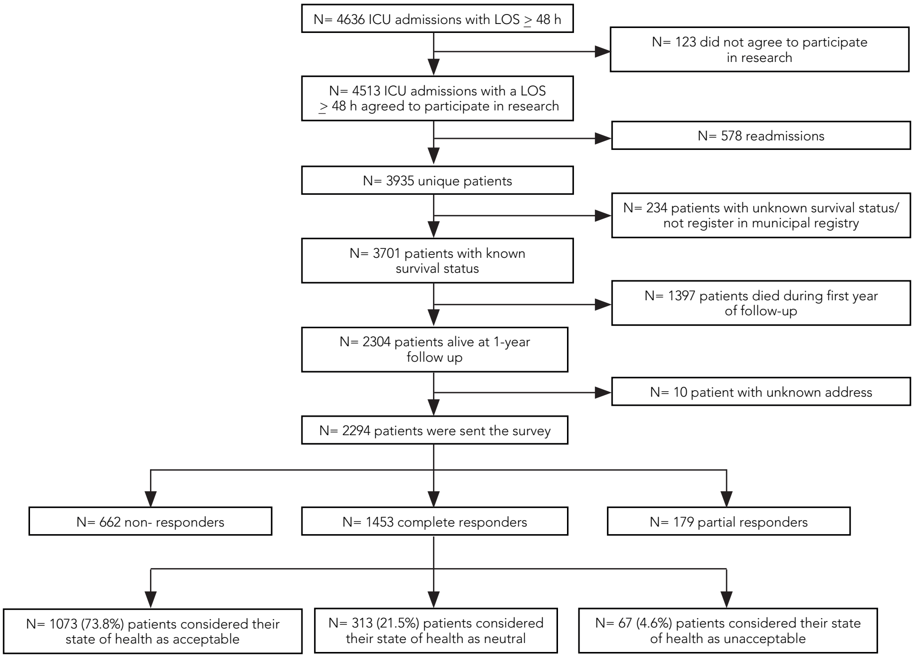


Figure 1. Flowchart of the enrolment process

Flowchart depicting the enrolment process, reasons for exclusion and follow-up of the enrolled patients. *ICU*= intensive care unit.

Acceptable state of health-statement	Acceptable (n=1073)	Neutral (n=313)	Unacceptable (n=67)	Total (n=1453)	P value
Male gender	710 (66.2)	187 (59.7)	37 (55.2)	934 (64.3)	0.032
Age at admission (years)	60 (49-70)	59 (50-69)	55 (44-67)	59 (49-70)	0.265
Living in a nursing home	36 (3.4)	29 (9.3)	7 (10.4)	72 (5.0)	<0.001*
ICU LOS (in days)	5.06 (3.16-9.42)	5.52 (3.07-9.84)	5.03 (2.96-10.59)	5.10 (3.08-9.61)	0.865
Type of admission					0.937
Elective surgery	287 (26.7)	86 (27.5)	18 (26.9)	391 (26.9)	
Emergency surgery	311 (29.0)	84 (26.8)	18 (26.9)	413 (28.4)	
Medical	467 (43.5)	143 (45.7)	31 (46.3)	641 (44.1)	
Number of comorbidities					0.855
0	677 (63.1)	199 (63.6)	43 (64.2)	919 (63.2)	
1	274 (25.5)	73 (23.3)	17 (25.4)	364 (25.1)	
2 or more	120 (11.2)	41 (13.1)	7 (10.4)	168 (11.6)	
APACHE score	59.00 (45-80)	59.00 (45-76)	55 (47-78)	59 (45-79)	0.222
SOFA highest score	13 (8-17)	11.5 (7-16)	12 (6-16)	12 (8-16)	0.013
CVVH	108 (10.1)	33 (10.5)	9 (13.4)	150 (10.3)	0.682

Table 1. Baseline characteristics

Baseline characteristics of patients who responded acceptable/neutral/unacceptable to the acceptable state of health- question. *Continuous data are presented as median (IQR (=interquartile range)). Categorical data are presented as n (%). ICU= intensive care unit, LOS = length of stay, COPD = Chronic Obstructive Pulmonary Disease, AIDS = Acquired Immune Deficiency Syndrome, APACHE = Acute Physiology and Chronic Health Evaluation, SOFA = Sepsis-related Organ Failure Assessment, CVVH =continuous venovenous hemofiltration. Chi square test was used for categorical data, one-way ANOVA for continuous data. P values <0.003 were considered to be statistically significant (*).*

Outcome data

Table 3 shows the distribution of the various PROMS for the three groups of respondents. The ICU survivors who reported an unacceptable outcome of ICU treatment reported an EQ-5D index value of 0.57 (99% CI 0.17-0.78) compared to an EQ-5D index value of 0.81 (99% CI 0.69-1.00) in ICU survivors reporting an acceptable or neutral outcome.

	Unacceptable (n=67)	Neutral (n=313)	Acceptable (n=1073)	Neutral+Acceptable (n=1386)
EQ-5D	0.569 (0.174-0.775)	0.773 (0.434-0.861)	0.843 (0.719-1.000)	0.811 (0.687-1.000)
Barthel Index	19 (15.5-20)	20 (16-20)	20 (19-20)	20 (19-20)
CFQ	27 (12-41.3)	23.5 (11-36)	20 (10-30)	21 (11-32)
HADS	18 (12.5-24.5)	14 (10-19)	11 (8-15)	11 (8-16)
IES	21 (0-36.8)	9 (0-25)	6 (0-17)	6 (0-19)

Table 3. Raw questionnaire scores related to self-reported outcome groups

Raw questionnaire scores of patients presented for the groups self-reporting their outcome as unacceptable, acceptable, neutral and the combined acceptable plus neutral group. *Data are presented as median (IQR (=interquartile range)). EQ-5D= EuroQoL-5 Dimension index value, CFQ= cognitive failures questionnaire, HADS= hospital anxiety and depression scale, IES= impact of event scale.*

Main results

Table 4 shows the analysis of patients who reported an unacceptable outcome of ICU treatment, compared to patients who responded neutral or acceptable. The unadjusted odds ratios showed a significant association between a more unfavorable value on the EQ-5D (OR 2.09, 99% CI 1.62-2.69), on the HADS (OR 2.20, 99% CI 1.60-3-02) and on the IES (OR 1.74, 99% CI 1.26-2.40) and self-reported unacceptable outcome. When adjusted for demographic factors alone or for both demographic and ICU factors, a lower EQ-5D index value, higher HADS score and higher IES score were significantly associated with a self-reported unacceptable outcome. The Barthel Index and Cognitive Failures Questionnaire had no effect on self-reported unacceptable outcome in any of the adjusted analyses.

When adjusting for the other components of PICS, along with demographic factors and ICU factors, only the HADS score was significantly associated with self-reported unacceptable outcome of ICU treatment with an OR of 2.06 (99% CI 1.18-3.61).

Supplementary analyses

The sensitivity analysis in which self-reported neutral and unacceptable outcome one year after ICU were combined and compared to the acceptable outcome group, showed the same significant association with the HADS score in the logistic regression analysis (Supplemental table S1).

In the multinomial regression analysis, neutral and unacceptable responding patients were compared with patients reporting an acceptable outcome (table S2). This analysis showed that the neutral response group differs from both the unacceptable outcome and acceptable outcome group. It also showed a much stronger effect of unfavorable EQ-5D and HADS scores in the unacceptable group compared to neutral responders.

The logistic regression analyses of the association between the EQ-5D domains and unacceptable outcome (table S3) shows an association of unfavorable scores in all domains with unacceptable outcome in both unadjusted and adjusted analyses. Impairment in usual activities (OR 2.14, CI 99% 1.48-3.09) and mood (OR 2.13, CI 99% 1.62-2.79) had the strongest association with unacceptable outcome.

We were unable to identify a discriminating EQ-5D index value that could define unacceptable outcome of ICU treatment one year after discharge (figure S1 and S2). In the receiver operating curve (ROC) statistics, the area under the curve was .706 and for the EQ-5D cut-off value of 0.72, the sensitivity and specificity were both 69%.

Unacceptable vs acceptable +neutral outcome of ICU treatment	OR unadjusted (99% CI)	p-value	OR adjusted for demographic factors (99% CI)	p-value	OR adjusted for demographic and ICU factors (99% CI)	p-value	OR adjusted for demographic, ICU factors and other questionnaires (99% CI)	p-value
EQ-5D	2.09 (1.62-2.69)	<0.001*	2.05 (1.56-2.70)	<0.001*	2.20 (1.64-2.94)	<0.001*		
Barthel Index	1.30 (0.97-1.73)	0.019	1.22 (0.85-1.75)	0.158	1.24 (0.85-1.82)	0.142	0.84 (0.42-1.67)	0.512
CFQ	1.43 (0.98-2.07)	0.014	1.38 (0.94-2.03)	0.031	1.40 (0.94-2.10)	0.031	0.84 (0.47-1.50)	0.439
HADS	2.20 (1.60-3.02)	<0.001*	2.04 (1.47-2.84)	<0.001*	2.05 (1.45-2.89)	<0.001*	2.06 (1.18-3.61)	0.001*
IES	1.74 (1.26-2.40)	<0.001*	1.64 (1.17-2.30)	<0.001*	1.57 (1.09-2.26)	0.002*	1.13 (0.68-1.88)	0.525

Table 4. Association between questionnaire scores and self-reported unacceptable outcome

Association between (standardized) questionnaire scores and self-reported unacceptable outcome of ICU treatment versus self-reported acceptable plus neutral outcome, expressed in adjusted odds ratios from multivariable logistic regression. Odds ratios are expressed for decreases in EQ-5D index value and Barthel Index and for increases in HADS, CFQ and IES scores. P-values <.003 are considered to be significant (*)

Demographic characteristics; age, gender and place of residence (home versus rehabilitation clinic or nursing home). ICU characteristics; type of admission, length of stay, comorbidities, APACHE score, highest SOFA score and use of continuous venovenous hemofiltration (CVVH).

99% CI= 99% confidence interval. OR= odds ratio. ICU= intensive care unit. EQ-5D= EuroQoL-5 Dimension, HADS= hospital anxiety and depression scale, CFQ= cognitive failures questionnaire, IES= impact of event scale

DISCUSSION

The aim of this study was to investigate the effect of overall HRQoL and of the components of PICS on the risk of a self-reported unacceptable outcome of ICU treatment. We found that a low overall HRQoL corresponds with a self-reported unacceptable outcome, but were unable to identify a cut-off value for the patient-reported outcome measure on overall HRQoL. Considering PICS, symptoms of anxiety and depression have the strongest association with self-reported unacceptable outcome one year after ICU discharge.

ICU survivors with a self-reported unacceptable outcome reported lower overall HRQoL index values. Interestingly, the majority of ICU survivors (74%) rate their health as being acceptable even with low overall HRQoL. In other words, some patients with severe impairments reflected by a low EQ-5D index value, report an acceptable outcome. This is illustrated by a great overlap in the distribution of EQ-5D index values between the group with unacceptable and acceptable/neutral outcome. We were therefore unable to identify an EQ-5D cut-off value defining an unacceptable outcome. This divergence implies unmeasured factors that impact how patients perceive their outcome in terms of acceptance. One explanation might be the disability paradox [22]. This phenomenon describes patients with severe illness whose appraisal of their quality of life is good or excellent. It indicates that quality of life reflects a balance of body and mind within a social context and environment. Some patients make the decision to live, rather than just to survive, and experience a better HRQoL. Secondly, the discrepancy could reflect the ability to adjust and give meaning to impairments, which has been described previously in ICU survivors [23].The so-called response shift refers to the change in the meaning of one's self-evaluation of quality of life as a result of changes in internal standards, values and the conceptualization of quality of life [24-26]. These aspects are not captured in the PROM on HRQoL, impeding straightforward interpretation in survivors of critical illness. From a clinical perspective, an EQ-5D cut-off value for poor ICU outcome should be treated with vigilance, although the association of the HRQoL scores and unacceptable outcome is illustrative [27, 28]. Studies on ICU outcome should preferably use both objective as well as subjective appraisal of wellbeing [10].

Focusing on the components of PICS, symptoms of anxiety and depression as measured by the HADS were found to be most explanatory for an unacceptable outcome of ICU treatment. This was confirmed by the multivariate analyses and the sensitivity analysis in which the HADS still had a strong effect. Post-traumatic stress disorder symptoms lost its significance after correcting for the other questionnaires, which is likely caused by the fact that the majority of patients who suffer from mental impairments have both symptoms of anxiety and depression, as well as post-traumatic stress [29]. Due to the known overlap in symptoms of anxiety and depression and the small sample of patients reporting an unacceptable outcome, more detailed analysis of the impact of each was considered unavailing.

Physical impairment, as measured by the Barthel Index, was not associated with self-reported unacceptable outcome after ICU treatment. However, more than 70% of all responding ICU survivors reported a Barthel Index score higher than 16 indicating functional independence in most daily life activities (table 3). It is known that the Barthel Index is less likely to measure differences in the higher range, possibly causing an overestimation of physical functioning [30]. The fact that former ICU patients considered physical outcome to be very important, stresses the need for more detailed research on the impact of physical sequelae [7, 10, 23].

Since persistent mental symptoms mostly impacted self-reported unacceptable outcome, strategies to reduce mental sequelae are likely to benefit health acceptance in ICU survivors. ICU diaries, reduced use of sedatives and early mobilization are proven interventions to decrease mental sequelae [31-33]. In addition, screening patients early after discharge can aid identifying patients at risk for mental disabilities [34].
However, appraisal of state of health reflects more than the PROMs measure, as illustrated by the wide distribution of overall HRQoL scores in relation to acceptable health status. Since resilience has been found to be inversely related to mental symptoms in ICU survivors, strategies to improve resilience might also be able to benefit state of health acceptance after ICU discharge [35]. Promoting coping skills and mindfulness training are promising interventions, however trials are still awaited [36, 37]. Its effect on decision-making on continuation of treatment, is yet neither evident.

To our knowledge, this is the first study to test whether it is justified to translate the results of validated questionnaires (PROMs) into acceptable or unacceptable outcome in former ICU patients [15]. We were able to show that a self-reported unacceptable outcome corresponds with a low overall HRQoL and is mainly explained by mental sequelae. One of the strengths of our study is that we were able to include a large number of patients. The fact that subjective well-being was assessed one year after discharge from the ICU is a strong feature. Since for most patients a new equilibrium is established after one year, the acquired data in this study can be considered legitimate.

This study also holds limitations. Firstly, this is a single-center study from the Netherlands, which may impede the generalizability of the findings. Secondly, the measurement of the outcome measures took place at only one time-point. The EQ-5D is known to vary over time and both under- as overestimation may have occurred. Thirdly, the incidence of cognitive disabilities might be incorrect due to the use of patient-reported questionnaires instead of neurocognitive testing [8]. Fourthly, we have categorized the patients who disagreed with the statement that their outcome was acceptable as the unacceptable group. There is, however, a fine difference between not agreeing that the outcome is acceptable and stating that it is unacceptable. Additionally, in the unacceptable group, more patients received help from caregivers with completing the questionnaire than in the neutral/acceptable group (46% versus 25%). It is possible that this reflects more severe disabilities in the unacceptable group. However, it is also possible that caregiver strain influenced the response to the question whether the outcome was acceptable [38]. Fifthly, only survivors being alive one year after discharge were questioned. It is conceivable that some patients who had experienced or feared an unacceptable outcome were not alive anymore at the time of follow-up, because they had requested withholding or withdrawal of care. Sixthly, despite the result of the sensitivity analysis we may have lost information by pooling the neutral response group with the acceptable outcome group. The multinomial regression analysis showed that the neutral response group differs from both the unacceptable outcome and acceptable outcome group. Seventhly, the rather conservative Bonferroni correction helped us to avoid false positive associations, but we may have missed some true associations. Lastly, the presence of missing values could cause issues. We are not informed on the distribution of missing patients' outcome. Our study could therefore have under- or overestimated the proportion of patients stating their health as unacceptable.

CONCLUSIONS

Although there is a strong association between low overall HRQoL and self-reported unacceptable outcome of ICU treatment, ICU patients with low overall HRQoL may still consider their outcome acceptable. The mental component of PICS, but not the physical and cognitive component, is strongly associated with self-reported unacceptable outcome of ICU treatment one year after discharge.

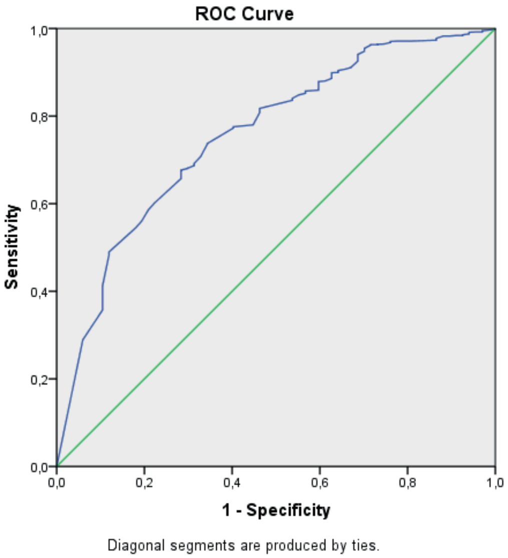
REFERENCES

1. Needham DM, Davidson J, Cohen H, et al (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 40:502–509. doi: 10.1097/CCM.0b013e318232da75
2. Jackson JC, Pandharipande PP, Girard TD, et al (2014) Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med 2:369–379. doi: 10.1016/S2213-2600(14)70051-7
3. Calvo-Ayala E, Khan BA, Farber MO, et al (2013) Interventions to Improve the Physical Function of ICU Survivors: A Systematic Review. Chest 144:1469–1480. doi: 10.1378/chest.13-0779
4. Pandharipande PP, Girard TD, Jackson JC, et al (2013) Long-Term Cognitive Impairment after Critical Illness. N Engl J Med 369:1306–1316. doi: 10.1056/NEJMoa1301372
5. Turnbull AE, Rabiee A, Davis WE, et al (2016) Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. Crit Care Med 44:1267–1277. doi: 10.1097/CCM.0000000000001651
6. Dinglas VD, Chessare CM, Davis WE, et al (2018) Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. Thorax 73:7–12. doi: 10.1136/thoraxjnl-2017-210234
7. Nedergaard HK, Haberlandt T, Reichmann PD, et al (2018) Patients' opinions on outcomes following critical illness. Acta Anaesthesiol Scand 62(4):531-9. doi: 10.1111/aas.13058
8. Wolters AE, Slooter AJC, van der Kooi AW, van Dijk D (2013) Cognitive impairment after intensive care unit admission: a systematic review. Intensive Care Med 39:376–386. doi: 10.1007/s00134-012-2784-9
9. Dawson J, Doll H, Fitzpatrick R, et al (2010) The routine use of patient reported outcome measures in healthcare settings. BMJ 340:c186–c186. doi: 10.1136/bmj.c186
10. Needham DM, Sepulveda KA, Dinglas VD, et al (2017) Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. Am J Respir Crit Care Med 196:1122–1130. doi: 10.1164/rccm.201702-0372OC
11. Robinson KA, Davis WE, Dinglas VD, et al (2017) A systematic review finds limited data on measurement properties of instruments measuring outcomes in adult intensive care unit survivors. J Clin Epidemiol 82:37–46. doi: 10.1016/j.jclinepi.2016.08.014
12. Lim WC, Black N, Lamping D, et al (2016) Conceptualizing and measuring health-related quality of life in critical care. J Crit Care 31:183–193. doi: 10.1016/j.jcrc.2015.10.020
13. König C, Matt B, Kortgen A, et al (2019) What matters most to sepsis survivors: a qualitative analysis to identify specific health-related quality of life domains. Qual Life Res 28:637. https://doi.org/10.1007/s11136-018-2028-8
14. Griffith DM, Salisbury LG, Lee RJ, et al (2018) Determinants of Health-Related Quality of Life After ICU: Importance of Patient Demographics, Previous Comorbidity, and Severity of Illness. Crit Care Med 46:594–601. doi: 10.1097/CCM.0000000000002952
15. Soliman IW (2018) Predicting long-term outcomes of intensive care patients. Chapter five; Hidden normativity in categorizations of functional outcomes in intensive care studies. Dissertation, University of Utrecht, the Netherlands
16. Rabin R, Gudex C, Selai C, Herdman M (2014) From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health 17:70–76. doi: 10.1016/j.jval.2013.10.006
17. Szende A, Janssen B, Cabases J (2014) Self-Reported Population Health: An International Perspective based on EQ-5D. Springer, Dordrecht. doi: https://doi.org/10.1007/978-94-007-7596-1
18. Mahoney FI, Barthel DW (1965) Functional evaluation: the Barthel Index. Md State Med J 14:61–65.
19. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR (1982) The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol 21 (Pt 1):1–16.

20. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370.
21. Horowitz M, Wilner N, Alvarez W (1979) Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209–218.
22. Albrecht GL, Devlieger PJ (1999) The disability paradox: high quality of life against all odds. Soc Sci Med 48:977–988.
23. Eakin MN, Patel Y, Mendez-Tellez P, et al (2017) Patients' outcomes after acute respiratory failure: A qualitative study with the promis framework. Am J Crit Care 26:456–465. doi: 10.4037/ajcc2017834
24. Rapkin BD, Schwartz CE (2004) Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. Health Qual Life Outcomes 2:14. doi: 10.1186/1477-7525-2-14
25. Hofhuis JGM, van Stel HF, Schrijvers AJP, et al (2009) Conceptual issues specifically related to health-related quality of life in critically ill patients. Crit Care 13:118. doi: 10.1186/cc7699
26. Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 48:1507–1515.
27. Soliman IW, de Lange DW, Peelen LM, et al (2015) Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care 30:181–186. doi: 10.1016/j.jcrc.2014.09.009
28. Benoit DD, Jensen HI, Malmgren J, et al (2018) Outcome in patients perceived as receiving excessive care across different ethical climates: a prospective study in 68 intensive care units in Europe and the USA. Intensive Care Med 44:1039–1049. doi: 10.1007/s00134-018-5231-8
29. Wolters AE, Peelen LM, Welling MC, et al (2016) Long-Term Mental Health Problems After Delirium in the ICU. Crit Care Med 44:1808–1813. doi: 10.1097/CCM.0000000000001861
30. Prodinger B, O'Connor RJ, Stucki G, Tennant A (2017) Establishing score equivalence of the Functional Independence Measure motor scale and the Barthel Index, utilising the International Classification of Functioning, Disability and Health and Rasch measurement theory. J Rehabil Med 49:416–422.
31. Eggmann S, Verra ML, Luder G, et al (2018) Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. PLoS ONE 13:e0207428. doi: 10.1371/journal.pone.0207428
32. Strøm T, Martinussen T, Toft P (2010) A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 375:475–480. doi: 10.1016/S0140-6736(09)62072-9
33. Jones C, Backman C, Capuzzo M, Egerod I (2010) Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. Crit Care 14(5):R168. doi: 10.1186/cc9260
34. Milton A, Brück E, Schandl A, et al (2017) Early psychological screening of intensive care unit survivors: A prospective cohort study. Crit Care 21:273. doi: 10.1186/s13054-017-1813-z
35. Maley JH, Brewster I, Mayoral I, et al (2016) Resilience in Survivors of Critical Illness in the Context of the Survivors' Experience and Recovery. Ann Am Thorac Soc 13:1351–1360. doi: 10.1513/AnnalsATS.201511-782OC
36. Cox CE, Porter LS, Buck PJ, et al (2014) Development and preliminary evaluation of a telephone-based mindfulness training intervention for survivors of critical illness. Ann Am Thorac Soc 11:173–181. doi: 10.1513/AnnalsATS.201308-283OC
37. Cox CE, Porter LS, Hough CL, et al (2012) Development and preliminary evaluation of a telephone-based coping skills training intervention for survivors of acute lung injury and their informal caregivers. Intensive Care Med 38:1289–1297. doi: 10.1007/s00134-012-2567-3
38. Sneeuw KCA, Sprangers MAG, Aaronson NK (2002) The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. J Clin Epidemiol 55:1130–1143.

4

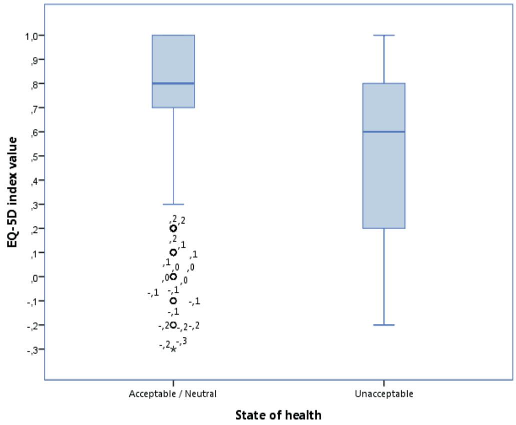
SUPPLEMENTAL MATERIAL



Diagonal segments are produced by ties.

Supplemental figure S1. ROC curves of self-reported unacceptable outcome

ROC curve of EQ-5D index values as a predictor for self-reported unacceptable outcome. Area under the curve 0.76. At the optimal EQ5D index value of 0.72, the sensitivity and specificity were both 69%.



Supplemental figure S2. Boxplots of EQ-5D index scores related to self-reported outcome

Boxplots of EQ-5D index scores related to self-reported neutral plus acceptable outcome and to self-reported unacceptable outcome in ICU survivors one year after ICU discharge

Unacceptable +neutral vs acceptable-outcome of health status after ICU treatment	OR unadjusted (99% CI)	p-value	OR adjusted for demographic factors (99% CI)	p-value	OR adjusted for demographic and ICU factors (99% CI)	p-value	OR adjusted for demographic, ICU factors and other questionnaires (99% CI)	p-value
EQ-5D	1.88 (1.61-2.19)	<0.001*	1.80 (1.53-2.12)	<0.001*	1.87 (1.57-2.22)	<0.001*		
Barthel Index	1.46 (1.25-1.72)	<0.001*	1.43(1.19-1.72)	<0.001*	1.43 (1.18-1.75)	<0.001*	1.31 (1.02-1.69)	0.005
CFQ	1.27 (1.07-1.52)	<0.001*	1.26 (1.05-1.50)	0.001*	1.29 (1.07-1.55)	0.001*	0.99 (0.77-1.27)	0.901
HADS	1.79 (1.51-2.12)	<0.001*	1.73 (1.46-2.06)	<0.001*	1.68 (1.40-2.01)	<0.001*	1.54 (1.18-2.01)	<0.001*
IES	1.33 (1.12-1.57)	<0.001*	1.31 (1.10-1.55)	<0.001*	1.29 (1.07-1.55)	<0.001*	1.06 (0.83-1.35)	0.518

Supplemental table S1. Association between questionnaire scores and self-reported neutral/unacceptable versus acceptable outcome (sensitivity analysis)

Multinomial regression Reference group: acceptable	OR unadjusted (99% CI) Compared to neutral	p-value	OR unadjusted (99% CI) Compared to unacceptable	p-value	OR adjusted for demographic factors (99% CI) Compared to neutral	p-value	OR adjusted for demographic factors (99% CI) Compared to unacceptable	p-value
EQ-5D	1.75 (1.49-2.07)	<0.001*	2.54 (1.95-3.33)	<0.001*	1.69 (1.42-2.00)	<0.001*	2.46 (1.85-3.28)	<0.001*
Barthel Index	1.46 (1.24-1.73)	<0.001*	1.48 (1.09-2.00)	0.001*	1.44 (1.19-1.75)	<0.001*	1.38 (0.95-2.00)	0.025
CFQ	1.24 (1.03-1.49)	0.003	1.50 (1.03-2.19)	0.006	1.23 (1.02-1.48)	0.005	1.45 (0.98-2.14)	0.014
HADS	1.66 (1.38-1.99)	<0.001*	2.58 (1.85-3.59)	<0.001*	1.63 (1.36-1.96)	<0.001*	2.38 (1.69-3.36)	<0.001*
IES	1.25 (1.04-1.49)	0.002*	1.84 (1.33-2.56)	<0.001*	1.24 (1.03-1.49)	0.003	1.73 (1.23-2.45)	<0.001*

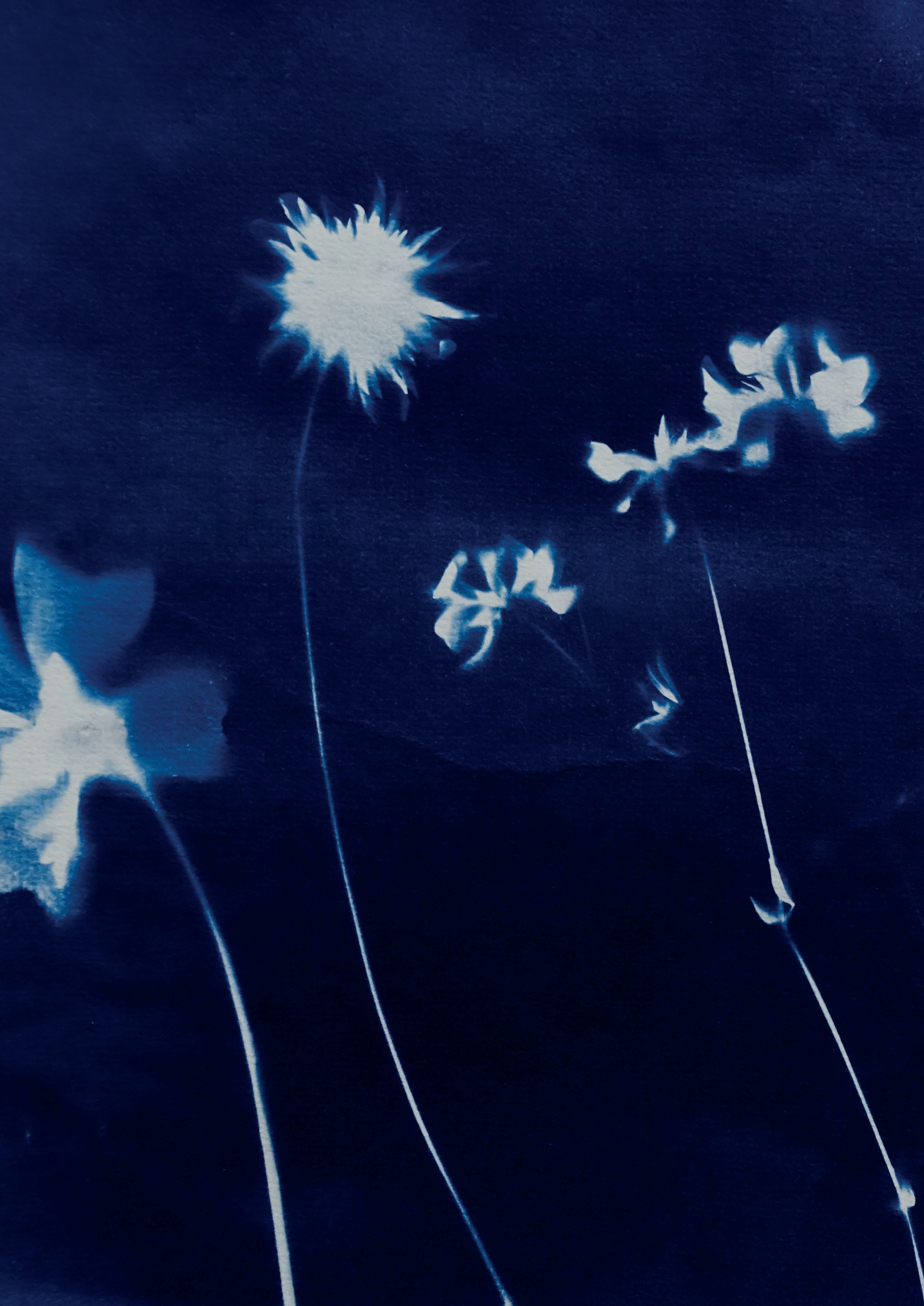
Multinomial regression Reference group: acceptable	OR adjusted for demographic and ICU factors (99% CI) Compared to neutral	p-value	OR adjusted for demographic and ICU factors (99% CI) Compared to unacceptable	p-value	OR adjusted for demographic, ICU factors and other questionnaires (99% CI) Compared to neutral	p-value	OR adjusted for demographic, ICU factors and other questionnaires (99% CI) Compared to unacceptable	p-value
EQ-5D	1.73 (1.44-2.08)	<0.001*	2.70 (1.98-3.68)	<0.001*	-	-	-	-
Barthel Index	1.45 (1.18-1.78)	<0.001*	1.42 (0.95-2.10)	0.023	1.37 (1.06-1.78)	0.002*	0.95 (0.47-1.90)	0.841
CFQ	1.25 (1.02-1.53)	0.004	1.47 (0.98-2.21)	0.015	1.00 (0.77-1.30)	0.984	0.83 (0.46-1.50)	0.421
HADS	1.57 (1.29-1.90)	<0.001*	2.37 (1.66-3.38)	<0.001*	1.43 (1.08-1.90)	0.001*	2.29-(1.30-4.05)	<0.001*
IES	1.23 (1.01-1.50)	0.007	1.66 (1.15-2.40)	<0.001*	1.05 (0.81-1.36)	0.635	1.16 (0.70-1.94)	0.445

Supplemental table S2. Association between questionnaire scores and self-reported outcome (multinomial regression analysis)
Association between (standardized) questionnaire scores of neutral or unacceptable outcome of ICU treatment vs acceptable outcome (reference), expressed in adjusted odds ratios. Odds ratios are expressed for decreases in EQ-5D and Barthel Index and for increases in HADS, CFQ and IES. P-values <.003 (*) are considered to be significant. *99% CI= 99% confidence interval. OR= odds ratio. ICU= intensive care unit. EQ-5D= EuroQoL-5 Dimension, CFQ= cognitive failures questionnaire, HADS= hospital anxiety and depression scale, IES= impact of event scale.*

Unacceptable vs acceptable +neutral outcome of ICU treatment	OR unadjusted (99% CI)	p-value	OR adjusted for demographic factors (99% CI)	p-value	OR adjusted for demographic and ICU factors (99% CI)	p-value
EQ-5D mobility	1.84 (1.38-2.46)	<0.001*	1.74 (1.26-2.40)	<0.001*	1.81 (1.29-2.55)	<0.001*
EQ-5D self-care	1.51 (1.18-1.93)	<0.001*	1.44 (1.07-1.92)	0.001*	1.48 (1.09-2.01)	0.001*
EQ-5D daily activities	2.01 (1.47-2.75)	<0.001*	2.00 (1.42-2.82)	<0.001*	2.14 (1.48-3.09)	<0.001*
EQ-5D pain	1.67 (1.24-2.24)	<0.001*	1.68 (1.23-2.29)	<0.001*	1.75 (1.26-2.43)	<0.001*
EQ-5D mood	2.10 (1.64-2.70)	<0.001*	2.05 (1.58-2.65)	<0.001*	2.13 (1.62-2.79)	<0.001*

Supplemental table S3. Association between domains of EQ-5D scores (mobility, self-care, daily activities, pain, mood) and unacceptable outcome versus neutral/acceptable outcome

Odds ratios are expressed for decreases in EQ5D domain score. P-values <.003 are considered to be significant (*) 99% CI= 99% confidence interval. OR= odds ratio. ICU= intensive care unit. EQ-5D= EuroQoL-5 Dimension.



Part two

Decision-making on Intensive Care treatment

5

Selecting and evaluating decision-making strategies in the intensive care unit: a systematic review

MC Kerckhoffs, M Kant, JJM van Delden, L Hooft,
J Kesecioglu, D van Dijk

Published in; Journal of Critical Care 2019

ABSTRACT

Purpose Many patients in the Intensive Care Unit (ICU) die after a decision to withhold or withdraw treatment. To ensure that for each patient the appropriate decision is taken, a careful decision-making process is required. This review identifies strategies that can be used to optimize the decision-making process for continuing versus limiting life sustaining treatment of ICU patients.

Methods We conducted a systematic review of the literature by searching PUBMED and EMBASE.

Results Thirty-two studies were included, with five categories of decision-making strategies (1) integrated communication, (2) consultative communication, (3) ethics consultation, (4) palliative care consultation and (5) decision aids. Many different outcome measures were used and none of them covered all aspects of decisions on continuing versus limiting life sustaining treatment. Integrated communication strategies had a positive effect on multiple outcome measures. Frequent, predefined family-meetings as well as triggered and integrated ethical or palliative consultation were able to reduce length of stay of patients who eventually died, without increasing overall mortality.

Conclusions The decision-making process in the ICU can be enhanced by frequent family-meetings with predefined topics. Ethical and palliative support is useful in specific situations. These interventions can reduce non-beneficial ICU treatment days.

INTRODUCTION

Physicians working in an Intensive Care Unit (ICU) are responsible for appropriate and proportional care for their patients. They evaluate the course of the disease, the effect of their treatment, and the prognosis of the patients with their team in order to advice or decide on the intensity of ICU treatment. In approximately 10% of all ICU patients the decision to forgo life sustaining treatment is made [1]. In the majority of patients who die in an ICU, a decision to withhold or withdraw life-sustaining therapy preceded death [2-5]. Previous studies, however, reported high variability in the proportion of ICU patients dying after some sort of limitation in life sustaining therapy [3]. These variations were observed between countries, within countries and even between physicians within the same ICU [5, 6].

In order to ensure that for each patient the most appropriate decision about continuing or limiting ICU treatment is made, a careful and preferably shared decision-making process is required. Shared decision-making ensures patients, or their surrogates, and clinicians to make evidence based and personalized health care decisions [7].
This decision-making process is complex and hard to define for the ICU setting. It minimally involves a stepwise process of gathering and interpretation of information, weighing different options and ultimately a (shared-) decision[7]. There is limited evidence on the required steps of the decision making process on continuing or limiting ICU treatment and how each step contributes to a proportionate process and optimal decision [8]. It is unclear if decision making benefits most from particular steps in the process, or merely by standardizing the process.

Another factor that adds to the complexity of identifying optimal decision-making is defining the right outcome measure for studies on this topic. Patient-related outcomes, surrogate decision-maker outcomes, healthcare utilization and process measures are all important outcomes that apply to the various parties involved in decision-making in the ICU. Reducing subjectivity and variability could be desirable form the caregivers' point of view, while patients and families might define optimal decision-making by satisfaction with the communication or reduced non-beneficial treatment days [9]. Since all stakeholders have their own perspective, study endpoints vary accordingly, hampering a straightforward comparison on the different decision-making strategies.

Given the observed variability in the incidence of decisions on limiting life sustaining therapy, as well as their complexity and their impact on patients and families, there is a need for a better understanding of how to optimize this process. Although the decision-making process may be largely intuitive, including family meetings and consultation of other stakeholders, focussing on the individual steps of this process could benefit the process as a whole.

The aim of this systematic review was to identify which strategies can be used to optimize the decision-making process for continuing versus limiting life sustaining treatment of ICU patients and to describe usable outcome measures.
Methods

METHODS

Study design

We conducted a systematic review of the literature after using the scoping review approach to define our research question. A scoping study is aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field. It is performed systematically and evidence is presented visually as a mapping or charting of the data [10, 11]. We followed the approach as suggested for conducting a systematic scoping review by the Arksey and O'Malley framework enhanced by Levac and further clarified by the Joanna Brigs Institute [11-13].

Search strategy

The search and selection of relevant studies was performed according to figure 1. The research team consisted of three ICU physicians, a medical student, a medical ethicist, and an epidemiologist experienced in commencing reviews and evidence synthesis. The search for relevant studies started with an iterative process of three steps. First the research team defined the research question and formulated keywords on patients, intervention and outcome. A preliminary search in Google Scholar and PubMed was performed and relevant articles were selected by two reviewers (MK, MCK). From these articles keywords were defined to use in the second and more extensive search. The research team was subsequently consulted, but added no additional keywords. The third and final search (December 2018) was conducted in PubMed and EMBASE without limits on the year of publication. Duplicates were removed after assimilation of all data using Covidence software and manually during title-abstract screening [14]. Covidence online software was used throughout the entire reviewing process to ensure a transparent and uniform practice.

[Supplement Table S1. Keywords used for PubMed and EMBASE search]

Eligibility

To be included in this review an article had to describe a strategy aimed at the process of decision-making on continuing or limiting life-sustaining treatment in the ICU.

The decision-making process was defined as the process in (1) in which information is communicated with the patient or his/her surrogates, (2) in which information on patients' prognosis and treatment preferences (living will, advance directives, advance care plan, conversation with the patient or its surrogates) is gathered and (3) that ultimately results in a decision on the goals of ICU care. Studies had to report the effect of the strategy to be included.

Only studies that included mainly ICU patients were eligible since end-of-life decision making in ambulatory or non-ICU settings differs significantly.

Studies published in languages other than English and studies in children were excluded.

Study selection

Two reviewers [MK, MCK] independently screened all titles and abstracts on in- and exclusion criteria (Table 1). The full text of all potentially relevant articles was screened by the two reviewers independently and in duplicate for eligibility. Consensus was reached on the inclusion and exclusion for all studies. After full text screening one of the reviewers [MCK] hand searched all references of the 10 most recent included articles.

[Supplement Table S2. Reasons for exclusion full text screened articles]

Inclusion criteria	Exclusion criteria
Studies concerning the process of making decisions on the intensity of ICU treatment	Studies focussing on end-of-life treatment or prognostication
Adult patients	Children
ICU patients	Non-ICU patients
Intervention studies	Reviews, case-reports, abstracts, editorials
English language	Other languages

Table 1. Inclusion and exclusion criteria

ICU Intensive Care Unit

RESULTS

Search results

The initial database search (figure 1) yielded 9525 results (updated December 2018), from which 2487 duplicates were removed. From the 7038 unique studies, 6707 were excluded after title-abstract screening. 331 studies were selected for full-text evaluation. For 56 studies the full-text articles could not be obtained. A review of these titles and abstracts showed a variety of strategies that were not unique and mentioned in other studies selected for full-text review. Therefore, excluding these studies was considered justified. From the remaining studies, 31 studies met the selection criteria. One study was added after reference screening.

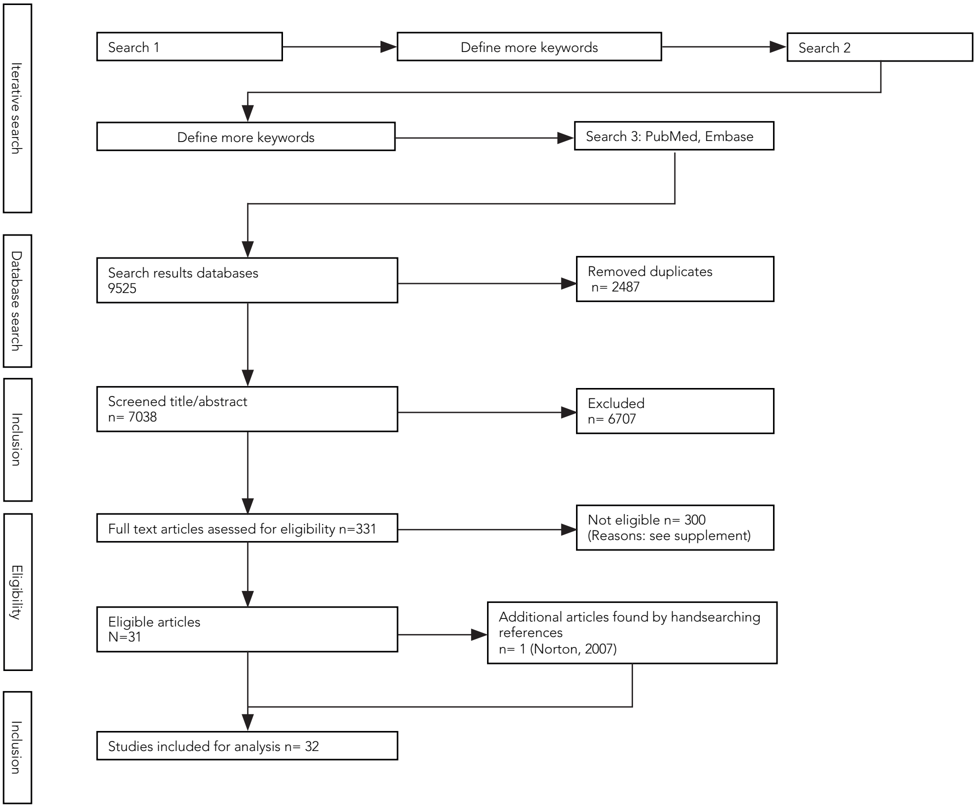


Figure 1. Search and selection of articles. The final search was performed December 2018

Characteristics of included studies

The 32 included studies were published between 1997 and 2018 and mainly performed in the United States (US) (n=28, 88%) [15,16]. Studies were performed in mixed ICUs as well as in specialized surgical, medical and neuro-medicine ICUs.

Most studies (n=19, 59%) used a pre- and post-intervention design to evaluate the effect of their strategy. Two of these studies included a long-term follow-up control group to evaluate enduring effect [17,18]. Randomized controlled trials and case-control design were both used in 7 (22%) studies.

Five different strategy categories could be distinguished; (1) strategies integrating communication within the standard ICU care, (2) strategies offering consultative communication support, (3) strategies comprising ethics consultation, (4) strategies comprising consulting/integrating palliative care and (5) strategies using decision aids. Eleven studies (34%) evaluated the effect of complex strategies comprising multiple aforementioned strategy categories.

The studied decision-support strategies targeted patients (n=19, 59%), surrogate decision makers (n=16, 50%), healthcare providers (n=8, 25%) and costs (n=6, 19%). Half of the studies included more than one target. The number of subjects studied varied across the studies from 17 to 2158 [19,20].

Outcome measures varied accordingly with the target of the strategy. However different outcomes were reported in studies targeting the same population. Most studies assessed patients discharged alive and patient who died in het ICU separately.

Quality assessment

Risk of biases was assessed using the Cochrane Risk of Bias tool for randomized trials and the Risk of Bias for nonrandomized studies (RoBANS) strategy for other study designs [21, 22]. Studies with a low risk of bias in all domains were considered to have an overall low risk of bias. Two studies fulfilled these criteria [16, 23]. Studies with a high risk of bias in any domain were considered high risk of bias. This applied to 18 (56%) studies. The remaining twelve studies (38%) were considered having unclear risk of biases. Results are shown in supplemental table S3 and S4.

Results by strategy category

Strategies integrating communication

Thirteen studies (41%) explored communication strategies integrated within the standard care and offered by ICU staff [4,16-18,24-32]. The majority evaluated a complex and intensive communication structure addressing surrogates.

Seven studies incorporated a communication strategy, containing both a structure as well as predefined topics to discuss [16, 18, 24, 25, 28-30]. These studies used a variety of endpoints described in table 2. Most commonly ICU length of stay was studied. This was reduced in five studies and remained unchanged in one study. Although measured differently, all studies showed beneficial effects on either time to decision making, the number of family meetings or documentation of goals. One study measured psychological distress in surrogates 6 months after discharge, which was not reduced with the communication-intervention [16].

Two tools were evaluated; the PACE (Psychological Assessment and Communication Evaluation) and VALUE communication tool [4, 17]. PACE resulted in an increased satisfaction with assessment and treatment of symptoms and VALUE in an increase in frequency of family updates with a higher nurse participation and more documented treatment goals. Family satisfaction was not influenced by this communication tool, however another nurse-led intervention study did find increased perceived quality of communication and patient-centeredness[16]. Family attendance during daily rounds was studied twice and increased knowledge and decreased the need for family meetings and nurses' workload. Family and physician satisfaction remained unchanged [27, 32]. One study studied the effect of the communication strategy on healthcare providers and found a reduction in the relative risk of developing depression and burnout [30].

Strategies offering consultative communication support

Four studies (13%) studied a communication strategy led by specialized non-ICU healthcare providers [20, 33-35]. Outcome measures were heterogeneous as shown in table 2. No distinct effect on goal of care discussions and documentation nor on patient and surrogate satisfaction could be extracted because of conflicting results. One study included administrative data and found a decrease in length of stay for ICU decedents and a decrease in ICU costs per day and in total for the intervention group only partly explained by decreased length of stay [35].

Strategies comprising ethics consultation

Ethics consultation was studied four times (13%) [36-39]. One study focused solely on supporting healthcare providers [36]. The remaining three studies were randomized controlled and studied ethics consultation offered to both healthcare providers, patients and surrogates [37-39]. Length of stay was reduced in three out of four studies, although one study only found this in patients who died in the ICU [39]. None of the studies found an effect on mortality.

Strategies concerning palliative care

Palliative care strategies were described in six studies (19%) either as an integrated or consultative strategy [23, 40-44]. Length of stay was evaluated in all studies and found to be decreased in four studies of which two showed the shorter length of stay only in patients who died in the ICU and one only for hospital length of stay [40, 42, 45].

The three studies evaluating the effect on surrogates all failed to improve either perceived quality of dying, satisfaction with care or depressive or anxiety symptoms [41-43]. Palliative care team-led meetings was studied once and increased Post Traumatic Stress Disorder (PTSD) symptoms [41]. Other endpoints were heterogeneous and studied only once. These are shown in table 2.

Strategies using decision aids

Four studies (13%) evaluated the use of a decision aid, either for the process of decision-making on intensity of care or focused on cardiopulmonary resuscitation (CPR) [19, 46-48]. The latter study used a 3-minute video about CPR and showed an increase in knowledge on CPR without an effect on code status.

One study handed the surrogates a personalised decision aid describing four domains of decision making enriched with individualised probabilistic information [19]. They found a positive effect on comprehension of prognosis, quality of communication and discussions about long-term patient outcome. The remaining two studies used a multifaceted strategy aimed at ICU staff. Their endpoints differed between ICU length of stay and costs (both decreased) and time to first consideration of level of treatment (decreased) [46, 47].

Results by outcome measure

Various outcome measures were used in the 32 included studies. Table 2 shows a mapping matrix in which the nine most studied outcomes are related to the five strategy categories. Since most studies included multiple outcome measures, articles can be cited more than once. Outcomes were aimed at patients, surrogates, health care workers, factors related to the process of decision-making, costs or combinations or these factors.

The most studied outcome was length of stay (18 times) [16, 18, 23-25, 28, 29, 35-43, 45, 46]. Thirteen out of 18 studies found a decreased length of stay, of which six found this effect only in decedents and one only for hospital length of stay [29, 35, 37, 39, 40, 42, 45]. The second most often studied outcome was satisfaction (12 times) [4, 16, 17, 19, 27, 31, 32, 34, 42, 43, 46, 49]. Satisfaction was assessed in patients, surrogates, nurses and physicians, evaluated various aspects of ICU care and used several questionnaires.

Strategy Outcome	Integrated communication	Consultative communication	Ethics consultation	Palliative care	Decision aid/ tool	Total
Length of stay[a]	White [16] (+) Lilly [18] (+) Ahrens [24] (+) Campbell [25] (+) Daly [28] (0) Quenot [29] (+)	Curtis [35] (+)	Dowdy [36] (+) Schneiderman [37] (+) Andereck [38] (0) Schneiderman [39] (+)	Norton [23] (0) Mosenthal [40] (+) Carson [41] (0) Braus [42] (+) Curtis [43] (+) O'Mahony [44] (0) Mun [45] (0)	Hatler [46] (+)	19
Satisfaction[b]	Higginson [4] (+) White [16] (+) Wysham [17] (0) Jacobowski[27] (0) de Havenon [31] (0) Allen [32] (0)	Burns [33] (0) Kaufer [34] (+)		Braus [42] (0) Curtis [43] (0)	Cox [19] (0) Hatler [46] (0)	12
Mortality[c]	White [16] (0) Lilly [18] (+) Ahrens [24] (0) Jacobowski [27] (0)		Andereck [38] (0) Schneiderman [39] (0)	Norton [23] (0) Mosenthal [40] (0) Carson [41] (0) Braus [42] (0)		10
Documented treatment goals[d]	Wysham [17] (+) Campbell [25] (+) Quenot [29] (+)	Teno [21] (+) Burns [33] (+)	Dowdy [36] (+)	Mosenthal [40] (0) Mun [45] (+)		8
Costs[e]	Ahrens [24] (+) Campbell [25] (0)	Curtis [35] (+)	Andereck [38] (0)		Cox [19] (+) Hatler [46] (+)	6
Family meetings[f]	Wysham [17] (+) Lilly [18] (+) Daly [28] (+) Allen [32] (+)			Braus [42] (+) Mun [45] (+)		6
Time to decision (making)[g]	Campbell [25] (+) Quenot [29] (+)	Curtis [35] (+)		Mosenthal [40] (+)	Jensen [47] (+)	5
Days on mechanical ventilation[h]			Schneiderman [37] (+) Andereck [38] (0) Schneiderman [39] (+)	Carson [41] (0)	Hatler [46] (0)	5
Psychological complaints[i]	White [16] (0) Quenot [30] (+)	Curtis [35] (0)		Carson [41] (-) Braus [42] (0)		5

Table 2. Mapping Matrix.

This mapping matrix illustrates the studied outcomes in relation to the strategy categories ordered by the frequency of the studied outcomes. Codes for effect for each study; (+) = beneficial effect, (0) = no effect, (-) = negative effect. Colour codes for the results: Green: the majority of studies report a beneficial effect. Grey: the majority of studies lacked to show effect. Yellow: equally distributed or beneficial effect. Red: minimal one study with a negative effect. [a] *Length of stay*: in ICU or in hospital, length of stay until death in ICU/hospital. [b] *Satisfaction*; satisfaction scores reported by patients. QODD (Quality Of Dying and Death survey) scores by nurses. FS-ICU scores (Family-Satisfaction in ICU), satisfaction with care/decision making/family meetings/communication reported by surrogates. Satisfaction reported by physicians. [c] *Mortality*; of all patients, decedents or patients discharged alive. [d] *Documented treatment goals*: number of patients with documented goals, time to documented treatment goals. [e] *Costs;* spared daily costs, total ICU costs per case, ICU cost per day, total (average) hospital costs. [f] *Family meetings*: time to first meeting, documented meetings, frequency of the meetings, length of the meetings. [g] *Time to decision (making);* time to first consideration on level of treatment, time to documented decision or time to withhold or withdraw treatment. [h] *Days on mechanical ventilation*; amount of days on ventilator or ventilator free days. [i] *Psychological complaints;* in surrogates or health care workers. Anxiety, depressive symptoms, PTSD symptoms, burnout symptoms.

Three studies were able to show an improvement in satisfaction [4, 16, 34]. Mortality was the third most often used outcome measure (10 studies)[16, 18, 23, 24, 27, 37, 38, 40-42]. It was unchanged in nine studies and reduced in one in which a reduction in mortality was achieved and sustained over the follow-up period [18]. Evaluation of costs was included in 6 studies of which four showed a reduction in costs [19, 24, 25, 35, 38, 46].

DISCUSSION

The aim of this systematic review was to identify strategies that can be used to optimize the decision-making process on continuing versus limiting life sustaining treatment of ICU patients and to map out strategies in relation to outcome measures.
We found 32 publications describing a strategy aimed at improving this decision-making process in adult ICU patients. Most publications had unclear or high risk of bias. Strategies could be grouped in five categories. Nine frequently used outcome measures could be distinguished.
The most effective strategies involve enhancing communication with patients and surrogates offered in close relation with the standard ICU care, which resulted in a lower number of non-beneficial treatment days.

Decision-making on continuing versus limiting life-sustaining treatment in the ICU is a complex process. Despite this complexity, half of the studies evaluated a single aspect or a simple change of the decision-making process. Surprisingly, some of these simple interventions had an impact on important outcome measures such as length of ICU stay of patients with a poor prognosis.

The simplified three steps of shared decision-making (gathering information, deliberating, deciding) are all dependent of the quality of communication[7]. It is therefore not surprising that in many studies, enhanced communication strategies had a positive effect on the decision-making process. Although family-meetings are common practice, improving the details can benefit the process of decision-making. First, using a standardised format comprising the structure and topics of the meeting [4, 17, 18, 24, 25, 27-29, 34] and making the communication protocol known to families, can aid patients and surrogates. Presenting the process of communication and decision-making together with individual prognostic information, may even function as a decision aid [19, 46, 47]. Although our review only involved printed documents,

tablet-based tools and websites are a promising method to aid surrogates in the decision-making process [50, 51].
Secondly, increasing the frequency of family-meetings was found to lead to more timely decisions and may save costs when non-beneficial treatment is withdrawn earlier [17, 25, 28, 32]. Thirdly, communication provided by consulting physicians or specialists was not superior to communication integrated in the ICU care and offered by ICU caregivers. This is an important finding from the perspective of costs and scarce resources and simplifies implementing communication strategies.
To make ethical and palliative support for ICU patients benefit decision-making, it should be triggered to the right patients and offered in close relation with the ICU team. The best triggers for palliative care however, are still a matter of debate [23, 36, 37, 39, 42, 52].

Evaluating a complex process like decision-making is difficult. This is reflected by the variety of outcome measures found in this review (Table 2). It is questionable if any outcome measure is truly capable to reflect the quality of the decision-making process. The perception of the most ideal decision-making process varies for the different stakeholders. A family centered outcome could entail the perceived quality of communication, or how well the decision corresponded with the patient's values, or the incidence of the post-intensive care syndrome of family members (PICS-F). In our review satisfaction with the decision making process was most often used as a surrogate-centered outcome, but this outcome measure failed to improve in most studies [4, 17, 19, 27, 31, 32, 34, 42, 43, 46, 49]. An explanation is that overall satisfaction measured in ICU surrogates is usually already high irrespective of the quality of decision-making. Questionnaires used to evaluate satisfaction might not be sensitive enough to truly reflect differences in perceived care. More specific questionnaires measuring quality of communication, the perception of patient centeredness, quality of decision-making or the elements of PICS-F might be more useful [53, 54].

Several studies in this review used the duration of ICU treatment of patients who eventually die in the ICU as outcome measure. In most of these studies, it proved to be possible to reduce the number of these non-beneficial treatment days. Since overall mortality was not increased in any of the studies, this is truly an effect of a more timely decision to limit treatment in patients with a poor prognosis [23, 24, 35, 37, 40, 42]. The fear that interventions targeted at decision-making lead to a self-fulfilling prophecy, namely more often withdrawal of treatment, seemed not justified. It is perhaps more likely that decision-making strategies promote awareness, than lead to injudicious decisions and increased mortality.

Future research

The biggest challenge for future research in decision-making in the ICU, is probably defining the right endpoints. It is clear that the complex process of decision-making cannot be evaluated with a single outcome measure. The results of our review suggest that the number of non-beneficial treatment days is a feasible and relevant outcome measure from both a patient, surrogate, caregivers and cost perspective. Other suggested outcome measures are symptoms of psychological distress of family members (PICS-F) and quality of communication [55]. Nurses, through their close interaction with the surrogates, could also rate quality of decision-making [43, 56].

Limitations

Our systematic review holds several limitations. Firstly, the risk of biases was valued unclear or high in 30 of 32 studies. Secondly, most studies are from the United States, impeding generalizability for non-US practice. Thirdly, categorizing the heterogeneous data was done by the authors and subjectivity could have affected the analyses. Fourthly, some studies were performed in an experimental setting and might not be applicable in clinical practice. Fifthly, the strategies and the outcome measures in the included studies were characterized by large heterogeneity, impeding the pooling of data. Lastly, since decision-making practices vary across ICUs, the added value of the proposed strategies will vary depending on existing decision-making procedures.

CONCLUSION

Enhancing the frequency and quality of communication between ICU caregivers and the patients' family with a standardized format improves the decision-making process for continuing versus limiting life sustaining treatment of ICU patients. Ethical and palliative support is useful in specific situations, when integrated in the standard ICU care. The multiple outcome measures that were found in this review illustrate the complexity of evaluating decision-making strategies in the ICU. Several studies used length of ICU stay of patients with a poor prognosis as outcome measure. Length of ICU stay in these patients was often reduced by changes in the decision-making process, whereas family satisfaction was generally not changed. Further research is needed to determine relevant outcomes that do justice to the complexity of decision-making on continuing versus limiting life sustaining treatment.

REFERENCES

1. Azoulay E, Metnitz B, Sprung CL, et al (2009) End-of-life practices in 282 intensive care units: data from the SAPS 3 database. Intensive Care Med 35:623–630. doi: 10.1007/s00134-008-1310-6
2. Sprung CL, Cohen SL, Sjokvist P, et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. doi: 10.1001/jama.290.6.790
3. Prendergast TJ, Claessens MT, Luce JM (1998) A national survey of end-of-life care for critically ill patients. Am J Resp Crit Care Med 158:1163–1167. doi: 10.1164/ajrccm.158.4.9801108
4. Higginson IJ, Koffman J, Hopkins P, et al (2013) Development and evaluation of the feasibility and effects on staff, patients, and families of a new tool, the Psychosocial Assessment and Communication Evaluation (PACE), to improve communication and palliative care in intensive care and during clinical uncertainty. BMC Med 11:213. doi: 10.1186/1741-7015-11-213
5. Mark NM, Rayner SG, Lee NJ, Curtis JR (2015) Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. Intensive Care Med 41:1572–1585. doi: 10.1007/s00134-015-3810-5
6. Barnato AE, Tate JA, Rodriguez KL, et al (2012) Norms of decision making in the ICU: a case study of two academic medical centers at the extremes of end-of-life treatment intensity. Intensive Care Med 38:1886–1896. doi: 10.1007/s00134-012-2661-6
7. Kon AA, Davidson JE, Morrison W, et al (2016) Shared Decision-Making in Intensive Care Units. Executive Summary of the American College of Critical Care Medicine and American Thoracic Society Policy Statement. Am J Resp Crit Care Med 193:1334–1336. doi: 10.1164/rccm.201602-0269ED
8. Scheunemann LP, Cunningham TV, Arnold RM, et al (2015) How clinicians discuss critically ill patients' preferences and values with surrogates: an empirical analysis. Crit Care Med 43:757–764. doi: 10.1097/CCM.0000000000000772
9. Wilkinson DJC, Truog RD (2013) The luck of the draw: physician-related variability in end-of-life decision-making in intensive care. Intensive Care Med 39:1128–1132. doi: 10.1007/s00134-013-2871-6
10. Colquhoun HL, Levac D, O'Brien KK, et al (2014) Scoping reviews: time for clarity in definition, methods, and reporting. J Clin Epidemiol 67:1291–1294. doi: 10.1016/j.jclinepi.2014.03.013
11. Peters MDJ, Godfrey CM, Khalil H, et al (2015) Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 13:141–146. doi: 10.1097/XEB.0000000000000050
12. Arksey H, O'Malley L (2007) Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 8:19–32. doi: 10.1080/1364557032000119616
13. Levac D, Colquhoun H, O'Brien KK (2010) Scoping studies: advancing the methodology. Implement Sci
14. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
15. Teno JM, Licks S, Lynn J, et al (1997) Do advance directives provide instructions that direct care? SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. J Am Geriatr Soc 45:508–512.
16. White DB, Angus DC, Shields AM, et al (2018) A randomized trial of a family-support intervention in intensive care units. N Engl J Med 378:2365–2375. doi: 10.1056/NEJMoa1802637
17. Wysham NG, Mularski RA, Schmidt DM, et al (2014) Long-term persistence of quality improvements for an intensive care unit communication initiative using the VALUE strategy. J Crit Care 29:450–454. doi: 10.1016/j.jcrc.2013.12.006
18. Lilly CM, Sonna LA, Haley KJ, Massaro AF (2003) Intensive communication: four-year follow-up from a clinical practice study. Crit Care Med 31:S394–9. doi: 10.1097/01.CCM.0000065279.77449.B4

19. Cox CE, Lewis CL, Hanson LC, et al (2012) Development and pilot testing of a decision aid for surrogates of patients with prolonged mechanical ventilation. Crit Care Med 40:2327–2334. doi: 10.1097/CCM.0b013e3182536a63
20. Teno J, Lynn J, Wenger N, et al (1997) Advance Directives for Seriously Ill Hospitalized Patients: Effectiveness with the Patient Self-Determination Act and the SUPPORT Intervention. J Am Geriatr Soc 45:500–507. doi: 10.1111/j.1532-5415.1997.tb05178.x
21. Kim SY, Park JE, Lee YJ, et al (2013) Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 66:408–414. doi: 10.1016/j.jclinepi.2012.09.016
22. Higgins JPT, Altman DG, Gøtzsche PC, et al (2011) The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. 343:d5928–d5928. doi: 10.1136/bmj.d5928
23. Norton SA, Hogan LA, Holloway RG, et al (2007) Proactive palliative care in the medical intensive care unit: Effects on length of stay for selected high-risk patients. Crit Care Med 35:1530–1535. doi: 10.1097/01.CCM.0000266533.06543.0C
24. Ahrens T, Yancey V, Kollef M (2003) Improving family communications at the end of life: implications for length of stay in the intensive care unit and resource use. Am J Crit Care 12:317–23– discussion 324.
25. Campbell ML, Guzman JA (2003) Impact of a proactive approach to improve end-of-life care in a medical ICU. Chest 123:266–271.
26. Lee Char SJ, Evans LR, Malvar GL, White DB (2010) A randomized trial of two methods to disclose prognosis to surrogate decision makers in intensive care units. Am J Resp Crit Care Med 182:905–909. doi: 10.1164/rccm.201002-0262OC
27. Jacobowski NL, Girard TD, Mulder JA, Ely EW (2010) Communication in critical care: family rounds in the intensive care unit. Am J Crit Care 19:421–430. doi: 10.4037/ajcc2010656
28. Daly BJ, Douglas SL, O’Toole E, et al (2010) Effectiveness trial of an intensive communication structure for families of long-stay ICU patients. Chest 138:1340–1348. doi: 10.1378/chest.10-0292
29. Quenot JP, Rigaud JP, Prin S, et al (2012) Impact of an intensive communication strategy on end-of-life practices in the intensive care unit. Intensive Care Med 38:145–152. doi: 10.1007/s00134-011-2405-z
30. Quenot JP, Rigaud JP, Prin S, et al (2012) Suffering among carers working in critical care can be reduced by an intensive communication strategy on end-of-life practices. Intensive Care Med 38:55–61. doi: 10.1007/s00134-011-2413-z
31. de Havenon A, Petersen C, Tanana M, et al (2015) A pilot study of audiovisual family meetings in the intensive care unit. J Crit Care 30:881–883. doi: 10.1016/j.jcrc.2015.05.027
32. Allen SR, Pascual J, Martin N, et al (2017) A novel method of optimizing patient- and family-centered care in the ICU. J Trauma Acute Care Surg 82:582–586. doi: 10.1097/TA.0000000000001332
33. Burns JP, Mello MM, Studdert DM, et al (2003) Results of a clinical trial on care improvement for the critically ill. Crit Care Med 31:2107–2117. doi: 10.1097/01.CCM.0000069732.65524.72
34. Kaufer M, Murphy P, Barker K, Mosenthal A (2008) Family Satisfaction Following the Death of a Loved One in an Inner City MICU. American Journal of Hospice and Palliative Medicine® 25:318–325. doi: 10.1177/1049909108319262
35. Curtis JR, Treece PD, Nielsen EL, et al (2016) Randomized Trial of Communication Facilitators to Reduce Family Distress and Intensity of End-of-Life Care. Am J Resp Crit Care Med 193:154–162. doi: 10.1164/rccm.201505-0900OC
36. Dowdy MD, Robertson C, Bander JA (1998) A study of proactive ethics consultation for critically and terminally ill patients with extended lengths of stay. Crit Care Med 26:252–259.
37. Schneiderman LJ, Gilmer T, Teetzel HD (2000) Impact of ethics consultations in the intensive care setting: a randomized, controlled trial. Crit Care Med 28:3920–3924.

38. Andereck WS, McGaughey JW, Schneiderman LJ, Jonsen AR (2014) Seeking to reduce nonbeneficial treatment in the ICU: an exploratory trial of proactive ethics intervention*. Crit Care Med 42:824–830. doi: 10.1097/CCM.0000000000000034
39. Schneiderman LJ, Gilmer T, Teetzel HD, et al (2003) Effect of ethics consultations on nonbeneficial life-sustaining treatments in the intensive care setting: a randomized controlled trial. JAMA 290:1166–1172. doi: 10.1001/jama.290.9.1166
40. Mosenthal AC, Murphy PA, Barker LK, et al (2008) Changing the culture around end-of-life care in the trauma intensive care unit. J Trauma 64:1587–1593. doi: 10.1097/TA.0b013e318174f112
41. Carson SS, Cox CE, Wallenstein S, et al (2016) Effect of Palliative Care-Led Meetings for Families of Patients With Chronic Critical Illness: A Randomized Clinical Trial. JAMA 316:51–62. doi: 10.1001/jama.2016.8474
42. Braus N, Campbell TC, Kwekkeboom KL, et al (2016) Prospective study of a proactive palliative care rounding intervention in a medical ICU. Intensive Care Med 42:54–62. doi: 10.1007/s00134-015-4098-1
43. Curtis JR, Treece PD, Nielsen EL, et al (2008) Integrating palliative and critical care: evaluation of a quality-improvement intervention. Am J Resp Crit Care Med 178:269–275. doi: 10.1164/rccm.200802-272OC
44. O'Mahony S, McHenry J, Blank AE, et al (2009) Preliminary report of the integration of a palliative care team into an intensive care unit. Palliat Med 24:154–165. doi: 10.1177/0269216309346540
45. Mun E, Ceria-Ulep C, Umbarger L, Nakatsuka C (2016) Trend of Decreased Length of Stay in the Intensive Care Unit (ICU) and in the Hospital with Palliative Care Integration into the ICU. Perm J 20:56–61. doi: 10.7812/TPP/16-036
46. Hatler CW, Grove C, Strickland S, et al (2012) The effect of completing a surrogacy information and decision-making tool upon admission to an intensive care unit on length of stay and charges. J Clin Ethics 23:129–138.
47. Jensen HI, Ammentorp J, Ording H (2013) Guidelines for withholding and withdrawing therapy in the ICU: impact on decision-making process and interdisciplinary collaboration. Heart Lung Vessel 5:158–167.
48. McCannon JB, O'Donnell WJ, Thompson BT, et al (2012) Augmenting Communication and Decision Making in the Intensive Care Unit with a Cardiopulmonary Resuscitation Video Decision Support Tool: A Temporal Intervention Study. J Palliat med 15:1382–1387. doi: 10.1089/jpm.2012.0215
49. Burns KEA, Rizvi L, Smith OM, et al (2015) Is there a role for physician involvement in introducing research to surrogate decision makers in the intensive care unit? (The Approach trial: a pilot mixed methods study). Intensive Care Med 41:58–67. doi: 10.1007/s00134-014-3558-3
50. Ernecoff NC, Witteman HO, Chon K, et al (2016) Key stakeholders' perceptions of the acceptability and usefulness of a tablet-based tool to improve communication and shared decision making in ICUs. J Crit Care 33:19–25. doi: 10.1016/j.jcrc.2016.01.030
51. Van Scoy LJ, Chiarolanzio PJ, Kim C, Heyland DK (2017) Development and initial evaluation of an online decision support tool for families of patients with critical illness: A multicenter pilot study. J Crit Care 39:18–24. doi: 10.1016/j.jcrc.2016.12.022
52. Wysham NG, Hua M, Hough CL, et al (2017) Improving ICU-Based Palliative Care Delivery: A Multicenter, Multidisciplinary Survey of Critical Care Clinician Attitudes and Beliefs. Crit Care Med 45:e372–e378. doi: 10.1097/CCM.0000000000002099
53. Engelberg R, Downey L, Curtis JR (2006) Psychometric characteristics of a quality of communication questionnaire assessing communication about end-of-life care. J Palliat Med 9:1086–1098. doi: 10.1089/jpm.2006.9.1086
54. Gerritsen RT, Jensen HI, Koopmans M, et al (2017) Quality of dying and death in the ICU. The euroQ2 project. J Crit Care 44:376–382. doi: 10.1016/j.jcrc.2017.12.015
55. Davidson JE, Aslakson RA, Long AC, et al (2017) Guidelines for Family-Centered Care in the Neonatal, Pediatric, and Adult ICU. Crit Care Med 45:103–128. doi: 10.1097/CCM.0000000000002169

56. Ramos KJ, Downey L, Nielsen EL, et al (2016) Using Nurse Ratings of Physician Communication in the ICU To Identify Potential Targets for Interventions To Improve End-of-Life Care. J Palliat Med 19:292–299. doi: 10.1089/jpm.2015.0155

SUPPLEMENTAL MATERIAL

PUBMED	Domain	“critical care”[MeSH] OR (“critical”[tiab] AND “care”[tiab]) OR “critical care”[tiab] OR (“intensive”[tiab] AND “care”[tiab]) OR “intensive care”[tiab]
	Intervention	“decision support techniques”[MeSH] OR “clinical decision making”[MeSH] OR “Decision Making”[Mesh] OR “Resuscitation Orders”[Mesh] OR “Patient Participation”[Mesh] OR “decision support”[tiab] OR “decision making”[tiab] OR “advance care planning”[MeSH Terms] OR “advance care”[tiab] OR “advance health”[tiab] OR (“advance” AND “directive”[tiab]) OR (“advance” AND “directives”[tiab]) OR (“shared” AND “decision”[tiab]) OR “family conference”[tiab] OR “ethical consultation”[tiab]
	outcome	“terminal care”[MeSH Terms] OR (“terminal”[tiab] AND “care”[tiab]) OR “terminal care”[tiab] OR (“end”[tiab] AND “life”[tiab] AND “care”[tiab]) OR “end of life care”[tiab] OR “end of life decision”[tiab] OR (“end of life”[tiab] AND “decision”[tiab]) OR “decisional conflict”[tiab] OR “treatment limitation”[tiab] OR “life sustaining”[tiab] OR “withhold”[tiab] OR “forgo”[tiab] OR “forgoing”[tiab] OR
EMBASE	Domain	(critical care: ti,ab OR intensive care; ti,ab)
	Intervention	(decision support: ti,ab OR decision support techniques: ti,ab OR decision support system: ti,ab OR decision making instrument; ti,ab OR decision making aid; ti,ab OR advance care planning; ti,ab OR advance directive: ti,ab OR advance care plan: ti,ab OR decision making: ti,ab OR shared decision making: ti,ab OR family conference: ti,ab OR ethic consultation: ti,ab
	outcome	terminal care: ti,ab OR end of life care: ti,ab OR end AND of AND life decision; ti,ab OR decisional conflict: ti,ab OR treatment limitation: ti,ab OR life-sustaining: ti,ab AND therapy: ti,ab OR therapy, ti,ab OR treatment: ti,ab

Table S1. Keywords used for PubMed and EMBASE search strategy

Number of studies	Reason
166	Wrong study design
56	No full text available
33	Not about (process of) decision making
18	(mostly) NON-ICU patients
10	Congress note/abstract/editorial
6	End of Life care
5	Wrong language
3	Duplicate
2	Triage/decision to admit or not to ICU
1	Pediatric population

Table S2. Reasons for exclusion

ICU Intensive Care Unit

First author	Year	Comparator	Sequence generation	Allocation concealment	Blinding of participants and personell	Blinding of outcome assessor	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall Risk of bias
Lee char	2010	Randomized control	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	**Unclear**
Curtis	2016	Randomized control	Low	Low	High	Low	Low	Low	Low	**High**
Schneiderman	2003	Randomized control	Low	Low	Unclear	Low	Low	Unclear	Low	**Unclear**
Andereck	2014	Randomized control	Unclear	Unclear	High	Low	Low	Unclear	Low	**High**
Schneiderman	2000	Randomization (block)	Unclear	Unclear	High	Low	Low	Low	High	**High**
Carson	2016	Randomized control	Low	Low	High	Low	Low	Low	Low	**High**
White	2018	Stepped-wedge cluster randomized	Low	Low	Low	Low	Low	Low	Low	**Low**

Table S3. Risk of Bias of randomized trails
Overall risk of bias is considered low if bias is **low** in all domains and **high** if risk of bias is high in any domain.

First author	Year	Selection of participants	Selection bias	Performance bias	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall Risk of bias
Ahrens	2003	Low	High	Low	Low	Unclear	Unclear	**High**
Allen	2017	Low	Low	Unclear	Unclear	Low	High	**High**
Braus	2016	Low	Low	Low	Low	Unclear	Unclear	**Unclear**
Burns	2003	Low	High	Low	Unclear	High	Low	**High**
Campbell	2003	High	Unclear	Unclear	Low	Low	Low	**High**
Cox	2012	Low	Low	Low	Unclear	Low	Unclear	**Unclear**
Curtis	2008	Low	Low	Low	Unclear	Unclear	Low	**Unclear**
Daly	2010	Low	Low	Low	Low	Low	Unclear	**Unclear**
De Havanon	2015	High	High	Low	Low	Unclear	Unclear	**High**
Dowdy	1998	Low	Low	Unclear	Low	Low	Low	**Unclear**
Halter	2012	High	Low	Unclear	Low	Unclear	Unclear	**Unclear**
Higginson	2013	Low	High	Low	Low	Unclear	Low	**High**
Jacobowski	2010	Low	Low	Low	Low	High	Low	**High**
Jensen	2013	High	High	Low	Low	Unclear	High	**High**
Kaufer	2008	High	Low	High	Low	High	Low	**High**
Lilly	2003	Low	Low	Low	Low	Low	High	**High**
McCannon	2012	Unclear	Unclear	Low	High	Low	Low	**High**
Mosenthal	2008	Low	Low	Low	Unclear	Low	Unclear	**Unclear**
Mun	2016	Unclear	Low	Unclear	Unclear	Unclear	Low	**Unclear**
Norton	2007	Low	Low	Low	Low	Low	Low	**Low**
O'Mahony	2009	Low	Unclear	Low	Low	Unclear	Low	**Unclear**
Quenot	2012	High	High	Low	Low	High	Unclear	**High**
Quenot	2012	Low	High	Low	Low	Low	Low	**High**
Teno	1997	Low	Unclear	Unclear	Unclear	Low	Low	**Unclear**
Wysham	2014	Low	Low	High	Unclear	Unclear	Low	**High**

Table S4. Risk of Bias of non-randomized trails
Overall risk of bias is considered low if bias is low in all key domains and high if risk of bias is high in any domain

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Ahrens (24)	medical ICU patients with high risk of dying	case- control	I = 43/ C = 108	USA	daily communication by physician and clinical nurse specialist with patient and/or surrogates	decreased hospital and ICU LoS, decreased costs	mortality
Campbell (25)	medical ICU patients with (1) global cerebral ischemia after cardiac arrest or (2) three or more organ systems in failure for minimal three days	case- control	I = 41/C = 40	USA	daily family meetings on prognosis and recommended change of treatment goals	(1) decreased LoS ICU and hospital, decreased time to comfort care (2) decreased time to decision, decreased LoS ICU	costs
Lilly (18)	medical ICU patients with predicted (1) admission >5 days (2) >25% mortality or (3) impossible to return home	pre-post- and 4-year follow-up	pre = 134/ post = 396/ 4-year follow-up =2361	USA	intensive communication < 72h with predefined objectives including defining clinical milestones and time-frame.	decreased ICU LoS, decreased ICU mortality, increased documented communication sessions	
Lee Char (26)	surrogate decision makers of mixed ICU patients	randomized control	I=83/ C= 86	USA	numeric prognostic statements	decreased discordance between physician and surrogates estimated prognosis	understanding the prognosis
Jacobowski (27)	medical ICU patients	pre-post	pre = 116/ post = 111	USA	family attendance and participation in daily interdisciplinary rounds		overall family satisfaction and decision making sub scores, ICU survival

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Daly (28)	surrogate of ICU patient with more than 72h mechanical ventilation and without decisional capacity	pre-post	I = 346/ C = 135	USA	family meeting within 5 days of ICU admission and at least weekly thereafter, with predefined objectives including medical update, values and preferences, goals of care; treatment plan; milestones to determine effectiveness	increased frequency and duration of family meetings	
Quenot (29)	ICU patients who died in the ICU/ hospital	pre-post	pre = 678/ post = 823	France	intensive strategy for communication on the level of therapeutic engagement according to clinical severity and expected prognosis	decreased time to initiation of decision making process, decreased time to decision, decreased LoS for descendents. More documented decisions, more often initiation of process by family-members or non-physician's caregivers	reasons to forgo treatment
Quenot (30)	healthcare workers in the ICU	pre-post	pre = 53/ post = 49	France	intensive communication strategy regarding both organizational factors and communication measures	decreased risk of burnout and depression	

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Higginson (4)	ICU staff and family members of medical and surgical ICU patients	case-control	I = 88/ C = 42	UK	Psychosocial Assessment and Communication Evaluation (PACE) 24-48h after admission	increased satisfaction with assessment and treatment of symptoms, higher perceived consistency of information provided	
Wysham (17)	medical-surgical ICU patients	pre-post- and 3-year follow-up	pre = 38/ post = 27/ follow up = 42	USA	daily discussions with the family using VALUE communication tool and documented in daily care plans	more often daily update with family, increased nurses' participation in update, more often goals and changes documented	family satisfaction, family conference rate
de Havenon (31)	family members of neuro-critical care ICU patients	Non-randomized control	I = 29 / C = 59	USA	audio-visual family meetings		satisfaction with the decision-making process
Allen (32)	Family members of surgical ICU patients	Pre-post	Pre= 886/ post= 847	USA	family attendance during daily rounds	family: increased knowledge on care plan, knows doctor. Less post-rounds family meetings. Nurses: Reduced workload	Physicians: satisfaction

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Teno (20)	patients with advanced stages of pre-specified diseases with an expected mortality rate of about 50% at 6 months	pre-post	I = 2158 / C = 1705	USA	SUPPORT intervention; patient-specific prognoses for survival and function, information about each patient's and surrogate's preferences. Facilitated communication by a specialized nurse. Option to complete a formal advance directive.	more documentation of existing advance directives in the medical record	awareness of advance directives, rates of completion of advance directives, CPR decision making
Burns (33)	medical/ surgical ICU patients with a high risk of conflict in decision making	case-control	I = 172 / C = 701	USA	Social workers interviewed families of patients at high risk for decisional conflict, provided feedback to the clinical team, presented a list with optional measures to address the problems identified from which the team could select	increased probability of a goal of care decision	patient or surrogate satisfaction with care

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Kaufer (34)	surrogates of patients died in the medical ICU	pre-post	Pre = 43/ post = 45	USA	Introduction of family support team and palliative care team: discuss palliative care patients at least 3 times per week, educational initiatives, facilitate family meetings and ensure formal documentation, follow-up of patients	increased satisfaction with the frequency of communication, overall satisfaction, accessibility of information, involvement in decision making, satisfaction with the death and dying process	
Curtis (35)	mixed ICU patients admitted > 24 hours; mechanically ventilated, Sequential Organ Failure Assessment (SOFA) score =/> 6 or criteria predicting >30% risk of hospital mortality	randomized control	I = 82 (surrogates 137) / C = 86 (surrogates 131)	USA	interviews by facilitators with families; meetings by facilitators with clinicians sharing family concerns, needs, and communication characteristics; provision of communication and emotional support; participation in family conferences; 24-hour follow-up with the family after discharge	decreased symptoms of depression, decreased time to withdrawal of treatment in patients who died, decreased LoS of patients who died, decreased ICU costs per day and in total	level of anxiety PTSD score, mortality

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Dowdy (36)	mechanical ventilation for >96 hrs in the ICU	pre-post	I= 31/ C= 31 (baseline = 37)	USA	pro-active ethics consultation to increase attention to key decision-making and communication: discussing advance directives, who is decision maker, diagnosis and prognosis	decreased ICU LoS, more treatment decisions made	
Schneiderman (37)	medical and pediatric ICU patients identified by the teams in whom value-based treatment conflicts arose	randomized control	I = 35 / C = 35	USA	pro-active ethics consultation for patients in whom value laden treatment conflicts were imminent or manifest	decreased days on mechanical ventilation, decreased ICU LoS for decedents	mortality
Schneiderman (39)	ICU patients with imminent or manifest value laden treatment conflicts	Random ized control	I = 276 / C = 270	USA	pro-active ethics consultation (ethical diagnosis, recommendations, documentation, follow-up)	for decedents: decreased LoS hospital, LoS ICU and days receiving mechanical ventilation	survivors: LoS, days receiving MV/art feeding

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Andereck (38)	medical/surgical ICU patients with LoS > 5 days	block-randomized	I = 174 / C = 210	USA	clinical ethicist meeting with patient and surrogates, facilitate communication, advice medical providers, document activities		mortality, ICU LoS, hospital LoS, days on mechanical ventilation, days on artificial feeding, costs, perception of quality of care by patients/surrogates/physicians/nurses, perception of suffering by nurses/physicians
O'Mahony (44)	mixed ICU	case-control	I = 22 / C= 43	USA	pro-active involvement of palliative care team: family meeting, advice on treatment of symptoms and limitations	less non-beneficial care, more use of opioids	ICU LoS
Norton (23)	five medical ICU patient groups with high risk of dying or adverse burden/benefit ratio	pre-post	pre = 65 / post = 126	USA	pro-active basic (advice in chart) or complete (active involvement) palliative care consultation	decreased ICU LoS, increased palliative care involvement	mortality, hospital LoS

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Mosenthal (40)	surgical ICU patients	pre-post	pre = 266 / post = 367	USA	integrated palliative care intervention for all trauma patients and families: assessment < 24h, interdisciplinary family meeting < 72h	decreased time to code change, shorter LoS in ICU and hospital for decedents, more discussion on pain and symptom management	mortality, DNR orders
Curtis (43)	family members and nurses of mixed-ICU patients who had died in the ICU or <24h after discharge	pre-post	Family: pre = 125 / post = 150 Nurses: pre = 216 / post = 307	USA	critical care clinician education in palliative care, training of ICU local champions, resolve unit-specific issues, feedback on quality-improvement data, system support	decreased ICU LoS, improved QODD scores nurses	QODD scores family members, family satisfaction with care
Carson (41)	surrogate decision makers of mixed ICU patients >7 days of MV	Random ized control	I = 163 / C = 149	USA	two/more meetings with palliative care team		HADS score, PTSD diagnostic cut-off, FS-ICU scores, duration of mechanical ventilation, hospital LoS, survival

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Braus (42)	medical ICU patients	pre-post	I = 103 / C = 100	USA	palliative care clinician interacting with the ICU physicians on daily rounds for patients who met palliative care triggers	decreased ICU LoS for decedents, hospital LOS for all patients, shorter time to first family meeting, more document family meetings and interdisciplinary meetings	frequency of full palliative care consultation, mortality, family satisfaction, symptoms of depression and PTSD
Mun (45)	Mixed ICU patients	Pre-post	pre= 194, post=198	USA	pro-active (triggered) palliative care consultation	decreased hospital LoS, goals of care and code-status identified in more patients, more family meetings, more palliative care brochures provided	ICU LoS
McCannon (48)	surrogates of medical ICU patients, < 72h after admission	pre-post	pre = 23 / post = 27	USA	3 minutes CPR video decision support tool	increased knowledge on CPR	patients with DNR code status
Cox (19)	surrogates of mixed ICU patients >10 days on mechanical ventilation	pre-post	I = 17 / C = 10	USA	decision aid containing four main domains of shared decision making	less physician–surrogate discordance for the expected 1-yr patient survival and functional independence, decreased decisional conflict scale scores, decreased hospital costs.	quality of communication scores, medical comprehension scores, discussions with physicians about expected long-term patient survival and functional status

First author	Population	Design	Sample size	Country	Intervention	Beneficial effect	No effect on
Hatler (46)	neuro ICU patients admitted >6 days or > 96h on mechanical ventilation	pre-post	pre = 105 / post = 98	USA	staff education on ethics, critical communication skills, early identification of families and staff in crisis, and use of a simple tool to document previously expressed care wishes, and information leaflet for patient/ surrogates	decreased hospital LoS, decreased hospital costs	patient satisfaction scores, ventilator free days, discharge locations
Jensen (47)	ICU patients	pre-post	I = 897 / C = 1665	Denmark	guidelines with five sections on decision-making: legal issues, definitions, issues regarding the process, practical advice and recommendations	for decedents in the ICU: LoS to first consideration on level of therapy and to withdrawal	patients with therapy withdrawn, nurses perceived involvement in the decision-making process
White (16)	ICU surrogates	Stepped-wedge randomized	I = 547 C = 873	USA	multicomponent family-support intervention with daily nurse- family check-ins, and clinician–family meetings within 48 hours after enrollment and every 5 to 7 days thereafter	quality of communication and patient family centeredness, LoS in ICU	HADS, IES

Table S5. Included studies; characteristics and results

ICU Intensive Care Unit, *I* = intervention, *C*= control, *USA* United States of America, *LoS* Length of Stay, *CPR* Cardiopulmonary Resuscitation, *PTSD* Post Traumatic Stress Disorder, *DNR* Do Not Resuscitate, *QODD* Quality of Dying and Death, *HADS* Hospital Anxiety and Depression Scale, *FS-ICU* Family Satisfaction in the Intensive Care Unit, *IES* Impact of Events Scale

6

A framework to support the process of decision-making on life-sustaining treatments in the intensive care unit: results of a Delphi study

MC Kerckhoffs, J Senekal, D van Dijk, A Artigas, J Butler,
A Michalsen, MMC van Mol, R Moreno, F Pais da Silva, E Picetti,
P Póvoa, A Robertsen, JJM van Delden

Published in; Critical Care Medicine 2020

ABSTRACT

Objective To develop a consensus framework that can guide the process of decision-making on continuing or limiting life-sustaining treatments in intensive care unit (ICU) patients, using evidence-based items, supported by caregivers, patients and surrogate decision makers from multiple countries.

Design A three-round web-based international Delphi consensus study with a priori consensus definition was conducted with experts from 13 countries. Participants reviewed items of the decision-making process on a 7-point Likert scale or with open ended questions. Questions concerned terminology, content and timing of decision-making steps. The summarized results (including mean scores) and expert suggestions were presented in the subsequent round for review.

Setting Web-based surveys of international participants representing Intensive Care Unit physicians, nurses, former Intensive Care Unit patients and surrogate-decision-makers.

Patients Not applicable

Interventions Not applicable

Measurements and main results In three rounds, respectively 28, 28 and 27 (of 33 invited) physicians together with 12, 10 and 7 (of 19 invited) nurses participated. Patients and surrogates were involved in round one and 12 of 27 responded. Caregivers were mostly working in university affiliated hospitals in Northern Europe. During the Delphi process, most items were modified in order to reach consensus. Seven items lacked consensus after three rounds. The final consensus framework comprises the content and timing of four elements; three elements focused on caregiver-surrogate communication (admission meeting, follow-up meeting, goals of care meeting) and one element (weekly time-out meeting) focused on assessing preferences, prognosis and proportionality of ICU treatment among professionals.

Conclusions Physicians, nurses, patients and surrogates, generated a consensus-based framework to guide the process of decision-making on continuing or limiting life-sustaining treatments in the ICU. Early, frequent and scheduled family-meetings combined with a repeated multidisciplinary time-out meeting may support decisions in relation to patient preferences, prognosis and proportionality.

INTRODUCTION

On almost 75.000 Intensive Care Unit (ICU) beds across Europe, critically ill patients are cared for every day [1]. On most of these days a decision to continue treatment is taken, implicitly or explicitly. In at least 10% of all ICU patients however, the decision is made to limit life-sustaining ICU treatments [2, 3]. While some decisions concerning life-prolonging therapies may seem straightforward, most decisions are the result of a complex process of decision-making.

In 2003 and 2019 the ETHICUS studies gave valuable insights into the variability and complexity of life-sustaining treatments decisions across European ICUs [3, 4]. The variability between and within countries on those decisions as well as heterogeneity in prevalence of withdrawal of life-sustaining treatments within one ICU, is only decreasing slowly [2, 4-6]. The reason for this variation is multifactorial. Patient related factors (i.e., age, co-morbidities), geographic factors (for example southern Europe versus central/northern Europe), and ICU characteristics all impact the tendency to make or avoid decisions on life-sustaining therapy [3, 4, 7-9]. In addition, physician related factors can cause discordances in prognostic estimates, and unknown preferences of the patient can cause hesitation in decision making [10-12].

Although decisions are inevitably individual, they should always be the result of a careful process. The decision-making process minimally involves a stepwise practice of gathering and interpreting information, weighing different options and ultimately taking a (shared-) evidence based and personalised decision [13]. Engaging in this process can both minimize subjectivity and biases as well as maximize ICU team, patient and surrogate involvement [10, 14].

There is limited evidence on the required elements of the decision making process on continuing or limiting ICU treatment and how each element contributes to a careful process and decision [15, 16]. Strategies based on frequent caregiver- family meetings with predefined topics and integrated within standard ICU care may improve process measures like ‘time to decision’ and reduce non-beneficial treatment days [16]. In addition it has been shown that adequate communication, including the opportunity to challenge the appropriateness of care within ICU teams, is a prerequisite for the delivery of appropriate care [17].

Since several strategies contributing to careful decision-making have been described in the past, we hypothesized that it would be possible to integrate this knowledge into a framework that can support the process of decision-making on treatment intensity in the ICU. The use of a framework promotes transparency of the process for all stakeholders, can minimize the effect of coincidence and can encourage patients and surrogates to participate in decision-making [18].

The aim of this study was to develop a framework that can support the decision-making process to continue, withhold or withdraw life-sustaining treatments in ICU patients.

MATERIALS AND METHODS

We conducted a three-round web-based Delphi consensus study, based on evidence on decision-making strategies, in accordance with guidelines and in analogy with recently performed ICU Delphi studies [16,19-22]. The Delphi technique is widely-used in health research to obtain consensus in serial surveys, referred to as rounds [23]. Key elements of the technique are 1) expert participants 2) anonymity and individuality 3) providing a summary of results of the former round at the start of the subsequent round.

Ethical approval was granted from the Institutional Review Board of the University Medical Centre Utrecht, The Netherlands (protocol number 16/508), University Hospital Ghent, Belgium (BC/2368 LBG) and the University Hospital Oslo, Norway (17/16124). Consent was waived, except for the Norwegian and Belgian participants who provided a written consent.

Expert panel recruitment

Experts were defined as having theoretical knowledge or practical experience with the decision-making process on continuing, withholding or withdrawing life-sustaining treatments in the ICU. To develop a framework that would comply with the needs of all stakeholders, the expert panel consisted of (1) ICU physicians, (2) ICU nurses and (3) former ICU patients and surrogate decision-makers. Physicians who were either member of the section on Ethics of the European Society of Intensive Care Medicine (ESICM) or known for their interest in ethics (clinically or scientifically) were primarily invited to participate by email. Snowball sampling, participants recommending acquaintances, was used to recruit additional physicians and nurses. Intended participants received an email containing a summary of the relevant literature and the purpose, design and time investment of the study.

The former ICU patients and surrogate decision-makers were invited through five participating hospitals in four countries. Patients were eligible if they had been admitted to the ICU for more than seven days in the past two years. Surrogate decision-makers were eligible when their family member met the former criteria and was discharged alive. For practical reasons, Dutch or English proficiency was required. Patients and surrogate decision-makers were treated as one expert group.

Delphi design

The study was designed to consist of three rounds. Between rounds, data were summarized and analysed anonymously by an independent researcher (JS) using Typeform and SPSS version 25 [24] (Figure 1). Refinements made to the survey or framework were discussed within the core research group (JS, MK, HvD, DvD). Only participants who completed the previous round were invited to subsequent rounds. Participation could be withdrawn at any time without reason. No financial compensation was offered.

Consensus was a priori defined as more than 70% agreement or a mean Likert score more than or equal to four (on a scale of 1 to 7). No consensus encompassed < 70% agreement or a mean Likert score of less than 4. Items with 30-70% consensus were refined based on recommendations and feedback from participants and presented in the subsequent round. Elements with less than 30% agreement were regarded as irrelevant and excluded.

Survey design

A complete description of the survey design is described in the supplemental digital content; methods.

An online survey was designed based on an outline of decision-making steps ('elements') for which the participants were asked to specify the content through defining 'items', timing and contributors (supplemental digital content Figure S1. framework-draft). The survey consisted of statements, questions using a seven point Likert-scale (seven is most positive) and open ended questions.

The online survey was pilot-tested in eight experts, professionals and surrogate decision-makers, not participating in the Delphi study itself. The survey could be completed via a personal access-code ensuring single completion.

Patients and surrogate decision-makers received a paper copy of the first round of the survey in laymen's terms with a pre-paid return-envelop. They were given the opportunity to reflect on the basic draft and encouraged to share their view on the

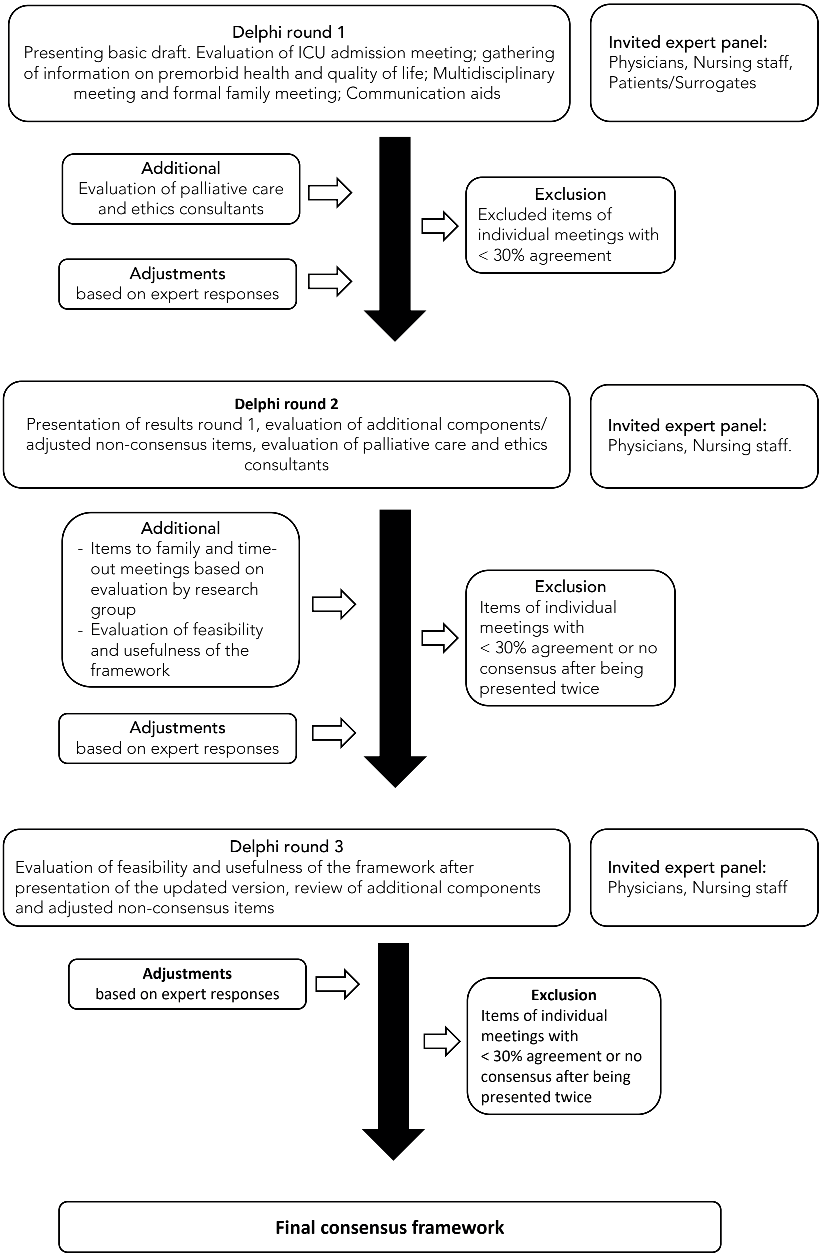


Figure 1. Flowchart Delphi process

Graphical representation of the methods of the Delphi consensus process.

decision-making process. It was pre-specified to involve them only in round one, to minimize the burden. To maximize their input, their survey was enriched with more open ended questions.

Round one aimed at getting insight into expert's views on the optimal ICU decision-making process, focused on communication, gathering of background information and the use of communication aids and tools. Importance and feasibility of each element were assessed.

During round two the ICU physicians and nurses were provided the results and feedback from the first round, revised items (without consensus) and additional items based on recommendations. Questions on the importance, feasibility, role and triggers to involve palliative care teams and ethics consultants were added.

During round three the refined version of the decision-making framework was presented for feedback regarding usefulness and feasibility. Round three also finalized evaluation of items without consensus as well as additional recommendations that had been made by participants.

Statistical reporting

Descriptive statistics (SPSS version 25) were used to analyse and report data, including percentage agreement, mean Likert score, equimedian (defined as the median weighted by size of group) and Inter Quartile Ranges (IQR) when appropriate.

RESULTS

Seventy-nine experts consented to participate after the invitational email, of which 28 physicians, 12 nurses and 12 patients and surrogate decision-makers completed round one (Table 1, details in supplemental digital content Table S1). The physicians and nurses were experienced caregivers, predominantly working in university affiliated hospitals. 92% of all experts were from Europe. Former ICU patients and surrogate decision-makers completing the survey were from the Netherlands, United Kingdom and Belgium.

Results are presented in figure 2A/B, table 2 and in the following paragraphs. Detailed results on each element are presented as supplemental digital content (Figure S2, Table S2).

In round one, 52 of the 79 invited experts responded (66%). Consensus was reached on importance and feasibility of an admission meeting, gathering of information regarding premorbid health and quality of life, a multidisciplinary meeting and a formal family meeting. No consensus was reached on their timing. Consulting the general practitioner and other specialists to gather background information was considered important. In addition, using family-meetings was chosen over questionnaires as a source of information. There was consensus on the use of an informational brochure and communication preparation tool, as opposed to the use of video. Excluded items referred to mandatory participants of individual meetings.

After round one, the framework was modified to a structure of four elements; three family-meetings and a multidisciplinary caregivers-meeting. This meeting was retitled "time-out meeting" to elucidate the goal of the meeting, namely to address whether to continue, withhold or withdraw life-sustaining treatments. The item on religion and cultural background was rephrased to assess inclusion in the framework. New propositions regarding the timing of the individual meetings were made based on responses. Four additional items of the admission-meeting and family-meetings, additional options to support the gathering of information as well as a recommendation for additional services available to patients/surrogates were added based on recommendations from participants.

In round two, 38 of 40 experts responded (95%). Consensus was reached on the four additional items included in the admission and formal family meeting and on three of four additional options to support the gathering of information. Neither additional services to support the family, nor the use of validated questionnaires to support gathering of information, reached consensus. Six of the thirteen previous non-consensus items, which were adjusted to choose optional versus mandatory inclusion in the framework, remained without consensus.

Importance, but not feasibility, of palliative care was established together with futility as a trigger. All other suggestions regarding palliative care did not achieve consensus. The importance and feasibility of the availability of an ethics consultant was established in an advisory role regarding ethics, policies and legal implications, as well as resolution of conflict.

Only the timing of the admission- and time-out meeting reached consensus.

After round two, the gathering of information was included as an item of the follow-up family meeting based on the suggestions of participants, where the timing was proposed to be day two or three. The "formal family meeting" was re-titled to "goals-of-care meeting" to emphasize the objective of this meeting. Three additional items related to prognosis and treatment limitations were added to the family- and time-out meeting.

Characteristic	Intensivists	ICU nurses	Patients/surrogates
Number invited	33	19	27
Number of participants first round (%)	28(85%)	12(63%)	12(44%)
Number of participants completed all three rounds (%)	27(96%)	7(58%)	N/A
Gender			
Male	20(74%)	2(17%)	Information not available
Years of experience in ICU			N/A
0 - 10 years	3(11%)	1(8%)	
11-20 years	9(33%)	3(25%)	
> 20 years	15(56%)	8(67%)	
Current practice			N/A
University affiliated hospital	22(81%)	9(75%)	
District/General hospital	4(15%)	3(25%)	
Private practice	1(4%)	0	
Characteristics of ICU (multiple options possible)			N/A
Mixed	22(81%)	8(67%)	
Medical	4(15%)	4(33%)	
Surgical	4(15%)	4(33%)	
Neuro	6(22%)	2(17%)	
Cardiothoracic	2(7%)	2(17%)	
Country of origin (Participants first round)			
Australia	2(7%)	1(8%)	0(0%)
Belgium	4(14%)	3(25%)	2(17%)
Denmark	1(4%)	0(0%)	0(0%)
Germany	1(4%)	1(8%)	0(0%)
Greece	0(0%)	1(8%)	0(0%)
Israel	1(4%)	0(0%)	0(0%)
Italy	5(18%)	1(8%)	0(0%)
Netherlands	4(14%)	2(17%)	9(75%)
Norway	2(7%)	2(17%)	0(0%)
Portugal	4(14%)	0(0%)	0(0%)
Spain	1(4%)	0(0%)	0(0%)
United Kingdom	2(7%)	1(8%)	1(8%)
United States	1(4%)	0(0%)	0(0%)

Table 1. Characteristics of experts

Demographic characteristics of intensivists available for 27 participants, data not available for one participant. *N/A; non-applicable, ICU; Intensive Care Unit*

The described role of palliative care was adjusted to evaluate whether a protocolised role in the decision-making process would be appropriate. The previously presented triggers were combined into "poor prognosis" as a single trigger. The trigger for ethics involvement was proposed to be conflict where other means had been ineffective. The use of video was rephrased to "include digital information resources", in order to include the use of internet resources.

In round three, 34 of 38 experts responded (89%). The framework was found useful and feasible to support the decision-making process in the ICU and it was established that the framework should be made available to patients and surrogate decision-makers. The three items on discussing prognosis and limitations of treatment during time-out- and goals-of-care meeting achieved consensus. Consensus was reached on recommending the availability of religious support, a social worker and psychologist to support the family as well as the use of digital information resources. It was established that the palliative care team should not have a mandatory protocolled role in the ICU. The minimum frequency of both the time-out and the goals-of-care meetings, were agreed upon to be weekly.

Statistics

For each option provided in the various rounds, the mean and equimedian on the 7-point Likert scale and percentage agreement on dichotomous questions were presented in the subsequent rounds. Data are presented in the supplemental digital content file table S2.

Practical implications concerning the use of the suggested framework

The final result of the three rounds is presented in figure 2A/B and consists of (in summary) (1) an ICU admission meeting; aimed to inform the family and clarify treatment goals and resuscitation status, 2) a family follow-up meeting; inform and gather information on pre-morbid functioning, 3) a goals-of-care meeting; defining milestones and treatment goals in relation to patient preferences and values, 4) a (recurrent) time-out meeting where caregivers address prognosis and proportionality together with goals and/or limitations of treatment. At admission, the framework would be offered to the patient/surrogate, informing them about the process of communication and decision-making steps including the agenda for each meeting. The local version of the framework can be enriched with available, recommended measures such as family support services.

Details per meeting	Round	1	2	3
ICU Admission meeting				
Content items	Update on current situation and disease/injury process	✓		
	Determine presence of pre-existing documented patient preferences	✓		
	Identify and confirm surrogate decision-maker/ legal representative	✓		
	Provision of information regarding ICU#	n/a	✓	
	Treatment plan and interventions#	n/a	✓	
	Potential outcomes and prognosis#	n/a	✓	
Timing	As soon as achievable within 24h	X	✓	
Follow-up family meeting (including gathering of information)				
Content items	Update similar to admission meeting	n/a	n/a	✓
	Independence with activities of daily living	✓		
	Frailty	✓		
	Cognition	✓		
	Pain and discomfort on a daily basis	✓		
	Religion and cultural background	X	✓	
Timing	Day 2 of ICU admission	X	X	✓
Time-out meeting				
Content items	Evaluate effectiveness of current management and control of symptoms (mandatory)	X	✓	
	Information regarding premorbid health and quality of life (mandatory)	X	✓	
	Discuss patient preferences	✓		
	Set treatment goals and milestones for evaluation	✓		
	Establish/review resuscitation status	✓		
	Prognosis and expected outcomes+	n/a	n/a	✓
	Establish limitations of treatment+	n/a	n/a	✓
Timing	5 -7 days after admission	X	✓	
	Minimum frequency weekly	n/a	X	✓
Goals-of-care meeting				
Content items	Update on current situation	✓		
	Identify milestones to indicate progress or failure	✓		
	Goals of care plan	✓		
	Limitations of treatment (if any)	✓		
	Identification of family needs and requirement for support#	n/a	✓	
	Prognosis and expected outcomes+	n/a	n/a	✓
Timing	Pre-determined and at physician discretion	n/a	✓	
	Frequency: minimum weekly	n/a	X	✓

Table 2. Summarized consensus process

Note that only selected items regarding content and timing which achieved consensus are presented.
Additional items added after round one,
+ Additional items added after round two. *n/a: non-applicable, ICU: Intensive Care Unit*

Decision-making framework Intensive Care Unit

ICU Admission family meeting

Intensivist
ICU nurse
Patient/family

< 24h

Update:
- Current situation and disease/injury
- Treatment plan and interventions
- Potential outcomes and prognosis (if possible)
- Information regarding the ICU

Identify:
- Surrogate decision-maker or legal representative
- The presence of pre-existing documented patient preferences (Advance health directive)

Address:
- Clarify and determine current resuscitation status

ICU follow-up family meeting

Intensivist
ICU nurse
Patient/family

< 2-3 days

Update:
- Current situation and disease/injury
- Treatment plan and interventions
- Potential outcomes and prognosis (if possible)

Identify:
Premorbid functioning;
Independence with activities of daily living, cognition, mobility, pain and discomfort, frailty, alcohol/drugs/smoking, anxiety and depression symptoms,
religion and cultural background

Address:
- The presence of pre-existing documented patient preferences (Advance health directive)
- The current resuscitation status

Additional resources for information on premorbid functioning:
Referring specialist/ General practitioner/ Other specialists known to patient/ Medical record/ Bedside information

Goals-of-care family meeting

Intensivist
ICU nurse
Patient/family

Optional;referring specialist trainee

< 5-7 days

In association with TIME-OUT meeting; repeat minimally weekly

Update family:
- Current situation
- Treatment plan
- Prognosis and expected outcomes

Identify:
- Milestones to indicate progress or failure
- Family needs and requirement for support

Address;
- Goals of care plan
- Limitations of treatment (if any)

TIME-OUT meeting

Intensivist
ICU nurse
Referring specialist

Optional: Other intensivists not attending to patient, other specialists , social worker

After 5-7 days

In association with goals of care family meeting; repeat weekly

Evaluate current management and progress:
- Current clinical status
- Effectiveness of current management and control of symptoms

Discuss:
- Premorbid health and quality of life
- Patient preferences
- Prognosis and expected outcomes

Address:
- Set treatment goals and milestones
- Establish limitations of treatment
- Review and establish resuscitation status

Consider using additional resources

Communication aids and tools:
- Information brochure
- Communication preparation tool
- Digital information resources

Ethics consultants

Palliative care as optional resource

Additional services:
- Social worker
- Religious support
- Psychologist

Figure 2 A/B. Consensus framework

Final framework resulting from the three rounds Delphi study, describing three elements of decision-making in the ICU. ICU Intensive Care Unit

DISCUSSION

We conducted a three-round International Delphi consensus study with physicians, nurses, former ICU patients and surrogate decision-makers from 13 countries, who co-created a decision-making framework describing the content and timing of four evidence- and practice-based decision-making steps.

Interpretation of the framework

The created framework should be considered as an indicative aid to enhance timely, personalized and proportional decision-making, allowing the opportunity to modify the timing of the various elements according to patient trajectory. Although our expert sample was relatively small and skewed towards experienced European caregivers, the content and timing of the four decision-making steps largely align with international evidence and practice.

The framework in relation to scientific evidence

The admission meeting, the follow-up meeting and the weekly goals-of-care meeting all emphasize the importance of communication with patients or surrogate decision-makers. This is supported by previous studies, as early patient and family participation improves satisfaction with decision making, decreases decisional conflict [25-28] and is associated with a decreased length of stay for patients who ultimately die in the ICU [29]. Moreover it may lead to a reduction in depressive symptoms in family members and ICU caregivers [30].

Another consistent item in the framework for each family meeting, is eliciting and reassessing patient treatment preferences. Studies have shown that this is currently often omitted [15, 31, 32].

The time-out meeting as the fourth element of the framework, can work as a cognitive aid. By discussing factors known to influence prognosis, physicians are stimulated to use analytical thinking before they use their intuition to estimate outcome for a specific patient [33, 34]. In addition, weighing risks and benefits helps to structure the decision-making process, can promote more unbiased decisions and improves prognostic accuracy [35].

The absence of palliative care team involvement in the framework is remarkable, since previous studies have shown its effect on length of stay and quality of communication [36-39]. A possible explanation is that evidence on palliative care interventions mainly arises from Northern America, while our experts were predominantly working in Europe. Delphi participants mentioned that intensivists should have these competences themselves.

The framework in practice

The timing of the various meetings may appear late. After multiple Delphi rounds, only a small minority perceived the meetings as being too late. Therefore, the suggested timing could be regarded as the latest suitable timing, also granting the opportunity to advance meetings according to patient trajectory.

In addition, the formal role of family members in decision making varies across countries and our expert sample may have not covered all strategies. Shared decision-making strategies, as opposed to paternalistic strategies, allows all stakeholders including the patient's substitutes to share responsibility [40]. This approach may promote earlier surrogate involvement than is suggested in the framework.

Since the experts were encouraged to draft a framework applicable to most ICU patients, some items were rejected for mandatory inclusion. However, addressing premorbid functioning at admission or evaluating burden and rehabilitation planning during the time-out meeting, can be very important and might be already valuable practice in some ICUs.

Strengths and weaknesses

This study has several strengths. First, we followed the reporting standard for Conducting and Reporting of Delphi Studies (CREDES) ensuring clear consensus criteria and descriptions of designing subsequent rounds [22]. Second, the survey was first piloted, to test understanding of the participants. Third, the items included in the framework are evidence-based [16]. Fourth, the Delphi experts originated from 13 countries reflecting different regions, various cultural backgrounds and several types of ICUs. Fifth, former ICU patients and surrogate decision-makers participated in the development of the framework ensuring compliance with patients' needs and expectations. Sixth, the use of refining comments, for example the use of additional resources to provide information on ICU admission was valued very important by patients and surrogate decision-makers, therefor re-presented in the next round and subsequently included in the framework.

This study also has limitations. First, by design the results are influenced by the participating experts. The snowball sampling method, might have introduced a sampling bias resulting in the majority of representatives being overall very experienced, from North-European countries and working in university affiliated hospitals, which might impede generalization in other regions worldwide. The lack on consensus on some items could reflect cultural differences regarding end-of-life decisions. Second, we are not informed about the background of the patient and surrogates and how decision-making was perceived in their situation. In addition, their response rate was lower than expected and they were only involved in the first round. Including patients and surrogate decision-makers in subsequent rounds could have influenced the framework, although most of their remarks are incorporated in the final version. Third, only 58% of nurses completed all three rounds.

Future research should especially consider the applicability of the framework in various regions throughout the world and the different perspectives of patients and surrogates (including surrogates of deceased patients).

CONCLUSION

International physicians, nurses, patients and surrogates, generated a consensus-based framework to guide the process of decision-making on continuing or limiting life-sustaining treatments in the ICU. Early, frequent and scheduled family-meetings combined with a repeated multidisciplinary time-out meeting may support decisions in relation to patient preferences, prognosis and proportionality.

Acknowledgements

The authors would like to acknowledge all participants;

T. Aasmundstad, J. van den Akker, T.S. Andersen, A. Artigas, J. Benbenishty, D. Benoit, T. Boeter, V. Bosschem, E. Bull, J. Butler, A. Carneiro, G. Citerio, R. Curtis, C. Danbury, L. De Bus, P. Depuyt, B. Frommlett, A. Galazzi, L. Gale, R. Gerritsen, G Grasselli, C. Groeninx van Zoelen, E. Indseth, N. Latronico, A. Michalsen, J. Millo, L. Mavrommati, M. Mol, R. Moreno, S. Oeyen, F. Pais Silva, E. Picetti, D. Poole, P. Povoa, M. Reade, A. Robertsen, D. Tjan, M. Trout, F. Van Lierde, C. Verdonck and all patients and surrogate decision-makers.

REFERENCES

1. Rhodes A, Ferdinande P, Flaatten H, et al (2012) The variability of critical care bed numbers in Europe. Intensive Care Med 38:1647–1653. doi: 10.1007/s00134-012-2627-8
2. Mark NM, Rayner SG, Lee NJ, Curtis JR (2015) Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. Intensive Care Med 41:1572–1585. doi: 10.1007/s00134-015-3810-5
3. Sprung CL, Cohen SL, Sjokvist P, et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. doi: 10.1001/jama.290.6.790
4. Sprung CL, Ricou B, Hartog CS, et al (2019) Changes in End-of-Life Practices in European Intensive Care Units From 1999 to 2016. JAMA 322:1692–1704. doi: 10.1001/jama.2019.14608
5. Barnato AE, Tate JA, Rodriguez KL, et al (2012) Norms of decision making in the ICU: a case study of two academic medical centers at the extremes of end-of-life treatment intensity. Intensive Care Med 38:1886–1896. doi: 10.1007/s00134-012-2661-6
6. Piers RD, Azoulay E, Ricou B, et al (2011) Perceptions of appropriateness of care among European and Israeli intensive care unit nurses and physicians. JAMA 306:2694–2703. doi: 10.1001/jama.2011.1888
7. Prendergast TJ, Claessens MT, Luce JM (1998) A national survey of end-of-life care for critically ill patients. Am J Resp Crit Care Med 158:1163–1167. doi: 10.1164/ajrccm.158.4.9801108
8. Azoulay E, Metnitz B, Sprung CL, et al (2009) End-of-life practices in 282 intensive care units: data from the SAPS 3 database. Intensive Care Med 35:623–630. doi: 10.1007/s00134-008-1310-6
9. Benoit DD, Jensen HI, Malmgren J, et al (2018) Outcome in patients perceived as receiving excessive care across different ethical climates: a prospective study in 68 intensive care units in Europe and the USA. Intensive Care Med 44:1039–1049. doi: 10.1007/s00134-018-5231-8
10. Wilkinson DJC, Truog RD (2013) The luck of the draw: physician-related variability in end-of-life decision-making in intensive care. Intensive Care Med 39:1128–1132. doi: 10.1007/s00134-013-2871-6
11. Poulton B, Ridley S, Mackenzie-Ross R, Rizvi S (2005) Variation in end-of-life decision making between critical care consultants. Anaesthesia 60:1101–1105. doi: 10.1111/j.1365-2044.2005.04333.x
12. Wilson ME, Rhudy LM, Ballinger BA, et al (2013) Factors that contribute to physician variability in decisions to limit life support in the ICU: a qualitative study. Intensive Care Med 39:1009–1018. doi: 10.1007/s00134-013-2896-x
13. Kon AA, Davidson JE, Morrison W, et al (2016) Shared Decision-Making in Intensive Care Units. Executive Summary of the American College of Critical Care Medicine and American Thoracic Society Policy Statement. Am J Resp Crit Care Med 193:1334–1336. doi: 10.1164/rccm.201602-0269ED
14. Cook D, Rocker G, Marshall J, et al (2003) Withdrawal of mechanical ventilation in anticipation of death in the intensive care unit. N Engl J Med 349:1123–1132. doi: 10.1056/NEJMoa030083
15. Scheunemann LP, Cunningham TV, Arnold RM, et al (2015) How clinicians discuss critically ill patients' preferences and values with surrogates: an empirical analysis. Crit Care Med 43:757–764. doi: 10.1097/CCM.0000000000000772
16. Kerckhoffs MC, Kant M, van Delden JJM, et al (2019) Selecting and evaluating decision-making strategies in the intensive care unit: A systematic review. J Crit Care 51:39–45. doi: 10.1016/j.jcrc.2019.01.029
17. Piers RD, Azoulay E, Ricou B, et al (2014) Inappropriate care in European ICUs: confronting views from nurses and junior and senior physicians. Chest 146:267–275. doi: 10.1378/chest.14-0256
18. Stacey D, Légaré F, Col NF, et al (2014) Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 1:CD001431. doi: 10.1002/14651858.CD001431.pub4

19. Turnbull AE, Sepulveda KA, Dinglas VD, et al (2017) Core Domains for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. Crit Care Med 45:1001–1010. doi: 10.1097/CCM.0000000000002435
20. Needham DM, Sepulveda KA, Dinglas VD, et al (2017) Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. Am J Resp Crit Care Med 196:1122–1130. doi: 10.1164/rccm.201702-0372OC
21. Diamond IR, Grant RC, Feldman BM, et al (2014) Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 67:401–409. doi: 10.1016/j.jclinepi.2013.12.002
22. Jünger S, Payne SA, Brine J, et al (2017) Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. Palliat Med 31:684–706. doi: 10.1177/0269216317690685
23. Linstone HA, Turoff M (2002) The Delphi method: Techniques and applications.
24. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY
25. Chiarchiaro J, Buddadhumaruk P, Arnold RM, White DB (2015) Prior Advance Care Planning is Associated with Less Decisional Conflict in Surrogates for the Critically Ill. Ann Am Thorac Soc 150804122022007. doi: 10.1513/AnnalsATS.201504-253OC
26. Lautrette A, Darmon M, Megarbane B, et al (2007) A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med 356:469–478. doi: 10.1056/NEJMoa063446
27. Kodali S, Stametz RA, Bengier AC, et al (2014) Family experience with intensive care unit care: association of self-reported family conferences and family satisfaction. J Crit Care 29:641–644. doi: 10.1016/j.jcrc.2014.03.012
28. Heyland DK, Rocker GM, Dodek PM, et al (2002) Family satisfaction with care in the intensive care unit: Results of a multiple center study*. Crit Care Med 30:1413.
29. Majesko A, Hong SY, Weissfeld L, White DB (2012) Identifying family members who may struggle in the role of surrogate decision maker. Crit Care Med 40:2281–2286. doi: 10.1097/CCM.0b013e3182533317
30. Quenot JP, Rigaud JP, Prin S, et al (2012) Suffering among carers working in critical care can be reduced by an intensive communication strategy on end-of-life practices. Intensive Care Med 38:55–61. doi: 10.1007/s00134-011-2413-z
31. Chiarchiaro J, Ernecoff NC, Scheunemann LP, et al (2017) Physicians Rarely Elicit Critically Ill Patients' Previously Expressed Treatment Preferences in Intensive Care Units. Am J Resp Crit Care Med 196:242–245. doi: 10.1164/rccm.201611-2242LE
32. Scheunemann LP, Ernecoff NC, Buddadhumaruk P, et al (2019) Clinician-Family Communication About Patients' Values and Preferences in Intensive Care Units. JAMA Intern Med. doi: 10.1001/jamainternmed.2019.0027
33. Saposnik G, Redelmeier D, Ruff CC, Tobler PN (2016) Cognitive biases associated with medical decisions: a systematic review. BMC Med Inform Decis Mak 16:138. doi: 10.1186/s12911-016-0377-1
34. Stiegler MP, Ruskin KJ (2012) Decision-making and safety in anesthesiology. Current opinion in anaesthesiology 25:724–729. doi: 10.1097/ACO.0b013e328359307a
35. Kahneman D (2012) Thinking Fast and Slow Penguin. ISBN 9780141033570. 213:563–564. doi: 10.1192/bjp.2018.109
36. Braus N, Campbell TC, Kwekkeboom KL, et al (2016) Prospective study of a proactive palliative care rounding intervention in a medical ICU. Intensive Care Med 42:54–62. doi: 10.1007/s00134-015-4098-1
37. Aslakson R, Cheng J, Vollenweider D, et al (2014) Evidence-based palliative care in the intensive care unit: a systematic review of interventions. J Palliat Med 17:219–235. doi: 10.1089/jpm.2013.0409
38. Mercadante S, Gregoretti C, Cortegiani A (2018) Palliative care in intensive care units: why, where, what, who, when, how. BMC Anesthesiol 18:255.

39. Curtis JR, Treece PD, Nielsen EL, et al (2016) Randomized Trial of Communication Facilitators to Reduce Family Distress and Intensity of End-of-Life Care. Am J Resp Crit Care Med 193:154–162. doi: 10.1164/rccm.201505-0900OC
40. Sprung CL, Truog RD, Curtis JR, et al (2014) Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. Am J Resp Crit Care Med 190(8):855-66 doi: 10.1164/rccm.201403-0593CC

SUPPLEMENTAL MATERIAL

- Methods section, detailed
- Figure S1. The framework-draft presented in round one
- Figure S2. Detailed results on handling of each element during the Delphi process
- Table S1. Delphi expert panel, detailed characteristics
- Table S2. Detailed description consensus process per round, including statistical reporting

METHODS

Survey design

An online survey was designed based on an outline of decision-making steps ('elements') for which the participants were asked to specify the content through defining 'items', timing and contributors *(supplemental digital content Figure S1. framework-draft)*.

The survey consisted of statements (agree/don't agree and optional/mandatory) and questions using a seven point Likert-scale (seven is most positive). Open ended questions were included in the first and second round to maximize input. To assess stability of the results, after each round the opportunity was granted for comments on or disagreement with items which achieved consensus in the previous round.

The online survey was pilot-tested in eight experts, professionals and surrogate decision-makers, not participating in the Delphi study itself. The survey could be completed via a personal access-code ensuring single completion.

Patients and surrogate decision-makers received a paper copy (in English or Dutch) of the first round of the survey in laymen's terms with a pre-paid return-envelop. They were given the opportunity to reflect on the basic draft and encouraged to share their view on the decision-making process. It was pre-specified to involve them only in round one, to minimize the burden. To maximize their input, their survey was enriched with more open ended questions.

Round one aimed at getting insight into expert's views on the optimal ICU decision-making process. Evaluation focused on communication in the setting of family- and multidisciplinary meetings, gathering of information on background (approach and key components), health and quality of life, and the use of communication aids and tools (informational brochure, video and a communication preparation tool).

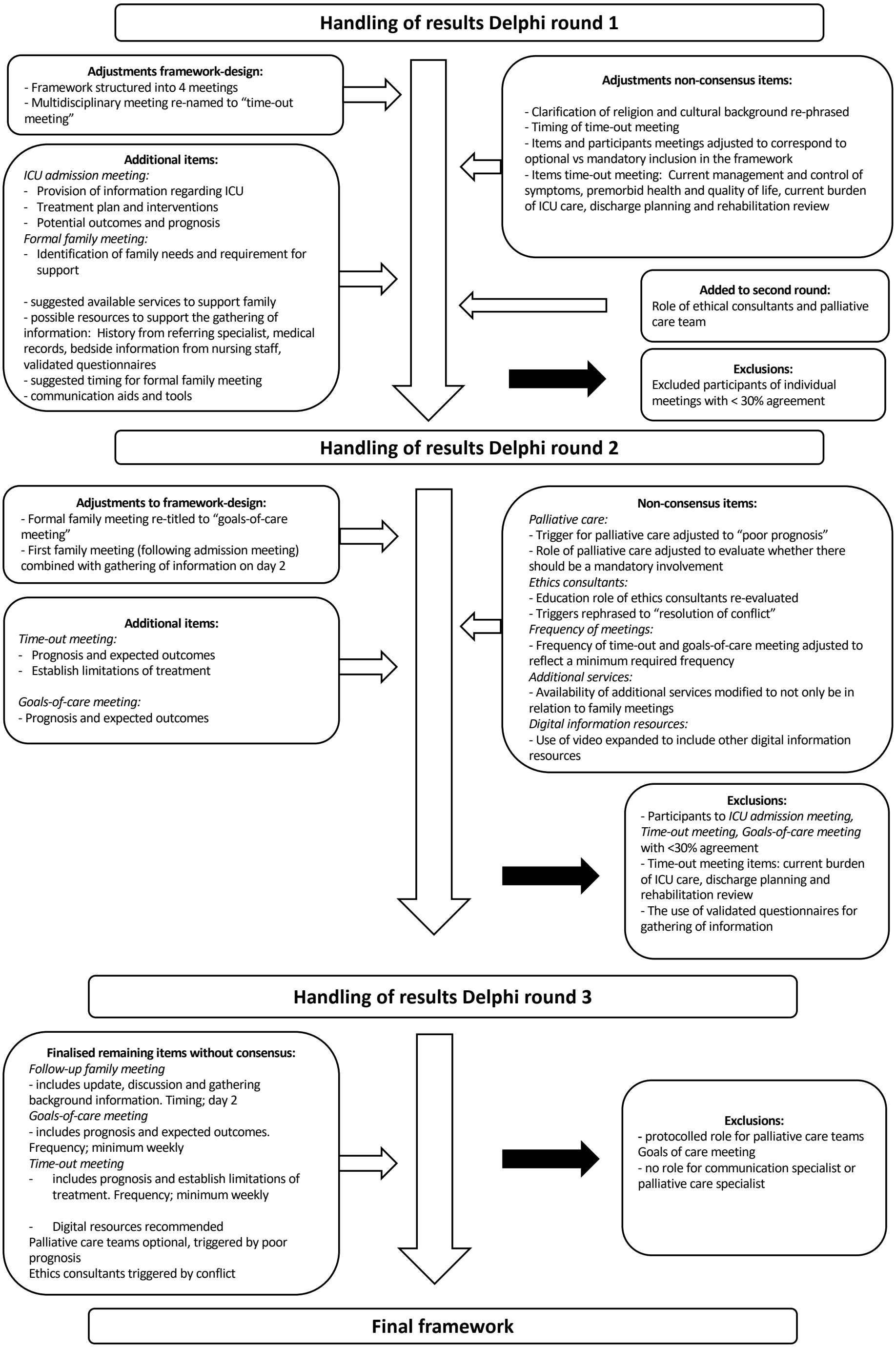
Importance and feasibility of each element were assessed. The suggested meetings were evaluated in terms of content, timing and participants.

During round two, the ICU physicians and nurses were provided the results and feedback from the first round, including the percentage agreement and mean Likert scores. Consensus items were presented to verify agreement with the suggestions. A revised version of items without consensus, as well as additional items based on recommendations, were presented for appraisal. Questions on the importance, feasibility, role and triggers to involve palliative care teams and ethics consultants were added.

During round three the aim was to reach final consensus on the content, timing and participants of each element included in the framework, as well as on suggested additional resources. The refined version of the decision-making framework, based on items that achieved consensus during previous rounds, was presented to the ICU physicians and nurses for feedback regarding usefulness and feasibility. Round three also finalized evaluation of items without consensus as well as additional recommendations that had been made by participants.

What and when	Who	Items
Admission meeting within 24 hours		**Update:** Current situation and disease/injury process **Identify:** Advance health directive and resuscitation status **Clarify:** Who is the surrogate decision maker
Information collection: Days 4/5 (informal)		**Background information:** Health before admission to hospital
Multidisciplinary meeting "Time-out" after 1 week  *Repeated weekly for long term patients*		**Update:** • Current status of illness • Burden of ICU treatment • Premorbid history • Resuscitation status and wishes **Identify:** Milestones **Clarify:** Treatment goals
Family meeting: Additional to multidisciplinary meeting *Repeated weekly for long term patients*		**Update:** Current situation **Identify:** Milestones **Clarify:** • Treatment plan • Goals of care

Figure S1. The framework-draft presented in round one



Handling of results Delphi round 1

Adjustments framework-design:
- Framework structured into 4 meetings
- Multidisciplinary meeting re-named to "time-out meeting"

Additional items:
ICU admission meeting:
- Provision of information regarding ICU
- Treatment plan and interventions
- Potential outcomes and prognosis

Formal family meeting:
- Identification of family needs and requirement for support

- suggested available services to support family
- possible resources to support the gathering of information: History from referring specialist, medical records, bedside information from nursing staff, validated questionnaires
- suggested timing for formal family meeting
- communication aids and tools

Adjustments non-consensus items:
- Clarification of religion and cultural background re-phrased
- Timing of time-out meeting
- Items and participants meetings adjusted to correspond to optional vs mandatory inclusion in the framework
- Items time-out meeting: Current management and control of symptoms, premorbid health and quality of life, current burden of ICU care, discharge planning and rehabilitation review

Added to second round:
Role of ethical consultants and palliative care team

Exclusions:
Excluded participants of individual meetings with < 30% agreement

Handling of results Delphi round 2

Adjustments to framework-design:
- Formal family meeting re-titled to "goals-of-care meeting"
- First family meeting (following admission meeting) combined with gathering of information on day 2

Additional items:
Time-out meeting:
- Prognosis and expected outcomes
- Establish limitations of treatment

Goals-of-care meeting:
- Prognosis and expected outcomes

Non-consensus items:
Palliative care:
- Trigger for palliative care adjusted to "poor prognosis"
- Role of palliative care adjusted to evaluate whether there should be a mandatory involvement

Ethics consultants:
- Education role of ethics consultants re-evaluated
- Triggers rephrased to "resolution of conflict"

Frequency of meetings:
- Frequency of time-out and goals-of-care meeting adjusted to reflect a minimum required frequency

Additional services:
- Availability of additional services modified to not only be in relation to family meetings

Digital information resources:
- Use of video expanded to include other digital information resources

Exclusions:
- Participants to *ICU admission meeting, Time-out meeting, Goals-of-care meeting* with <30% agreement
- Time-out meeting items: current burden of ICU care, discharge planning and rehabilitation review
- The use of validated questionnaires for gathering of information

Handling of results Delphi round 3

Finalised remaining items without consensus:
Follow-up family meeting
- includes update, discussion and gathering background information. Timing; day 2

Goals-of-care meeting
- includes prognosis and expected outcomes. Frequency; minimum weekly

Time-out meeting
- includes prognosis and establish limitations of treatment. Frequency; minimum weekly

- Digital resources recommended

Palliative care teams optional, triggered by poor prognosis
Ethics consultants triggered by conflict

Exclusions:
- protocolled role for palliative care teams Goals of care meeting
- no role for communication specialist or palliative care specialist

Final framework

Figure S2. Detailed results on handling of each element during the Delphi process

Characteristic	Intensivists			ICU nurses			Patients/surrogates	
Number invited	33			19			27	
Number of participants first round (%) *{Expert panel}*	28(85%)			12(63%)			12(44%)	
Number of expert panel who completed all three rounds (%)	27(96%)			7(58%)			*n/a*	
Country of origin	Invited	1st round {Expert panel}	Participated all 3 rounds (96.4%)	Invited	1st round {Expert panel}	Participated all 3 rounds (58%)	Invited	Participated
Australia	2(6%)	2(7%)	2(7.1%)	2(11%)	1(8%)	1(8%)	0(0%)	
Belgium	5(15%)	4(14%)	4(14.3%)	5(26%)	3(25%)	1(8%)	11(41%)	2(17%)
Denmark	1(3%)	1(4%)	1(3.6%)	1(5%)	0(0%)	0(0%)	0(0%)	
Germany	1(3%)	1(4%)	1(3.6%)	1(5%)	1(8%)	0(0%)	0(0%)	
Greece	0(0%)	0(0%)	0(0%)	1(5%)	1(8%)	1(8%)	0(0%)	
Israel	1(3%)	1(4%)	1(3.6%)	0(0%)	0(0%)	0(0%)	0(0%)	
Italy	6(18%)	5(18%)	5(17.9%)	1(5%)	1(8%)	0(0%)	0(0%)	
Netherlands	6(18%)	4(14%)	3(10.7%)	5(26%)	2(17%)	2(17%)	11(41%)	9(75%)
Norway	2(6%)	2(7%)	2(7.1%)	2(11%)	2(17%)	2(17%)	4(15%)	0(0%)
Portugal	5(15%)	4(14%)	4(14.3%)	0(0%)	0(0%)	0(0%)	0(0%)	
Spain	1(3%)	1(4%)	1(3.6%)	0(0%)	0(0%)	0(0%)	0(0%)	
United Kingdom	2(6%)	2(7%)	2(7.1%)	1(5%)	1(8%)	0(0%)	1(3%)	1(8%)
United States	1(3%)	1(4%)	1(3.6%)	0(0%)	0(0%)	0(0%)	0(0%)	
Gender*								
Male	20(74.1%)			2(16.7%)			Information not available	
Years of experience in ICU*							*n/a*	
< 10 years	3(11.1%)			1(8.3%)				
10-20 years	9(33.3%)			3(25%)				
> 20 years	15(55.6%)			8(66.7%)				
Current practice*							*n/a*	
Academic /Teaching Hospital	22(81.5%)			9(75%)				
District/General	4(14.8%)			3(25%)				
Private practice	1(3.7%)			0(0%)				
Characteristics of ICU* (*multiple options possible*)							*n/a*	
Mixed	22(81.5%)			8(66.7%)				
Medical	4(14.8%)			4(33.3%)				
Surgical	4(14.8%)			4(33.3%)				
Neuro	6(22.2%)			2(16.7%)				
Cardiothoracic	2(7.4%)			2(16.7%)				

Supplemental digital content; Table S1. Delphi expert panel, detailed characteristics

*Data missing for one intensivist participant. *ICU Intensive Care Unit n/a non-applicable*

	ICU Admission meeting					
	Agreement			Consensus per round		
				One	Two	Three
	Mean	Equimedian	IQR			
Importance	6.35	7	1	✓		
Feasibility	5.48	6	2	✓		
Items						
	Percentage agreement					
Update on current situation and disease/injury process	100%			✓		
Determine presence of pre-existing document patient preferences	89.75%			✓		
Clarify and determine current resuscitation status	94.25%			✓		
Identify and confirm surrogate decision-maker/ legal representative	90.1%			✓		
	Mean	**Equimedian**	**IQR**			
Provision of information regarding ICU	5.93	6	1	n/a	✓	
Treatment plan and interventions	6.17	6	1	n/a	✓	
Potential outcomes and prognosis	5.93	7	2	n/a	✓	
Who						
	Percentage agreement					
Intensivist	95.85%			✓		
ICU nurse	96.15%			✓		
ICU trainee	Optional 67.8%			X	X	
Referring specialist	Optional 61.5%			X	X	
Timing						
	Mean	**Equimedian**	**IQR**			
As soon as achievable within 24h	6.55	7	1	X	✓	

Table S2.1

Gathering of information on premorbid health and quality of life						
	Agreement			Consensus per round		
				One	Two	Three
	Mean	Equimedian	IQR			
Importance	6.50	7	1	✓		
Feasibility	5.53	6	2	✓		
Items						
	Percentage agreement					
Independence with activities of daily living	95.85%			✓		
Mobility	90.3%			✓		
Frailty	71.75%			✓		
Cognition	89.8%			✓		
Pain and discomfort on a daily basis	80.55%			✓		
Anxiety and depression on a daily basis	75%			✓		
Alcohol, drugs and smoking	72.7%			✓		
	Mean	Equimedian	IQR			
Religion and cultural background	5.07	6	3	X	✓	
Approach						
	Percentage agreement					
Meeting with intensivist, ICU nurse and family +/- patient	88.9%			X	✓	
	Mean	Equimedian	IQR			
Meeting to include update and discussion similar to admission meeting	5.78	6	1	*n/a*	*n/a*	✓
Additional approach/resources						
	Percentage agreement					
History from referring specialist	89.65%			*n/a*	✓	
Medical records	92.85%			*n/a*	✓	
Bedside information	82.5%			*n/a*	✓	
Validated questionnaires	31.05%			X	X	
	Mean	Equimedian	IQR			
General practitioner importance	5.49	6	3	✓		
Other consultants known to patient: importance	5.03	6	2	✓		
Timing						
Combine with first family meeting on day 2	5.84	6	2	X	X	✓

Table S2.2

	Goals-of-care meeting					
	Agreement			Consensus per round		
				One	Two	Three
	Mean	Equimedian	IQR			
Importance	6.37	7	1	✓		
Feasibility	5.96	7	1	✓		
Items						
	Percentage agreement					
Update on current status	97%			✓		
Discuss treatment plan	81.75%			✓		
Clarify goals of care plan	91.65%			✓		
Identify milestones to indicate progress or failure	92%			✓		
Clarify limitations of treatment	100%			✓		
	Mean	Equimedian	IQR			
Identification of family needs and requirement for support	5.75	6	2	*n/a*	✓	
Prognosis and expected outcomes	6.4	7	1	*n/a*	*n/a*	✓
Timing						
	Percentage agreement					
Pre-determined and at physician discretion	75.5%				✓	
	Mean	Equimedian	IQR			
Frequency: minimum weekly	6.33	7	1			✓
Who						
	Percentage agreement					
Intensivist	91.67%			✓		
Nursing staff	82.1%			✓		
Patient	80.1%			✓		
Surrogate decision-maker/ legal representative	95.85%			✓		
Extended family members	Optional 58.95%			X	X	
ICU trainee	Optional 75.7%			X	✓	
Referring specialist	Optional 79.3%			X	✓	
Additional services						
	Mean	Equimedian	IQR			
Recommended	6.05	6	2	*n/a*	X	✓
	Percentage agreement					
Social worker	78.95%			*n/a*	✓	
Religious support	84.5%			*n/a*	X	✓
Psychologist	82.45%			*n/a*	X	✓
Communication facilitator	58.6%			*n/a*	X	X
Palliative care specialist	41.4%			*n/a*	X	X

Table S2.3

Time-out meeting						
	Agreement			Consensus per round		
				One	Two	Three
	Mean	Equimedian	IQR			
Importance	6.31	7	1	✓		
Feasibility	5.33	6	3	✓		
Items						
	Percentage agreement					
Update on current clinical status	96.3%			✓		
Provision of information regarding premorbid health	84.65% (Mandatory inclusion)			X	✓	
Discuss patient preferences	90.3%			✓		
Establish/review resuscitation status	84.75%			✓		
Set treatment goals and milestones for evaluation	90.3%			✓		
Evaluate current burden of ICU care	68.55% (Mandatory inclusion)			X	X	
Evaluate effectiveness of symptom management	75.7% (Mandatory inclusion)			X	✓	
Discharge planning and rehab review	63.55% (Mandatory inclusion)			X	X	
	Mean	Equimedian	IQR			
Prognosis and expected outcomes	6.21	7	1	*n/a*	*n/a*	✓
Establish limitations of treatment	6.17	6	1	*n/a*	*n/a*	✓
Timing						
	Mean	Equimedian	IQR			
5 – 7 days after admission	5.46	6	3	X	✓	
Minimum frequency weekly	6.4	7	1	*n/a*	X	✓
Who						
	Percentage agreement					
Intensivist attending to patient	100%			✓		
Nursing staff	100%			✓		
Referring specialist	77.8%			✓		
Intensivists not attending to patient	70.7% (Optional)			X	✓	
Other specialists (not referring)	77.85% (Optional)			*n/a*	✓	
Physiotherapist	51.8% (Optional)			X	X	
Social worker	70.7% (Optional)			X	✓	

Table S2.4

Communication aids and tools						
	Agreement			Consensus per round		
				One	Two	Three
Information brochure						
	Percentage agreement					
Recommended in framework	98.2%			*n/a*	✓	
	Mean	Equimedian	IQR			
Feasibility	5.73	6	2	✓		
Communication preparation tool						
	Mean	Equimedian	IQR			
Recommended in framework	5.13	6	2	*n/a*	✓	
Feasibility	4.03	4	2	✓		
Digital information resources including video						
	Mean	Equimedian	IQR			
Recommended	4.53	4	3	*n/a*	*n/a*	✓
Feasibility	4.85	6	3	X	*n/a*	✓

Table S2.5

	Palliative care				
	Agreement			**Consensus per round**	
				Round two	**Round three**
	Mean	**Equimedian**	**IQR**		
Importance	4.5	5	3	✓	
Feasibility as an optional resource	5.26	6	3	X	✓
Protocolled role	3.39	4	4.25	X	X
Triggers:					
	Percentage agreement				
Futility	73.35%			✓	
	Mean	**Equimedian**	**IQR**		
Poor prognosis	4.42	5	3	X	✓

Table S2.6

Ethics consultants					
	Agreement			Consensus per round	
				Round two	Round three
	Mean	Equimedian	IQR		
Importance	4.56	5	3	✓	
Feasibility	4.22	5	4	✓	
Role:					
	Percentage agreement				
Resolution of conflict	76.4%			✓	
Advisory role ethics, policies, legal implications	88.2%			✓	
	Mean	**Equimedian**	**IQR**		
Education not included	4.22	4	3.5	X	✓
Trigger:					
Conflict not resolved through usual measures	5.65	6	1.5	X	✓

Table S2.7 Detailed description consensus process per round, including statistical reporting

7

The effect of a weekly 'time-out' meeting on length of stay and 90-day mortality in Intensive Care Unit patients

MC Kerckhoffs, SMA Dijkstra- Kersten, OL Cremer,
DW de Lange, AJC Slooter, JJM van Delden, D van Dijk

In preparation

ABSTRACT

Introduction Decision-making on life-sustaining treatments in the Intensive Care Unit (ICU) should be grounded in estimates on prognosis and patient preferences in order to prevent unwanted or disproportional treatments. To enhance their identification, we implemented a protocolised weekly multi-disciplinary time-out meeting, addressing the items of prognosis and preferences. We hypothesized that earlier identification of patients with a poor prognosis or non-goal-concordant care, would reduce ICU length-of-stay (LOS), without affecting 90-day mortality.

Methods This single center interventional before-after study was conducted in a university-affiliated ICU in the Netherlands, in which we implemented a decision-making framework that included questionnaires on pre-morbid health and patient preferences together with a weekly multi-disciplinary time-out meeting. All patients with an ICU LOS of ≥ 7 days were included. The primary outcome was the ICU LOS for patients who died within 90 days of admission. Secondary outcomes included ICU and hospital mortality and ICU LOS in survivors. We used multivariable analyses to adjust for age, SOFA score at day 7, and the number of co-morbidities.

Results In the before and after group, 478 respectively 381 patients were included, who were comparable at baseline, except that the after-group had significantly more-co-morbidities. Following the intervention, the ICU LOS for patients who died within 90 days increased (median 0 in both periods, IQR 0-7.1 versus IQR 0-10.6, p = .002). Hospital mortality was 115 (24.3%) and 112 (29.9%) (adjusted OR 1.32; 95% CI 0.85-2.06) and 90-day mortality 131 (27.6%) and 137 (36.6%) (adjusted OR 1.47; 95% CI 1.05-2.06) before and after the intervention, respectively. Length of stay in 90-day survivors remained similar (median 12.9 days, IQR 8.9-22.0 and 12.6 days, IQR 8.6-20.9).

Conclusion Implementation of a decision-making framework to address prognosis and preferences using a protocolised weekly time-out meeting, was associated with an increased ICU LOS for patients who died within 90 days and an increased mortality at day 90.

INTRODUCTION

In intensive care medicine, decision-making whether to continue, withhold or withdraw treatment is daily practice. For most patients, admitted to the intensive care unit (ICU) for only a few days, such decisions are straightforward. Most patients clearly benefit from ICU treatment, whereas in the minority it becomes apparent quite early that they will not survive. Some patients however, experience persistent organ failure necessitating a prolonged stay in the ICU [1-4]. In these patients, the process of decision-making is more complex and challenging. Previous studies have shown a persistent variability in the tendency to discuss and install treatment limitations between countries, within countries and even within a single ICU [5-11]. Avoiding decision-making, carries the risk of unjustified continuation of unlimited ICU treatment, and may result in disproportionate and non-beneficial ICU treatment, increased suffering and high health care consumption [12-14]. This can be harmful for the patient, the surrogates, health care workers and society [15-17].

Decision-making on restriction of life-sustaining treatments implies combining the anticipated prognosis with patient preferences in order to provide goal-concordant care, i.e. aligned with personal values and preferences regarding long-term outcome [18]. Prognostication in patients with a prolonged stay in the ICU is particularly important since they experience, on average, increased mortality and decreased functional recovery and quality of life [3, 19-28]. Factors that influence long-term outcome, like premorbid health, co-morbidities, frailty and quality of life should therefore be addressed [20, 29-34].

Patient values and preferences, including goals concerning functional outcomes, have to be elicited from the beginning of ICU treatment onwards in order to provide goal-concordant care [22, 35]. In current practice, even in patients with a high risk of death, preferences are only discussed in one third of family conversations [36-38]. Unknown patients preferences and uncertain long-term outcomes, can be reasons for the clinician to refrain from initiating the discussion whether unrestricted ICU treatment is still appropriate [39, 40]. Communication interventions aimed at surrogate decision-makers might, on the contrary, enhance decision-making and reduce ICU LOS for patients with a poor prognosis [41, 42]. An optimal decision-making process on continuing or restricting ICU treatment, therefore requires that the discussion is initiated, that prognostic factors are addressed and that patient preferences are elicited and integrated in the discussion with surrogate decision-makers. In addition, the process should reduce arbitrariness and cognitive biases trough deliberate consideration with colleagues and the use of tools like checklists [43-45].

We developed a decision-making framework consisting of a weekly multi-disciplinary time-out meeting, addressing the items of prognosis and patient preferences in a standardized format. We hypothesized that with introducing weekly goals-of-care discussions, patients with a poor prognosis or non-goal-concordant care would be identified earlier, leading to a reduction of ICU LOS for patients with a poor prognosis, without an effect on 90-day mortality.

METHODS

Study design and setting

This single center pragmatic interventional before-after study was conducted in the ICU of a university affiliated referral center and teaching hospital in the Netherlands (University Medical Center Utrecht). This is an adult, mixed ICU with approximately 2200 admissions annually, including medical patients and cardiac, neuro, trauma, gastro-intestinal and transplant surgery. The institutional review board of the University Medical Center Utrecht waived the need for approval (protocol number 19/664).

Intervention

A decision-making framework was introduced January 2017 (figure 1). This consisted of the following components. Firstly, after four days in the ICU, the nurse handed out a set of surveys to surrogates of the patient to evaluate pre-morbid health related quality of life (using the EQ5D-3L questionnaire [46, 47]), functional (in)dependence (using the Barthel questionnaire [48]) and frailty (using the Clinical Frailty Scale (CSF) [29]). Resulting health indexes were entered into the electronic health record. On day 7, the general practitioner (GP) was consulted by telephone for additional information on pre-morbid functioning and to verify the existence of advance directives or known treatment preferences. Second, on the first weekday following 7 days of ICU admission, a 10-minute time slot was reserved for a 'time-out' during the daily multi-disciplinary meeting. The time-out describes a protocolised assessment of the patient and requires physicians to formally decide to continue, limit or withdraw ICU treatments based on input in four categories; 1) current medical situation. This included the severity of suffering as perceived and documented by the nursing staff, and quantified with a number from 0 to 4 (4 being worst score), 2) pre-morbid health scores for HRQoL, functional (in)dependence and frailty, 3) additional information from the GP included existing advance directives/advance care planning, 4) estimated prognosis in terms of survival and quality of life. The discussion was concluded with the determination of treatment goals, including possible limitations of care. The conclusion was noted in the electronic health record and a family-meeting was planned to discuss and finalize goals-of-care and treatment limitations.

The time-out meeting is attended by at least five senior ICU consultants, several registrars and trainees, consultants and the responsible ICU nurse. A physician's suggestion to withdraw treatment, required consensus from all physicians present before discussing it with surrogates. After the first time-out meeting, an ICU physician was assigned to be the contact-person for the family. To ensure continuity in the decision-making process, this physician was preferably involved in subsequent time-out meetings, that were repeated weekly.

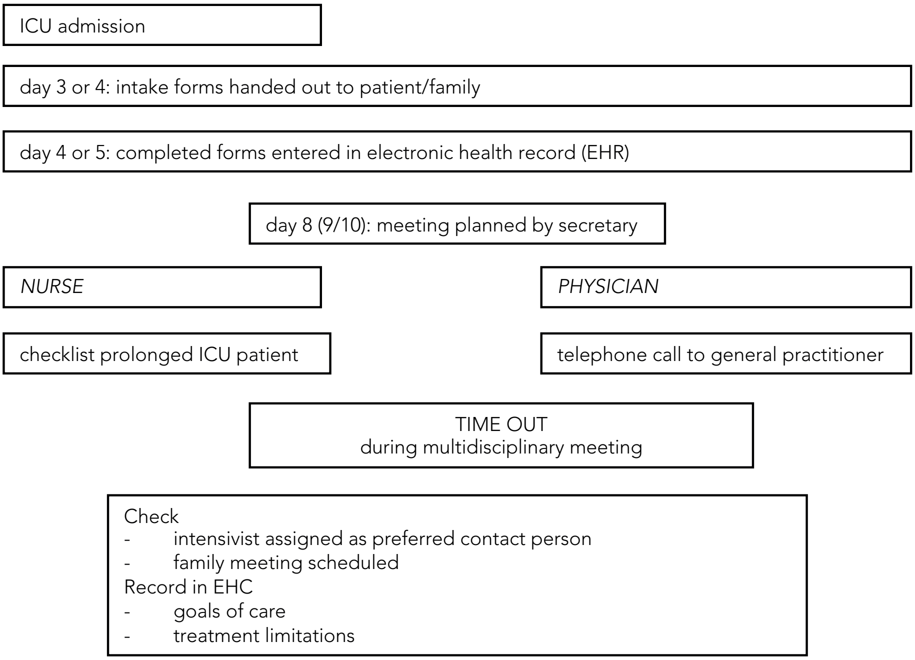


Figure 1. Decision-making framework as introduced in 2017

Participants

All patients who had an ICU admission of at least 7 consecutive days (index admission) were included. Patients were excluded if under 16 years of age, not traceable through the municipal registry or if they opted out for participation in scientific studies.

Outcome variables

The primary outcome measure of this study was the ICU LOS for patients who died within 90 days after ICU admission, in the tables referred to as 'hypothetically non-beneficial ICU days'. For all patients who survived 90-days after ICU admission, this was set to zero. In case of a readmission within 90 days, all days spent in the ICU were summed.

Secondary outcomes were ICU mortality, hospital mortality, length of ICU stay, number of family meetings and treatment limitations during ICU admission.

Data source and management

Baseline characteristics were collected through the electronic health record, date of death trough the Dutch municipal population register. We used observation windows of 18 months both before and after the intervention, following exclusion of all data that were collected during the 6-month period immediately surrounding implementation.

Baseline patient characteristics included age, sex, co-morbidities (categorized as 0/1/2 or more) and admission characteristics (type of admission, APACHE IV score). Disease severity was described with the SOFA on day 7. The number of family meetings and treatment limitations during admission were recorded. To measure exposure to the intervention, we assessed the electronic health record for the questionnaires and reported if the time-out meeting recorded.

Statistical analysis

Baseline characteristics were compared between the phase before and after implementation of the intervention by chi-square test for categorical data, independent t-test for normally distributed data, and Mann-Whitney U for non-normally distributed data.

The primary and secondary outcomes in the pre- and post-intervention phases were first compared by an independent t-test, Mann-Whitney U test or chi square test, where appropriate. Second, to correct for differences in admission characteristics, the effect of the intervention on ICU mortality, hospital mortality, and 90-day mortality was examined by logistic regression analyses and adjusted for age, SOFA score at day 7, and number of comorbidities. Third, the median (IQR) number of 'hypothetically non-beneficial' ICU days, median (IQR) ICU length of stay, mortality rates, and patient characteristics were plotted for each 3-months period to display trends that had already set in before the intervention was commenced and to assess the stability of the effect over time.

We conducted two sensitivity analyses for the primary endpoint. The 'hypothetically non-beneficial' ICU days were set to 90 days, opposed to 0 days, for a) patients who died in the ICU after 90 days, and b) patients who were still admitted in the ICU after 90 days. We performed a post-hoc analysis with the exclusion of patients admitted directly after heart- or lung-transplantation. Time series analyses were performed to assess temporal trends.

All statistical analyses were performed using SPSS version 25 [49]. A p-value < .05 (two-sided) was considered statistically significant.

RESULTS

We studied 478 and 381 patients having an ICU admission of >7 days during the 18-month observation window before and after implementation of the decision-making framework, respectively. These included patients represented 18% and 14.7% of total ICU admissions during that time period. Eleven patients (respectively 4 and 7) were not in the municipal registry and therefore excluded, leaving 474 ('before cohort') and 374 ('after cohort') patients for analysis. Missing mortality was not related to the intervention phase. In the intervention phase, the questionnaires were reported in 77% of patients' electronic health records. In 60% of patients, the intervention was mentioned in the electronic health record.

The baseline characteristics of the patients are shown in table 1. Patients were comparable in age, type of admission and severity of illness in the before and after phase, but the after group had significantly more comorbidities (p = 0.003). The supplemental data file shows characteristics in three-month time-intervals (Supplemental figures S1-S3).

The median number of 'hypothetically non-beneficial' ICU days increased significantly after the intervention, from 0.0 (IQR 0-7.1) to 0.0 (IQR 0-10.6) (p = .002) (Table 2). Comparable results were found in the two planned sensitivity analyses and the post-hoc analysis.

Baseline characteristics of ICU patients admitted ≥ 7 days	Before N = 474	After N = 374	P value
Age, mean (SD)	57.8 (15.6)	59.7 (15.0)	.063
Male, n (%)	314 (66.2%)	258 (69.0%)	.398
APACHE III score, mean (SD)	71.5 (26.5)	73.5 (24.8)	.294
Days with mechanical ventilation (med, IQR)	11 (8-19)	11 (8-17)	.637
Type of admission, n (%)			.286
Medical	266 (56.1%)	210 (56.3%)	
Acute surgery	140 (29.5%)	122 (32.7%)	
Elective surgery	68 (14.3%)	41 (11.0%)	
Number of comorbidities, n (%)			.003*
0	238 (50.2%)	146 (39.0%)	
1	124 (26.2%)	132 (35.3%)	
≥2	112 (23.6%)	96 (25.7%)	
SOFA score day 7, mean (SD)	6.6 (3.6)	6.8 (3.7)	.340
Highest SOFA score, mean (SD)	10.6 (3.7)	10.8 (3.5)	.417

Table 1. Baseline characteristics

SD standard deviation, APACHE Acute Physiology And Chronic Health Evaluation, IQR Inter Quartile Range, SOFA Severity of Organ Failure

In a per-protocol analysis, the patients with documented exposure to the intervention had more 'hypothetically non-beneficial' ICU treatment days, a higher 90 day-mortality, more family meetings and a longer ICU LOS (supplemental table S2).

The 90-day mortality differed significantly between the two phases (131 (27.6%) and 137 (36.6%) respectively, p = .005). There was no difference in ICU mortality, hospital mortality or in the length of stay in the ICU in the two phases (table 2). In the supplemental data, figures show the outcomes in three-month time-intervals (supplemental figure S4-S7).

The odds ratios for ICU and hospital-mortality after the intervention were 1.42 (0.96-2.11) and 1.38 (0.99-1.92) and the adjusted odds ratios respectively 1.32 (95% CI 0.85-2.06) and 1.29 (95% CI 0.89-1.85), which were not statistically significant (table 3). For 90-day mortality the unadjusted OR was 1.55 (1.14-2.13) and the adjusted OR 1.47 (95%

CI 1.05-2.06) which remained to differ significantly between the intervention phases (p = .026).

After the implementation of the decision-making framework, more patients received treatment limitations (18.2% versus 14.1%, p = .060), only comfort care (17.4% versus 14.3%, p = .060) or were discharged with anticipated death during hospital admission (8.8% versus 5.7%, p < .001). Post-hoc logistic regression analyses showed that these differences remained significant after correction for differences in prognostic characteristics (SOFA at day 7, number of comorbidities, and age). After the implementation of the decision-making framework, more family meetings per patient were reported (median 4, IQR 2-6 versus median 4, IQR 2-7, p = .013). Post-hoc logistic regression analyses showed that this difference was not explained by the differences in prognostic characteristics between the two phases (5% decrease in regression coefficient).

Outcome variable	Before N = 474	After N = 374	P value
'hypothetically non-beneficial' ICU days, median (IQR)	0.0 (0.0 - 7.1)	0.0 (0.0 - 10.6)	.002*
ICU mortality	77 (16.2%)	74 (19.8%)	.181
Hospital mortality	115 (24.3%)	112 (29.9%)	.063
90-day mortality after ICU admission	131 (27.6%)	137 (36.6%)	.005*
ICU LOS all patients, median (IQR)	12.7 (8.9-20.6)	12.8 (9.0-21.9)	.796
ICU LOS for patients who died in ICU, median (IQR)	12.6 (8.2 – 23.4)	14.5 (11.0 -25.0)	.118
ICU LOS 90-day survivors, median (IQR)	12.9 (8.9-22.0)	12.6 (8.6-20.9)	.415
Documented family conversations per patient, median (IQR)	4 (2 - 6)	4 (2 - 7)	.013*
Patients with treatment limitations (n, %)	67 (14.1%)	68 (18.2%)	.060*
Patients with comfort care only (n, %)	68 (14.3%)	65 (17.4%)	.060*

Table 2. Primary and secondary outcomes

ICU Intensive Care Unit, *IQR* interquartile range, *LOS* Length of Stay

Mortality	Crude OR	95% CI	p-value	Adjusted OR[1]	95% CI	p-value
ICU	1.42	0.96 to 2.11	.083	1.32	0.85 to 2.06	.212
Hospital	1.38	0.99 to 1.92	.059	1.29	0.89 to 1.85	.171
90 day	1.55	1.14 to 2.13	.006*	1.47	1.05 to 2.06	.026*

Table 3. Odds ratio's for mortality following the implementation of the intervention

[1]Adjusted for prognostic differences (age, SOFA day 7, comorbidities)
OR odds ratios, *CI* Confidence Interval, *ICU* Intensive Care Unit

DISCUSSION

In this single-center before-after study, we found that the implementation of a decision-making framework addressing the items of prognosis and preferences within a weekly multi-disciplinary time-out meeting was associated with an increased ICU LOS for patients who died within 90 days of ICU admission.

This unexpected finding may illustrate that decisions to limit life support were postponed, resulting in a longer continuation of ICU treatments in patients who die within 90 days of ICU admission, than was previously common. This could be explained by multiple factors. The intervention prompted physicians to include pre-morbid health, quality of life and patient preferences in decisions concerning life-sustaining ICU treatments. Increased understanding of the patient might have encouraged physicians to promote continuation of care. Also, a methodically addressed prognosis, might provide a more optimistic prognostic outlook than professional expertise would have suggested in the phase before the decision-making framework was implemented. In addition, having a weekly evaluation planned, may have prevented other physicians to initiate ad hoc discussions on the appropriateness to continue life-sustaining treatments. Moreover, assigning an ICU physician as contact-person for the family gives an emotional connection that could cause an escalation of commitment [50, 51]. This concept describes the tendency to allow previous investments to influence future decisions [52]. A tendency to postpone decisions to forego life support, may have started already in the first week of ICU admission, because the mortality of patients with an admission shorter than 7 days was lower in the period after implementing the intervention, whereas the mortality of the study population (patients admitted for at least 7 days) increased. The mortality of all patients together (with ICU LOS shorter and longer than 7 days) remained similar in the two study periods (supplemental data table S1).

The changed role of families in eliciting preferences and defining goals of care during family meetings, could also have added to a longer continuation of ICU treatment, either because care became better aligned with preferences, or because a poor prognosis was insufficiently disclosed during the shared-decision-making process. The poor prognosis was reflected by a significantly higher post-discharge (90-day) mortality, probably since these ICU survivors may not have had the physiological reserve to survive the first months after discharge.

Residual confounding is another explanation. It is known that long-term mortality is mostly influenced by pre-morbid health [20, 29-34]. Although the patients in the two phases differed significantly in their number of co-morbidities, the mortality-risk remained statistically significant higher after adjusting for the number of co-morbidities. The sensitivity analysis excluding post-transplant patients, neither explained the difference. However, we could have missed confounding factors. In the after group, patients could have been more frail, a multidimensional syndrome describing reduced physiological reserves, poorly reflected by comorbidities only and known to be associated with a worse long-term prognosis [29, 53, 54]. In addition, a change in ICU team composition, a decreased ward capacity to admit ICU patients and a different selection of surgical patients could also have influenced outcomes.

In this study, we defined our primary outcome as a reduction of days in the ICU for patients who die within 90 days, based on previous research [55]. In this definition, our study results are negative. However, it remains an individual consideration whether ICU care is non-beneficial, even in patients with a poor prognosis. Non-beneficial ICU care from a patient perspective, would be ICU care where the burden outweighs benefits or that is unable to reach future goals, i.e. is non goal-concordant [14, 18, 56]. Although we found that in 60% of patients the 'time-out' meeting was reported in the electronic health record, we are not informed about the extent to which ICU treatments were aligned with patients' goals. The intervention could have had a positive effect on goal-concordant care, even in patients for whom an ICU admission ultimately resulted in death at 90-days.

Future directions

Although the intervention had other effects than anticipated, there is broad consensus that the burden and benefits of ICU care should be repeatedly evaluated during admission [22, 35]. Our framework was designed to ensure that ICU physicians at least weekly evaluate prognosis, proportionality and patient preferences within their multidisciplinary team. Modifications of the used decision-making framework, for example with regard to timing, frequency and patient/surrogate participation may change its effects. The time-out meeting could be planned as soon as all relevant information that influences (long-term) prognosis is available instead of reserving it for patient with a LOS of 7 days. Waiving the need for unanimous consensus to withdraw treatments, could reduce the weight of the opinion to continue treatment and improve balanced decision-making. In addition, a weekly meeting might not be capable to capture the changing prognosis and understanding of prognosis that occurs with critically ill patients. More flexibility concerning the repeated time-out meeting could be considered. Finally, the decision-making framework primarily intended to support ICU physicians in their decision-making process. Although patient preferences were collected and addressed within the time-out meeting, the role of patients or surrogate decision-makers during subsequent family meeting was not described in the intervention. To be able to provide ICU care that is aligned with patient-preferences, the goal-of-care meeting with the patient or surrogates should be explicitly addressed in future interventions.

Future research should include the assessment of goal-concordance of ICU care as an outcome measure. Although this assessment is difficult, reviewing patient records, evaluate the quality of serious illness communication and include a post-discharge assessment of perceived goal-concordant care in a qualitative study, can enhance the understanding of how a decision-making framework can support goal-concordant decision-making [57].

Strengths and limitations

Strengths of this study are firstly that by protocol treatment decisions were made by multiple physicians and withdrawal of treatment required consensus from all physicians present. In previous outcome studies, the treating physicians may be regarded as a confounder by introducing physician related factors concerning decision-making [11, 40, 63]. Secondly, relating ‘hypothetically non-beneficial’ ICU days to 90-day mortality is more relevant than ICU or hospital mortality since a large portion of mortality occurs in the first months after discharge [25]. Thirdly, using the same time-frame in the before and after phase minimized the effect of seasonal influences on admission diagnosis.

This study also holds limitations. Firstly, this was a single-center study in the Netherlands, which impedes generalizability to ICUs around the world where shared decision-making is already more common than paternalistic decision-making. Secondly, the before-after design may have introduced unknown confounding since patients may differ in various time-periods. Thirdly, we were not informed about the actual number of conducted time-out meetings since we had to use the note in the electronic health record as a surrogate. If 60% is the correct percentage of patients who received the intervention, then the adherence to the protocol was relatively low since in 77% of patients the questionnaires on pre-morbid health were reported.

CONCLUSION

The use of a decision-making framework addressing the items of prognosis and preferences within a weekly repeated multi-disciplinary time-out meeting, was unable to reduce the ICU length of stay for patients who died within 90 days of ICU admission. With comparable ICU and hospital mortality, the 90-day mortality increased. Further studies have to address goal-concordant care in addition to mortality, to fully comprehend the effect of the intervention from a patient perspective.

REFERENCES

1. Kahn JM, Le T, Angus DC, et al (2015) The epidemiology of chronic critical Illness in the United States. Crit Care Med 43:282–287. doi: 10.1097/CCM.0000000000000710
2. Yearbook Stichting NICE 2018. http://www.stichting-nice.nl/doc/jaarboek-2018-web.pdf. accessed November 2019
3. Iwashyna TJ, Hodgson CL, Pilcher D, et al (2016) Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. Lancet Respir Med 4:566–573. doi: 10.1016/S2213-2600(16)30098-4
4. Bagshaw SM, Stelfox HT, Iwashyna TJ, et al (2018) Timing of onset of persistent critical illness: a multi-centre retrospective cohort study. Intensive Care Med 182:446–11. doi: 10.1007/s00134-018-5440-1
5. Sprung CL, Cohen SL, Sjokvist P, et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. doi: 10.1001/jama.290.6.790
6. Sprung CL, Ricou B, Hartog CS, et al (2019) Changes in End-of-Life Practices in European Intensive Care Units From 1999 to 2016. JAMA 322:1692–1704. doi: 10.1001/jama.2019.14608
7. Mark NM, Rayner SG, Lee NJ, Curtis JR (2015) Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. Intensive Care Med 41:1572–1585. doi: 10.1007/s00134-015-3810-5
8. Piers RD, Azoulay E, Ricou B, et al (2011) Perceptions of appropriateness of care among European and Israeli intensive care unit nurses and physicians. JAMA 306:2694–2703. doi: 10.1001/jama.2011.1888
9. Schenker Y, Tiver GA, Hong SY, White DB (2012) Association between physicians' beliefs and the option of comfort care for critically ill patients. Intensive Care Med 38:1607–1615. doi: 10.1007/s00134-012-2671-4
10. Guidet B, Flaatten H, Boumendil A, et al (2018) Withholding or withdrawing of life-sustaining therapy in older adults (≥ 80 years) admitted to the intensive care unit. Intensive Care Med 44:1027–1038. doi: 10.1007/s00134-018-5196-7
11. Kerlin MP, Epstein A, Kahn JM, et al (2018) Physician-Level Variation in Outcomes of Mechanically Ventilated Patients. Ann Am Thorac Soc 15:371–379. doi: 10.1513/AnnalsATS.201711-867OC
12. Wintermann G-B, Weidner K, Strauß B, et al (2016) Predictors of posttraumatic stress and quality of life in family members of chronically critically ill patients after intensive care. Ann Intensive Care 6:69. doi: 10.1186/s13613-016-0174-0
13. Cameron JI, Chu LM, Matté A, et al (2016) One-Year Outcomes in Caregivers of Critically Ill Patients. NEJM 374:1831–1841. doi: 10.1056/NEJMoa1511160
14. Huynh TN, Kleerup EC, Wiley JF, et al (2013) The frequency and cost of treatment perceived to be futile in critical care. JAMA Intern Med 173:1887–1894. doi: 10.1001/jamainternmed.2013.10261
15. Piers RD, Azoulay E, Ricou B, et al (2014) Inappropriate care in European ICUs: confronting views from nurses and junior and senior physicians. Chest 146:267–275. doi: 10.1378/chest.14-0256
16. Lambden JP, Chamberlin P, Kozlov E, et al (2018) Association of Perceived Futile or Potentially Inappropriate Care With Burnout and Thoughts of Quitting Among Health-Care Providers. Am J Hosp Palliat Care 36:1049909118792517–206. doi: 10.1177/1049909118792517
17. Chamberlin P, Lambden J, Kozlov E, et al (2019) Clinicians' Perceptions of Futile or Potentially Inappropriate Care and Associations with Avoidant Behaviors and Burnout. J Palliat Med 22:1039–1045. doi: 10.1089/jpm.2018.0385
18. Turnbull AE, Hartog CS (2017) Goal-concordant care in the ICU: a conceptual framework for future research. Intensive Care Med 43:1847–1849. doi: 10.1007/s00134-017-4873-2
19. Hill AD, Fowler RA, Pinto R, et al (2016) Long-term outcomes and healthcare utilization following critical illness – a population-based study. Critical Care 2016 20:1 20:76. doi: 10.1186/s13054-016-1248-y

20. Szakmany T, Walters AM, Pugh R, et al (2019) Risk Factors for 1-Year Mortality and Hospital Utilization Patterns in Critical Care Survivors: A Retrospective, Observational, Population-Based Data Linkage Study. Crit Care Med 47:15–22. doi: 10.1097/CCM.0000000000003424
21. Wunsch H, Guerra C, Barnato AE, et al (2010) Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA 303:849–856. doi: 10.1001/jama.2010.216
22. Dinglas VD, Chessare CM, Davis WE, et al (2018) Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. Thorax 73:7–12. doi: 10.1136/thoraxjnl-2017-210234
23. Williams TA, Dobb GJ, Finn JC, et al (2008) Determinants of long-term survival after intensive care. Crit Care Med 36:1523–1530. doi: 10.1097/CCM.0b013e318170a405
24. Reardon PM, Fernando SM, Van Katwyk S, et al (2018) Characteristics, Outcomes, and Cost Patterns of High-Cost Patients in the Intensive Care Unit. Crit Care Res Pract 2018:5452683–7. doi: 10.1155/2018/5452683
25. Brinkman S, de Jonge E, Abu-Hanna A, et al (2013) Mortality after hospital discharge in ICU patients. Crit Care Med 41:1229–1236. doi: 10.1097/CCM.0b013e31827ca4e1
26. Keenan SP, Dodek P, Chan K, et al (2002) Intensive care unit admission has minimal impact on long-term mortality. Crit Care Med 30:501–507.
27. Gardner AK, Ghita GL, Wang Z, et al (2019) The Development of Chronic Critical Illness Determines Physical Function, Quality of Life, and Long-Term Survival Among Early Survivors of Sepsis in Surgical ICUs*. Crit Care Med 47:566–573. doi: 10.1097/CCM.0000000000003655
28. Brown SM, Wilson E, Presson AP, et al (2017) Predictors of 6-month health utility outcomes in survivors of acute respiratory distress syndrome. Thorax 72:311–317. doi: 10.1136/thoraxjnl-2016-208560
29. Muscedere J, Waters B, Varambally A, et al (2017) The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med 43:1105–1122. doi: 10.1007/s00134-017-4867-0
30. Lone NI, Gillies MA, Haddow C, et al (2016) Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. Am J Resp Crit Care Med 194:198–208. doi: 10.1164/rccm.201511-2234OC
31. Ferrante LE, Pisani MA, Murphy TE, et al (2016) Factors Associated with Functional Recovery among Older Intensive Care Unit Survivors. Am J Resp Crit Care Med 194:299–307. doi: 10.1164/rccm.201506-1256OC
32. Bagshaw SM, Stelfox HT, Johnson JA, et al (2015) Long-term association between frailty and health-related quality of life among survivors of critical illness: a prospective multicenter cohort study. Crit Care Med 43:973–982. doi: 10.1097/CCM.0000000000000860
33. Gayat E, Cariou A, Deye N, et al (2018) Determinants of long-term outcome in ICU survivors: Results from the FROG-ICU study. Crit Care 22:8. doi: 10.1186/s13054-017-1922-8
34. Oeyen S, Vermeulen K, Benoit D, et al (2018) Development of a prediction model for long-term quality of life in critically ill patients. J Crit Care 43:133–138. doi: 10.1016/j.jcrc.2017.09.006
35. Turnbull AE, Sepulveda KA, Dinglas VD, et al (2017) Core Domains for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. Crit Care Med 45:1001–1010. doi: 10.1097/CCM.0000000000002435
36. Scheunemann LP, Cunningham TV, Arnold RM, et al (2015) How clinicians discuss critically ill patients' preferences and values with surrogates: an empirical analysis. Crit Care Med 43:757–764. doi: 10.1097/CCM.0000000000000772
37. Scheunemann LP, Ernecoff NC, Buddadhumaruk P, et al (2019) Clinician-Family Communication About Patients' Values and Preferences in Intensive Care Units. JAMA Intern Med. doi: 10.1001/jamainternmed.2019.0027
38. Douglas SL, Daly BJ, Lipson AR (2012) Neglect of quality-of-life considerations in intensive care unit family meetings for long-stay intensive care unit patients. Crit Care Med 40:461–467. doi: 10.1097/CCM.0b013e318232d8c4

39. Turnbull AE, Davis WE, Needham DM, et al (2016) Intensivist-reported Facilitators and Barriers to Discussing Post-Discharge Outcomes with Intensive Care Unit Surrogates. A Qualitative Study. Ann Am Thorac Soc 13:1546–1552. doi: 10.1513/AnnalsATS.201603-212OC
40. Visser M, Deliens L, Houttekier D (2014) Physician-related barriers to communication and patient- and family-centred decision-making towards the end of life in intensive care: a systematic review. Crit Care 18:604. doi: 10.1186/s13054-014-0604-z
41. Lee HW, Park Y, Jang EJ, Lee YJ (2019) Intensive care unit length of stay is reduced by protocolized family support intervention: a systematic review and meta-analysis. Intensive Care Med 45:1072–1081. doi: 10.1007/s00134-019-05681-3
42. Bibas L, Peretz-Larochelle M, Adhikari NK, et al (2019) Association of Surrogate Decision-making Interventions for Critically Ill Adults with Patient, Family, and Resource Use Outcomes: A Systematic Review and Meta-analysis. JAMA Netw Open 2:e197229–e197229. doi: 10.1001/jamanetworkopen.2019.7229
43. Ely JW, Graber ML, Croskerry P (2011) Checklists to reduce diagnostic errors. Acad Med 86:307–313. doi: 10.1097/ACM.0b013e31820824cd
44. Turnbull AE, Krall JR, Ruhl AP, et al (2014) A scenario-based, randomized trial of patient values and functional prognosis on intensivist intent to discuss withdrawing life support. Crit Care Med 42:1455–1462. doi: 10.1097/CCM.0000000000000227
45. Graber ML, Kissam S, Payne VL, et al (2012) Cognitive interventions to reduce diagnostic error: a narrative review. BMJ Qual Saf 21:535–557. doi: 10.1136/bmjqs-2011-000149
46. Rabin R, Gudex C, Selai C, Herdman M (2014) From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health 17:70–76. doi: 10.1016/j.jval.2013.10.006
47. Lamers LM, McDonnell J, Stalmeier PFM, et al (2006) The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ 15:1121–1132. doi: 10.1002/hec.1124
48. Mahony FI, Barthel DW, (1965) Functional Evaluation: the Barthel Index. Md State Med J 14:61-65.
49. IBM Corp. (2017) IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY
50. Gunia BC, Sivanathan N, Galinsky AD (2009) Vicarious entrapment: Your sunk costs, my escalation of commitment. Journal of Experimental Social Psychology 45:1238–1244. doi: 10.1016/j.jesp.2009.07.004
51. Braxton CC, Robinson CN, Awad SS (2017) Escalation of Commitment in the Surgical ICU. Crit Care Med 45:e433–e436. doi: 10.1097/CCM.0000000000002261
52. Bornstein BH, Emler AC (2001) Rationality in medical decision making: a review of the literature on doctors’ decision-making biases. J Eval Clin Pract 7:97–107.
53. Bagshaw M, Majumdar SR, Rolfson DB, et al (2016) A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care 20:175. doi: 10.1186/s13054-016-1338-x
54. Brummel NE, Bell SP, Girard TD, et al (2017) Frailty and Subsequent Disability and Mortality among Patients with Critical Illness. Am J Resp Crit Care Med 196:64–72. doi: 10.1164/rccm.201605-0939OC
55. Kerckhoffs MC, Kant M, van Delden JJM, et al (2019) Selecting and evaluating decision-making strategies in the intensive care unit: A systematic review. J Crit Care 51:39–45. doi: 10.1016/j.jcrc.2019.01.029
56. Downar J, You JJ, Bagshaw SM, et al (2015) Nonbeneficial treatment Canada: definitions, causes, and potential solutions from the perspective of healthcare practitioners*. Crit Care Med 43:270–281. doi: 10.1097/CCM.0000000000000704
57. Sanders JJ, Curtis JR, Tulsky JA (2018) Achieving Goal-Concordant Care: A Conceptual Model and Approach to Measuring Serious Illness Communication and Its Impact. J Palliat Med 21:S17–S27. doi: 10.1089/jpm.2017.0459

SUPPLEMENTAL DATA

Supplemental table S1. Description of ICU characteristics of all patients in the periods before and after the implementation of the interventions

Supplemental table S2. Per-protocol analysis of patients with and without documented exposure to the intervention

SOFA Severity of Organ Failure, SD standard deviation, APACHE Acute Physiology And Chronic Health Evaluation, IQR Inter Quartile Range, ICU Intensive Care Unit, LOS Length Of Stay, EHR Electronic Health Record

	July 2015-December 2016	July 2017-December 2018
Total number of admissions (%)	3198	3182
ICU mortality all patients	295 (9.2%)	287 (9.0%)
Number of admissions with LOS < 7 days (%)	2720 (85%)	2801 (88%)
ICU mortality patients with LOS < 7 days (%)	217 (8%)	213 (7.6%)
Number of admissions with LOS ≥7 days (%)	478 (14,9%)	381 (12%)
ICU mortality patients with LOS ≥ 7 days (%)	77 (16.2%)	74 (19.8%)

Supplemental table S1. Description of ICU characteristics of all patients in the periods before and after the implementation of the interventions

	With intervention noted in EHR (n= 255)	Without intervention noted in EHR (n=149)	*P* value
SOFA score day (mean, SD)	7.3 (3.8)	6.2 (3.4)	.010*
Co-morbidities, n (%)	146 (64.9%)	82 (55.0%)	.056
Days with mechanical ventilation (median, IQR)	14 (11 - 24)	8 (6 - 11)	<.001*
APACHE III score (mean, SD)	75.6 (24.1)	70.6 (25.5)	.079
ICU LOS (median, IQR)	15.9 (11.7-28.3)	9.0 (7.5-12.5)	<.001*
90-day mortality, n (%)	90 (40.0%)	47 (31.5%)	.097
Number of 'hypothetically non-beneficial' ICU days (median, IQR)	0 (0-14.5)	0 (0-7.8)	.002*
Number of documented family conversations per patient (median, IQR)	5 (3-8)	3 (1-5)	<.001*

Supplemental table S2. Per-protocol analysis of patients with and without documented exposure to the intervention

SOFA Severity of Organ Failure, *SD* standard deviation, *APACHE* Acute Physiology And Chronic Health Evaluation, IQR Inter Quartile Range, *ICU* Intensive Care Unit, *LOS* Length Of Stay, EHR Electronic Health Record

SUPPLEMENTAL FIGURES

Displaying characteristics/outcome in 3-month periods
Figure S1-S3; baseline characteristics
Figure S4-S7; primary and secondary outcomes

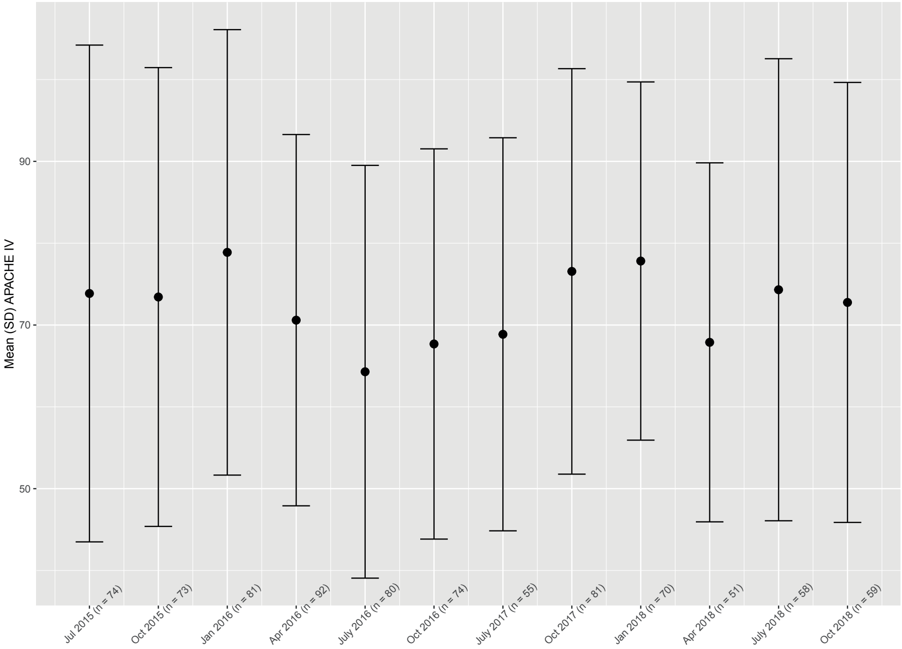


Figure S1. Apache IV score

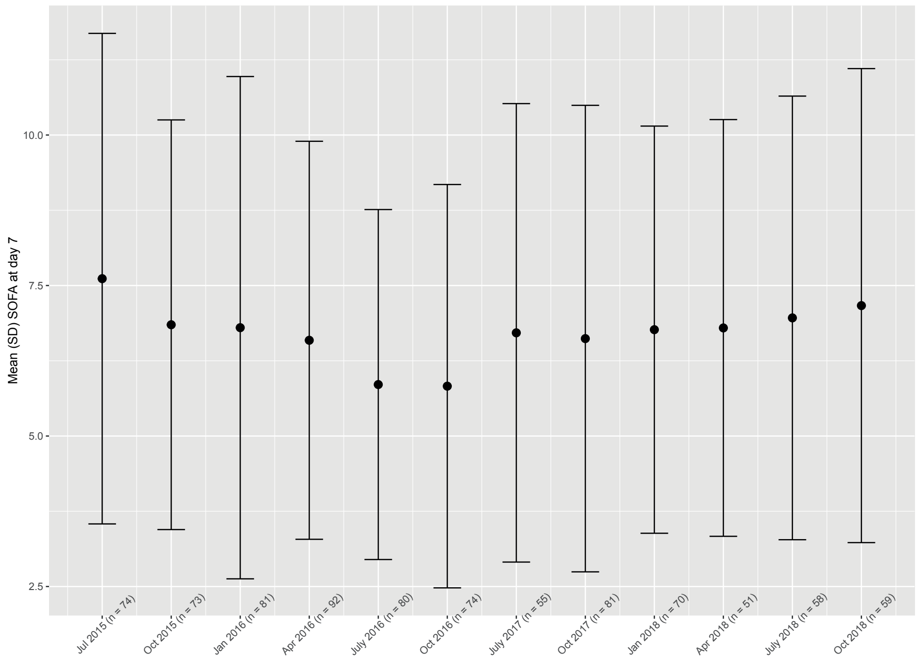


Figure S2. SOFA score at day 7

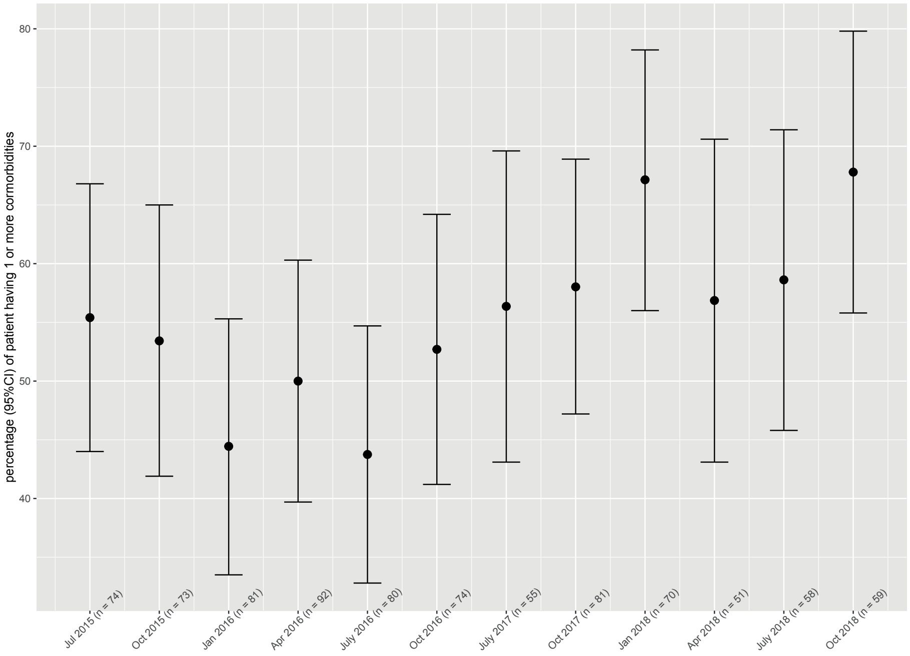


Figure S3. Percentage of patients with >1 co-morbidities

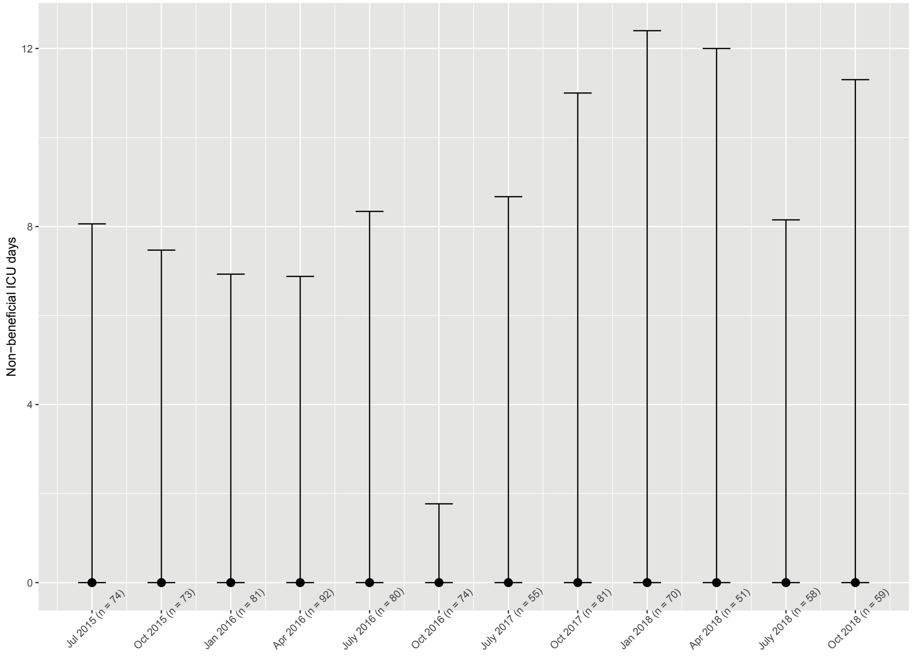


Figure S4. Number of 'hypothetically non-beneficial' days

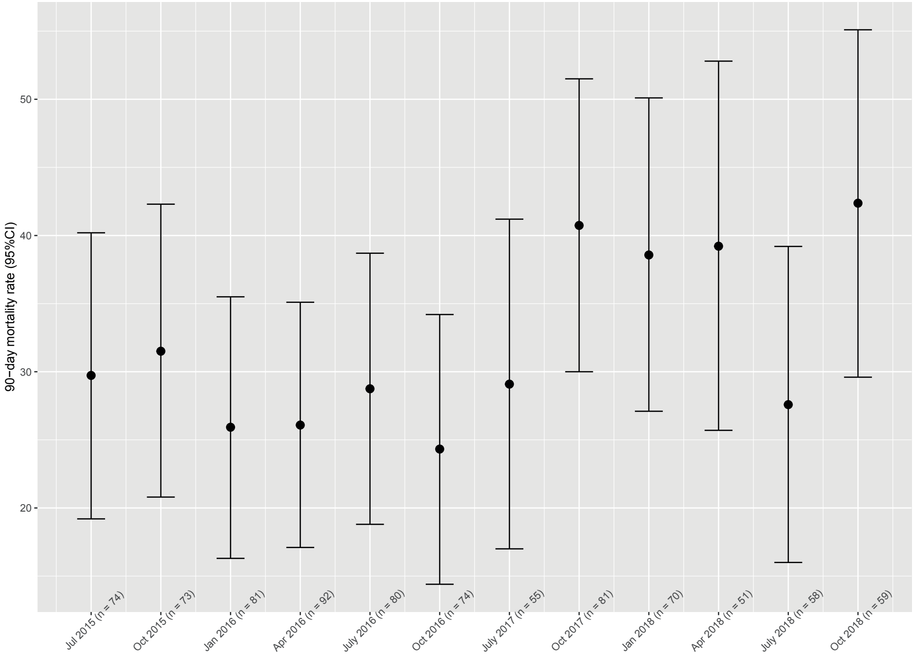


Figure S5. 90-day mortality

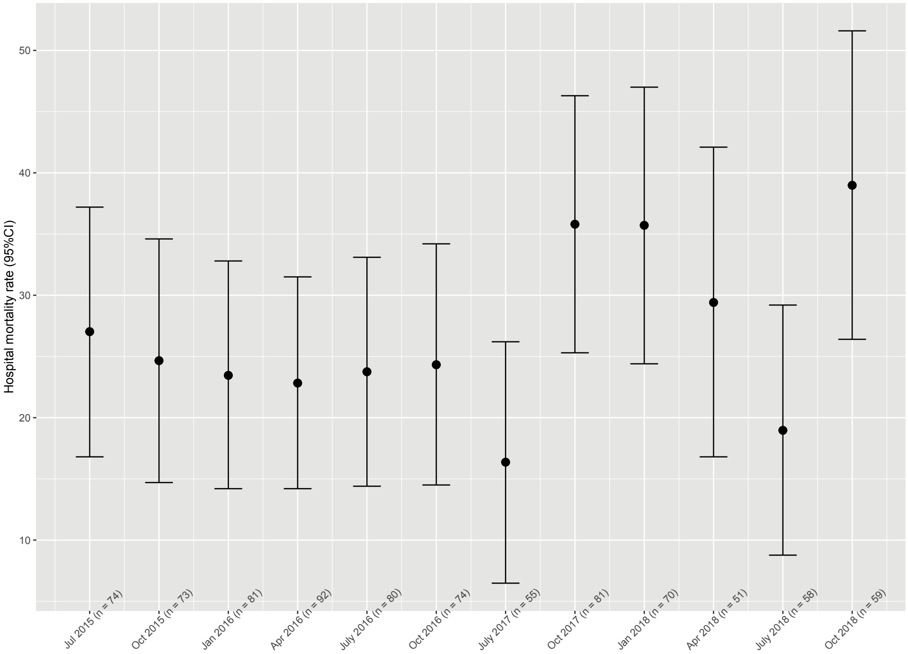


Figure S6. Hospital mortality

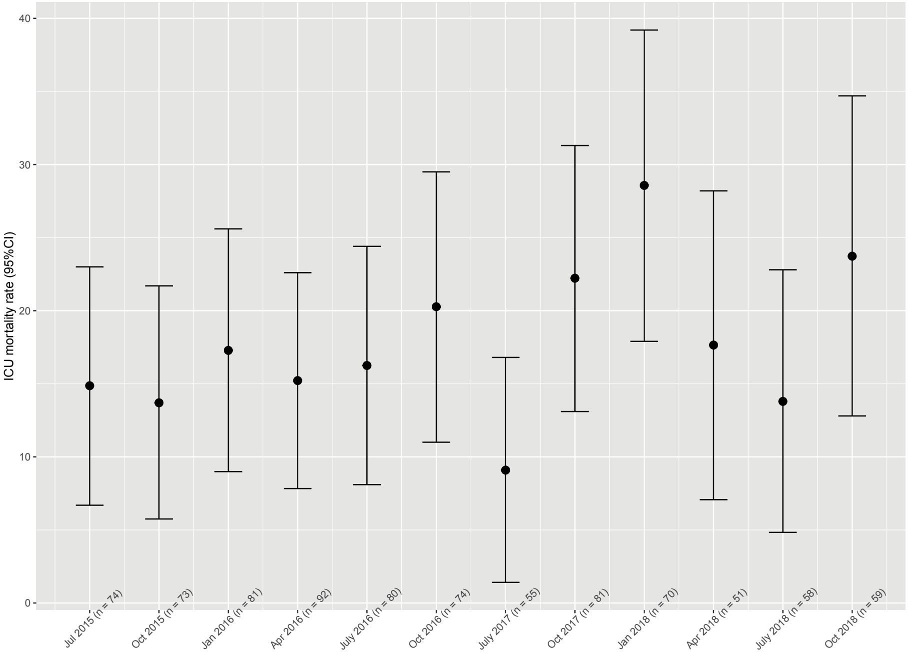


Figure S7. ICU mortality

8

General discussion

MC Kerckhoffs

GENERAL DISCUSSION

Treatment in the Intensive Care Unit (ICU) saves many lives. At the same time, an ICU treatment is burdensome and the outcome can be disappointing. Many patients suffer from the ICU treatment itself in terms of anxiety, discomfort and pain. Some patients will die during their ICU admission, while others survive with persistent morbidity or reduced quality of life[1]. The additional burden on surrogates and caregivers, high costs and limited capacity of ICU beds further emphasizes the need for carefully tailored ICU care [2-6].

ICU treatments are ideally given to patients who are likely to survive with an outcome that they perceive as acceptable. Therefore, ICU physicians should, together with patients and surrogates, identify both these patients as well as the patients who are unlikely to benefit from the ICU treatment. Decision-making on continuing versus forgoing life-sustaining ICU treatments follows this shared assessment of proportionality.

There is a large and multifactorial variability in decision-making strategies concerning life-sustaining treatments between and within ICUs [7-11]. Differences are influenced by cultural, legal and personal factors which can for instance affect the initiation of discussing goals-of-care or the practice of decision-making (shared versus paternalistic). Cognitive biases, like tolerance of risk or ambiguity, overconfidence, psychological commitment or insecurity on long-term outcome, can either predispose or indispose physicians to limit treatments [12-18]. Since the majority of patients who die the ICU, do so after a decision to withhold or withdraw life-sustaining therapy, the importance of a transparent, unbiased and careful decision-making process is evident [7, 10, 19-21].

Every decision on the proportionality and desirability of ICU treatments leans on the predicted outcome. Physicians however, are not very good at estimating long-term survival and quality of life [22-25]. Predominantly, since there is no reliable model to predict long-term outcome during the ICU admission available. But also, because personality, biases and the lack of feedback on long-term outcome prediction, affect how physicians estimate outcome [26]. At the same time, there is broad consensus which factors concerning current health and pre-morbid functioning affect long-term outcome, albeit it is unclear what their precise predictive value is and how their predictive abilities develop during the ICU admission [27, 28].

Desirability of a treatment is ultimately defined by the patient. However, preferences are often not elicited [lee 2020] and not always followed [29-32]. Physicians and nurses frequently report to deliver ICU treatments [4, 9, 33, 34] that they perceive to be not aligned with preferences [4, 28, 34].

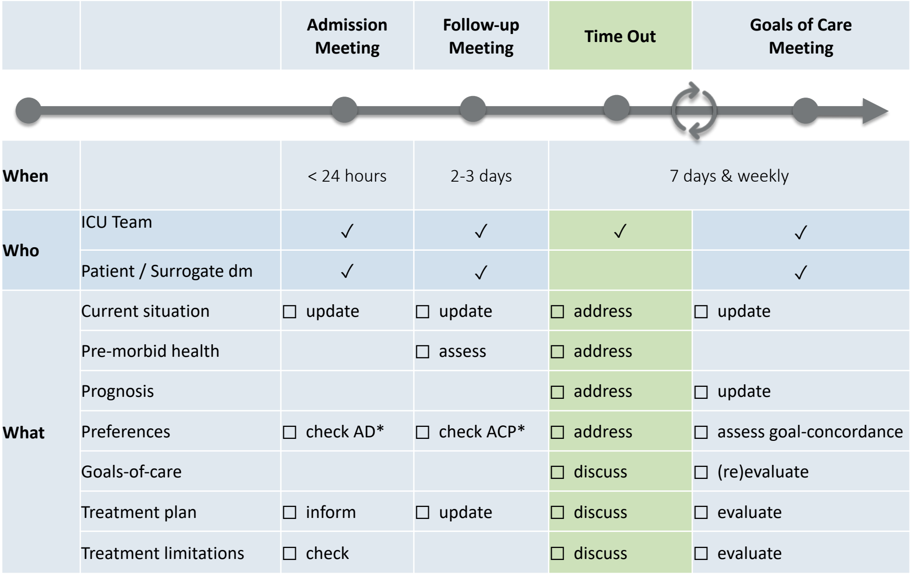
The uncertainty in prognosis, physician-related variability and unknown preferences in decision-making in ICU patients, carries the risk of unwanted or disproportional continuation of ICU treatment. With the ambition to promote proportional ICU treatments aligned with individual preferences, we hypothesized that we had to improve the process of decision-making concerning life-sustaining ICU treatments.

Since prognostication is imperative to assess proportionality and goal-concordance, we had several research questions. What is the longterm outcome of ICU patients? How do different predictive characteristics perform during consecutive days in the ICU? And what is the effect of persistent disabilities on self-reported quality of life in ICU survivors? We found that 8% of all ICU patients die during their ICU admission. After one year, 20% of all admitted ICU patients have deceased. For patients with an ICU length of stay (LOS) of more than one week, ICU mortality was 20% and one-year mortality 40%, with the highest mortality observed within the first 3 months after discharge [35]. We were able to illustrate that for patients with an ICU LOS of at least 3 days, one-year mortality is more reliably predicted when using antecedent patient characteristics (i.e. age, co-morbidities) than when using acute illness characteristics. Moreover, many ICU survivors suffer long-term physical, cognitive and/or mental disabilities. This results in a decreased health related quality of life one year after discharge in a substantial number of ICU survivors [1]. They remain to experience a decreased health related quality of life with variable subjective appraisal of their outcome. A decreased quality of life was mostly associated with mental disabilities [36].

To use prognosis in decision-making on life-sustaining ICU treatments, it should be integrated in a process of shared decision-making that addresses both prognosis as well as preferences. Although shared decision-making and advance care planning are quite well described, we wondered how these decision-making process relate to decision-making on life-sustaining treatments in the ICU setting [37-39]. Our questions were; which strategies and elements are useful in decision-making in the ICU and how should they be evaluated? How do the different participants of shared decision-makings propose to use the various elements of decision-making? With this input, we wondered if a decision-making framework could reduce days admitted in the ICU for patients who die within 90 days?

We found that enhanced communication strategies offered by ICU caregivers positively affected the decision-making process. Increasing the frequency of family-meetings, using a standardised format (including structure and topics of the meeting) [20, 40-47] and making the communication protocol known to families was found to lead to more timely decision-making. [40, 42, 44, 48]. The studied suggested that reducing ICU length of stay for patients who will eventually die in the ICU, seemed both feasible and relevant.

The international group of ICU physicians, ICU nurses, former ICU patients and surrogate decision-makers subsequently co-created a decision-making framework within a Delphi design [49]. In three rounds, they reached consensus on the content and timing of four evidence- and practice-based decision-making steps; 1) an ICU admission meeting; aimed to inform the family and clarify treatment goals and resuscitation status, 2) a family follow-up meeting; inform and gather information on pre-morbid functioning, 3) a goals-of-care meeting; defining milestones and treatment



		Admission Meeting	**Follow-up Meeting**	**Time Out**	**Goals of Care Meeting**
When		< 24 hours	2-3 days	7 days & weekly	
Who	ICU Team	✓	✓	✓	✓
	Patient / Surrogate dm	✓	✓		✓
What	Current situation	☐ update	☐ update	☐ address	☐ update
	Pre-morbid health		☐ assess	☐ address	
	Prognosis			☐ address	☐ update
	Preferences	☐ check AD*	☐ check ACP*	☐ address	☐ assess goal-concordance
	Goals-of-care			☐ discuss	☐ (re)evaluate
	Treatment plan	☐ inform	☐ update	☐ discuss	☐ evaluate
	Treatment limitations	☐ check		☐ discuss	☐ evaluate

* *Surrogate dm* surrogate decision-maker, *AD* advance directive, *ACP* advance care planning

Figure 1. Simplified decision-making framework

Surrogate DM Surrogate decision-maker, AD Advance Directive, ACP Advance Care Planning goals in relation to patient preferences and values, 4) a (recurrent) time-out meeting where caregivers evaluate prognosis and proportionality together with goals and/or limitations of treatment (figure 1).

The shared conclusion of our findings was that decision-making on life-sustaining ICU treatments aims to promote proportional and goal-concordant ICU care, i.e. aligned with patient values and aimed at realizing patient-specific goals concerning survival, functional-outcomes and participation in society [50-52]. This implies that the fit between prognosis and preferences has to be (regularly) assessed during the ICU admission within a process of shared decision-making.

This insight suggested that the current practice of decision-making on life-sustaining ICU treatments in the ICU, could be improved by a uniform process that elicits and combines prognosis and preferences. Therefore, we evaluated a simplified version of the consensus decision-making framework in practice. The framework provided a structure of family meetings combined with a protocolised weekly evaluation of the appropriateness of ICU treatments. During this evaluation, current health and prognostic items like frailty, functional (in)dependence, quality of life and severity of organ failure are systematically assessed. These are paired with the burden of the ICU treatment and related to patient preferences in order to assess proportionality and goal-concordance [26, 53]. We evaluated the efficacy of the framework within a before-after study, on length of ICU stay for patients who died within 90 days. We were surprised by the findings that decision-making seemed to be postponed from early in the ICU admission to beyond 7 days with an increased 90-day mortality and an increased ICU length of stay for these patients. Although residual confounding might partly explain our results, other explanations could lay in increased hesitance to take decisions caused by an unclear prognosis or unknown preferences. The structure prescribing a weekly evaluation planned, may have prevented more ad hoc decisions to limit life-sustaining treatments. The changed role of families in eliciting preferences and defining goals of care during family meetings, could have also resulted in care that became better aligned with preferences even for patients who died within 90 days.

Although the benefits of the framework were not unambiguous, there remain enough arguments to use a framework that can support decision-making on continuing or forgoing life-sustaining ICU treatments.

ARGUMENTS TO USE A DECISION-MAKING FRAMEWORK

The framework was built on two pillars; standardizing and individualizing. The use of the decision-making framework ensures a standardized format to assess the appropriateness of life-sustaining ICU treatment based on individual prognostic factors and personal preferences. Professional expertise or intuition is paired with more objective prognostic items. The repeated character of the goals-of-care meeting, requires every physician to repeatedly assess benefits and harms in a comparable manner. The goals-of-care notes in the electronic health record can provide continuity even when physicians rotate.

Together with the standardization of the process, the framework promotes more individualized decisions. Prognostication can be improved by integrating antecedent patient characteristics in long-term outcome prediction. For patients who are treated in the ICU for a few days, these pre-morbid characteristics like co-morbidities, functional dependency and frailty are more predictive of long-term survival than acute illness characteristics [54-59].

The framework further ensures that preferences are elicited, in order to be able to align ICU care with future goals-of-care. Making this a mandatory item is important since, even in patients with a high risk of death, preferences and quality of life considerations are only discussed in the minority of ICU family meetings [29-31]. Moreover, patients who defined goals-of-care in the prehospital setting, did not automatically receive less aggressive ICU care [32].

The use of the framework offers several other advantages. When physicians are prompted to consider (long-term) outcome, they are more inclined to disclose prognosis to surrogates [60, 61]. In addition, providing the framework as a communication preparation tool to surrogate decision-makers, can prepare them for family meetings. Together with frequent meetings, this can increase surrogate participation, promote the alignment of care with preferences and reduce non-beneficial ICU treatments [62]. Finally, the framework can promote communication on decision-making within ICU teams, which has been shown to reduce the number of patients with perceived disproportional care [4, 28, 34].

CONSIDERATIONS WHEN USING A DECISION-MAKING FRAMEWORK

The framework can support standardized and individualized decision-making, but the complexity of decision-making on life-sustaining treatments in ICU patients implies important considerations.

First, the use of a decision-making framework may result in a prolonged continuation of ICU treatments like we found in our study. This can reflect improved involvement of patients and/or surrogates in decision-making and enhanced goal-concordant care. It could likewise reflect that decision-making is avoided when prognosis and/or preferences are unclear or unknown. Users have to be aware that the framework does not intend to shift the decision-making responsibility completely towards patients and/or surrogates. Physicians and surrogate decision-makers should jointly take decisions, to prevent the request for unlimited ICU treatments dictated by insecurity or feelings of guilt and fear. It remains a shared responsibility to prevent disproportionate care. Primarily for the patient, but also to minimize moral distress and the risk of burnout for caregivers [6, 63, 64].

Second, ICU patients are often incapable to participate in decision-making on life-sustaining treatments. Aligning care with patient preferences, then relies on previously expressed goals-of-care or advance directives. Some patients may have engaged in advance care planning (ACP) at an earlier stage [37, 38]. Some may have documented advance directives, while others have only engaged in future goals-of-care conversations with family-members.

In patients without documented goals-of-care or advance directives, surrogate-decision makers are inclined to express patient-preferences. However, studies report that one third of surrogates incorrectly predicts treatment preferences, both under- and overestimating preferences [71-73]. In addition, advance directives that have been defined some time before the actual ICU admission, should be carefully interpreted. People change their opinion on life-sustaining treatments, where often less intensive treatments are preferred when outcome estimates become more pessimistic [74]. Changings factors like generic health status, mobility, mental health and marital status, may influence these preferences [75]. Whether advance directives exist or surrogate decision-makers express preferences, trying to understand the line of reasoning can help to interpret patient preferences within the context of the ICU.

Third, it is important to understand how the individual patient may appraise their functional outcome. Multiple studies showed a decreased health related quality of life (HRQoL) in ICU survivors [1, 65]. Concurrently, some studies report that patients are generally satisfied with their health status or even self-report an increased quality of life [23, 36, 65]. This positive appraisal of quality of life, despite impairments is called the disability paradox and explained by the response shift [66, 67]. This phenomenon has been described in ICU survivors [68] and reflects someone's ability to adjust and give meaning to impairments. It indicates that quality of life reflects a balance of body and mind within a social context and environment [67, 69, 70]. Patients who can or learn to adjust to new impairments, may appraise their survivorship more positively than others.

The most important consideration when using the decision-making framework relates to effectiveness. Although the holy grail of ICU care is to provide goal-concordant care, the process of decision-making itself could benefit from improvements. But what defines good decision-making and how should a complex intervention like a decision-making framework be evaluated in terms of success? The perception of the most ideal decision-making process measures varies for the different stakeholders. Reducing subjectivity and variability is desirable form the caregivers' point of view, while patients and families might want to improve communication. When a decision-making framework is implemented in practice, it should be clear what the framework intends to improve. In different settings, countries or cultures, the shortcomings in the process of decision-making might need a different approach and measurement of impact.

FUTURE DIRECTIONS FOR DECISION-MAKING ON CONTINUING OR LIMITING ICU CARE

Decision-aid

This thesis lays the fundaments of a decision-making framework that includes items of prognosis, proportionality and preferences applicable to patients treated in the ICU. The framework we have evaluated, postposed decision-making with an increased 90-day mortality. One hypothesis to explain this finding, could be that the framework led to unjustified optimistic prognostic estimates. With this in mind, the supportive character of the framework might have to change into a more informative shared-decision-making aid. This might be able to improve physicians' understanding of the individual outcome and decrease the discrepancy of outcome estimates between physicians and surrogates to facilitate well informed decision-making [76].

According to the International Patient Decision Aids Standards (IPDAS) Collaboration, decision aids are evidence-based tools designed to help patients make specific and deliberated choices in conjunction with clinicians' counselling [77]. People exposed to decision aids are more knowledgeable, have improved risk perceptions and have a more active role in decision making. There is growing evidence that decision aids may improve value-congruent choices without adverse effects on satisfaction [78]. To make the framework function as a decision-aid in the ICU, the relevant prognostic items in the framework have to be translated into a personalized estimate on (long-term) outcome. This outcome prediction should be evidence-based with enough certainty, easily available and simple to comprehend by professional caregivers, patients and surrogates.

For physicians to include prognostic information in decision-making, the outcome predictions have to be trustworthy. Physicians will need to understand which factors are incorporated in the prediction-model, how these factors affect the outcome prediction and what the confidence intervals of the predictions are. In addition, the prediction model should be dynamic to do justice to the changing physiology of ICU patients over time.

For patients and surrogates, the decision-aid has to facilitate goals-of-care conversations. It should include prognostic information and stimulate users to assess which aspects of outcome are most important to their loved one [79]. Prognostic information has been proven to be helpful and appreciated by surrogates, who prefer prognostic information even when there is uncertainty on the outcome [76, 80]. Prognosis should however be presented in a format that is easy to understand and leads to valid risk and benefit perceptions [81, 82]. Natural frequencies are probably better understood than probabilities, but further research is needed to explore the optimal format for surrogates with varying numeracy [83, 84]. In addition, the efficacy of using decision-aids in surrogates, instead of patients, has to be explored, since previous studies have showed that designing an effective tool is difficult [85].

In practice, multiple options to use a decision-aid are possible. In a simple design, the ICU physician could present the individual outcome estimates during the family meeting in print or digitally to promote the critical appraisal of information. A digital format could enable the physician to 'live' illustrate the contribution of each prognostic factor on mortality and morbidity. In subsequent meetings, an updated outcome estimate can be discussed, giving insight in changing prognosis over time. Solely disclosing prognosis however, might be insufficient to change decision-making practice [60].

A more comprehensive option would be an ACP tool, an online decision-aid that prepares surrogate decision-makers for goals-of-care discussions. In this format, the decision-aid can stimulate surrogates to define what aspects of outcome are most important to the ICU patient they are representing. By participating in this process in advance, goal-of-care meetings can be more powerful and effective [84].

Advance care planning

Deciding whether life-sustaining ICU treatments are justified, always requires input on preferences regarding long-term outcome and future goals. Since ICU patients are most often incapable of decision-making themselves, surrogate decision-makers have to voice the preferences of their loved one. It is very helpful for surrogate decision-makers and clinicians, if the patient has engaged in advance care planning (ACP) before the ICU admission and expressed or documented preferences [37, 38]. If future goals or advance directives are known, it enhances goal-concordant ICU care and reduces decisional-conflict in surrogate decision-makers [86]. Therefore, an important future directive is to draw attention to the concept of ACP throughout the whole trajectory of the patient. Currently, many studies are conducted that evaluate the effect of promoting ACP in the pre-hospital setting and in the outpatient clinic. Especially in patients at risk for a ICU admission or with a poor life-expectancy, conversations on future-goals-of care can prepare patients and surrogates for future decision-making [87, 88]. ICU physicians should claim their role in decision-making situations where patients and professional caregivers cannot reach consensus or when there is doubt whether ICU treatments can reach patient specific goals.

Besides promoting ACP before the ICU admission, future effort has to focus on the participation of patients and/or surrogate decision-makers in the process of ACP during the ICU admission. Enhancing a decision-making framework with clear shared-decision making objectives, has a large potential to improve goal-concordant care. This might need more than a checklist addressing relevant items and training communication skills. Building an alliance with palliative care teams might be (temporarily) needed to truly change the culture of paternalistic decision-making into shared and advance care planning [89-92].

Physician-related factors

With the use of the decision-making framework, decisions on life-sustaining ICU treatments were taken during a weekly multi-disciplinary goals-of-care meeting with the input of four to six physicians. One of the assets of the meeting was the reduction of physician-related factors to affect decision-making on life-sustaining ICU treatments. Treatment-limitations always required consensus and the weekly character prevented ad hoc decision-making on limiting life-sustaining treatments. The practice of weekly decision-making during a time-out meeting, was however associated with a longer ICU admission for patients who died within three months. This might be explained by an effect called irrational escalation or escalation of treatments. The emotional or psychological connection between the physician and patient or surrogates can cause this phenomenon, which describes the tendency to allow previous investments to have an irrational influence on future decisions [93]. A physician who has been involved in previous decisions to continue treatments, is more likely to persist in this decision. ICU teams have to be aware of this effect and could consider to rotate the responsible physician in some patients, to stimulate more objective decision-making.

Cultural interpretation

Culture-related factors affecting decision-making in the ICU are of great importance in preference-sensitive decisions on life-sustaining treatments. Cultural differences affect both the decision-making process as well as how the outcome of an individual patient will be perceived. In the Netherlands, decisions on life-sustaining treatments are usually made by a team of physicians and a somewhat paternalistic decision-making style is common. The use of the framework, in which a shared-decision making style is promoted, could have different effects in countries and cultures where shared decision-making is already common practice. In addition, cultural aspects influence which outcome is considered (un)acceptable. Being fully dependent of care for example, can be valued higher in some cultures than in others. Understandably, deciding whether continuous ICU treatment is justified, will differ accordingly.

Appraisal

ICU physicians aim to provide ICU treatments to patients who will survive with an outcome that they will consider acceptable. During decision-making in the ICU, an acceptable outcome is considered a quality of life that is congruent with the patient's wishes. However, the concept of quality of life is complex. It is multi-dimensional (physical, mental, etc.), dynamic and consists of both objective and subjective components. Some ICU survivors will be able to re-evaluate their quality of life and will be satisfied with a new health state, while others will not. Understanding if the patient will have the ability to cope with persisting disabilities could enhance incorporating future quality of life in decision-making on life-sustaining ICU treatments. Therefore, future studies have to unravel which patient-related, social or cultural factors positively affect adaptation. In addition, if we could understand which of these factors are modifiable during or after the ICU admission, we could improve the long-term quality of life of ICU survivors.

CONCLUSION

The use of a decision-making framework in the ICU, can ensure that for each ICU patient prognosis, proportionality and preferences are addressed. A standardized shared-decision-making process that combines individual items concerning prognosis and preferences with current health and suffering, has the potential to provide proportional and goal-concordant ICU care.

REFERENCES

1. Soliman IW, de Lange DW, Peelen LM, et al (2015) Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care 30:181–186. doi: 10.1016/j.jcrc.2014.09.009
2. Wintermann G-B, Weidner K, Strauß B, et al (2016) Predictors of posttraumatic stress and quality of life in family members of chronically critically ill patients after intensive care. Ann Intensive Care 6:69. doi: 10.1186/s13613-016-0174-0
3. Cameron JI, Chu LM, Matté A, et al (2016) One-Year Outcomes in Caregivers of Critically Ill Patients. http://dxdoiorg/101056/NEJMoa1511160 374:1831–1841. doi: 10.1056/NEJMoa1511160
4. Piers RD, Azoulay E, Ricou B, et al (2014) Inappropriate care in European ICUs: confronting views from nurses and junior and senior physicians. Chest 146:267–275. doi: 10.1378/chest.14-0256
5. Lambden JP, Chamberlin P, Kozlov E, et al (2018) Association of Perceived Futile or Potentially Inappropriate Care With Burnout and Thoughts of Quitting Among Health-Care Providers. Am J Hosp Palliat Care 36:1049909118792517–206. doi: 10.1177/1049909118792517
6. Chamberlin P, Lambden J, Kozlov E, et al (2019) Clinicians' Perceptions of Futile or Potentially Inappropriate Care and Associations with Avoidant Behaviors and Burnout. J Palliat Med 22:1039–1045. doi: 10.1089/jpm.2018.0385
7. Mark NM, Rayner SG, Lee NJ, Curtis JR (2015) Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. Intensive Care Med 41:1572–1585. doi: 10.1007/s00134-015-3810-5
8. Barnato AE, Tate JA, Rodriguez KL, et al (2012) Norms of decision making in the ICU: a case study of two academic medical centers at the extremes of end-of-life treatment intensity. Intensive Care Med 38:1886–1896. doi: 10.1007/s00134-012-2661-6
9. Piers RD, Azoulay E, Ricou B, et al (2011) Perceptions of appropriateness of care among European and Israeli intensive care unit nurses and physicians. JAMA 306:2694–2703. doi: 10.1001/jama.2011.1888
10. Sprung CL, Cohen SL, Sjokvist P, et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. doi: 10.1001/jama.290.6.790
11. Myburgh J, Abillama F, Chiumello D, et al (2016) End-of-life care in the intensive care unit: Report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care 34:125–130. doi: 10.1016/j.jcrc.2016.04.017
12. Turnbull AE, Davis WE, Needham DM, et al (2016) Intensivist-reported Facilitators and Barriers to Discussing Post-Discharge Outcomes with Intensive Care Unit Surrogates. A Qualitative Study. Ann Am Thorac Soc 13:1546–1552. doi: 10.1513/AnnalsATS.201603-212OC
13. Visser M, Deliens L, Houttekier D (2014) Physician-related barriers to communication and patient- and family-centred decision-making towards the end of life in intensive care: a systematic review. Crit Care 18:604. doi: 10.1186/s13054-014-0604-z
14. Saposnik G, Redelmeier D, Ruff CC, Tobler PN (2016) Cognitive biases associated with medical decisions: a systematic review. BMC Med Inform Decis Mak 16:138. doi: 10.1186/s12911-016-0377-1
15. Stiegler MP, Ruskin KJ (2012) Decision-making and safety in anesthesiology. Current opinion in anaesthesiology 25:724–729. doi: 10.1097/ACO.0b013e328359307a
16. Braxton CC, Robinson CN, Awad SS (2017) Escalation of Commitment in the Surgical ICU. Crit Care Med 45:e433–e436. doi: 10.1097/CCM.0000000000002261
17. Kollef MH, Ward S (1999) The influence of access to a private attending physician on the withdrawal of life-sustaining therapies in the intensive care unit. Crit Care Med 27:2125.
18. Braverman JA, Blumenthal-Barby JS (2012) Assessment of the sunk-cost effect in clinical decision-making. Soc Sci Med 75:186–192. doi: 10.1016/j.socscimed.2012.03.006

19. Prendergast TJ, Claessens MT, Luce JM (1998) A national survey of end-of-life care for critically ill patients. American Journal of Respiratory and Critical Care Medicine 158:1163–1167. doi: 10.1164/ajrccm.158.4.9801108
20. Higginson IJ, Koffman J, Hopkins P, et al (2013) Development and evaluation of the feasibility and effects on staff, patients, and families of a new tool, the Psychosocial Assessment and Communication Evaluation (PACE), to improve communication and palliative care in intensive care and during clinical uncertainty. BMC Med 11:213. doi: 10.1186/1741-7015-11-213
21. Sprung CL, Ricou B, Hartog CS, et al (2019) Changes in End-of-Life Practices in European Intensive Care Units From 1999 to 2016. JAMA 322:1692–1704. doi: 10.1001/jama.2019.14608
22. Detsky ME, Harhay MO, Bayard DF, et al (2017) Discriminative Accuracy of Physician and Nurse Predictions for Survival and Functional Outcomes 6 Months After an ICU Admission. JAMA 317:2187–2195. doi: 10.1001/jama.2017.4078
23. Detsky ME, Kohn R, Delman AM, et al (2018) Patients' perceptions and ICU clinicians predictions of quality of life following critical illness. J Crit Care 48:352–356. doi: 10.1016/j.jcrc.2018.09.034
24. Soliman IW, Cremer OL, de Lange DW, et al (2018) The ability of intensive care unit physicians to estimate long-term prognosis in survivors of critical illness. J Crit Care 43:148–155. doi: 10.1016/j.jcrc.2017.09.007
25. Meadow W, Pohlman A, Frain L, et al (2011) Power and limitations of daily prognostications of death in the medical intensive care unit. Crit Care Med 39:474–479. doi: 10.1097/CCM.0b013e318205df9b
26. Kahneman D (2012) Thinking Fast and Slow By Daniel Kahneman. Penguin. 2012. £10.99 (pb). 512 pp. ISBN 9780141033570. 213:563–564. doi: 10.1192/bjp.2018.109
27. Sprung CL, Truog RD, Curtis JR, et al (2014) Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. In: Am. J. Respir. Crit. Care Med. American Thoracic Society, pp 855–866
28. Quenot J-P, Large A, Meunier-Beillard N, et al (2019) What are the characteristics that lead physicians to perceive an ICU stay as non-beneficial for the patient? PLoS ONE 14:e0222039. doi: 10.1371/journal.pone.0222039
29. Scheunemann LP, Cunningham TV, Arnold RM, et al (2015) How clinicians discuss critically ill patients' preferences and values with surrogates: an empirical analysis. Crit Care Med 43:757–764. doi: 10.1097/CCM.0000000000000772
30. Scheunemann LP, Ernecoff NC, Buddadhumaruk P, et al (2019) Clinician-Family Communication About Patients' Values and Preferences in Intensive Care Units. JAMA Intern Med. doi: 10.1001/jamainternmed.2019.0027
31. Douglas SL, Daly BJ, Lipson AR (2012) Neglect of quality-of-life considerations in intensive care unit family meetings for long-stay intensive care unit patients. Crit Care Med 40:461–467. doi: 10.1097/CCM.0b013e318232d8c4
32. Hartog CS, Peschel I, Schwarzkopf D, et al (2014) Are written advance directives helpful to guide end-of-life therapy in the intensive care unit? A retrospective matched-cohort study. J Crit Care 29:128–133. doi: 10.1016/j.jcrc.2013.08.024
33. Benoit DD, Jensen HI, Malmgren J, et al (2018) Outcome in patients perceived as receiving excessive care across different ethical climates: a prospective study in 68 intensive care units in Europe and the USA. Intensive Care Med 44:1039–1049. doi: 10.1007/s00134-018-5231-8
34. Huynh TN, Kleerup EC, Wiley JF, et al (2013) The frequency and cost of treatment perceived to be futile in critical care. JAMA Intern Med 173:1887–1894. doi: 10.1001/jamainternmed.2013.10261
35. Brinkman S, de Jonge E, Abu-Hanna A, et al (2013) Mortality after hospital discharge in ICU patients. Crit Care Med 41:1229–1236. doi: 10.1097/CCM.0b013e31827ca4e1

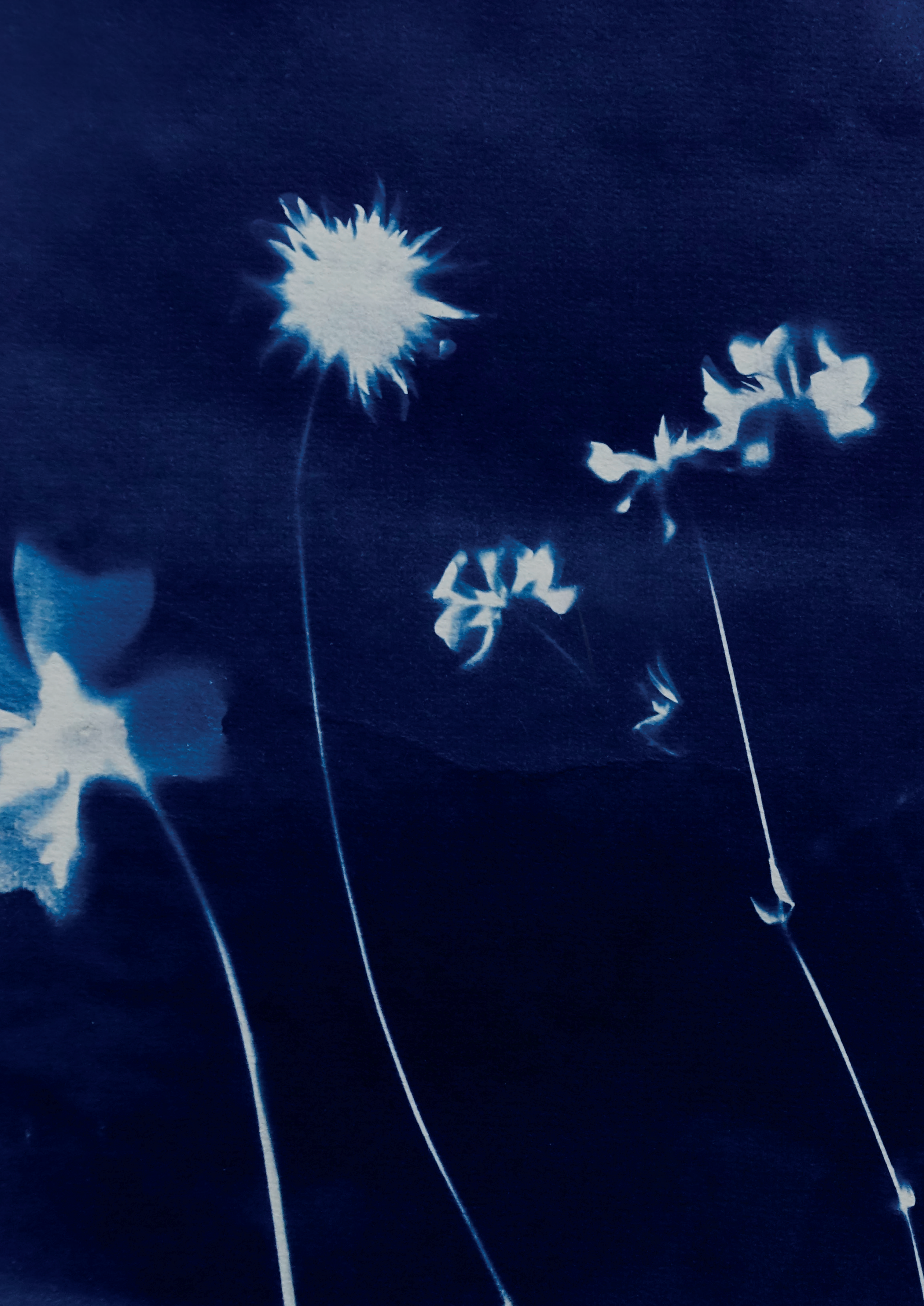
36. Kerckhoffs MC, Kosasi FFL, Soliman IW, et al (2019) Determinants of self-reported unacceptable outcome of intensive care treatment 1 year after discharge. Intensive Care Med 40:502–9. doi: 10.1007/s00134-019-05583-4
37. Rietjens JAC, Sudore RL, Connolly M, et al (2017) Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. Lancet Oncol 18:e543–e551. doi: 10.1016/S1470-2045(17)30582-X
38. Sudore RL, Lum HD, You JJ, et al (2017) Defining Advance Care Planning for Adults: A Consensus Definition From a Multidisciplinary Delphi Panel. J Pain Symptom Manage 53:821–832.e1. doi: 10.1016/j.jpainsymman.2016.12.331
39. Kon AA, Davidson JE, Morrison W, et al (2016) Shared Decision-Making in Intensive Care Units. Executive Summary of the American College of Critical Care Medicine and American Thoracic Society Policy Statement. American Journal of Respiratory and Critical Care Medicine 193:1334–1336. doi: 10.1164/rccm.201602-0269ED
40. Wysham NG, Mularski RA, Schmidt DM, et al (2014) Long-term persistence of quality improvements for an intensive care unit communication initiative using the VALUE strategy. J Crit Care 29:450–454. doi: 10.1016/j.jcrc.2013.12.006
41. Lilly CM, Sonna LA, Haley KJ, Massaro AF (2003) Intensive communication: four-year follow-up from a clinical practice study. Crit Care Med 31:S394–9. doi: 10.1097/01.CCM.0000065279.77449.B4
42. Daly BJ, Douglas SL, O'Toole E, et al (2010) Effectiveness trial of an intensive communication structure for families of long-stay ICU patients. Chest 138:1340–1348. doi: 10.1378/chest.10-0292
43. Ahrens T, Yancey V, Kollef M (2003) Improving family communications at the end of life: implications for length of stay in the intensive care unit and resource use. Am J Crit Care 12:317–23– discussion 324.
44. Campbell ML, Guzman JA (2003) Impact of a proactive approach to improve end-of-life care in a medical ICU. Chest 123:266–271.
45. Jacobowski NL, Girard TD, Mulder JA, Ely EW (2010) Communication in critical care: family rounds in the intensive care unit. Am J Crit Care 19:421–430. doi: 10.4037/ajcc2010656
46. Quenot JP, Rigaud JP, Prin S, et al (2012) Impact of an intensive communication strategy on end-of-life practices in the intensive care unit. Intensive Care Med 38:145–152. doi: 10.1007/s00134-011-2405-z
47. Kaufer M, Murphy P, Barker K, Mosenthal A (2008) Family Satisfaction Following the Death of a Loved One in an Inner City MICU. American Journal of Hospice and Palliative Medicine® 25:318–325. doi: 10.1177/1049909108319262
48. Allen SR, Pascual J, Martin N, et al (2017) A novel method of optimizing patient- and family-centered care in the ICU. J Trauma Acute Care Surg 82:582–586. doi: 10.1097/TA.0000000000001332
49. Linstone HA, Turoff M (2002) The Delphi method: Techniques and applications.
50. Sanders JJ, Curtis JR, Tulsky JA (2018) Achieving Goal-Concordant Care: A Conceptual Model and Approach to Measuring Serious Illness Communication and Its Impact. J Palliat Med 21:S17–S27. doi: 10.1089/jpm.2017.0459
51. Turnbull AE, Hartog CS (2017) Goal-concordant care in the ICU: a conceptual framework for future research. Intensive Care Med 43:1847–1849. doi: 10.1007/s00134-017-4873-2
52. Dinglas VD, Chessare CM, Davis WE, et al (2018) Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. Thorax 73:7–12. doi: 10.1136/thoraxjnl-2017-210234
53. Minne L, Toma T, de Jonge E, Abu-Hanna A (2013) Assessing and combining repeated prognosis of physicians and temporal models in the intensive care. Artificial Intelligence in Medicine 57:111–117. doi: 10.1016/j.artmed.2012.08.005

54. Muscedere J, Waters B, Varambally A, et al (2017) The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med 43:1105–1122. doi: 10.1007/s00134-017-4867-0
55. Lone NI, Gillies MA, Haddow C, et al (2016) Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. American Journal of Respiratory and Critical Care Medicine 194:198–208. doi: 10.1164/rccm.201511-2234OC
56. Ferrante LE, Pisani MA, Murphy TE, et al (2016) Factors Associated with Functional Recovery among Older Intensive Care Unit Survivors. American Journal of Respiratory and Critical Care Medicine 194:299–307. doi: 10.1164/rccm.201506-1256OC
57. Bagshaw SM, Stelfox HT, Johnson JA, et al (2015) Long-term association between frailty and health-related quality of life among survivors of critical illness: a prospective multicenter cohort study. Crit Care Med 43:973–982. doi: 10.1097/CCM.0000000000000860
58. Gayat E, Cariou A, Deye N, et al (2018) Determinants of long-term outcome in ICU survivors: Results from the FROG-ICU study. Crit Care 22:8. doi: 10.1186/s13054-017-1922-8
59. Szakmany T, Walters AM, Pugh R, et al (2019) Risk Factors for 1-Year Mortality and Hospital Utilization Patterns in Critical Care Survivors: A Retrospective, Observational, Population-Based Data Linkage Study. Crit Care Med 47:15–22. doi: 10.1097/CCM.0000000000003424
60. Turnbull AE, Hayes MM, Brower RG, et al (2019) Effect of Documenting Prognosis on the Information Provided to ICU Proxies: A Randomized Trial. Crit Care Med 47:757–764. doi: 10.1097/CCM.0000000000003731
61. Turnbull AE, Krall JR, Ruhl AP, et al (2014) A scenario-based, randomized trial of patient values and functional prognosis on intensivist intent to discuss withdrawing life support. Crit Care Med 42:1455–1462. doi: 10.1097/CCM.0000000000000227
62. Bibas L, Peretz-Larochelle M, Adhikari NK, et al (2019) Association of Surrogate Decision-making Interventions for Critically Ill Adults with Patient, Family, and Resource Use Outcomes: A Systematic Review and Meta-analysis. JAMA Netw Open 2:e197229–e197229. doi: 10.1001/jamanetworkopen.2019.7229
63. Quenot JP, Rigaud JP, Prin S, et al (2012) Suffering among carers working in critical care can be reduced by an intensive communication strategy on end-of-life practices. Intensive Care Med 38:55–61. doi: 10.1007/s00134-011-2413-z
64. Fumis RRL, Junqueira Amarante GA, de Fátima Nascimento A, Vieira Junior JM (2017) Moral distress and its contribution to the development of burnout syndrome among critical care providers. Ann Intensive Care 7:71–8. doi: 10.1186/s13613-017-0293-2
65. Cuthbertson BH, Elders A, Hall S, et al (2013) Mortality and quality of life in the five years after severe sepsis. Crit Care 17:R70. doi: 10.1186/cc12616
66. Albrecht GL, Devlieger PJ (1999) The disability paradox: high quality of life against all odds. Soc Sci Med 48:977–988.
67. Rapkin BD, Schwartz CE (2004) Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. Health Qual Life Outcomes 2:14. doi: 10.1186/1477-7525-2-14
68. Eakin MN, Patel Y, Mendez-Tellez P, et al (2017) Patients’ outcomes after acute respiratory failure: A qualitative study with the promis framework. Am J Crit Care 26:456–465. doi: 10.4037/ajcc2017834
69. Hofhuis JGM, van Stel HF, Schrijvers AJP, et al (2009) Conceptual issues specifically related to health-related quality of life in critically ill patients. Crit Care 13:118. doi: 10.1186/cc7699
70. Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 48:1507–1515.
71. Shalowitz DI, Garrett-Mayer E, Wendler D (2006) The accuracy of surrogate decision makers: a systematic review. Arch Intern Med 166:493–497. doi: 10.1001/archinte.166.5.493
72. Alagappan M, Richardson MT, Schoen MK, et al (2018) A Three-Step Letter Advance Directive Procedure to Facilitate Patient-Proxy Alignment in Advance Care Planning. J Palliat Med 21:1749–1754. doi: 10.1089/jpm.2018.0150

73. Fried TR, Zenoni M, Iannone L, et al (2017) Engagement in Advance Care Planning and Surrogates' Knowledge of Patients' Treatment Goals. J Am Geriatr Soc 65:1712–1718. doi: 10.1111/jgs.14858
74. Houben CHM, Spruit MA, Schols JMGA, et al (2017) Instability of Willingness to Accept Life-Sustaining Treatments in Patients With Advanced Chronic Organ Failure During 1 Year. Chest 151:1081–1087. doi: 10.1016/j.chest.2016.12.003
75. Janssen DJA, Spruit MA, Schols JMGA, et al (2012) Predicting changes in preferences for life-sustaining treatment among patients with advanced chronic organ failure. Chest 141:1251–1259. doi: 10.1378/chest.11-1472
76. Lee Char SJ, Evans LR, Malvar GL, White DB (2010) A randomized trial of two methods to disclose prognosis to surrogate decision makers in intensive care units. American Journal of Respiratory and Critical Care Medicine 182:905–909. doi: 10.1164/rccm.201002-0262OC
77. Joseph-Williams N, Newcombe R, Politi M, et al (2014) Toward Minimum Standards for Certifying Patient Decision Aids: A Modified Delphi Consensus Process. Med Decis Making 34:699–710. doi: 10.1177/0272989X13501721
78. Stacey D, Légaré F, Lewis K, et al (2017) Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 4:CD001431. doi: 10.1002/14651858.CD001431.pub5
79. Scalia P, Durand M-A, Kremer J, et al (2018) Online, Interactive Option Grid Patient Decision Aids and their Effect on User Preferences. Med Decis Making 38:56–68. doi: 10.1177/0272989X17734538
80. Evans LR, Boyd EA, Malvar G, et al (2009) Surrogate decision-makers' perspectives on discussing prognosis in the face of uncertainty. American Journal of Respiratory and Critical Care Medicine 179:48–53. doi: 10.1164/rccm.200806-969OC
81. Peters E, Hart PS, Fraenkel L (2011) Informing patients: the influence of numeracy, framing, and format of side effect information on risk perceptions. Med Decis Making 31:432–436. doi: 10.1177/0272989X10391672
82. Akl EA, Oxman AD, Herrin J, et al (2007) Using different statistical formats for presenting health information. Cochrane Database of Systematic Reviews 324:827. doi: 10.1002/14651858.CD006776
83. Akl EA, Oxman AD, Herrin J, et al (2011) Using alternative statistical formats for presenting risks and risk reductions. Cochrane Database Syst Rev 58:CD006776. doi: 10.1002/14651858.CD006776.pub2
84. Witteman HO, Gavaruzzi T, Scherer LD, et al (2016) Effects of Design Features of Explicit Values Clarification Methods: A Systematic Review. Med Decis Making 36:760–776. doi: 10.1177/0272989X16634085
85. Cox CE, White DB, Hough CL, et al (2019) Effects of a Personalized Web-Based Decision Aid for Surrogate Decision Makers of Patients With Prolonged Mechanical Ventilation: A Randomized Clinical Trial. Ann Intern Med 170:285–297. doi: 10.7326/M18-2335
86. Chiarchiaro J, Buddadhumaruk P, Arnold RM, White DB (2015) Prior Advance Care Planning Is Associated with Less Decisional Conflict among Surrogates for Critically Ill Patients. Ann Am Thorac Soc 12:1528–1533. doi: 10.1513/AnnalsATS.201504-253OC
87. Kleinpell R, Sessler CN, Wiencek C, Moss M (2019) Choosing Wisely in Critical Care: Results of a National Survey From the Critical Care Societies Collaborative. Crit Care Med 47:331–336. doi: 10.1097/CCM.0000000000003496
88. Downar J, You JJ, Bagshaw SM, et al (2015) Nonbeneficial treatment Canada: definitions, causes, and potential solutions from the perspective of healthcare practitioners*. Crit Care Med 43:270–281. doi: 10.1097/CCM.0000000000000704
89. Braus N, Campbell TC, Kwekkeboom KL, et al (2016) Prospective study of a proactive palliative care rounding intervention in a medical ICU. Intensive Care Med 42:54–62. doi: 10.1007/s00134-015-4098-1

90. Aslakson R, Cheng J, Vollenweider D, et al (2014) Evidence-based palliative care in the intensive care unit: a systematic review of interventions. J Palliat Med 17:219–235. doi: 10.1089/jpm.2013.0409
91. Mercadante S, Gregoretti C, Cortegiani A (2018) Palliative care in intensive care units: why, where, what, who, when, how. BMC Anesthesiol 18:255.
92. Curtis JR, Treece PD, Nielsen EL, et al (2016) Randomized Trial of Communication Facilitators to Reduce Family Distress and Intensity of End-of-Life Care. American Journal of Respiratory and Critical Care Medicine 193:154–162. doi: 10.1164/rccm.201505-0900OC
93. Bornstein BH, Emler AC (2001) Rationality in medical decision making: a review of the literature on doctors' decision-making biases. J Eval Clin Pract 7:97–107.

8



Summary

Nederlandse samenvatting

Appendices

List of publications

Dankwoord

Curriculum vitae

SUMMARY

Each year around 80.000 patients are treated in a Dutch Intensive Care Unit (ICU) [1]. Although most patients survive, mortality during and after the ICU remains significant [2]. Besides the burden caused by the ICU treatment itself, more than one third of ICU survivors suffer from the sequelae of critical illness. These comprise of impairments in physical, cognitive and/or mental health, often referred to as the Post Intensive Care Syndrome (PICS), and lead to increased hospital resource use and decreased quality of life [3-6].

Since ICU treatment can be burdensome and the outcome may be disappointing, the benefit and harm of an ICU treatment should be assessed repeatedly [7]. Prognosis, proportionality and patient preferences should be aligned in order to provide proportional and goal-concordant care. This means that the ICU treatment must have the potential to realize patient-specific goals concerning survival, functional-outcomes and participation in society [8-10].

Although in the majority of patients who die in an ICU, a decision to withhold or withdraw life-sustaining therapy preceded death, previous studies reported high variability in the tendency to limit life sustaining therapy [11-14]. These variations were observed between countries, within countries and even between physicians within the same ICU [14,15]. Avoiding decision-making about limiting life support carries the risk of unjustified continuation of unlimited ICU treatment, potentially resulting in unwanted or disproportionate ICU treatment [16-20]. To prevent unjustified ICU treatments, ICU physicians are repeatedly challenged to evaluate the fit between prognosis and patient preferences. This should be done within a process of careful and shared decision-making, in which clinicians and patients or their surrogate decision-makers make rational, evidence based and individualized health care decisions [7]. For each individual ICU patient, the relevant information concerning prognosis, proportionality and patient preferences has to be integrated in the decision-making process on continuing or limiting life-sustaining treatments.

PART ONE. LONGTERM OUTCOMES OF ICU PATIENTS

In the first part of this thesis we explored the prognosis of ICU patients. In **chapter two**, we provide an overview of long-term outcomes of the heterogeneous group of ICU patients. Mortality in the ICU ranges from 8% of all patients to 20% of patients with an ICU stay of 7 days onwards. One third to half of ICU survivors suffer from the sequelae of ICU treatment, marked by an increased hospital resource use, decreased quality of life and newly acquired physical, cognitive or mental disabilities that persist after discharge.

Additionally, we wanted to understand how predictive factors perform during the ICU admission. In **chapter three** we showed that in the Dutch ICU population, antecedent patient factors (like age and co-morbidities) outperform acute admission characteristics (like diagnosis and severity of illness) in predicting one-year mortality for patients with an ICU length of stay of at least three days. For hospital mortality, this crossover was found for patients with a length of stay of seven days and onwards. After one week, length of stay in the ICU itself can not be used to predict mortality.

In the **fourth chapter**, we focussed on quality of life in ICU survivors by analysing the results of patient reported outcome measures filled out one year after ICU discharge. We showed that ICU survivors with a self-reported unacceptable outcome reported lower overall health related quality of life (measured with the EQ5D), mostly explained by symptoms of anxiety and depression. However, even with low overall health related quality of life, the majority of ICU survivors rated their health as being acceptable therefor lacking a EQ5D-score cut-off value indicating unacceptable outcome. We suggested that this divergence implies unmeasured factors that impact how patients perceive their outcome in terms of acceptance and illustrates that some patients have the the ability to adjust and give meaning to impairments [22-24].

PART TWO DECISION-MAKING ON INTENSIVE CARE TREATMENT

The second part of this thesis is dedicated to the process of decision-making on life-sustaining treatments in ICU patients.
The **fifth chapter** describes a review of 32 publications describing strategies aimed at improving the decision-making process on continuing versus limiting life-sustaining treatment in ICU patients. Despite the complexity, half of the studies evaluated a single aspect of the decision-making process. We found that the most effective strategies involved enhancing communication with patients and surrogates. Improving family-meetings by using a standardised format comprising the structure and topics of the meeting, making the communication protocol known to families and increasing the frequency of family-meetings was found to lead to more timely decisions. The review revealed the difficulty defining an outcome measure that is capable to reflect a true improvement in the quality of the decision-making process. The reduction of ICU length of stay for patients who eventually die in the ICU, seemed both valuable as well as feasible.

In **chapter six**, ICU physicians, ICU nurses, former ICU patients and surrogate decision-makers from 13 countries co-created a decision-making framework aimed to support and improve the decision-making process for ICU patients. In a three round Delphi study they reached consensus on a decision-making framework with four elements. Three refer to family-meetings; 1) an ICU admission meeting; aimed to inform the family and clarify treatment goals and resuscitation status, 2) a family follow-up meeting; inform and gather information on pre-morbid functioning, 3) a goals-of-care meeting; defining milestones and treatment goals in relation to patient preferences and values. The fourth element describes a (recurrent) time-out meeting where professional caregivers address prognosis and proportionality together with goals and/or limitations of treatment.

The **seventh chapter** describes the effect of the time-out meeting on length of ICU stay for patients who died within 90 days of ICU admission. A time-out meeting was held for every patient admitted in the ICU for at least 7 days and repeatedly weekly. During a multi-disciplinary meeting with consultants, nurses and ICU physicians, aspects that affect outcome (pre-morbid functioning and prognosis), current suffering and previously expressed preferences concerning outcome were addressed. We found that the use of the time-out meeting was associated with postponed decision-making, illustrated by an increased ICU length of stay for patients who died within 90 days. Systematic assessment of prognostic factors, increased understanding of the patient and his/her preferences and the weekly nature of the meeting, could have influenced this reduced tendency to limit life sustaining ICU treatments. Although in 60% of patients the time-out was noted in the electronic health record, we were not informed about goal-concordance of ICU care.

In the **chapter eight** we discuss the benefits, considerations and future opportunities of a ICU decision-making framework to support decision-making to continue or limit life-sustaining ICU treatments.

CONCLUSION

Deciding on life-sustaining ICU treatments requires the integration of prognosis and preferences in order to provide proportional and goal-concordant ICU care. During the ICU admission, the estimate of prognosis mostly requires knowledge on pre-morbid health. In addition, should the alignment of outcome with preferences, include the estimated appraisal of functional disabilities and quality of life. The use of a decision-making framework promotes a standardized process and an individualized assessment of prognosis, proportionality and preferences for every ICU patient. Its use can encourage goal-concordant ICU care and has the potential to prevent unwanted or non-beneficial care.

REFERENCES

1. http://www.stichting-nice.nl/doc/jaarboek-2018-web.pdf. Accessed March 2020
2. Brinkman S, de Jonge E, Abu-Hanna A, et al (2013) Mortality after hospital discharge in ICU patients. Crit Care Med 41:1229–1236. doi: 10.1097/CCM.0b013e31827ca4e1
3. Soliman IW, de Lange DW, Peelen LM, et al (2015) Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care 30:181–186. doi: 10.1016/j.jcrc.2014.09.009
4. Hofhuis JGM, van Stel HF, Schrijvers AJP, et al (2015) ICU survivors show no decline in health-related quality of life after 5 years. Intensive Care Med 41:495–504. doi: 10.1007/s00134-015-3669-5
5. Herridge MS, Tansey CM, Matté A, et al (2011) Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med 364:1293–1304. doi: 10.1056/NEJMoa1011802
6. Needham DM, Davidson J, Cohen H, et al (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 40:502–509. doi: 10.1097/CCM.0b013e318232da75
7. Kon AA, Davidson JE, Morrison W, et al (2016) Shared Decision-Making in Intensive Care Units. Executive Summary of the American College of Critical Care Medicine and American Thoracic Society Policy Statement. American Journal of Respiratory and Critical Care Medicine 193:1334–1336. doi: 10.1164/rccm.201602-0269ED
8. Sanders JJ, Curtis JR, Tulsky JA (2018) Achieving Goal-Concordant Care: A Conceptual Model and Approach to Measuring Serious Illness Communication and Its Impact. J Palliat Med 21:S17–S27. doi: 10.1089/jpm.2017.0459
9. Turnbull AE, Hartog CS (2017) Goal-concordant care in the ICU: a conceptual framework for future research. Intensive Care Med 43:1847–1849. doi: 10.1007/s00134-017-4873-2
10. Dinglas VD, Chessare CM, Davis WE, et al (2018) Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. Thorax 73:7–12. doi: 10.1136/thoraxjnl-2017-210234
11. Sprung CL, Cohen SL, Sjokvist P, et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. doi: 10.1001/jama.290.6.790
12. Prendergast TJ, Claessens MT, Luce JM (1998) A national survey of end-of-life care for critically ill patients. American Journal of Respiratory and Critical Care Medicine 158:1163–1167. doi: 10.1164/ajrccm.158.4.9801108
13. Higginson IJ, Koffman J, Hopkins P, et al (2013) Development and evaluation of the feasibility and effects on staff, patients, and families of a new tool, the Psychosocial Assessment and Communication Evaluation (PACE), to improve communication and palliative care in intensive care and during clinical uncertainty. BMC Med 11:213. doi: 10.1186/1741-7015-11-213
14. Mark NM, Rayner SG, Lee NJ, Curtis JR (2015) Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. Intensive Care Med 41:1572–1585. doi: 10.1007/s00134-015-3810-5
15. Barnato AE, Tate JA, Rodriguez KL, et al (2012) Norms of decision making in the ICU: a case study of two academic medical centers at the extremes of end-of-life treatment intensity. Intensive Care Med 38:1886–1896. doi: 10.1007/s00134-012-2661-6
16. Benoit DD, Jensen HI, Malmgren J, et al (2018) Outcome in patients perceived as receiving excessive care across different ethical climates: a prospective study in 68 intensive care units in Europe and the USA. Intensive Care Med 44:1039–1049. doi: 10.1007/s00134-018-5231-8
17. Piers RD, Azoulay E, Ricou B, et al (2014) Inappropriate care in European ICUs: confronting views from nurses and junior and senior physicians. Chest 146:267–275. doi: 10.1378/chest.14-0256
18. Piers RD, Azoulay E, Ricou B, et al (2011) Perceptions of appropriateness of care among European and Israeli intensive care unit nurses and physicians. JAMA 306:2694–2703. doi: 10.1001/jama.2011.1888

19. Huynh TN, Kleerup EC, Wiley JF, et al (2013) The frequency and cost of treatment perceived to be futile in critical care. JAMA Intern Med 173:1887–1894. doi: 10.1001/jamainternmed.2013.10261
20. Quenot J-P, Large A, Meunier-Beillard N, et al (2019) What are the characteristics that lead physicians to perceive an ICU stay as non-beneficial for the patient? PLoS ONE 14:e0222039. doi: 10.1371/journal.pone.0222039
21. Albrecht GL, Devlieger PJ (1999) The disability paradox: high quality of life against all odds. Soc Sci Med 48:977–988.
22. Rapkin BD, Schwartz CE (2004) Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. Health Qual Life Outcomes 2:14. doi: 10.1186/1477-7525-2-14
23. Hofhuis JGM, van Stel HF, Schrijvers AJP, et al (2009) Conceptual issues specifically related to health-related quality of life in critically ill patients. Crit Care 13:118. doi: 10.1186/cc7699
24. Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 48:1507–1515.

NEDERLANDSE SAMENVATTING

Elk jaar worden er in Nederland rond 80.000 patiënten op een Intensive Care (IC) behandeld. Deze patiënten vormen een heterogene groep. Ze verschillen in leeftijd, mate van kwetsbaarheid, co-morbiditeit en ziekte-ernst. Sommige van hen worden gepland op de IC opgenomen na een ingreep, terwijl anderen acuut op de IC worden opgenomen. Ook de kans op een goede uitkomst varieert. Hoewel de meerderheid van deze patiënten overleeft, zal een deel tijdens of kort na de IC opname komen te overlijden. Van de patiënten die overleven, houdt bovendien 30 tot 50% klachten die het gevolg zijn van de IC behandeling. Dit kunnen zowel lichamelijke, cognitieve als mentale klachten zijn, die in de literatuur vaak gezamenlijk het post-IC syndroom (PICS) worden genoemd. Ook hebben patiënten die een IC opname hebben doorgemaakt, in de periode erna meer ziekenhuisopnames en een verminderde kwaliteit van leven. Naast dat een IC behandeling niet altijd het gewenste resultaat heeft, is de IC behandeling zelf ook belastend. Veel patiënten ervaren tijdens een IC opname episodes van pijn, benauwdheid en/of verwardheid.

Om bovengenoemde redenen, moeten de voor- en nadelen van de IC behandeling steeds opnieuw kritisch tegen elkaar worden afgewogen. Prognose en voorkeuren van elke individuele patiënt moeten met elkaar in overeenstemming zijn, zodat de IC behandeling steeds gericht blijft op het halen van doelen die de individuele patiënt voor de toekomst wenst. In het Engels wordt hiervoor de term ‘goal-concordant’ gebruikt; de IC behandeling moet redelijkerwijs in staat zijn om patiënt-specifieke doelen te behalen op het gebied van overleving, functioneren en participatie in de maatschappij. Als er tijdens een IC opname geen momenten zijn waarop de prognose, proportionaliteit van de behandeling en patiënt voorkeuren worden geëvalueerd, bestaat het risico dat de behandeling ongewild of onterecht wordt doorgezet, of juist te snel wordt gestaakt.

Tussen landen, binnen landen en zelfs binnen één IC, wordt verschillend omgegaan met besluitvorming rondom het doorgaan, beperken of staken van de IC behandeling. Tegelijkertijd overlijden patiënten op de IC zelden zonder dat er een beslissing om de behandeling te beperken of stoppen aan is voorafgegaan. Daarnaast laten studies zien dat intensivisten en verpleegkundigen regelmatig het gevoel hebben dat ze disproportionele zorg leveren: zorg die niet past bij de wensen van de patiënt ten aanzien van toekomstig functioneren, of waarbij het lijden niet in verhouding staat tot de verwachte uitkomst.

Een zorgvuldig besluitvormingsproces waarbij de intensivist met de patiënt of zijn vertegenwoordiger de prognose en behandelwensen bespreekt om te komen tot een gezamenlijk besluit om de IC behandeling al dan niet door te zetten, is dan ook voor elke IC patiënt belangrijk.

DEEL 1. LANGETERMIJN UITKOMSTEN VAN IC PATIËNTEN

Kennis over de prognose is essentieel om de proportionaliteit en wenselijkheid van een IC behandeling te kunnen beoordelen. Helaas bestaat er geen model dat de (langetermijn) prognose van de individuele IC patiënt betrouwbaar kan voorspellen. Wel wordt steeds duidelijker dat patiëntkenmerken als kwetsbaarheid en pre-morbide functioneren, van grote invloed zijn op de overleving op de langere termijn. Hoe de verschillende factoren zich tot elkaar verhouden en zich ontwikkelen in relatie tot de ligduur, is nog niet bekend. Ook is het nog onduidelijk hoe beperkingen in het kader van PICS, de kwaliteit van leven van patiënten die een IC opname hebben overleefd beïnvloeden.

In **hoofdstuk twee** beschrijven we de langetermijn uitkomsten van IC patiënten. De IC mortaliteit van alle patiënten die op een IC worden behandeld is 8%, terwijl 20% in het eerste jaar overlijdt. Deze sterfte verdubbelt bij een opname van meer dan een week. De opnamediagnose, een acute of geplande opname en of een patiënt gezond was voorafgaand aan de IC opname heeft allemaal invloed op de kans op sterfte. Een derde tot de helft van de patiënten die de IC opname overleeft, houdt lichamelijke, cognitieve of mentale klachten. Slechts de helft van de patiënten die de IC overleeft kan terugkeren naar zijn of haar werk en veel patiënten rapporteren een verminderde kwaliteit van leven.

Omdat je tijdens de IC opname patiënten met een goede prognose wil kunnen onderscheiden van patiënten met een slechte prognose, onderzochten we in het **derde hoofdstuk** de voorspellende waarde van verschillende factoren op 1-jaars overleving en ziekenhuisoverleving tijdens opeenvolgende dagen op de IC. De eerste dagen bleken de acute kenmerken (zoals opnamediagnose en ziekte-ernst) de overleving het beste te voorspellen. Voor patiënten met een opnameduur van 3 dagen of langer, voorspelden patiëntkenmerken (zoals leeftijd en co-morbiditeit) de 1-jaars overleving echter beter dan de acute kenmerken. Voor ziekenhuisoverleving, lag het omslagpunt bij een opnameduur van 7 dagen. Ook vonden we dat na een week op de IC, de opnameduur geen effect had op ziekenhuis- of 1-jaarsoverleving.

In **hoofdstuk vier** gaan we dieper in op het effect van functionele beperkingen op de kwaliteit van leven van de patiënten die de IC opname hebben overleefd. We vonden dat voormalig IC patiënten die hun uitkomst niet acceptabel vonden, ook op de kwaliteit van leven vragenlijst lager scoorden. Angst en depressieve klachten verklaarden deze lagere waardering het beste. We konden geen afkapwaarde van deze kwaliteit van leven score (EQ5D index) definiëren die betrouwbaar correleerde met een niet-acceptabele uitkomst van de IC behandeling. Zelfs met een lage EQ5D-score, waardeerde drie kwart van de IC overlevers hun uitkomst als acceptabel. Deze vermeende discrepantie staat bekend als de 'disability-paradox' en kan verklaard worden door de 'response shift'. Mensen kunnen hun leven, ook met beperkingen, opnieuw waarderen als ze de veerkracht hebben om hun standaarden en waarden aan te passen.

DEEL 2. BESLUITVORMING RONDOM HET VOORTZETTEN OF BEPERKEN VAN DE IC BEHANDELING

De inschatting of een IC behandeling proportioneel is, vraagt om de beoordeling van de langetermijn uitkomst tegen de achtergrond van het huidige lijden en de wensen ten aanzien van toekomstig functioneren. Hiervoor moeten de behandelwensen van een patiënt helder worden gemaakt, een proces wat 'advance care planning' (ACP) of anticiperende besluitvormig wordt genoemd. Er is nog veel onduidelijk over hoe gedeelde en anticiperende besluitvorming op de IC het beste kan worden vormgegeven.

Het **vijfde hoofdstuk** geeft een overzicht van de interventies gericht op besluitvorming over levensreddende behandelingen op de IC, die eerder zijn onderzocht. De meest veelbelovende strategieën behelsden het verbeteren van de communicatie met patiënten en hun naasten. Meer familie-gesprekken met een vaste structuur, inclusief vaststaande onderwerpen, kan bijdragen aan tijdige besluitvorming. Deze review maakte ook duidelijk hoe moeilijk het is om een complex proces als besluitvorming, te beoordelen op één eindpunt dat tegelijkertijd recht moet doen aan de verschillende gezichtspunten van de deelnemers. We concludeerden dat een afname van de ligduur op de IC voor patiënten die uiteindelijk op de IC komen te overlijden, een redelijke en meetbare uitkomst zou kunnen zijn.

In het **zesde hoofdstuk** legden we in een Delphi studie de gevonden interventies voor aan experts uit 13 landen. In drie rondes bereikten IC artsen, IC verpleegkundigen, voormalig IC patiënten en naasten van voormalig IC patiënten consensus over een instrument dat het nemen van besluiten over doorgaan, beperken of staken van IC behandelingen tijdens de IC opname kan ondersteunen. Het ontwikkelde instrument bestaat uit vier elementen, waarvan drie contactmomenten met de (vertegenwoordiger van) de patient;1) een opnamegesprek; informeren en pre-existente behandelcode verifiëren, 2) een vervolggesprek; informeren en informatie over pre-morbide functioneren verzamelen, 3) behandeldoelen gesprek; mijlpalen en behandeldoelen afstemmen op de patiëntvoorkeuren. Het vierde element beschrijft een wekelijks evaluatie moment (een time-out) door de professionals waar prognostische items en individuele behandelwensen en –grenzen besproken worden om tot een behandelvoorstel te komen. Het instrument beoogt om besluiten over doorgaan, beperken of staken van IC behandelingen, in overeenstemming te brengen met prognose, proportionaliteit en patiëntvoorkeuren.

In **hoofdstuk zeven** beschrijven we het effect van de time-out meeting op de IC opnameduur voor patiënten die binnen 90 dagen na IC opname overlijden. Bij patiënten met een IC opname duur vanaf 7 dagen, werd tijdens een time-out met intensivisten, consulenten en de IC verpleegkundige, de proportionaliteit en wenselijkheid van de IC behandeling op een standaardiseerde wijze besproken. Het besluitvormingsinstrument bleek in de voor-na studie geassocieerd met uitstel van besluiten om de IC behandeling te beperken of te staken. We vonden een langere ligduur voor patiënten die 90 dagen na IC opname waren overleden en een hogere 90-dagen mortaliteit. Bij patiënten met een korte IC opname duur (< 7 dagen), was de mortaliteit juist afgenomen. Alhoewel niet-gerelateerde factoren kunnen hebben bijdragen aan het geobserveerde verschil, zou het methodisch nagaan van de prognose en wensen van de patiënt kunnen hebben geleid tot uitstel van besluiten om de behandeling te beperken of staken.

Het is nog niet zo gemakkelijk om de prognose te bepalen en die te gebruiken in een gestandaardiseerd besluitvormingsproces. In **hoofdstuk acht** beschrijven we de kansen, risico's en toekomstige toepassingen van een besluitvormingsinstrument voor IC patiënten. Met betrouwbare prognostische informatie en met voldoende kennis van de wensen van de patiënt, kan de IC zorg nog beter worden afgestemd op persoonlijke doelen. Daarnaast kan een gestandaardiseerd besluitvormingsproces waarin een team van professionals samen met de patiënt of zijn vertegenwoordiger, de individuele prognostische factoren en persoonlijke voorkeuren expliciet integreert in de besluitvorming, bijdragen aan het voorkomen van ongewenste of niet-zinvolle IC zorg.

9

APPENDICES

11a Intake forms; used to gather background information to support the time-out meeting
11b Besluitvormingsinstrument Nederlands

UMC Utrecht

PATIENTENSTICKER
(OOK PLAKKEN OP LAATSTE
BLAD)

Geachte heer of mevrouw,

Uw familielid of naaste is opgenomen op de Intensive Care. Wij doen er alles aan om onze zorg zo optimaal mogelijk te maken. Daarvoor is het van belang om een beeld te hebben van functioneren van onze patiënten vóór IC opname. Daarom willen wij u vragen of u de bijgevoegde vragenlijst in wilt vullen en daarbij te antwoorden wat het beste past bij uw familielid of naaste. Wij noemen uw familielid of naaste in deze vragenlijst ‘uw naaste’. Per vraag is maar één antwoord mogelijk, tenzij anders wordt vermeld.
Het kan voorkomen dat vragen in de afgelopen dagen misschien al gesteld of besproken zijn.
Na het invullen van de vragenlijst bespreekt u deze na met een arts of verpleegkundige. Als u nog vragen heeft, kunt u ze tijdens dat gesprek stellen.
Namens het behandelteam van artsen en verpleegkundigen; bedankt voor uw tijd.

1.1 Dit formulier is ingevuld door:	
Naam	………………………………………......
Relatie tot patiënt ***(bv partner, broer, vriendin)***	………………………………………......
Invuldatum formulier	………….-…………….-…………..

1.2 Wat was de opnamedatum in het ziekenhuis? **Hiermee bedoelen wij de aaneengesloten ziekteperiode (dit hoeft dus niet in het UMC Utrecht te zijn)**
………….-…………….-…………..

1.3 Kunnen wij Nederlands met uw naaste spreken?	
Ja	☐ (1)
Nee, hij/zij spreekt en verstaat alleen (taal invullen): **……………………………………………...………………………………………………** **……………………………………………..……………………………………………**	☐ (2)

1.4 Waar woonde uw naaste voor opname in het ziekenhuis?	
Zelfstandig thuis	☐ (1)
Thuis, maar met aanpassingen en verzorging	☐ (2)
Welke zorg kreeg uw naaste (bv mantelzorg, hulp bij lichamelijke verzorging, boodschappen, huishouden):……………………………………………………. **……………………………………………...………………………………………………**	

In een revalidatietehuis met als doel straks weer zelfstandig thuis te zijn	☐ (3)
In een verzorgingshuis of verpleegtehuis	☐ (4)
Naam instelling of organisatie die zorg verleent evt met contactpersoon/telefoonnummer: ……………………………………………………………………………………… ……………………………………………………………………………………… ……………………………………………………………………………………… ………………………………………………………………………………………	

1.5 Wat is de sociale situatie?	
Alleenstaand	☐ (1)
Getrouwd/langdurige relatie, met kinderen	☐ (2)
Getrouwd/langdurige relatie, zonder kinderen	☐ (3)
Geen relatie, wel kinderen	☐ (4)
Eventuele toelichting: ……………………………………………………………………………………… ………………………………………………………………………………………	

1.6 Wat is of was zijn/haar beroep?
…… ……
1.7 Wat deed uw naaste in zijn/haar vrije tijd graag?
…… ………………………………………………………………………………………

1.8 Heeft uw naaste een dieet? Hoe was de eetlust?
…… ………………………………………………………………………………………

1.9 Gebruikt uw naaste alcohol?	
Nee, geheel niet	☐ (1)
Ja, 0-2 eenheden per dag	☐ (2)
Ja, >2 eenheden per dag	☐ (3)
Onbekend	☐ (9)
Eventuele toelichting: ………………………………………………………………………………………	

1.10 Rookt uw naaste?	
Nee, nooit gerookt	☐ (1)
In het verleden (> 3 maanden geleden)	☐ (2)
Ja, hij/zij rookt of is < 3 maanden geleden gestopt	☐ (3)
Onbekend	☐ (9)
Eventuele toelichting (hoeveelheid, hoe vaak): …… ………………………………………………………………………………	

1.11 Gebruikt uw naaste drugs?	
Nee	☐ (1)
Ja, namelijk: ………………………………………………………………………………………………	☐ (2)
Onbekend	☐ (9)
Eventuele toelichting (hoeveelheid, hoe vaak): …… ………………………………………………………………………………	

Er volgt nu een aantal vragen over het algemeen lichamelijk en geestelijk functioneren van uw naaste zoals dat was tot circa een maand vóór de huidige ziekenhuisopname.
Als u het antwoord niet weet, kunt u 'onbekend' aankruisen in de bovenste regel.

2.1 Hoe gaan dagelijkse activiteiten? Onbekend ☐ (9) (bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)	
Geen problemen met dagelijkse activiteiten	☐ (1)
Enige problemen met dagelijkse activiteiten	☐ (2)
Niet in staat dagelijkse activiteiten uit te voeren	☐ (3)

2.2 Had uw naaste hulpmiddelen thuis? Kruis aan wat reeds van toepassing was: (meerdere antwoorden mogelijk) Onbekend ☐ (9)	
Bril/lenzen	☐
Gehoortoestel	☐
Kunstgebit	☐
Kunstvoeding via een (PEG) sonde	☐
Dagelijks extra zuurstof via een neusbrilletje of masker	☐
Anders namelijk: ……………………………………………………………………………… ………………………………………………………………………………………………	

2.3.1 Had uw naaste problemen met lopen?	**Onbekend ☐ (9)**
Geen problemen met lopen	☐ (1)
Enkele problemen met lopen: ***ga naar vraag 2.3.2***	☐ (2)
Vrijwel volledig bedlegerig	☐ (3)

2.3.2 Bij problemen met lopen , welk hulpmiddel gebruikt uw naaste?	**Onbekend ☐ (9)**
Loopt met hulp van een ander of een hulpmiddel zoals een rollator	☐ (1)
Zelfstandig in rolstoel	☐ (2)

2.4 Als uw naaste zelfstandig of met hulp kan lopen: Lukt trappen lopen?	**Onbekend ☐ (9)**
Ja, hij/zij kan zelfstandig de trap op en af	☐ (1)
Met hulp; verbaal of lichamelijk	☐ (2)
Nee, daar is hij/zij niet toe in staat	☐ (3)

2.5 Hoe gaat uw naaste van bed naar stoel en terug?	**Onbekend ☐ (9)**
Zelfstandig	☐ (1)
Daarbij is weinig hulp nodig	☐ (2)
Daarbij is veel hulp nodig	☐ (3)
Daar is hij/zij niet toe in staat	☐ (4)

2.6. Hoe gaat het wassen of aankleden?	**Onbekend ☐ (9)**
Geen problemen met wassen of aankleden	☐ (1)
Enige problemen met wassen of aankleden	☐ (2)
Niet in staatzichzelf te wassen of aan te kleden	☐ (3)

2.7 Hoe gaat het me de persoonlijke verzorging?	**Onbekend ☐ (9)**
Zelfstandig in verzorging van gezicht, tanden, haar en scheren	☐ (1)
Volledig hulpbehoevend	☐ (2)

2.8 Hoe gaat het met baden of douchen?	**Onbekend ☐ (9)**
Zelfstandig	☐ (1)
Volledig hulpbehoevend	☐ (2)

2.9 Hoe gaat het aan-/uitkleden?	**Onbekend ☐ (9)**
Zelfstandig	☐ (1)
Vrijwel volledig hulpbehoevend	☐ (2)
Volledig hulpbehoevend	☐ (3)

2.10 Hoeveel hulp heeft uw naaste nodig bij het eten?	**Onbekend ☐ (9)**
Zelfstandig	☐ (1)
Hulp nodig bij snijden en smeren	☐ (2)
Hij/zij is vrijwel volledig hulpbehoevend	☐ (3)

2.11 Wat is van toepassing op zijn/haar toiletbezoek?	**Onbekend ☐ (9)**
Zelfstandig	☐ (1)
Weinig hulpbehoevend	☐ (2)
Vrijwel volledig hulpbehoevend	☐ (3)

2.12 Wat is van toepassing op zijn/haar ontlasting?	**Onbekend ☐ (9)**
Geen problemen met de ontlasting	☐ (1)
Soms incontinent	☐ (2)
Incontinent	☐ (3)

2.13 Wat is van toepassing op zijn/haar urine?	**Onbekend ☐ (9)**
Geen problemen	☐ (1)
Soms incontinent	☐ (2)
Katheter of incontinent	☐ (3)

2.14 Heeft uw naaste chronisch pijn of andere klachten?	**Onbekend ☐ (9)**
Geen pijn of andere klachten	☐ (1)
Matige pijn of andere klachten	☐ (2)
Zeer ernstige pijn of andere klachten	☐ (3)
Eventuele toelichting: ……………………………………………………………………………………………… ……………………………………………………………………………………………… ………………………………………………………………………………………………	

2.15 Wat is over het algemeen zijn/haar stemming?	**Onbekend ☐ (9)**
Niet angstig of somber	☐ (1)
Matig angstig of somber	☐ (2)
Erg angstig of somber	☐ (3)

2.16 Wat is over het algemeen zijn/haar denkvermogen *(bijvoorbeeld: herinneren, concentreren, IQ-niveau)* **Onbekend ☐ (9)**	
Geen beperkingen in denkvermogen	☐ (1)
Enige beperkingen in denkvermogen	☐ (2)
Ernstige beperkingen in denkvermogen	☐ (3)

2.17 Heeft uw naaste een religie of levensovertuiging?

………

………

………

2.18 Welke uitgangspunten/waarden zijn op dit moment belangrijk voor uw naaste? *Wat geeft steun, houvast of troost?*

………

………

………

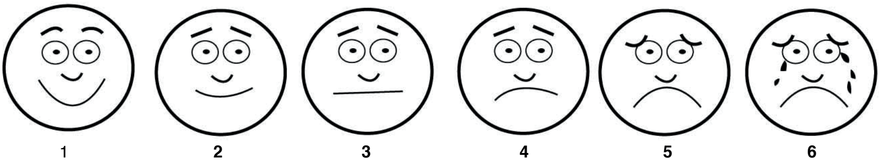
2.19 Welke muziek of radiozender luistert u naaste graag?

………

………

2.20 Kunt u op onderstaande schaal omcirkelen welk gezicht het beste overeenkomt met hoeveel plezier uw naaste had in het leven voor opname op de IC?

Levenslustig	**Overwegend somber**



2.21 Is er nog andere informatie die belangrijk kan zijn voor de artsen en verpleegkundigen?

……

……

……

3. Welke van de volgende afbeeldingen past bij het beste bij de situatie van uw naaste voor opname? Er is één antwoord mogelijk. Dementie kunt u apart noteren

	**Zeer Fit –** Mensen die krachtig, actief, energiek en gemotiveerd zijn. Deze mensen oefenen gewoonlijk regelmatig. Ze behoren tot de fitste van hun leeftijd.	☐ (1)
	**Fit –** Mensen die geen actieve ziektesymptomen hebben, maar minder fit zijn dan categorie ‘zeer fit’. Ze bewegen vaak of zijn meer actief tijdens seizoensgebonden activiteiten.	☐ (2)
	**Zelfredzaam –** Mensen wiens medische problemen goed onder controle zijn, maar niet regelmatig actief zijn, behalve routine wandelingen.	☐ (3)
	**Risico voor kwetsbaarheid –** Hoewel ze niet afhankelijk zijn van anderen voor de dagelijkse hulp, hebben ze vaak klachten die activiteiten beperken. Een veelgehoorde klacht is: ‘traag’, en/ of moe zijn gedurende de dag.	☐ (4)
	**Licht kwetsbaar –** Deze mensen zijn vaak duidelijk trager en hebben hulp nodig bij complexere dagelijkse activiteiten (financiën, vervoer, zwaar huishoudelijk werk, medicatie). Typisch is dat de lichte kwetsbaarheid winkelen, alleen buiten wandelen, maaltijdbereiding en huishoudelijk werk in toenemende mate belemmert.	☐ (5)
	**Matig kwetsbaar –** Mensen hebben hulp nodig bij alle activiteiten buitenshuis en bij het huishouden. Binnenshuis hebben ze vaak problemen met traplopen en hebben hulp nodig bij het douchen en mogelijk minimale hulp (aansporen) bij het aankleden.	☐ (6)
	**Ernstig kwetsbaar –** Volledig afhankelijk van persoonlijke verzorging, ongeacht de reden (fysiek of mentaal). Ze lijken stabiel en geen hoog risico te hebben op overlijden (binnen 6 maanden).	☐ (7)
	**Zeer ernstig kwetsbaar –** Volledig afhankelijk, het einde van het leven nadert. Typisch is dat ze niet meer kunnen herstellen, zelfs niet van een milde ziekte.	☐ (8)

	**Terminaal** – Het einde van het leven nadert. Deze categorie is alleen van toepassing op mensen met een levensverwachting van minder dan 6 maanden en die niet op een andere manier duidelijk kwetsbaar zijn.	☐ (9)

Heeft uw naaste dementie? Geef hier aan welke ernst:

☐ **Milde dementie**	(5)
☐ **Matige dementie**	(6)
☐ **Ernstige dementie**	(7)

Milde dementie : het vergeten van de details van een recente gebeurtenis, maar de gebeurtenis zelf herinneren ze wel, ze herhalen dezelfde vraag/ verhaal en trekken zich terug uit het sociale leven.

Matige dementie : recente gebeurtenissen worden slecht onthouden, hoewel ze schijnbaar de gebeurtenissen uit het verleden in het leven goed kunnen herinneren. Persoonlijke zorg is mogelijk met aansporing.

Ernstige dementie : volledig afhankelijk van zorg

4. De vragen op deze pagina gaan nog wat uitgebreider in op het denkvermogen.

Het gaat hierbij om het denkvermogen van uw naaste vóór de huidige ziekenhuisopname, vergeleken met 10 jaar geleden. Per onderdeel (1 t/m16) is één antwoordoptie mogelijk.

		Veel Beter (1)	**Iets beter (2)**	**Niet veranderd (3)**	**Iets slechter (4)**	**Veel slechter (5)**
4.1	Feiten herinneren over familieleden en vrienden, zoals beroepen, verjaardagen of adressen.	☐	☐	☐	☐	☐
4.2	Herinneren wat er pas geleden is gebeurd.	☐	☐	☐	☐	☐
4.3	Gesprekken herinneren van een paar dagen geleden.	☐	☐	☐	☐	☐
4.4	Onthouden van adres en telefoonnummer.	☐	☐	☐	☐	☐
4.5	Onthouden welke dag en maand het is.	☐	☐	☐	☐	☐
4.6	Onthouden waar iets normaal gesproken ligt.	☐	☐	☐	☐	☐
4.7	Iets weten te vinden dat niet op z'n gewone plek ligt.	☐	☐	☐	☐	☐
4.8	Omgaan met bekende huishoudelijke apparaten.	☐	☐	☐	☐	☐
4.9	Leren omgaan met nieuwe huishoudelijke apparaten.	☐	☐	☐	☐	☐
4.10	Nieuwe dingen leren in het algemeen.	☐	☐	☐	☐	☐
4.11	Het verhaal kunnen volgen in een boek of op TV.	☐	☐	☐	☐	☐
4.12	Beslissingen nemen over alledaagse dingen.	☐	☐	☐	☐	☐
4.13	Omgaan met geld voor de boodschappen.	☐	☐	☐	☐	☐
4.14	Geldzaken regelen, zoals het pensioen, bankzaken.	☐	☐	☐	☐	☐
4.15	Andere alledaagse rekenproblemen oplossen, zoals hoeveel eten er gekocht moet worden, weten wanneer familieleden of vrienden voor het laatst op bezoek zijn geweest.	☐	☐	☐	☐	☐
4.16	Het gezonde verstand gebruiken om te begrijpen wat er gebeurt en de zaken op een rijtje te zetten.	☐	☐	☐	☐	☐
4.17	**Onbekend**: ik kan geen van deze vragen over mijn naaste beantwoorden			☐		

Flowchart familie gesprekken

IC opname gesprek

Intensivist
Verpleegkundige
Patient/familie

< 24h

Verstrek informatie:
- Huidige medische situatie
- Behandelplan en interventies
- Mogelijke uitkomsten van behandeling
- Algemene informatie over de IC

Vraag naar:
- Wie is vertegenwoordiger van de patiënt
- Eventuele wilsverklaringen of uitingen van patiënt omtrent behandelbeperking

IC follow-up gesprek

Intensivist
Verpleegkundige
Patient/familie

< 2-3 dagen

Verstrek informatie:
- Huidige medische situatie
- Behandelplan en interventies
- Mogelijke uitkomsten van behandeling

Vraag naar:
- Functioneren voorafgaand aan deze opname
- ADL-zelfstandigheid, cognitie, mobiliteit, pijn, frailty, alcohol/drugs/roken, angst en depressie, religie en culturele achtergrond
- Behandeldoelen; acceptabele uitkomsten

Aanvullende bronnen van informatie over functioneren en behandelwensen:
Poortspecialist / huisarts / andere specialisten / medische status

Wekelijks familiegesprek over behandeldoelen

Intensivist
Verpleegkundige
Patient/familie

Optioneel: poortspecialist

< 5-7 dagen

Aansluitend op time-out.
Herhaal wekelijks

Verstrek informatie:
- Huidige medische situatie
- Behandelplan en interventies
- Prognose
- Voorstel team n.a.v. van time-out

Vraag naar:
- Reactie op uitkomst time-out
- Behoefte aan ondersteuning van de familie

Stel gezamenlijk vast:
- Doelen van de IC behandeling
- Eventuele behandelbeperkingen

TIME-OUT
Intensive Care

Intensivist
Verpleegkundige
Poortspecialist

Optioneel: andere artsen, maatschappelijk werk, revalidatie, fysiotherapie

< 5-7 dagen

Herhaal wekelijks

Bespreek pre-existent functioneren:
- Gebruik input van familie en huisarts
- Door patient ervaren kwaliteit van leven
- Zelfstandigheid; “frailty”

Bespreek huidige toestand:
- Gebruik input van IC verpleegkundige
- Medische situatie: diagnose en behandeling
- Lijdt patient onder de IC behandeling?

Bespreek behandeldoelen:
- Gebruik input van familie en huisarts
- Wat is een acceptabele uitkomst?
- Is de wens tot behandelbeperking geuit?

Bespreek prognose na ziekenhuis ontslag:
- Gebruik prognostische modellen
- Schatting 1 jaars overleving
- Kan patient revalideren en terug naar huis?

Conclusie:
- Bepaal behandedoelen en een eventuele tussentijdse mijlpaal
- Zijn behandelbeperkingen gewenst?
- Wanneer is het volgende familie gesprek?

LIST OF PUBLICATIONS

This thesis

Kerckhoffs, M.C., Soliman, I.W., Wolters, A.E., Kok, L, Schaaf, M., van Dijk, D.
Long-term outcome of Intensive Care Unit treatment.
Neth J Med. 2016; 160:A9653

Kerckhoffs, M.C., Brinkman, S., de Keizer, N.F., Soliman, I.W., de Lange, D.W., van Delden, J.J.M., van Dijk, D.
The performance of acute versus antecedent patient characteristics for 1-year mortality prediction during intensive care unit admission: a national cohort study.
Crit Care 2020; 24, 330

Kerckhoffs, M.C., Kosasi, F.L., Soliman, I.W, van Delden, J. J.M., Cremer, O.L., de Lange, D.W., Slooter, A.J.C., Kesecioglu, J., van Dijk, D.
Determinants of self-reported unacceptable outcome of intensive care treatment one year after discharge.
Intensive Care Med. 2019 Jun;45(6):806-814.

Kerckhoffs, M.C., Kant, M., van Delden, J. J.M., Hooft, L., Kesecioglu, J., van Dijk, D.
Selecting and evaluating decision-making strategies in the intensive care unit: a systematic review
J Crit Care. 2019 Jun;51:39-45.

Kerckhoffs, M.C., Senekal, J., van Dijk, D., Artigas, A., Butler, J., Michalsen, A., van Mol, M.M.C., Moreno, R., Pais da Silva, F., Picetti, E., Póvoa, P., Robertsen, A., van Delden, J. J.M.
A framework to support the process of decision-making on life-sustaining treatments in the intensive care unit: results of a Delphi study.
Crit Care Med 2020 May;48(5):645-653

Related publications

Haas, L.E.M., Kerckhoffs, M.C., Bakhshi-Raiez, F., Emmelot-Vonk, M.H., de Lange, D.W.
The admission of very old patients to our intensive care units: a review.
Neth J Crit Care January 2020;28(1): 6 – 12

Dijkstra-Kersten S.M.A., Kok L., Kerckhoffs M.C., Cremer O.L., de Lange D.W., van Dijk D., Needham D.M., Slooter A.J.C.
Neuropsychiatric outcome in subgroups of Intensive Care Unit survivors: Implications for after-care.
J Crit Care. 2020 Feb;55:171-176.

Haas, L.E.M., Kerckhoffs, M.C., Emmelot-Vonk, M.H., de Lange, D.W., van Dijk, D.
Too old for the intensive care unit? Backgrounds and challenges.
Neth J Med 2019;163:D4021

Kerckhoffs, M.C.
ICU aftercare, doing the right thing, the wrong way?
Neth J Crit Care 2019;27(5): 184 - 5

Other publications

Kerckhoffs, M.C., van der Sluijs, A.F., Binnekade, J.M., Dongelmans, D.A.
Improving patient safety in the ICU by prospective identification of missing safety barriers using the bow-tie prospective risk analysis model.
J Patient Saf. 2013 Sep;9(3):154-9.

Kerckhoffs, M.C., Hoskam, J.A., ten Tije, A.J.
Non-traumatic rupture of the spleen.
Neth J Med. 2011;155:A2935.

de Jongh, S, Kerckhoffs, M.C., Grootenhuis, M.A., Bakker, H.D., Heymans, H.S., Last, B.F.
Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolaemia and their parents.
Acta Paediatr. 2003 Sep;92(9):1096-101.

DANKWOORD

Het is af. Na momenten van intense blijdschap en grote frustraties, is er nu een proefschrift. Dit was er natuurlijk nooit gekomen zonder de hulp, coaching en medeleven van velen. Dank daarvoor!

Dit proefschrift heb ik afgerond in 2020, het jaar waarin COVID-19 de wereld op zijn kop zette. Ook het jaar waarin de heftigheid van een IC opname en bijbehorende nasleep bekendheid kreeg en het beroep intensivist ineens tot de verbeelding sprak.
Het is daarom extra jammer dat ik jullie bij mijn verdediging niet in levenden lijve zal/heb kunnen enthousiasmeren over de onderwerpen van mijn proefschrift. Als alternatief vind je op mijn website icudecisionmaking.com meer uitleg en informatie.

Professor van Dijk, beste Diederik, toen ik na mijn zwangerschapsverlof in 2014 terugkwam, kwam het onderwerp promoveren voor het eerst ter sprake. Na wat aarzelingen begon ik er een jaar later aan. En alhoewel de opstart me moeite kostte (je allereerste feedback luidde "in de wetenschap komt perfectionisme meer van pas dan efficiëntie"), kreeg ik er steeds meer plezier in. Dankzij jouw immer optimistische begeleiding ben ik de combinatie van kliniek en wetenschap juist heel erg gaan waarderen. Bedankt dat je met veel droge humor en een vleugje calvinisme naast een uitstekende promotor ook een prettige collega bent. Ik hoop nog jaren met je samen te mogen werken.

Professor van Delden, beste Hans, het was meteen duidelijk dat jij mijn tweede promotor moest worden. Als medisch ethicus, als arts, als wetenschapper en als mens heb je dan ook een zeer waardevolle bijdrage geleverd aan mijn onderzoek. Hoe jij de afgelopen jaren steeds kritisch de ethische kant van mijn plannen beschouwde, heb ik zeer gewaardeerd. Al waren je aantekeningen meestal minimaal een half jaar geleden opgeschreven, jij wist meteen weer de juiste vragen te stellen om mij op scherp te zetten. Veel dank voor deze fijne samenwerking.

Prof. dr. J.M.A. Visser-Meily, prof. dr. E. de Jonge, prof. dr. S. Van de Vathorst, prof. dr. H.A.H. Kaasjager, prof. dr. D. Benoit, dank voor uw bereidheid zitting te nemen in mijn beoordelingscommissie.

Professor Kesecioglu, beste Jozef, als afdelingshoofd heb jij voor ieder staflid een plan en voor mij was dat promoveren. Dank voor de lichte druk die je daarvoor hebt uitgeoefend. Ik ben blij dat ik het gedaan heb.

Professor de Smet, beste Annemarie, het is een mooi dat wij een krachtige vrouw aan het roer van onze divisie hebben. Dank voor je interesse en support.

Long-term follow-uppers; Dylan, Olaf, Arjen, Wietze, Jacqueline en Sandra. Dank voor jullie snelle, kritische en waardevolle feedback op mijn manuscripten. En dank voor de motiverende kopjes koffie. Het was ontzettend leerzaam om met jullie samen te werken en na te denken over onze follow-up. Hopelijk volgen er nog veel meer mooie projecten.

Ivo, Felicia, Jannien, Matthijs, Sylvia en Sandra, dank voor jullie hulp! Ivo, mijn voorganger in deze onderzoekslijn. Dank voor je epidemiologische kennis en bereidheid om me weer eens een statistische toets uit te leggen. Felicia, door jouw inzet en toewijding hebben we van jouw wetenschapsstage zo'n mooi artikel kunnen maken. Tot binnenkort op de IC! Matthijs, wat goed dat jij nu gaat promoveren binnen de divisie vitale functies. Jannien, als Zuid-Afrikaanse vanuit Australië via de UK naar NL komen voor de liefde, verdient heel veel lof en respect. Ik hoop dat je de komende jaren vooral kunt gaan genieten van je gezin, waar ook ter wereld. Sandra, dat je zelfs tijdens je verhuizing nog mijn data wil checken, zegt genoeg. Dank je!

Lennie, in 2005 nam ik pieper *1255 van je over in het 'Gooische Reservaat' en nu ben je vandaag mijn paranimf. Jij bent niet alleen een fijne collega, je bent mijn failure-friend, uitstekende promotie-coach, gezellige kamer- en reisgenoot en super barista. Tijdens het promotietraject kon jij elke keer met een korte analyse mijn probleem in het juiste perspectief plaatsen. Dat maakt jou zo'n getalenteerde wetenschapper. Ik kan niet wachten tot ik voor jou een film mag maken.
Inge, het is mooi hoe wij ons over dezelfde dingen kunnen verbazen, opwinden en lachen. Dat jij als mijn andere kamergenoot, mijn paranimf wil zijn, waardeer ik zeer.
Jeannine, het is fijn om in dezelfde levensfase, ook allerlei ambities met elkaar te delen. Die ambities bespreken onder het genot van een wijntje, houden we erin. En dan wel graag coronaloos.

De andere stafleden van de IC; Marjel, Dirk, Maarten, Alex, Joris, Nuray, Marc, Maaike, Marjon en de PAs; Sanul, Lidwina, Mariska, Esther en Pieter, dank voor jullie bemoediging en medeleven. We zijn een fijne groep collega's omdat ieder zijn of haar kwaliteiten kan inzetten en we met elkaar kunnen lachen.

Alle IC verpleegkundigen van het UMCU, wat is het toch leuk om met jullie te werken! Ook op de drukste dagen wordt er gelachen en is er interesse in elkaar. Jullie kritische vragen over wel of niet doorbehandelen bij onze IC patiënten, liggen aan de basis van dit proefschrift.

Rosalie, Christine en Astrid. Zonder jullie zou het secretariaat een saaie boel zijn. Even bijkletsen na de vakanties, het wel en wee van de families bespreken en tussendoor nog de administratie, roosters en planning scherp houden, jullie doen (of deden) het. Bedankt!

MMALS, mijn lieve vriendinnen Marije, Anke, Lotte en Sara. Sinds Berlijn eten we bijna elke maand met elkaar. Jullie vriendschap is me heel dierbaar. De mooie gesprekken die we met elkaar hebben, geven onze vriendschap waarde. Hopelijk blijven we dit nog heel lang volhouden.

Pomme, Mariëlle, Yolanda. Als sinds onze studie zijn we vriendinnen. Uitgewaaierd in verschillende vakgebieden en allemaal Amsterdam uit, delen we een mooie vriendschap. Gelukkig wonen we nog steeds op date- en eet-afstand!

Simone, Francien, Leontien en Floor. Ik verraad liever niet hoe lang we al samen tennissen, maar dat tennissen niet mijn corebusiness is moge duidelijk zijn. Met elkaar ons lief en leed bespreken onder het genot van een koffie of biertje, vind ik elke week weer fijn. Dank voor jullie gezelligheid én interesse in mijn wetenschappelijke ambities.

Pinkstervrienden, in ons 10^{e} Pinksterweekend stuurde ik het manuscript voor dit proefschrift in. Dank voor jullie medeleven en interesse, maar veel meer nog voor de vriendschappen. Zo soepel als deze weekendjes gaan, zelfs met 1,5 meter afstand en 21 (!) kinderen, is echt uniek. Zonder iemand tekort te willen doen, een speciale vermelding voor Lotte&Remko, Sara&Jeroen en Machteld&Armand. Onze vakanties samen zijn altijd goed. Met lekker eten, goede wijn en een finca, tent of camper komen wij een heel eind. Wat fijn om zulke dierbare vrienden te hebben.

Familie Lens, ik kreeg er met Carl een hele fijne familie bij. Jullie warmte, oprechte interesse in mij en mijn promotietraject waardeer ik enorm.
Robert, dat Christine dit niet kan meemaken is ongelooflijk verdrietig. Ik had heel graag met jullie samen in het bos over mijn proefschrift gesproken. Weet dat jij voor de kinderen altijd opa Robert zal blijven.

Leon en Taylor, mijn broer en schoonzus aan de andere kant van de oceaan. Al scheidt een oceaan ons fysiek, we blijven bij elkaar betrokken. De kans dat jullie bij mijn promotie kunnen zijn, is inmiddels zo goed als uitgesloten (reisbeperkingen ivm het coronavirus, zie eerder). Daar balen we allemaal van, maar het is niet anders. Weet dat ik van jullie hou en me verheug op de kleine Kerckhoffs-Robinson.

Lieve mama, ik ben ongelooflijk trots op jou. Ondanks ons grote verdriet over het verlies van papa, heb jij Leon en mij liefdevol opgevoed tot de gelukkige mensen die we nu zijn. Ook vandaag doet het pijn dat hij er niet meer is. Maar de dankbaarheid dat wij hier nu samen zijn, overheerst. Dank je wel, ik hou van je.

Carl, liefde van mijn leven! Jouw onvoorwaardelijke liefde en support zijn van onschatbare waarde en dat geldt voor veel meer dan alleen voor deze promotie. Dat wij ook nog zulke fantastisch leuke kinderen hebben, maakt mij elke dag gelukkig.
Lieve Lieuwe, Mette en Leonoor, de promotie is af. Ik hou van jullie en hoop nog vele mooie avonturen met jullie te mogen beleven.

CURRICULUM VITAE

Monika Cecilia Kerckhoffs was born October 17th 1978 in Schiedam. In 1997 she graduated from the Dominicus College (Gymnasium) in Nijmegen. In the same year, she moved to Amsterdam to start her medical studies at the University of Amsterdam. During her medical training, she participated in research on Familial Hypercholesterolemia, conducted her master thesis in Ethiopia and ended her training with a clinical rotation in Namibia. She graduated cum laude in 2004.

In 2005 she started as a resident in internal medicine in Gooi Noord, Blaricum (dr. H.P.M. Muller) where she got excited to specialize in intensive care medicine. After returning to the Academic Medical Center in Amsterdam, she completed her training in internal medicine (prof. dr. P. Speelman) and her intensive care residency (prof. dr. M.B. Vroom) in 2011. Earlier that year she had obtained the European Diploma in Intensive Care (EDICI+II). In 2012 she started as an internist-intensivist in the University Medical Center in Utrecht.

Monika started her PhD in 2015 under the supervision of prof. dr. D. van Dijk and prof. dr. J.J.M. van Delden and received a research grant from the European Society of Intensive Care Medicine (ESICM) in 2017.

In the UMC Utrecht Monika coordinates the training of fellows and residents in intensive care medicine as deputy program director and conducts internal audits in other medical specialties. In addition, she performs quality audits for the Dutch Society of Intensive Care Medicine (NVIC) and is a member of the section on Ethics of the ESICM.

Monika is married to Carl Lens and together they have three fantastic children, Lieuwe (2010), Mette (2011) and Leonoor (2014).