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The MONITOR-IC study, a mixed method prospective multicenter controlled cohort study assessing five-year outcomes of ICU survivors and related healthcare costs: a study protocol

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ABSTRACT

Introduction: Due to advances in critical care medicine, more patients survive their critical illness. However, intensive care unit (ICU) survivors often experience long-term physical, cognitive and mental problems, summarized as post intensive care syndrome (PICS), impacting their health related quality of life (HRQoL). In what frequency PICS occurs, and to what extent this influences ICU survivors' HRQoL, is mostly unknown.
The aims of this study are therefore to study the: 1) five-year patient outcomes, 2) predictors for PICS, 3) ratio between HRQoL of ICU-survivors and healthcare related costs, and 4) care and support needs.

Methods: The MONITOR-IC study is a multicenter prospective controlled cohort study, carried out in ICU units in four Dutch hospitals. Patients will be included between July 2016 and July 2021 and followed for five years. We estimated to include 12,000 ICU-patients. Primary outcomes; HRQoL and physical, cognitive and mental symptoms. Secondary outcomes; ICU survivors' care and support needs, their healthcare use and related costs. A control cohort of otherwise seriously ill patients will be assembled to compare long-term patient reported outcomes.
We will use a mixed methods design, including questionnaires, medical data from patient records, cost data from health insurance companies and interviews with patients and family members.

Ethics and dissemination: Insights from this study will be used to inform ICU-patients and their family members about long-term consequences of ICU care, and to develop prediction and screening instruments to detect patients at risk for PICS. Subsequently, tailored interventions can be developed and implemented to prevent and mitigate long-term consequences. Additionally, insights into the ratio between HRQoL of ICU-patients and related healthcare costs during five-years after ICU admission, can be used to discuss the added value of ICU care from a community perspective.
The study has been approved by the Medical Ethical Reviewing Committee (2016-2289).

KEYWORDS

Cohort studies; Critical care; Follow-up studies; Intensive Care Units; Long-term outcome; Outcome Assessment; Post intensive care syndrome; Quality of life

STRENGHTS AND LIMITATIONS OF THIS STUDY

- The strength of the MONITOR-IC study is the thorough and comprehensive methodological approach, inclusion of thousands of ICU patients, five year follow-up, use of mixed methods and the combination of data regarding patients' HRQoL, healthcare use and patients needs.
- The baseline questionnaire includes questions relating to the patient's situation before the ICU admission. Therefore, we are able to compare the experienced post IC symptoms and related HRQoL with the situation before the admission.
- We aimed to included more than 12,000 patients. However, patients have to fill in eight questionnaires during five years. High loss to follow up rates are likely due to high mortality rates.
- Moreover, PICS does not only occur among ICU survivors, but also among their family members and relatives, also called PICS-Family (PICS-F). At the time of writing this protocol, we decided to focus on ICU survivors, and not their family members. In the future extension of this study, family members might be included as well.

INTRODUCTION

The number of patients admitted to the Intensive Care Unit (ICU) is increasing every year.[1] Meanwhile, advances in medical technologies allow more patients to survive their critical illness.[2] With this growing number of ICU survivors, there is an urgent need to shift our focus from short-term mortality to long-term outcomes of ICU survivors.[1 3]

In 2002, the members of the international surviving intensive care Roundtable already discussed whether ICU survivors have optimal long-term outcomes, and whether decisions regarding ICU care would change with increasing knowledge of outcomes[4] and the associated costs.[3] Costs of ICU care are high; 20% of the total hospital budget, with cost per day between three-and fivefold greater in ICU departments than in general wards.[5] These high costs are due to the need for highly trained staff, expensive modern equipment, and intensive use of diagnostic tests, pharmaceuticals and interventions.[6] Although economic evaluation of care in the ICU is often ethically difficult,[6] understanding of the costs and consequences associated with technologies, services and programs aimed at reducing mortality and morbidity of critically ill patients is important.[6 7]

Over the last two decades, it has become more and more clear how devastating and long-lasting the post-discharge consequences can be, and what the impact is on ICU survivors and their family.[8] These long-term consequences are called post-intensive care syndrome (PICS), defined as 'new or worsening impairment in physical, cognitive, or mental health status arising and persisting after hospitalisation for critical illness.[2] Examples of these physical impairments are pain, breathing difficulties, fatigue and loss of bodyweight resulting in physical weakness and problems in daily functioning and activities.[1 8 9] A total of 10 to 75% of the ICU survivors are still suffering from these difficulties one year later.[10] Cognitive problems, such as problems with memory, processing, planning and problem solving, are seen in 30-80% of the ICU survivors.[2 8] Although these impairments can improve over several months, they can persist for many years as well.[11] In addition, mental impairment, such as depression, anxiety and sleep disturbances, are common.[1 2 12] Up to 50% of the ICU survivors suffer from symptoms of posttraumatic stress disorder (PTSD), which can persist for 8 years.[2] Moreover, ICU survivors experience a significant socio-economic burden, because of long-term sick leave, early retirement and need for assistance at home which is primarily given by informal caregivers, impacting on family income.[13 14] Furthermore, ICU survivors experience a lower quality of life,[15] leading to high utilization of healthcare services and related costs.[13 16]

Although some risk factors for PICS are known (such as immobility, pre-existing impairments, age, sedation, duration of mechanical ventilation, delirium and sepsis),[3 11 17] continued investigation of risk factors and underlying mechanisms is essential to understand which subgroups of patients are prone to develop PICS.[3 11] Interventions and strategies to

prevent or mitigate PICS, such as ICU diaries, early mobilisation, post-discharge rehabilitations and follow up consultations with specialised nurses for ICU survivors, were recently described.[1 18-22] However, conclusive evidence for these interventions is lacking or limited.[2 18 19 21] Moreover, the majority of the healthcare professionals is still not aware of PICS, and interventions available for ICU survivors are therefore often not provided.[1 3]
More insight is necessary to better define the scope of long-term ICU symptoms and associated healthcare costs.[3] Incidence rates of PICS differ largely in studies, which is due to differences in study patient populations, co-morbidities, measurement tools and timeframes.[2] Additionally, previous studies addressing PICS often have limited focus or methodological limitations such as small sample sizes, low response rates, short follow-up, use of non-validated or unreliable instruments, no control group and absence of a pre-admission (baseline) measurement.[23-28]
For this reason, we set up a controlled cohort study called the MONITOR-IC. In this study, with a five years follow-up, we aim to study the ICU survivors' long-term outcomes, their HRQoL and their needs, in order to identify specific types of patients who are at risk for specific impairments, factors affecting their recovery and to target effective interventions both in the ICU and later during the fragile recovery period.[3 8 29] Additionally, we aim to get more insight into the ratio between the HRQoL and related healthcare costs to discuss the added value of ICU care from a community perspective.

OBJECTIVES

Overarching objective

To obtain more insight into the long-term outcomes and HRQoL of ICU survivors during five years following ICU admission, in order to ultimately improve care for ICU patients.

Specific research questions

1. What are the post intensive care symptoms that patients experience during five years after ICU admissions and what is their HRQoL?
2. What are important predictors for PICS?
3. What is the ratio between HRQoL and healthcare related costs?
4. What are the care and support needs of ICU survivors during five years after ICU admission?

METHODS/DESIGN

Study design and setting

The MONITOR-IC study is a multicenter prospective controlled cohort study in which long-term outcomes of ICU patients are studied for a period of five year.

The study will be carried out in ICUs of four hospitals in the Netherlands; one academic hospital, one teaching and two non-teaching hospitals. ICU patients will be recruited between July 2016 and July 2021 with a subsequent follow-up for five years.
Mixed methods will be used to collect data, including questionnaires, medical data from patient records, cost data from health insurance companies and interviews with ICU survivors and their family members.
To study if the long-term effects are unique for ICU survivors, we also include a control cohort of seriously ill patients, who were not or less than 12 hours admitted to the ICU.

Study population and eligible criteria

ICU patients are eligible to participate when they are 16 years or older; admitted at least 12 hours to a trauma, medical, neurosurgery or cardiac surgery ICU; and gave written informed consent (or by their legal representative).
Patients are eligible for the control cohort when they are 16 years or older and admitted either to the ICU for less than 12 hours, or to the Post Anaesthesia Care Unit (PACU), the medium care or ICU step-down unit.
Patients are not eligible for the study when they have a life expectance of <48 hours; receive palliative care; are admitted for a donor procedure; cannot read and speak the Dutch language; or are not able to fill in the questionnaire and do not have family members/ legal representatives either.

Assuming an annual hospital admissions of approximately 2,500 patients in the academic hospital and 2,200 patients in the three other hospitals, 23500 patients could be included during the five years. Expecting an inclusion rate of 60%, we estimate to include 12,000 patients. In the control cohort, we will include approximately 3000 patients during the next four years.

Patient recruitment

Patients scheduled for ICU admission after elective surgery, will be recruited at the outpatient clinic (anaesthesiology or cardiac surgery) (Figure 1). Patients with a non-scheduled admission will be recruited at the ICU. Patients will receive information by ICU nurses and intensivists regarding the aim, content and relevance of the study, and will be asked for participation. Informed consent is asked for the questionnaires, data from the patients' individual medical record and data from their health insurance company. In case patients are unable to give consent, their legal representative will be asked.

[Figure 1]

Outcomes measures

The primary outcomes of the MONITOR-IC study are the HRQoL among ICU survivors and their physical (fatigue, vulnerability and frailty), cognitive and mental (anxiety, depression and stress) impairments. Secondary outcomes are the patients' care and support needs, their healthcare use, and related costs.

Data collection

Different methods will be used to collect data among ICU patients, including questionnaires, patients' medical record (MR), database of healthcare cost data of Dutch health insurance companies (Vektis) and interviews with patients and their family members (Table 1).

Table 1: Research questions and methods

Research question	Methods
1. What are the post intensive care symptoms that patients experience during five years after ICU admission and what is their HRQoL?	Questionnaires MR
2.What are important predictors for PICS?	Questionnaires MR
3.What is the ratio between HRQoL and healthcare related costs?	Questionnaires Health insurance database
4.What are the care and support needs of ICU survivors during five years after hospital admission?	Questionnaires Interviews with ICU survivors and their family members

Questionnaires

All patients will be approached to fill in the paper based or online questionnaire (depending on their or legal representative preferences) in total eight times: at ICU admission (T0), at hospital discharge (T1), after 3 months (T2), 12 months (T3), 24 months (T4), 36 months (T5), 48 months (T6) and 60 months after ICU admission (T7).

The components in the questionnaire vary at different measurement points (Table 2). The main components are:

- Patients' *health status* and *HRQoL* are assessed using the SF-36[30] and the EQ-5D-5L.[31] The SF-36[30] consist of 36 questions aggregated into eight domains: 1) physical functioning, 2) role limitations because of physical health problems, 3) bodily pain, 4) social functioning, 5) general mental health, 6) role limitations because of emotional problems, 7) vitality and 8) general health perceptions. Each domain is scored from 0

(worst score) to 100 (best score). The Sf-36 yields eight domain scores and two summary scores: the physical component summary (PCS) and mental component summary (MCS) scores.

The EQ-5D-5L[31] comprises a 5-item questionnaire consisting of five domains: 1) mobility, 2) self-care, 3) usual activities, 4) pain and discomfort and 5) anxiety and depression. The EQ-5D-5L also comprises a visual analogue scale (VAS) to record perceptions of the participants own current overall health.

- *Physical impairments* are assed using the Clinical Frailty Score (CFS)[32] to assess vulnerability and frailty; a 9-point scale ranging from 1 'Very fit' to 9 'Terminally ill'. Fatigue is measured using the CIS-8, a subscale of the Checklist Individual Strength (CIS-20),[33] consisting of eight questions relating to experienced fatigue using a 7-point scale: 1 (yes, that is true) to 7 (no, that is not true). A score of 35 or more indicates sever fatigue.

- *Cognitive impairments* are measured using the validated abbreviated[34] Cognitive Failure Questionnaire (CFQ).[35] This short form scale consists of 14 items, instead of 25. Each item is scored on a 5 point sale, ranging from 0 (never) to 4 (very often).

- *Mental impairments* are assed using the Hospital Anxiety and Depression Scale (HADS) to determine the levels of anxiety and depression.[36] The scale consists of 14 questions: seven regarding anxiety (HADS-A) and seven regarding depression (HADS-D). Each item on the questionnaire is scored on a 4-point scale, ranging from 0-3. Scores range between 0 and 21 for depression and for anxiety. Higher scores indicate higher symptom frequencies: 0-7 is normal, 8-10 is mild, 11-14 is moderate and 15-21 is severe. Subjective distress, caused by traumatic events, will be measured using the Impact of Event Scale Revised (IES-R).[37] This lists consists of 22 questions, with a 5-point scale ranging from 0 (not at all) to 4 (extremely). Total scores range from 0 to 88, with score of 33 or above as best cut off for a probable diagnosis of PTSD.

- *Care needs* and *support from professionals and informal caregivers* are measured using questions created by our research team, inspired by previous studies among chronic patients.[38] Examples of included questions are: Do you need extra support in your daily activities? What kind of support do you get at this moment?

- *Social consequences* are measured using the novel question set designed by Griffiths et al., (2013)[13] to determine changes in family circumstances, socio-economic stability and care requirements.

Medical record

Patients' demographics and information regarding diagnosis and treatment, such as primary conditions, pre-existing co-morbidity, disease severity, sepsis, (re)admission, mechanical ventilation, length of ICU stay, delirium and medication will be extracted from the medical record (Table 2).

Health insurance data

Healthcare use and related costs, covered by the Dutch healthcare insurance, will be retrieved from Vektis; a Dutch organization which collects and manage health insurance claimed data of all health insurance companies in the Netherlands.[39] This data is collected based on the Diagnosis Treatment Combination (DTC); a total set of activities carried out by the hospital and medical specialists. Additionally, data is collected regarding nursing days, visits at the outpatient clinic and emergency department, nursing homes, ambulance transport, consultation with general practitioner, paramedical care (including physiotherapist, occupational therapist, dietician and speech therapist), prescribed medication, mental healthcare and revalidation. The Vektis database contains data from all for healthcare insured citizens and covers 99% of the total Dutch population. Using patient's unique insurance number we are able to merge patient's insurance data with the questionnaire data and medical data from the medical record at patient level.
Care delivered by community nurses and informal caregivers is not included in the Vektis database and will be studied via the questionnaire.

Interviews

To get insight into the experiences of ICU survivors during five years after ICU admission and their need for support, face to face semi-structured interviews will be conducted with ICU survivors and their family members. Interviews will take place at the participants' preferred location (home or clinic). Interviews will be conducted until data saturation is reached. Patients will be purposively sampled based on various experienced outcomes and experienced needs. Experienced and trained researchers will conduct the face-to-face interviews using a topic guide. This guide will be developed using the current literature and experience of the research team and covers the following subjects: experiences with the ICU admission and follow-up, experienced problems and needs for support. All interviews will be audio recorded and transcribed verbatim.

Table 2. Overview of used scales in the questionnaire and timeframe

Methods	Outcome	Used scales	T0	T1	T2	T3	T4	T5	T6	T7
			(ICU-) admission	Discharge hospital	3 months	12 months	24 months	36 months	48 months	60 months
Questionnaire	Demographic data		X							
	Health status and HRQoL	SF-36	X		X	X	X	X	X	X
		EQ-5D	X		X	X	X	X	X	X
	Physical impairments	CFS	X	X	X	X	X	X	X	X
		CIS-8	X		X	X	X			
	Cognitive impairments	CFQ-14	X		X	X	X			X
	Mental impairments	HADS	X		X	X	X			X
		IES-R			X	X	X			X
	New symptoms after ICU admission				X	X	X	X	X	X
	Care needs and professionals support/ informal caregivers				X	X	X			X
	Social consequences					X	X			X

Analysis

Questionnaires, medical record and health insurance data

During the data collection, data are checked on a regular basis to identify out-of-range answers, inconsistent responses, and missing data. Data from the questionnaires, medical record and healthcare insurance data will be merged at patient level. Descriptive statistics will be used to describe baseline characteristics and the incidence of long-term outcomes. Regression analysis will be used to determine associations between patient characteristics, treatment, and long-term outcomes. In order to predict PICS, a prediction model will be developed. Multivariable linear (for continuous outcome variables) and logistic (for dichotomous outcome variables) regression analysis will be performed. Linear and logistic multilevel models will be used to compare long-term outcomes between the study population (cohort) and control cohort group. Software Package for the Social Sciences (SPSS) will be used for data analysis.

Interviews

For the analysis of the interview data, the constant comparative method[40] will be used. Relevant data will be identified and structured by open, axial and selective coding. Two researchers will independently code the transcripts to minimize subjectivity in findings. Data analysis will be supported with the use of Atlas.ti, a qualitative data analysis program.

Ethics

The MONITOR-IC study will be conducted complying the Dutch Personal data protection act. The study has been approved by the Medical Ethical Reviewing Committee region Arnhem-Nijmegen (2016-2289). The study will be registered in the ClinicalTrials.gov database.

Relevance of findings

The MONITOR-IC study will generate more insight into the long-term outcomes of ICU survivors, their healthcare use and their needs (Box 1). This knowledge is of importance for patients, healthcare professionals, managers and health insurers to develop and evaluate the (after)care for ICU patients taking their health status and needs into account.
Patients and their family members could be better informed about the possible long-term physical, cognitive, mental and social consequences after ICU discharge. Moreover, the inclusion of thousands of ICU patients in this study, allows us to study several patient subgroups; for example the quality of life and specific care needs of patients after sepsis, acute respiratory distress syndrome or delirium. Using these disease specific insights,

prediction and screening instruments can be developed to determine patients at risk for long-term consequences. Subsequently, interventions, such as diaries, early mobilisation and follow-up consultations for patients and their family members, can be established and implemented to prevent or mitigate long-term consequences. Furthermore, long-term effects of important changes in health policy will be visible, whereby evaluation of effectiveness and efficacy of (changes in) policy on micro, meso and macro level is possible. Healthcare professionals will be better able to weigh up the options in the decision making process concerning ICU admission, treatment options and the added value for individual patients, which will improve shared decision making with patients and their families as well. Finally, this study gives more perspectives into the ratio between the patients' HRQoL and healthcare costs. Over the last decades, the ICU care is overwhelmed with new and also costly technologies and therapies, resulting in increasing costs, but without actually insight in the added value for patient and their health outcomes. Consequently, an open ethical dialogue, based on this ratio and what this ratio might be, is then possible.

Box 1 Relevance of study

1. Information about long-term outcomes for patients and their family members
2. Support for treatment choices for multiple medical specialties, in particular intensive care
3. Coordination of care by personalised follow up care for post ICU patients
4. Adjustments in healthcare policy for post ICU patients
5. Screenings instrument for early signs and symptoms
6. Establishing and implementing interventions to prevent or mitigate long-term consequences
7. Information for health insurance companies for purchasing care and professional associations for guideline development
8. Detecting unnecessary ICU care
9. Evaluation of changes in ICU healthcare policy on long term effects

The strength of the MONITOR-IC study is the thorough and comprehensive methodological approach, inclusion of thousands of ICU patients, five year follow-up, use of mixed methods and the combination of data regarding patients' HRQoL, healthcare use and patients needs. Moreover, the baseline questionnaire includes questions relating to the patient's situation before the ICU admission. Therefore, we are able to compare the experienced post IC symptoms and related HRQoL with the situation before the admission.

There are also some limitations that need to be addressed. We aimed to included more than 12,000 patients. However, patients have to fill in eight questionnaires during five years. High loss to follow up rates are likely due to high mortality rates.[41] Moreover, PICS does not only occur among ICU survivors, but also among their family members and relatives, also called PICS-Family (PICS-F).[42] These long-term consequences in families of survivors and non-survivors consist of psychological, physical and social consequences as well.[43-45] Outcomes

such as anxiety, depression, posttraumatic stress, loss of employment, financial burden and lifestyle interference are common.[44] It is important to increase awareness of these possible long-term consequences on family members as well.[2] However, at the time of writing this protocol, we decided to focus on ICU survivors, and not their family members. In the future extension of this study, family members might be included as well.

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Authors' contribution

JvdH, MvdB, MZ, HV and WG contributed to the design of the study. WG drafted the manuscript. JvdH, MvdB, MZ and HV were involved in the editing of the manuscript. All authors read and approved the final manuscript.

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Competing interest agreement

The authors declare they have no competing interest.

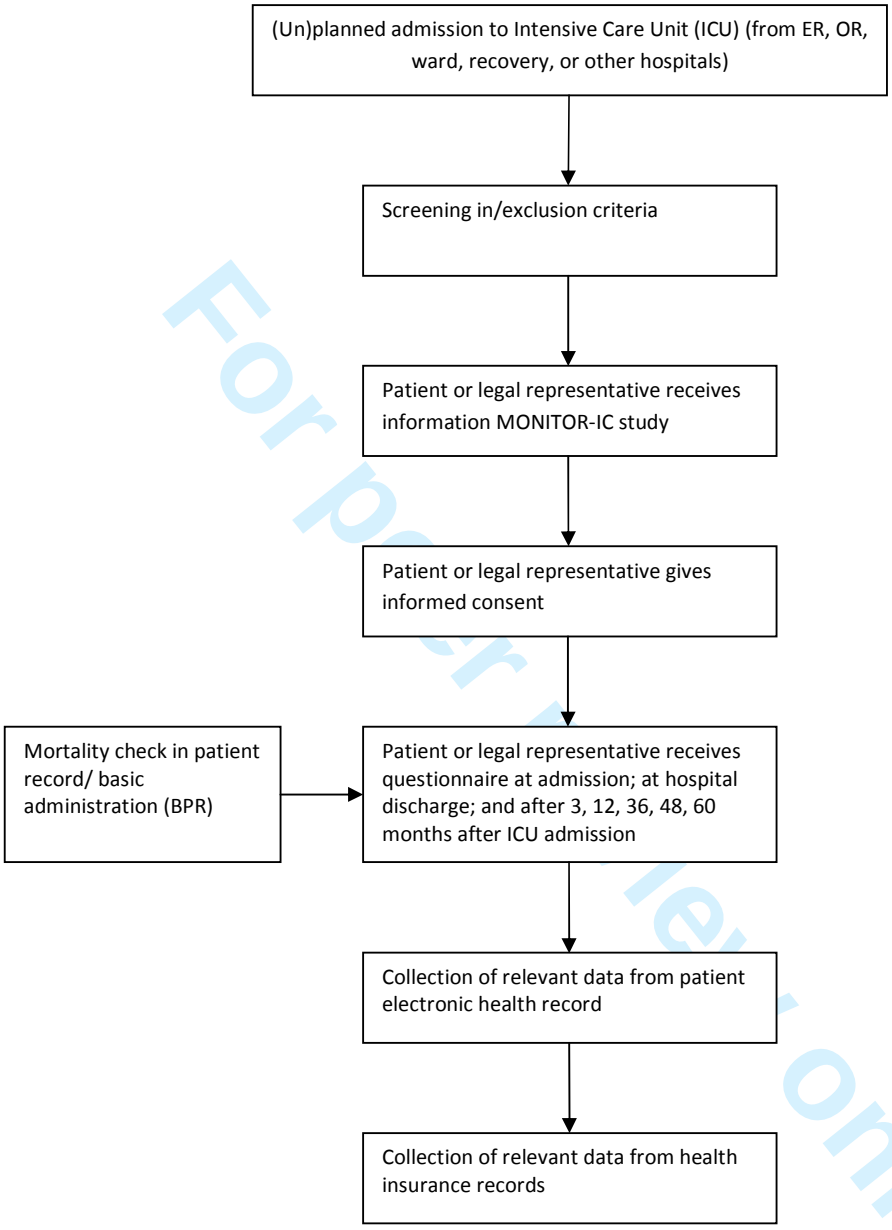
References

1. Svenningsen H, Langhorn L, Agard AS, et al. Post-ICU symptoms, consequences, and follow-up: an integrative review. *Nursing in critical care* 2015 doi: 10.1111/nicc.12165
2. Harvey MA, Davidson JE. Postintensive Care Syndrome: Right Care, Right Nowand Later. *Critical care medicine* 2016;44(2):381-5.
3. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical care medicine* 2012;40(2):502-9.
4. Angus DC, Carlet J, Brussels Roundtable P. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med* 2003;29(3):368-77.

5. Tan SS, Bakker J, Hoogendoorn ME, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. *Value Health* 2012;15(1):81-6.
6. Talmor D, Shapiro N, Greenberg D, et al. When is critical care medicine cost-effective? A systematic review of the cost-effectiveness literature. *Critical care medicine* 2006;34(11):2738-47.
7. Conti M, Merlani P, Ricou B. Prognosis and quality of life of elderly patients after intensive care. *Swiss Med Wkly* 2012;142:w13671.
8. Jutte JE, Erb CT, Jackson JC. Physical, Cognitive, and Psychological Disability Following Critical Illness: What Is the Risk? *Seminars in respiratory and critical care medicine* 2015;36(6):943-58. doi: 10.1055/s-0035-1566002
9. van der Schaaf M, Beelen A, Dongelmans DA, et al. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. *J Rehabil Med* 2009;41(5):360-6.
10. Harvey MA. Mitigating PICS 2016 [4-4-2017]. Available from: http://www.sccm.org/Communications/Critical-Connections/Archives/Pages/Mitigating-PICS.aspx.
11. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Critical care medicine* 2011;39(2):371-9.
12. Wade DM, Howell DC, Weinman JA, et al. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16(5):R192.
13. Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. *Crit Care* 2013;17(3):R100. doi: 10.1186/cc12745
14. Norman BC, Jackson JC, Graves JA, et al. Employment Outcomes After Critical Illness: An Analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors Cohort. *Critical care medicine* 2016;44(11):2003-09. doi: 10.1097/CCM.0000000000001849
15. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. *Critical care medicine* 2010;38(12):2386-400. doi: 10.1097/CCM.0b013e3181f3dec5
16. Hill AD, Fowler RA, Pinto R, et al. Long-term outcomes and healthcare utilization following critical illness--a population-based study. *Crit Care* 2016;20:76. doi: 10.1186/s13054-016-1248-y
17. Latronico N, Herridge M, Hopkins RO, et al. The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med* 2017
18. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ* 2009;339:b3723. doi: 10.1136/bmj.b3723
19. Jensen JF, Egerod I, Bestle MH, et al. A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multicenter randomized controlled trial, the RAPIT study. *Intensive Care Med* 2016;42(11):1733-43. doi: 10.1007/s00134-016-4522-1
20. Jones C, Backman C, Capuzzo M, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care* 2010;14(5):R168. doi: 10.1186/cc9260
21. Mehlhorn J, Freytag A, Schmidt K, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. *Critical care medicine* 2014;42(5):1263-71. doi: 10.1097/CCM.0000000000000148
22. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373(9678):1874-82. doi: 10.1016/S0140-6736(09)60658-9
23. Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care* 2010;14(1):R6. doi: 10.1186/cc8848

24. de Rooij SE, Govers AC, Korevaar JC, et al. Cognitive, functional, and quality-of-life outcomes of patients aged 80 and older who survived at least 1 year after planned or unplanned surgery or medical intensive care treatment. *J Am Geriatr Soc* 2008;56(5):816-22.
25. Hofhuis JG, Spronk PE, van Stel HF, et al. The impact of critical illness on perceived health-related quality of life during ICU treatment, hospital stay, and after hospital discharge: a long-term follow-up study. *Chest* 2008;133(2):377-85. doi: 10.1378/chest.07-1217
26. Kaarlola A, Pettila V, Kekki P. Quality of life six years after intensive care. *Intensive Care Med* 2003;29(8):1294-9.
27. Orwelius L, Nordlund A, Nordlund P, 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(2):R67.
28. Wu A, Gao F. Long-term outcomes in survivors from critical illness. *Anaesthesia* 2004;59(11):1049-52.
29. Van Der Schaaf M, Bakhshi-Raiez F, Van Der Steen M, et al. Recommendations for intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. *Minerva anestesiologica* 2015;81(2):135-44.
30. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.
31. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36.
32. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2005;173(5):489-95. doi: 10.1503/cmaj.050051
33. Vercoulen JH, Swanink CM, Fennis JF, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38(5):383-92.
34. Wassenaar A, de Reus J, Donders ART, et al. Development and validation of the abbreviated Cognitive Failure Questionnaire in Intensive Care Unit patients: a multicenter cohort study. *Submitted* 2017
35. Broadbent DE, Cooper PF, FitzGerald P, et al. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol* 1982;21 (Pt 1):1-16.
36. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.
37. Weiss DS, Marmar CR. Chapter: The Impact of Event Scale-Revised. 1997. Assessing psychological trauma and PTSD. New York, NY: Guilford Press; US 1997:399-411.
38. Nivel. Nationaal Panel Chronisch zieken en Gehandicapten Utrecht 2017 [Available from: https://www.nivel.nl/nl/panels/nationaal-panel-chronisch-zieken-en-gehandicapten-0.
39. Vektis. Vektis: informatie TTP voor de zorg Zeist [Available from: https://www.vektis.nl/.
40. Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality & Quantity* 2002;36:391-409.
41. Williams TA, Leslie GD. Challenges and possible solutions for long-term follow-up of patients surviving critical illness. *Australian critical care : official journal of the Confederation of Australian Critical Care Nurses* 2011;24(3):175-85.
42. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. *Critical care medicine* 2012;40(2):618-24.
43. Cameron JI, Chu LM, Matte A, et al. One-Year Outcomes in Caregivers of Critically Ill Patients. *The New England journal of medicine* 2016;374(19):1831-41. doi: 10.1056/NEJMoa1511160
44. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, et al. Reported burden on informal caregivers of ICU survivors: a literature review. *Crit Care* 2016;20:16.
45. Wintermann GB, Weidner K, Strauss B, et al. Predictors of posttraumatic stress and quality of life in family members of chronically critically ill patients after intensive care. *Annals of intensive care* 2016;6(1):69. doi: 10.1186/s13613-016-0174-0

Figure 1: Flow chart patient inclusion and data collection



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The MONITOR-IC study, a mixed methods prospective multicenter controlled cohort study assessing five-year outcomes of ICU survivors and related healthcare costs: a study protocol

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The MONITOR-IC study, a mixed methods prospective multicenter controlled cohort study assessing five-year outcomes of ICU survivors and related healthcare costs: a study protocol

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ABSTRACT

Introduction: Due to advances in critical care medicine, more patients survive their critical illness. However, intensive care unit (ICU) survivors often experience long-term physical, cognitive and mental problems, summarized as post intensive care syndrome (PICS), impacting their health related quality of life (HRQoL). In what frequency PICS occurs, and to what extent this influences ICU survivors' HRQoL, is mostly unknown.
The aims of this study are therefore to study the: 1) five-year patient outcomes, 2) predictors for PICS, 3) ratio between HRQoL of ICU-survivors and healthcare related costs, and 4) care and support needs.

Methods: The MONITOR-IC study is a multicenter prospective controlled cohort study, carried out in ICU units in four Dutch hospitals. Patients will be included between July 2016 and July 2021 and followed for five years. We estimated to include 12,000 ICU-patients. Outcomes are the HRQoL, physical, cognitive and mental symptoms, ICU survivors' care and support needs, healthcare use and related costs. A control cohort of otherwise seriously ill patients will be assembled to compare long-term patient reported outcomes.
We will use a mixed methods design, including questionnaires, medical data from patient records, cost data from health insurance companies and interviews with patients and family members.

Ethics and dissemination: Insights from this study will be used to inform ICU-patients and their family members about long-term consequences of ICU care, and to develop prediction and screening instruments to detect patients at risk for PICS. Subsequently, tailored interventions can be developed and implemented to prevent and mitigate long-term consequences. Additionally, insights into the ratio between HRQoL of ICU-patients and related healthcare costs during five-years after ICU admission, can be used to discuss the added value of ICU care from a community perspective.

The study has been approved by the research ethics committee of the Radboud University Medical Center (2016-2724).

KEYWORDS

Cohort studies; Critical care; Intensive Care Units; Long-term outcome; Post intensive care syndrome; Quality of life

STRENGHTS AND LIMITATIONS OF THIS STUDY

- The strength of the MONITOR-IC study is the thorough and comprehensive methodological approach, inclusion of thousands of ICU patients, five year follow-up, use of mixed methods and the combination of data regarding patients' HRQoL, healthcare use and patients needs.
- The baseline questionnaire includes questions relating to the patient's situation before the ICU admission. Therefore, we are able to compare the experienced post ICU symptoms and related HRQoL with the situation before the admission.
- We aimed to included more than 12,000 patients. However, patients have to fill in eight questionnaires during five years. High loss to follow up rates are likely due to high mortality rates.
- The symptoms and consequences are based on the reported outcomes by patients themselves. This could lead to bias, due to over- or underestimation of their own symptoms, for example their cognitive functioning.
- Moreover, PICS does not only occur among ICU survivors, but also among their family members and relatives, also called PICS-Family (PICS-F). At the time of writing this protocol, we decided to focus on ICU survivors, and not their family members.

INTRODUCTION

The number of patients admitted to the Intensive Care Unit (ICU) is increasing every year.[1] Meanwhile, advances in medical technologies allow more patients to survive their critical illness.[2] With this growing number of ICU survivors, there is an urgent need to shift our focus from short-term mortality to long-term outcomes of ICU survivors.[1 3]

In 2002, the members of the international surviving intensive care Roundtable already discussed whether ICU survivors have optimal long-term outcomes, and whether decisions regarding ICU care would change with increasing knowledge of outcomes[4] and the associated costs.[3] Costs of ICU care are high; 20% of the total hospital budget, with cost per day between three-and fivefold greater in ICU departments than in general wards.[5] These high costs are due to the need for highly trained staff, expensive modern equipment, and intensive use of diagnostic tests, pharmaceuticals and interventions.[6] Although economic evaluation of care in the ICU is often ethically difficult,[6] understanding of the costs and consequences associated with technologies, services and programs aimed at reducing mortality and morbidity of critically ill patients is important.[6 7]

Over the last two decades, it has become more and more clear how devastating and long-lasting the post-discharge consequences can be, and what the impact is on ICU survivors and their family.[8] These long-term consequences are called post-intensive care syndrome (PICS), defined as 'new or worsening impairment in physical, cognitive, or mental health status arising and persisting after hospitalisation for critical illness.[2] Examples of these physical impairments are pain, breathing difficulties, fatigue and loss of bodyweight resulting in physical weakness and problems in daily functioning and activities.[1 8-10 11] A total of 10 to 75% of the ICU survivors are still suffering from these difficulties one year later.[12] Cognitive problems, such as problems with memory, processing, planning and problem solving, are seen in 30-80% of the ICU survivors.[2 8] Although these impairments can improve over several months, they can persist for many years as well.[10] In addition, mental impairment, such as depression,[13] anxiety,[14] and sleep disturbances are common.[1 2] In 25% of the ICU survivors, posttraumatic stress disorder symptoms (PTSD) occur at 1 year follow-up.[15] These PTSD symptoms can persist for 8 years.[2] Moreover, ICU survivors experience a significant socio-economic burden, because of long-term sick leave, early retirement and need for assistance at home which is primarily given by informal caregivers, impacting on family income.[16 17] Furthermore, ICU survivors experience a lower quality of life,[18] leading to high utilization of healthcare services and related costs.[16 19]

Although some risk factors for PICS are known (such as immobility, pre-existing impairments, age, sedation, duration of mechanical ventilation, delirium and sepsis),[3 10 20] continued investigation of risk factors and underlying mechanisms is essential to understand which subgroups of patients are prone to develop PICS.[3 10] Interventions and strategies to

prevent or mitigate PICS, such as ICU diaries, early mobilisation, post-discharge rehabilitations and follow-up consultations with specialised nurses for ICU survivors, were recently described.[1 21-25] However, conclusive evidence for these interventions is lacking or limited.[24 26-29] Moreover, the majority of the healthcare professionals is still not aware of PICS, and interventions available for ICU survivors are therefore often not provided.[1 3]

More insight is necessary to better define the scope of long-term ICU symptoms and associated healthcare costs.[3] Incidence rates of PICS differ largely in studies, which is due to differences in study patient populations, co-morbidities, measurement tools and timeframes.[2] Additionally, previous studies addressing PICS often have limited focus or methodological limitations such as small sample sizes, low response rates, short follow-up, use of non-validated or unreliable instruments, no control group and absence of a pre-admission (baseline) measurement.[30-35]

For this reason, we set up a controlled cohort study called the MONITOR-IC. In this study, with a five years follow-up, we aim to study the ICU survivors' long-term outcomes, their HRQoL and their needs, in order to identify specific types of patients who are at risk for specific impairments, factors affecting their recovery and to target effective interventions both in the ICU and later during the fragile recovery period.[3 8 36] Additionally, we aim to get more insight into the ratio between the HRQoL and related healthcare costs to discuss the added value of ICU care from a community perspective.

OBJECTIVES

Overarching objective

To quantify and describe the extent of the physical, mental and cognitive long-term outcomes and HRQoL of ICU survivors during five years following ICU admission, in order to ultimately improve care for ICU patients.

Specific research questions

1. What are the post intensive care symptoms that patients experience during five years after ICU admissions and what is their HRQoL?
2. What are important predictors for the various physical, cognitive and mental long-term outcomes?
3. What is the ratio between HRQoL and healthcare related costs?
4. What are the care and support needs of ICU survivors during five years after ICU admission?

METHODS/DESIGN

Study design and setting

The MONITOR-IC study is a multicenter prospective controlled cohort study in which long-term outcomes of ICU patients are studied for a period of five year.

The study will be carried out in ICUs of four hospitals in the Netherlands; one academic hospital, one teaching and two non-teaching hospitals. ICU patients will be recruited between July 2016 and July 2021 with a subsequent follow-up for five years. Mixed methods will be used to collect data, including questionnaires, medical data from patient records, cost data from health insurance companies and interviews with ICU survivors and their family members.

To compare the outcomes, such as the quality of life and experienced symptoms of ICU patients with non-ICU patients, we will set up a control group as well.

Study population and eligible criteria

ICU patients are eligible to participate when they are 16 years or older; admitted at least 12 hours to a trauma, medical, neurosurgery or cardiac surgery ICU; and gave written informed consent (or by their legal representative).

Patients are eligible for the control cohort when they are 16 years or older and admitted either to the ICU for less than 12 hours, or to the Post Anaesthesia Care Unit (PACU), the Medium Care or high dependency unit for instance for monitoring during short interventions, such as bronchoalveolar lavage or insertion of a central venous catheter.

Patients are not eligible for the study when they have a life expectance of <48 hours; receive palliative care; are admitted for a donor procedure; cannot read and speak the Dutch language; or are not able to fill in the questionnaire and do not have family members/ legal representatives either.

For the MONITOR-IC study we estimated to include 12.000 patients. This estimation is based on: 1) the initial ICU admissions in the academic hospital and the three other participating hospitals together (2,500 and 2,200 respectively per year), and 2) an estimated response rate of 60%, which is based on previous conducted ICU studies.[37 38]

In the control cohort, we will include approximately 3000 patients during the next four years.

Patient recruitment

Patients scheduled for ICU admission after elective surgery, will be recruited at the outpatient clinic (anaesthesiology or cardiac surgery) (Figure 1). Patients with a non-scheduled admission will be recruited at the ICU. Patients will receive information by ICU nurses and

intensivists regarding the aim, content and relevance of the study, and will be asked for participation. Informed consent is asked for the questionnaires, data from the patients' individual medical record and data from their health insurance company. In case patients are unable to give consent, their legal representative will be asked.

[Figure 1: Flow chart patient inclusion and data collection]

Outcomes measures

The outcomes of the MONITOR-IC study are the HRQoL among ICU survivors and their physical (fatigue, vulnerability and frailty), cognitive and mental (anxiety, depression and stress) impairments. Additional outcomes are the patients' care and support needs, their healthcare use, and related costs.

Data collection

Different methods will be used to collect data among ICU patients, including questionnaires, patients' medical records (MR), database of healthcare cost data of Dutch health insurance companies and interviews with patients and their family members (Table 1).

Table 1: Research questions and methods

Research question	Methods
1. What are the post intensive care symptoms that patients experience during five years after ICU admission and what is their HRQoL?	Questionnaires MR
2.What are important predictors for the various physical, cognitive and mental long-term outcomes?	Questionnaires MR
3.What is the ratio between HRQoL and healthcare related costs?	Questionnaires Health insurance database
4.What are the care and support needs of ICU survivors during five years after ICU admission?	Questionnaires Interviews with ICU survivors and their family members

Questionnaires

All patients, or their relatives in case patients are not able to fill in the questionnaire themselves, will be approached to fill in the self-administered paper based or online questionnaire (depending on their preferences) in total eight times: at ICU admission (T0), at hospital discharge (T1), after 3 months (T2), 12 months (T3), 24 months (T4), 36 months (T5), 48 months (T6) and 60 months after ICU admission (T7). To get insight into the situation before the ICU admission, the baseline questionnaire (T0) is provided when the patients is asked for informed consent. This could be preoperatively for the planned admissions or after admission at the ICU. Then, patients are asked to rate their situation before the ICU admission.

The investigators keep track on when patients should receive the next questionnaire or the postal or telephone reminders after four and six weeks.

The questionnaire is established in close collaboration with worldwide experts in the fields of ICU long-term outcomes and the FCIC (Family and Patient Centered Intensive Care), the Dutch foundation for ICU survivors and their family members.

The components in the questionnaire vary at different measurement points (see Table 2 and for more information regarding the domains and items see Supplement 1), but contains the following:

- *Patients' health status and HRQoL* will be assessed using the SF-36[39] and the EQ-5D-5L.[40] Both questionnaires are validated instruments and applicable in different countries and languages. The SF-36 is a comprehensive instrument, measuring the general health status and quality of life, consisting of eight different health domains. The EQ-5D-5L is a simple instrument to measure the HRQoL.[4] Although the SF-36 is the most often used questionnaires measuring quality of life in intensive care patients,[41] the EQ-5D-5L is added since this questionnaire can be best used for the calculation of quality adjusted survival, a key measure of health effects for cost effectiveness assessments.[4]

- *Patients' level of frailty and vulnerability* will be assed using the Clinical Frailty Score (CFS).[42] Frailty is common in critically ill patients and is associated with poorer outcomes in terms of ICU and hospital mortality, impairment in HRQoL and functional dependence.[43] The CFS is simple, short and reliably measures frailty and using the CFS it is possible to predicts outcomes more effectively.[44]
  The level of *fatigue,* which is not well covered by the other included questionnaires, will be measured using the CIS-8, a subscale of the Checklist Individual Strength (CIS-20),[45] and is among used ICU patients before.[37]

- Critical illness and ICU treatment are associated with long-term *cognitive impairment,*[46] which will be measured using the validated abbreviated 14-item Cognitive Failure Questionnaire (CFQ-14).[47] The original CFQ-25 [48] is often used to screen ICU survivors for cognitive problems, however, the number of questions and missing values are a limitation.[47] Therefore we have chosen for the shorter version which is highly correlated with the original questionnaire.[48]

- The *mental impairments* will be assed using the Hospital Anxiety and Depression Scale (HADS) to determine the levels of anxiety and depression.[49] The HADS is the most often used questionnaire to measure symptoms of anxiety and depression in ICU survivors.[41]

Subjective distress, caused by traumatic events, will be measured using the Impact of Event Scale Revised (IES-R),[50] a standardized measure of PTSD symptoms.

- *Care needs* and *support from professionals and informal caregivers* will be measured using questions created by our research team, former ICU patients and members of the FCIC, and by previous studies among chronic patients.[51]
  Social consequences will be measured using the novel question set designed by Griffiths et al., (2013)[16] to determine changes in family circumstances, socio-economic stability and care requirements.

Although we are aware of the overlap between the used questionnaires, it will allows us to check the reliability. More information regarding the questionnaires, domains and scores, see supplement 1.

Medical data

Patients' demographics and information regarding their diagnosis and treatment, such as primary conditions, pre-existing co-morbidity, disease severity, sepsis, (re)admission, length of mechanical ventilation, length of ICU stay, delirium (CAM-ICU), pain (CPOT), expected mortality (based on the APACHE II, SAPS II, MPM II and APACHE III-IV models and medication, will be extracted from their medical record and the Dutch National Intensive Care Evaluation (NICE) registry.[52]

Health insurance data

Healthcare use and related costs, covered by the Dutch healthcare insurance, will be retrieved from Vektis; a Dutch organization which collects and manage health insurance claimed data of all health insurance companies in the Netherlands.[53] This data is collected based on the Diagnosis Treatment Combination (DTC); a total set of activities carried out by the hospital and medical specialists. Additionally, data is collected regarding nursing days, visits at the outpatient clinic and emergency department, nursing homes, ambulance transport, consultation with general practitioner, paramedical care (including physiotherapist, occupational therapist, dietician and speech therapist), prescribed medication, mental healthcare and revalidation. The Vektis database contains data from all for healthcare insured citizens and covers 99% of the total Dutch population. Using patient's unique insurance number we are able to merge patient's insurance data with the questionnaire data and medical data from the medical record at patient level.
Care delivered by community nurses and informal caregivers is not included in the Vektis database and will be studied via the questionnaire.

Interviews

To get insight into the experiences of ICU survivors during five years after ICU admission and their need for support, face to face semi-structured interviews will be conducted with ICU survivors and their family members. Interviews will take place at the participants' preferred location (home or clinic). Interviews will be conducted until data saturation is reached. Patients will be purposively sampled based on various experienced outcomes, such as the quality of life, daily functioning, anxiety, depression, and their experienced needs for more information or emotional support. Experienced and trained researchers will conduct the interviews using a topic guide. This guide will be developed using the current literature and experience of the research team and will cover the following subjects: experiences with the ICU admission and follow-up, experienced problems and needs for support. All interviews will be audio recorded and transcribed verbatim.

Table 2. Overview of used scales in the questionnaire and timeframe

Methods	Outcome	Used scales	T0	T1	T2	T3	T4	T5	T6	T7
			(ICU-) admission	Discharge hospital	3 months	12 months	24 months	36 months	48 months	60 months
Questionnaire	Demographic data		X							
	Health status and HRQoL	SF-36	X		X	X	X	X	X	X
		EQ-5D	X		X	X	X	X	X	X
	Physical impairments	CFS	X	X	X	X	X	X	X	X
		CIS-8	X		X	X	X			
	Cognitive impairments	CFQ-14	X		X	X	X			X
	Mental impairments	HADS	X		X	X	X			X
		IES-R			X	X	X			X
	New symptoms after ICU admission				X	X	X	X	X	X
	Care needs and professionals support/ informal caregivers				X	X	X			X
	Social consequences					X	X			X

Analysis

Questionnaires, medical record and health insurance data

During the data collection, data are checked on a regular basis to identify out-of-range answers, inconsistent responses, and missing data. Data from the questionnaires, medical record and healthcare insurance data will be merged at patient level. Descriptive statistics will be used to describe baseline characteristics and the incidence of long-term outcomes. Regression analysis will be used to determine associations between patient characteristics, treatment, and long-term outcomes. Subgroups will be identified based on their illness and condition (for example sepsis, delirium, co morbidities, ARDS), treatment (for example length of ICU stay, duration of mechanical ventilation, dialysis) and social demographics (age, gender, education, family setting etc).

In order to predict the various physical, cognitive and mental long-term outcomes, multiple prediction models will be developed. Multivariable linear (for continuous outcome variables) and logistic (for dichotomous outcome variables) regression analysis will be performed. Linear and logistic multilevel models will be used to compare long-term outcomes between the study population (cohort) and control cohort group.

To determine the ratio between HRQoL and patient outcomes and the health related costs, quality adjusted life years (QALYs) will be calculated. QALYs are a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. QALYs are calculated by estimating the years of life remaining for particular treatment and weighting each year with a quality of life score.[54] Software Package for the Social Sciences (SPSS) will be used for data analysis.

Interviews

For the analysis of the interview data, the constant comparative method[55] will be used. Relevant data will be identified and structured by open, axial and selective coding.

Two researchers will independently code the transcripts to minimize subjectivity in findings. The differences and similarities between the codes will be discussed together, and in case of disagreement, a third researcher will be involved. In the meetings with the team, the codebook will be refined and emerging categories and themes will be discussed.

Data analysis will be supported with the use of Atlas.ti, a qualitative data analysis program.

Ethics

The MONITOR-IC study will be conducted complying the Dutch Personal data protection act. The study has been approved by the research ethics committee of the Radboud University Medical Center, CMO region Arnhem- Nijmegen (2016-2724). The study will be registered in the ClinicalTrials.gov database.

Relevance of findings

The results of the MONITOR-IC study will be disseminated through international and national publications and presentations. We will quantify and describe the extent of the physical, cognitive and mental long-term outcomes of ICU survivors, their healthcare use and their needs (Box 1).

This knowledge is of importance for patients, healthcare professionals, managers and health insurers to develop and evaluate the (after)care for ICU patients taking their health status and needs into account. Patients and their family members could be better informed about the possible long-term physical, cognitive, mental and social consequences after ICU discharge. Moreover, the inclusion of thousands of ICU patients in this study, allows us to study several patient subgroups; for example the quality of life and specific care needs of patients after sepsis, acute respiratory distress syndrome or delirium. Using these disease specific insights, prediction and screening instruments can be developed to determine patients at risk for long-term consequences. Subsequently, interventions, such as diaries, early mobilisation and follow-up consultations for patients and their family members, could be adjusted, established and implemented to prevent or mitigate long-term consequences. Furthermore, long-term effects of important changes in health policy will be visible, whereby evaluation of effectiveness and efficacy of (changes in) policy on micro, meso and macro level is possible. Healthcare professionals will be better able to weigh up the options in the decision making process concerning ICU admission, treatment options and the added value for individual patients, which will improve shared decision making with patients and their families as well.

Finally, this study gives more perspectives into the ratio between the patients' HRQoL and healthcare costs. Over the last decades, the ICU care is overwhelmed with new and also costly technologies and therapies, resulting in increasing costs, but without actually insight in the added value for patient and their health outcomes. Consequently, an open ethical dialogue, based on this ratio and what this ratio might be, is then possible.

Box 1 Relevance of study

1. Information about long-term outcomes for patients and their family members
2. Support for treatment choices for multiple medical specialties, in particular intensive care
3. Coordination of care by personalised follow-up care for post ICU patients
4. Adjustments in healthcare policy for post ICU patients
5. Screenings instrument for early signs and symptoms
6. Establishing and implementing interventions to prevent or mitigate long-term consequences
7. Information for health insurance companies for purchasing care and professional associations for guideline development
8. Detecting unnecessary ICU care
9. Evaluation of changes in ICU healthcare policy on long term effects

The strength of the MONITOR-IC study is the thorough and comprehensive methodological approach, inclusion of thousands of ICU patients, five year follow-up, use of mixed methods and the combination of data regarding patients' HRQoL, healthcare use and patients needs. Moreover, the baseline questionnaire includes questions relating to the patient's situation before the ICU admission. Therefore, we are able to compare the experienced post IC symptoms and related HRQoL with the situation before the admission.

There are also some limitations that need to be addressed. We aimed to included more than 12,000 patients. However, patients have to fill in eight questionnaires during five years. High loss to follow-up rates are likely due to high mortality rates.[56] Furthermore, the post- ICU symptoms and consequences are based on the reported outcomes by patients themselves. This could lead to bias, due to over- or underestimation of their own symptoms, for example their cognitive functioning. Using the data of the health insurances companies regarding for example patients' visits to the general practitioner or medical specialist, we try to overcome this. Moreover, PICS does not only occur among ICU survivors, but also among their family members and relatives, also called PICS-Family (PICS-F).[57] These long-term consequences in families of survivors and non-survivors consist of psychological, physical and social consequences as well.[58-60] Although it is important to increase awareness of these possible long-term consequences on family members,[2] we decided to focus only on the ICU survivors. In the future extension of this study, family members might be included as well.

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Authors' contribution

JvdH, MvdB, MZ, HV and WG contributed to the design of the study. WG drafted the manuscript. JvdH, MvdB, MZ and HV were involved in the editing of the manuscript. All authors read and approved the final manuscript.

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Competing interest agreement

The authors declare they have no competing interest.

Data sharing

Additional data is available on request.

References

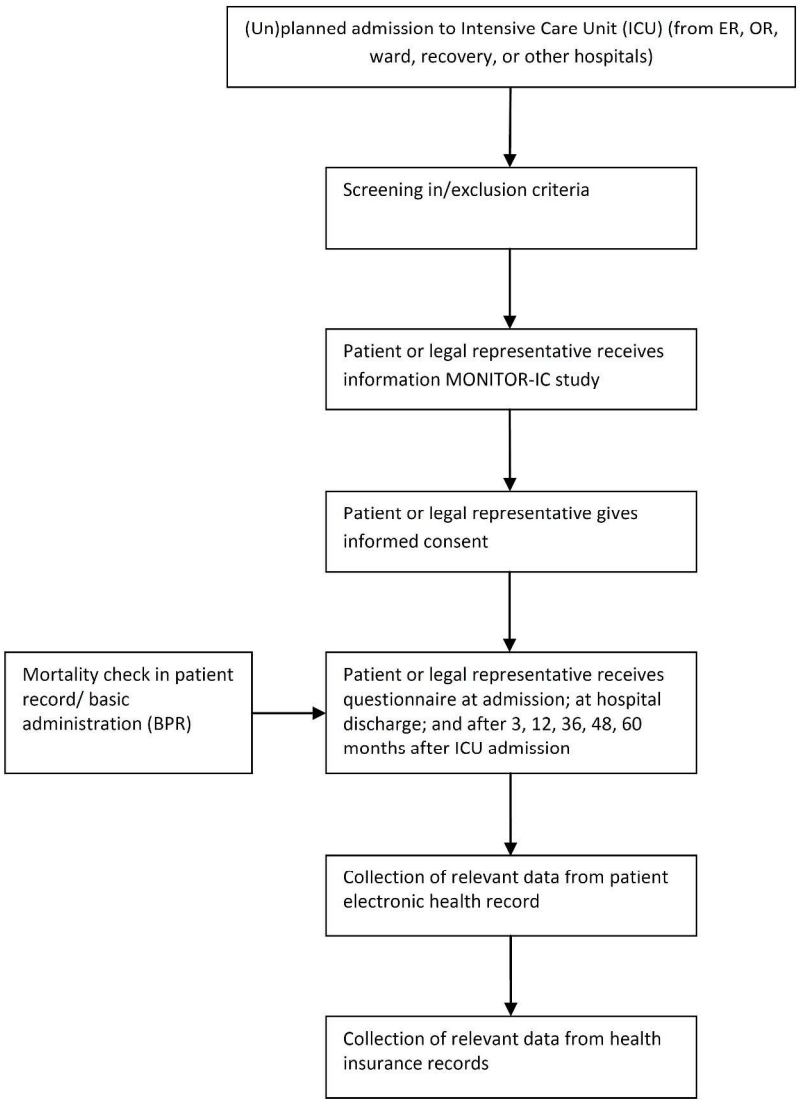
1. Svenningsen H, Langhorn L, Agard AS, et al. Post-ICU symptoms, consequences, and follow-up: an integrative review. *Nursing in critical care* 2015 doi: 10.1111/nicc.12165
2. Harvey MA, Davidson JE. Postintensive Care Syndrome: Right Care, Right Nowand Later. *Critical care medicine* 2016;44(2):381-5.
3. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical care medicine* 2012;40(2):502-9.
4. Angus DC, Carlet J, Brussels Roundtable P. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med* 2003;29(3):368-77.
5. Tan SS, Bakker J, Hoogendoorn ME, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. *Value Health* 2012;15(1):81-6.
6. Talmor D, Shapiro N, Greenberg D, et al. When is critical care medicine cost-effective? A systematic review of the cost-effectiveness literature. *Critical care medicine* 2006;34(11):2738-47.
7. Conti M, Merlani P, Ricou B. Prognosis and quality of life of elderly patients after intensive care. *Swiss Med Wkly* 2012;142:w13671.
8. Jutte JE, Erb CT, Jackson JC. Physical, Cognitive, and Psychological Disability Following Critical Illness: What Is the Risk? *Seminars in respiratory and critical care medicine* 2015;36(6):943-58. doi: 10.1055/s-0035-1566002
9. van der Schaaf M, Beelen A, Dongelmans DA, et al. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. *J Rehabil Med* 2009;41(5):360-6.
10. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Critical care medicine* 2011;39(2):371-9.
11. Granja C, Amaro A, Dias C, et al. Outcome of ICU survivors: a comprehensive review. The role of patient-reported outcome studies. *Acta Anaesthesiol Scand* 2012;56(9):1092-103. doi: 10.1111/j.1399-6576.2012.02686.x
12. Harvey MA. Mitigating PICS 2016 [4-4-2017]. Available from: http://www.sccm.org/Communications/Critical-Connections/Archives/Pages/Mitigating-PICS.aspx.
13. Rabiee A, Nikayin S, Hashem MD, et al. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. *Critical care medicine* 2016;44(9):1744-53. doi: 10.1097/CCM.0000000000001811
14. Nikayin S, Rabiee A, Hashem MD, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2016;43:23-29. doi: 10.1016/j.genhosppsych.2016.08.005
15. Parker AM, Sricharoenchai T, Raparla S, et al. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Critical care medicine* 2015;43(5):1121-9. doi: 10.1097/CCM.0000000000000882
16. Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. *Crit Care* 2013;17(3):R100. doi: 10.1186/cc12745
17. Norman BC, Jackson JC, Graves JA, et al. Employment Outcomes After Critical Illness: An Analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors Cohort. *Critical care medicine* 2016;44(11):2003-09. doi: 10.1097/CCM.0000000000001849
18. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. *Critical care medicine* 2010;38(12):2386-400. doi: 10.1097/CCM.0b013e3181f3dec5

19. Hill AD, Fowler RA, Pinto R, et al. Long-term outcomes and healthcare utilization following critical illness--a population-based study. *Crit Care* 2016;20:76. doi: 10.1186/s13054-016-1248-y
20. Latronico N, Herridge M, Hopkins RO, et al. The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med* 2017
21. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ* 2009;339:b3723. doi: 10.1136/bmj.b3723
22. Jensen JF, Egerod I, Bestle MH, et al. A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multicenter randomized controlled trial, the RAPIT study. *Intensive Care Med* 2016;42(11):1733-43. doi: 10.1007/s00134-016-4522-1
23. Jones C, Backman C, Capuzzo M, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care* 2010;14(5):R168. doi: 10.1186/cc9260
24. Mehlhorn J, Freytag A, Schmidt K, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. *Critical care medicine* 2014;42(5):1263-71. doi: 10.1097/CCM.0000000000000148
25. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373(9678):1874-82. doi: 10.1016/S0140-6736(09)60658-9
26. Aitken LM, Rattray J, Hull A, et al. The use of diaries in psychological recovery from intensive care. *Crit Care* 2013;17(6):253. doi: 10.1186/cc13164
27. Jensen JF, Thomsen T, Overgaard D, et al. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. *Intensive Care Med* 2015;41(5):763-75. doi: 10.1007/s00134-015-3689-1
28. Ullman AJ, Aitken LM, Rattray J, et al. Diaries for recovery from critical illness. *The Cochrane database of systematic reviews* 2014(12):CD010468. doi: 10.1002/14651858.CD010468.pub2
29. Tipping CJ, Harrold M, Holland A, et al. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. *Intensive Care Med* 2016 doi: 10.1007/s00134-016-4612-0
30. Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care* 2010;14(1):R6. doi: 10.1186/cc8848
31. de Rooij SE, Govers AC, Korevaar JC, et al. Cognitive, functional, and quality-of-life outcomes of patients aged 80 and older who survived at least 1 year after planned or unplanned surgery or medical intensive care treatment. *J Am Geriatr Soc* 2008;56(5):816-22.
32. Hofhuis JG, Spronk PE, van Stel HF, et al. The impact of critical illness on perceived health-related quality of life during ICU treatment, hospital stay, and after hospital discharge: a long-term follow-up study. *Chest* 2008;133(2):377-85.
33. Kaarlola A, Pettila V, Kekki P. Quality of life six years after intensive care. *Intensive Care Med* 2003;29(8):1294-9.
34. Orwelius L, Nordlund A, Nordlund P, 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(2):R67.
35. Wu A, Gao F. Long-term outcomes in survivors from critical illness. *Anaesthesia* 2004;59(11):1049-52.
36. Van Der Schaaf M, Bakhshi-Raiez F, Van Der Steen M, et al. Recommendations for intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. *Minerva anestesiologica* 2015;81(2):135-44.
37. van den Boogaard M, Schoonhoven L, Evers AW, et al. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Critical care medicine* 2012;40(1):112-8. doi: 10.1097/CCM.0b013e31822e9fc9

38. Wolters AE, van Dijk D, Pasma W, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. *Crit Care* 2014;18(3):R125. doi: 10.1186/cc13929
39. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.
40. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36.
41. Turnbull AE, Rabiee A, Davis WE, et al. Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. *Critical care medicine* 2016;44(7):1267-77. doi: 10.1097/CCM.0000000000001651
42. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2005;173(5):489-95. doi: 10.1503/cmaj.050051
43. Bagshaw SM, Stelfox HT, Johnson JA, et al. Long-term association between frailty and health-related quality of life among survivors of critical illness: a prospective multicenter cohort study. *Critical care medicine* 2015;43(5):973-82.
44. Le Maguet P, Roquilly A, Lasocki S, et al. Prevalence and impact of frailty on mortality in elderly ICU patients: a prospective, multicenter, observational study. *Intensive Care Med* 2014;40(5):674-82. doi: 10.1007/s00134-014-3253-4
45. Vercoulen JH, Swanink CM, Fennis JF, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38(5):383-92.
46. Wolters AE, Slooter AJ, van der Kooi AW, et al. Cognitive impairment after intensive care unit admission: a systematic review. *Intensive Care Med* 2013;39(3):376-86. doi: 10.1007/s00134-012-2784-9
47. Wassenaar A, de Reus J, Donders ART, et al. Development and validation of the abbreviated Cognitive Failure Questionnaire in Intensive Care Unit patients: a multicenter cohort study. *Submitted* 2017
48. Broadbent DE, Cooper PF, FitzGerald P, et al. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol* 1982;21 (Pt 1):1-16.
49. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.
50. Weiss DS, Marmar CR. Chapter: The Impact of Event Scale-Revised. 1997. Assessing psychological trauma and PTSD. New York, NY: Guilford Press; US 1997:399-411.
51. Nivel. Nationaal Panel Chronisch zieken en Gehandicapten Utrecht 2017 [Available from: https://www.nivel.nl/nl/panels/nationaal-panel-chronisch-zieken-en-gehandicapten-0.
52. NICE S. Nationale Intensive Care Evaluatie Amsterdam [Available from: https://www.stichting-nice.nl/.
53. Vektis. Vektis: informatie TTP voor de zorg Zeist [Available from: https://www.vektis.nl/.
54. NICE. National Institute for Health and Care Excellence London2017 [Available from: https://www.nice.org.uk/glossary?letter=q.
55. Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality & Quantity* 2002;36:391-409.
56. Williams TA, Leslie GD. Challenges and possible solutions for long-term follow-up of patients surviving critical illness. *Australian critical care : official journal of the Confederation of Australian Critical Care Nurses* 2011;24(3):175-85.
57. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. *Critical care medicine* 2012;40(2):618-24.
58. Cameron JI, Chu LM, Matte A, et al. One-Year Outcomes in Caregivers of Critically Ill Patients. *The New England journal of medicine* 2016;374(19):1831-41. doi: 10.1056/NEJMoa1511160
59. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, et al. Reported burden on informal caregivers of ICU survivors: a literature review. *Crit Care* 2016;20:16.

60. Wintermann GB, Weidner K, Strauss B, et al. Predictors of posttraumatic stress and quality of life in family members of chronically critically ill patients after intensive care. *Annals of intensive care* 2016;6(1):69. doi: 10.1186/s13613-016-0174-0

Figure 1: Flow chart patient inclusion and data collection



982x1413mm (96 x 96 DPI)

Supplementary 1 Overview of validated instruments

Item	Questionnaire	Questions	Domains	Score
Health status and related quality of life	SF-36 (Short Form Health Survey)[39]	36	1. Physical functioning (10 items) 2. Role limitations because of physical health problems (4 items) 3. Bodily pain (2 items) 4. Social functioning (2 items) 5. General mental health (5 items) 6. Role limitations because of emotional problems (3 items) 7. Vitality (4 items) 8. General health perceptions (5 items) Change in general health (1 item)	35 of the 36 items are used for the calculation of the eight domain scores and two summary scores: the physical component summary (PCS) and mental component summary (MCS) scores. Each domain is scored from 0 (worst score) to 100 (best score). The lower the score, the more disability.
	EQ-5D-5L[40]	5	1. Mobility (1 item) 2. Self-care (1 item) 3. Usual activities (1 item) 4. Pain and discomfort (1 item) 5. Anxiety and depression (1 item) The EQ-5D-5L also comprises a visual analogue scale (VAS) to record perceptions of the participants own current overall health.	Each domain is scored on a five point scale. The range of the VAS scale is from 0 to 100.
Physical impairments	CFS (Clinical Frailty Score)[42]	1	Frailty (1 item)	One 9-point scale ranging from 1 'Very fit' to 9 'Terminally ill'.
	CIS-8 (Subscale of the Checklist Individual Strength, CIS-20)[45]	8	Fatigue (8 items)	A 7 point scale, ranging from 'No that is not right' (1) to 'Yes that is right'(7). A total sum score of 35 or more indicates sever fatigue.
Cognitive impairments	CFQ-14 (Abbreviated versions of the Cognitive Failure Questionnaire)[47 48]	14	1.Memory (4 items) 2.Distractibility (5 items) 3.Social blunders (4 items) 4.Names (1 item)	Each item is scored on a 5 point sale, ranging from 0 (never) to 4 (very often). A total sum is calculated and a higher score indicates more cognitive failure.
Mental impairments	HADS (Hospital Anxiety and Depression Scale)[49]	14	1. Anxiety (HADS-A) (7 items) 2. Depression (HADS-D) (7 items)	Each item on the questionnaire is scored on a 4-point scale, ranging from 0-3. Scores range between 0 and 21 for depression and for anxiety. Higher scores indicate higher symptom frequencies: 0-7 is normal, 8-10 is mild, 11-14 is moderate and 15-21 is severe.
	IES-R (Impact of Event Scale Revised) [50]	22	Subjective stress, caused by traumatic events	This lists consists of 22 questions, with a 5-point scale ranging from 0 (not at all) to 4 (extremely). Total scores range from 0 to 88, with score of 33 or above as best cut off for a probable diagnosis of PTSD.