Journal of Critical Care 65 (2021) 76–83

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Development of a practically usable prediction model for quality of life of ICU survivors: A sub-analysis of the MONITOR-IC prospective cohort study

Nina Wubben, MSc [a], Mark van den Boogaard, RN, PhD [a], Jordache Ramjith, MSc [b], Laurens L.A. Bisschops, MD, PhD [a], Tim Frenzel, MD, PhD [a], Johannes G. van der Hoeven, MD, PhD [a], Marieke Zegers, PhD [a,*]

[a] Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Intensive Care Medicine, Nijmegen, the Netherlands
[b] Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Health Evidence, Nijmegen, the Netherlands

ARTICLE INFO

Available online xxxx

Keywords:
Quality of life
Critical care
Prediction modelling
Survivors
Critical care outcomes
Prognosis

ABSTRACT

Purpose: As the goal of ICU treatment is survival in good health, we aimed to develop a prediction model for ICU survivors' change in quality of life (QoL) one year after ICU admission.
Materials & methods: This is a sub-study of the prospective cohort MONITOR-IC study. Adults admitted ≥12 h to the ICU of a university hospital between July 2016–January 2019 were included. Moribund patients were excluded. Change in QoL one year after ICU admission was quantified using the EuroQol five-dimensional (EQ-5D-5L) questionnaire, and Short-Form 36 (SF-36). Multivariable linear regression analysis and best subsets regression analysis (SRA) were used. Models were internally validated by bootstrapping.
Results: The PREdicting PAtients' long-term outcome for Recovery (PREPARE) model was developed ($n = 1308$ ICU survivors). The EQ-5D-models had better predictive performance than the SF-36-models. Explained variance (adjusted R^2) of the best model (33 predictors) was 58.0%. SRA reduced the number of predictors to 5 (adjusted $R^2 = 55.3\%$, SE = 0.3), including QoL, diagnosis of a Cardiovascular Incident and frailty before admission, sex, and ICU-admission following planned surgery.
Conclusions: Though more long-term data are needed to ascertain model accuracy, in future, the PREPARE model may be used to better inform and prepare patients and their families for ICU recovery.

1. Introduction

Every year, millions of patients are admitted to an intensive care unit (ICU) worldwide. Due to advances in critical care medicine the number of patients that survive their critical illness has been steadily increasing [1]. However, over the last two decades, it has become more clear how devastating and long-lasting the consequences of critical illness can be for ICU survivors and their families. Physical, mental, and cognitive health symptoms can persist for months or even years post-discharge, severely affecting quality of life (QoL). Many patients and families are unaware of this fact, and are often too optimistic about long-term health expectations, underestimating the possible time and effort needed to return to their previous health state and associated life activities [2,3].

As highlighted by the COVID-19 pandemic [4], incorporating QoL aspects in decision making is incredibly important [5]. Expected ICU survivors need conversations about good quality of survivorship: what it entails for a particular person, whether it can be achieved, and what is necessary to achieve it.

Long-term prognoses are often based on caregivers' expert opinion and experience. Even though this is of invaluable importance in clinical practice, ICU physicians and nursing staff cannot always reliably predict future QoL [6-8]. At the same time, patients and families do not always feel comfortable speaking up about their concerns and preferences without invitation [9,10]. As it is not only the patient's survival that matters, but also their QoL, taking a more holistic point of view and broadening focus from being primarily on vital parameters is essential.

Abbreviations: PREPARE, PREdicting PAtients' long-term outcome for Recovery; ICU, Intensive Care Unit; QoL, Quality of Life; SRA, Subsets Regression Analysis; EQ-5D-5L, EuroQol five-dimensional questionnaire; SF-36, Short-Form 36 questionnaire; PROM, Patient Reported Outcome Measure; CMO, Committee on Research Involving Human Subjects; PCS, Physical Component Summary (of the SF-36 questionnaire); MCS, Mental Component Summary (of the SF-36 questionnaire); EHR, Electronic Health Record; CFS, Clinical Frailty Scale; VAS, Visual Analogue Scale; APACHE, Acute Physiology and Chronic Health Evaluation; NICE, (Dutch) National Intensive Care Evaluation registry; AIC, Akaike's Information Criterion; a-R^2, adjusted R^2; MSE, Mean Square Error; SE, Standard Error; VIF, Variance Inflation Factor; CVA, Cerebro Vascular Accident.

* Corresponding author at: Radboudumc, Department of Intensive Care Medicine, internal postal code: 707 P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.
E-mail address: marieke.zegers@radboudumc.nl (M. Zegers).

https://doi.org/10.1016/j.jcrc.2021.04.019
0883-9441/

Therefore, to improve communication between the patient and their family and ICU clinicians regarding long-term outcomes of critical illness and ICU treatment, an increased use of patient reported outcome measures (PROMs) is needed. Prediction models can aid the incorporation of PROMs in clinical decision making, and provide a more tailored prognosis regarding long-term health outcome.

Prediction modelling within the ICU has been predominantly focused on modelling short-term mortality [11,12]. Few models consider long-term health outcomes [13-15], let alone long-term QoL [16], and a clear path towards their use in the ICU is often rare. Existing models can be used to predict the chances of survival, but when survival is apparent, conversations about the QoL after the ICU need long-term data on ICU survivors to inform patients about the road to recovery and to provide ICU physicians with more outcome information to guide their ICU decision making and achieve goal-concordant care. Therefore, the aim of the present study was to develop a model to predict the change in QoL of ICU survivors one year after ICU admission, with the clear goal of its use in clinical practice.

2. Materials & methods

2.1. Study design and population

Data were obtained through an ongoing multicenter prospective cohort study (MONITOR-IC study), in which long-term outcomes of ICU patients are measured up to five years after ICU admission (ClinicalTrials.gov: NCT03246334). ICU patients aged 16 years or older were excluded when they had been admitted to the ICU for less than 12 h, had a life expectancy of less than 48 h, or could not read or speak the Dutch language. The MONITOR-IC study protocol has been previously published and can be referred to for further detail [17].

For this ancillary study, data of patients who were admitted to one of the five adult units of the intensive care department of a university hospital between July 2016 and January 2019 were used. The intensive care department regularly treats patients after complex cardiac surgery. It also has a unit specifically designed for patients who have difficulty being weaned from ventilation. The study population included medical, planned and emergency surgery admission types. The follow-up period was one year.

Possible predictors and other specific points of interest were discussed with two members of the patient organization (www.fcic.nl) before analysis and model development began. Post-analysis, the finished prediction model was again discussed with a patient organization representative.

The study has been approved by the research ethics committee of the Radboud University Medical Centre, CMO region Arnhem-Nijmegen (number 2016–2724). All patients, or their legal representative, provided written informed consent.

2.2. Data collection

Patients were asked to complete self-administered questionnaires regarding their health status before and one year after ICU admission. In the case of unplanned ICU admissions, patients or proxies were asked to recall their health situation before admission and complete the questionnaire retrospectively as soon as possible after admission. Patients with a planned ICU admission filled in the baseline questionnaire at the outpatient clinic before ICU admission. E-mail and telephone reminders were used in the case of non-response for 4 or 6 weeks, respectively. After 90 days of non-response, patients were excluded.

2.2.1. Outcome measure

The outcome measure, change in QoL one year after ICU admission, was calculated as the QoL one year after ICU admission minus the QoL before ICU admission (at baseline). A positive change in QoL meant a QoL improvement, and a negative change in QoL meant a decrease. It was quantified using both the EQ-5D-5L questionnaire [18], and the Short-Form 36 (SF-36) questionnaire [19], as specifically calibrated for the Dutch population [20]. Both questionnaires are oft-used measurements of QoL in ICUs [21,22]. Both were used for initial analyses to see which model would perform better, after which one was chosen for continued main analyses.

The EQ-5D is generally used in health technology assessment studies, though it is still frequently used in ICU research [21]. It consists of five questions each highlighting different aspects of QoL. The Dutch EQ-5D-5L range is −0.446 to 1 [20], a higher score means a better QoL. Its minimal clinically important difference is 0.08 [23].

The SF-36 is a staple of ICU QoL research [22]. Its 36 questions are used to describe both the physical and the mental health aspects of QoL, compiled into the physical component summary (PCS) and the mental component summary (MCS). Both the PCS and MCS range from 0 to 100, a higher score means a better QoL.

2.2.2. Predictors

Candidate predictors consisted of PROMs and other variables that were part of the questionnaire filled in by the patients or proxies as part of the MONITOR-IC study, and of medical patient characteristics collected in the electronic health record (EHR). Two of the PROMs used as candidate predictors in this study were frailty, measured using the Dutch Clinical Frailty Scale (CFS) (range: (1 [very fit] – 9 [terminally ill]) [24], and the Visual Analog Scale (VAS, a part of the EQ-5D, a measure of overall QoL experience) (both assessed by patients or proxies themselves). Examples of other questionnaire variables are marital status and education level (categorized according to highest finished level of education as low [unfinished primary education, primary education, lower-level secondary education], middle [intermediate general secondary education, secondary vocational education, pre-university education], or high [high professional education or academic education]). All PROMs and other variables collected in the MONITOR-IC database can be found in the study protocol [17]. EHR data included information about the first 24 h of a patient's admission to the ICU, as well as hospital and ICU length of stay. This was supplemented with the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score and physiological factors like blood pressure. All of these variables were collected by the Dutch National Intensive Care Evaluation registry (NICE: https://stichting-nice.nl/), with standardized definitions as specified in their data dictionary.

A preselection of possible predictors was executed based on expert opinion [25], future model ease-of-use and existing literature [21,26-28]. The full list of candidate predictors can be found in the Additional Files (Additional File 1).

2.3. Statistical analysis

The aim was to achieve the best predictive performance as opposed to explain associations between the predictors and the outcome. Predictive performance was primarily expressed as the explained variance (R^2). This aim guided all of the analysis decisions [29].

Complete case analysis was applied, meaning that the prediction model has explicitly been developed using survivor data. Multiple imputation was applied to account for independent variable missing values, but did not significantly change predictive performance.

In order to satisfy the regression assumption of normal dependent variable distribution, the outcome measure was defined as change in QoL after one year, i.e. QoL one year after ICU admission minus QoL before ICU admission (at baseline). To produce both a statistically sound and practically useable prediction model for ICU survivors' change in QoL after one year, multivariable linear regression analysis was applied to find the model that best fit the data, followed by best subsets regression analysis (SRA). Calibration plots can be found in the Additional Files (Additional File 3).

2.3.1. Linear regression modelling: choosing the best fit model

To obtain the model that best fit the data with respect to Akaike's Information Criterion (AIC) [30], a stepwise selection procedure was performed. This model is subsequently referred to as the best fit model. The adjusted R^2 (a-R^2) and mean square error (MSE) were calculated to indicate the predictive performance of the model.

2.3.2. Best subsets regression modelling: choosing the best practical model

SRA was used to identify the best practical model for use in daily clinical practice, and to compare its performance to the best fit model. This study considered a 'practical' model to be easy to use and thus small in terms of the number of predictors needed, while still providing an adequate predictive performance. SRA is a means for model selection that consists of testing all possible combinations of predictor variables while restricting the number of variables allowed in the prediction model. The R function regsubsets from the R package leaps was used to identify different best models of different sizes, ranging from the best one-variable model up to the best ten-variable model [31]. The best practical model was chosen based on expert-led discussion combined with the predictive performance, defined as the a-R^2 increase in the amount of variation explained in the model per predictor added.

2.3.3. Internal validation

For all models, interval validation was performed through bootstrap sampling [32]. The model was fit on the bootstrap dataset for each of the 2000 bootstrap samples. The outcomes on the full dataset were predicted and the R^2 and MSE from these predictions were calculated. Then, the mean R^2 and MSE across bootstrap samples as well as standard errors (SEs) were calculated. Good internal validation would result in mean bootstrap R^2's that are similar to the model a-R^2, and low SEs.

Classification tables for each bootstrap model to visualize the data fit can be viewed in the Additional Files (Additional File 4). For these, we categorized observed and predicted change in QoL score in three categories (<-0.2, -0.2–0.2, and > 0.2) and tabulated them. The variance inflation factor (VIF) was used to identify multicollinearity in the models. Variables with VIF > 5 were removed from the model.

Some additional analyses were explored for the purpose of exploring the consequences of our choice of outcome measurement and complete case analysis strategy. These can be viewed in Additional Files 4 and 5. These include the analysis using the SF-36 questionnaire to quantify QoL and a prediction model using EQ-5D including confirmed deaths (i.e. non-survivors).

All analyses were performed in R, version 3.6.2, using the readxl, MASS, haven, tidyr, ggplot2, plyr, gamlss, lmtest, foreign, varhandle, leaps and xlsx packages [31,33-42]. The Transparent Reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) was used to check that reporting adhered to their recommendations for the reporting of studies developing a prediction model [43].

3. Results

Between July 2016 and January 2019 a total of 4315 patients were admitted to a university hospital, of whom a total of 2291 patients were included in the MONITOR-IC study. Of these, 780 (34.0%) were excluded from this study because their one-year outcome measurements were missing, either due to death ($n = 184$, 8.0%), a wish to discontinue study participation ($n = 291$, 12.7%), noncompletion of questionnaire ($n = 36$, 1.6%) or other, unknown reasons ($n = 269$, 11.7%), resulting in a dataset of 1511 patients, of whom 1308 records had no other missing non-outcome data (Fig. 1).

3.1. Baseline patients characteristics

The median age of the study population was 65.0 years (interquartile range [IQR] = 57–71) and the majority was male (67.9%). Their median QoL, as quantified using the EQ-5D describing the period before ICU admission, was 0.8 (IQR = 0.7–0.9). A histogram of the changes in QoL measured by the EQ-5D can be found in Additional File 2. Over two thirds of the sample were admitted for planned surgery (72.7%). The median APACHE-IV score was 48.0 (IQR = 38–60). All baseline study population characteristics can be found in Table 1.

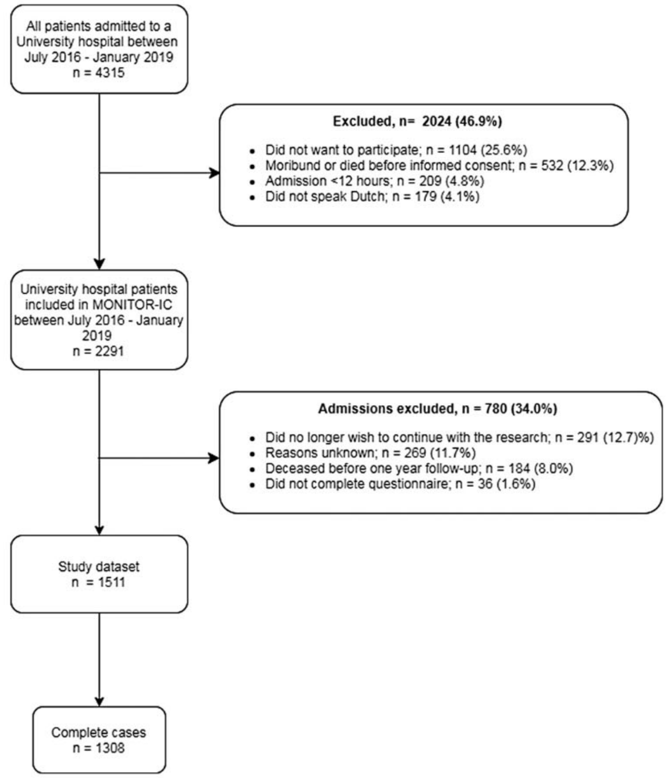

Fig. 1. Study population flowchart.

3.2. Quality of life outcome measure

Two practical prediction models were developed using the SF-36, to describe the change in PCS and MCS score. The best change in PCS model had an a-$R^2 = 40.6\%$, and the best change in MCS model had an $R^2 = 38.6\%$, more details can be found in the Additional Files (Additional File 5). The EQ-5D yielded better results in terms of predictive performance (a-$R^2 = 55.3\%$) and was preferred to the SF-36 due to the smaller size of the questionnaire. It was therefore selected for further analysis.

While the main goal was to develop a prediction model for ICU survivors, this study explored the option the EQ-5D questionnaire provides to give confirmed deaths a value of '0'. Due to the increased heterogeneity in the outcome measure variation, this yielded a lower predictive performance (a-$R^2 = 35.0$). See Additional File 6 for full results.

3.3. Best fit model (EQ-5D)

A total of 69 candidate predictors (excluding variable categories) were included in the linear regression analysis (Additional File 1). Stepwise selection resulted in a model with 34 predictors as the best fitting model (lowest AIC). Minimum thrombocyte level in first 24 h was removed due to evidence of multicollinearity, and the model was refit with 33 predictors. The strongest predictor in this best fit model was the baseline EQ-5D QoL score ($\beta = -0.79$, 95% CI: -0.83 to -0.75), a higher score was associated with a lower change in QoL after one year. Other negatively associated predictors were being admitted with a cerebrovascular accident (CVA) (which includes a cerebral embolism,

Table 1
Patient characteristics at baseline (ICU admission).

Variable	Median (25th–75th percentile) or N (%)
Sex: male	888 (67.9)
Age	65.0 (57.0–71.0)
Frailty	3 (2.0–3.0)
EQ-5D-5L score	0.8 (0.7–0.9)
SF-36 PCS score	41.9 (32.3–51.1)
SF-36 MCS score	52.0 (41.4–57.6)
APACHE IV score	48.0 (38.0–60.0)
Education level:	
• High	376 (28.7)
• Medium	574 (43.9)
• Low	358 (27.4)
Admission type:	
• Planned Surgery	951 (72.7)
• Emergency surgery	140 (10.7)
• Medical	217 (16.6)
Mechanically ventilated 24 h after admission	1020 (78.0)
Comorbidity (chronic conditions):	
• Immunological insufficiency	66 (5.0)
• Malignant hematological disease	18 (1.4)
• Metastasized neoplasm	58 (4.4)
• Cirrhosis	0 (0)
• Chronic cardiovascular insufficiency	37 (2.8)
• Chronic respiratory insufficiency	16 (1.2)
• Chronic renal insufficiency	21 (1.6)
Highest Sequential Organ Failure Assessment (SOFA) score	7.0 (5.0–9.0)
Length of mechanical ventilation (days)	1.0 (1.0–2.0)
ICU length of stay (days)	1.0 (1.0–2.0)
Hospital length of stay (days)	8.0 (6.0–13.0)

Abbreviations: PCS = SF-36 Physical Component Summary, MCS = SF-36 Mental Component Summary.

occlusion, bleeding or infarction prevalent before or within one hour of admission) (β = −0.11, 95% CI: −0.18 to −0.04)), chronic respiratory insufficiency (β = −0.15, 95% CI: −0.24 to −0.06) and a higher frailty score (β = −0.01, 95% CI: −0.02 to -0.01). Male sex was associated with a higher change in EQ-5D score after one year (β = 0.05, 95% CI: 0.03–0.07). The full summary of the best fit regression model is depicted in Table 2.

3.4. Best subsets regression analysis

If, through SRA, the number of predictors in the model was restricted to one, the model was most likely to include the baseline EQ-5D QoL score. The a-R^2 ranged from 51.1% for the smallest model, to an a-R^2 value of 58.0% for the largest model. The a-R^2's for all models were similar to their bootstrap mean R^2, showing good internal validation. Starting from the four-predictor model, adding more predictors to the smallest model added only minimal improvement in terms of predictive performance. After discussions within the multidisciplinary team, it was decided that using the five-variable model would offer a predictive performance approaching the full model while not forcing us to compromise on ease-of-use or nuance, and was selected as the final model. There was no evidence of multicollinearity, with variance inflation factors <2 for all variables across the 10 models. The full summary of the best subsets regression analysis can be found in Table 3.

3.5. Best practical model analysis

The five predictors most likely to be included in the best subsets model restricted to five predictors were studied with linear regression analysis. Baseline EQ-5D QoL score was negatively associated with the outcome (β = −0.76, 95% CI: −0.81 to −0.72), as were frailty score (β = −0.02, 95% CI: −0.03 to −0.01) and having been admitted with a cerebral vascular accident (CVA) (β = −0.14, 95% CI: −0.20 – −0.07). Male sex and being admitted from the operating room from

Table 2
Best fit prediction model for Change in QoL summary, including 33 predictors.

Predictor	Coefficient	95% CI	*p*-value
Baseline EQ-5D score	−0.79	−0.83 to −0.75	<0.001
Age at baseline	−0.00	−0.00 to −0.00	0.13
Sex: male	0.05	0.03–0.07	<0.001
Weight	−0.00	−0.00–0.00	0.09
Frailty	−0.01	−0.02 to −0.01	<0.001
Education level			
• High education	0.03	0.00–0.06	0.02
• Medium education	0.03	0.01–0.05	0.01
Admission type			
• Planned surgery	0.03	−0.01–0.07	0.10
Admission source (from same hospital):			
• CCU, ICU or Special Care Unit	0.10	0.01–0.18	0.02
• Operating room from nursing ward	0.03	−0.00–0.01	0.07
Dysrhythmia	0.03	−0.01–0.07	0.12
CVA (present at admission)	−0.11	−0.18 to −0.04	0.00
Intracranial mass effect	−0.07	−0.14–0.00	0.06
Chronic respiratory insufficiency	−0.15	−0.24 to −0.06	0.00
Acute renal failure	−0.05	−0.11–0.01	0.11
Chronic COPD	−0.03	−0.06 to −0.01	0.12
Minimum heartrate in first 24 h	−0.00	−0.00 to −0.00	0.04
Maximum heartrate in first 24 h	0.00	−0.00–0.00	0.18
Minimum systolic blood pressure in first 24 h	0.00	−0.00–0.00	0.09
Maximum systolic blood pressure in first 24 h	−0.00	−0.00–0.00	0.10
Mean minimum blood pressure in first 24 h	−0.00	−0.00–0.00	0.15
Minimum temperature in first 24 h	−0.01	−0.02 to −0.00	0.13
Maximum potassium level in first 24 h	−0.02	−0.04–0.00	0.02
Maximum sodium level in first 24 h	−0.00	−0.01 to −0.00	0.02
Maximum bicarbonate level in first 24 h	−0.00	−0.01 to −0.00	0.03
Bilirubin level in first 24 h	0.00	0.00–0.00	0.03
Minimum albumin level in first 24 h	−0.00	−0.00–0.00	0.10
Maximum albumin level in first 24 h	0.00	−0.00–0.00	0.36
Maximum thrombocyte level in first 24 h	0.00	−0.00–0.00	0.20
Maximum glucose level in first 24 h	−0.00	−0.01–0.00	0.05
APACHE probability score at baseline	0.21	0.08–0.34	0.00
APACHE IV probability score at baseline	−0.21	−0.32 to −0.10	<0.001
One previous admission to the ICU	−0.05	−0.09 to −0.01	0.02

Abbreviations: CCU = coronary care unit, CVA = Cardiovascular Accident, COPD = Chronic Obstructive Pulmonary disease, APACHE = Acute Physiology and Chronic Health Evaluation.

the nursing ward within the same hospital were positively associated with the outcome (β = 0.05, 95% CI: 0.03–0.07) and β = 0.07, 95% CI: 0.05–0.10), respectively.

This best practical model, named PREPARE (PREdicting PAtient's long-term outcome for REcovery) had an a-R^2 of 55.3%. A visual demonstration of the best practical model can be viewed in Fig. 2. The red dot points to the predicted change in QoL after one year for a fictional patient. An example of its possible use is detailed in the figure description.

The calibration plot shows that the relationship between the predicted changes in EQ-5D and the actual changes in EQ-5D is linear with slope = 1 (95% CI: 0.95–1.05) and intercept = 0 (95% CI: −0.01–0.01), indicating that the model is well calibrated. The calibration plot can be viewed in the Additional Files (Additional File 3).

The classification table for the PREPARE model shows that the model correctly classifies higher differences in EQ-5D score better than lower differences. Though this also occurred in the full model, this is more pronounced in the PREPARE model. All classification tables can be viewed in the Additional Files (Additional Files 4, 5, 6).

Table 3
Best subsets regression analysis summary.

Variable name ↓	Number of variables in model →	1	2	3	4	5	6	7	8	9	10	Best fit: 33
Baseline EQ-5D-5L score		■	■	■	■	■	■	■	■	■	■	■
Admission source: Operating room*			■	■	■	■	■	■	■	■	■	■
Sex: male				■	■	■	■	■	■	■	■	■
Frailty					■	■	■	■	■	■	■	■
CVA (present at admission)						■	■	■	■	■	■	■
Chronic respiratory insufficiency							■	■	■	■	■	■
Maximum sodium levels in first 24 hours								■	■	■	■	■
One previous ICU admission									■	■	■	■
Minimum heartrate in first 24 hours										■	■	■
Bilirubin levels in first 24 hours											■	■
Model Adjusted R^2 %		51.1	53.1	54.0	54.8	55.3	55.6	55.7	55.9	56.0	56.2	58.0
Mean Square Error of prediction (model)		0.033	0.032	0.031	0.030	0.030	0.030	0.030	0.030	0.030	0.029	0.029
Mean bootstrap R^2 % (SE)		51.0 (0.13)	53.0 (0.14)	54.0 (0.15)	54.7 (0.16)	55.1 (0.25)	55.3 (0.26)	55.5 (0.27)	55.7 (0.27)	55.8 (0.28)	55.9 (0.34)	57.6 (0.45)

* *Admitted from Operating room from nursing ward, same hospital.* This indicates an ICU admission after elective surgery.
Abbreviations: CVA = Cardiovascular accident

4. Discussion

In this study, a prediction model for change in ICU survivors' QoL one year after ICU admission was developed that has both predictive value and is well calibrated, as supported by internal validation. The small number of predictors, all available within the first 24 h of admission, increase the feasibility of eventually using the PREPARE model in clinical practice. Moreover, the prediction model based on the less-burdensome five-question EQ-5D questionnaire had better predictive value than the longer SF-36 QoL questionnaire, which is more commonly used in the ICU [21,22].

Prediction models focusing purely on QoL, and not on mortality, are rare in critical care. In many places, collecting long-term outcomes post-ICU is not routinely done. Using this information in clinical practice goes even further. A timely and continuous conversation about long-term outcomes is an indispensable part of future intensive care medicine for the growing numbers of ICU survivors who need to reckon with the fact that their lives might not be the same as before the ICU. Incorporating a prediction model in physician-family conversation as an enrichment to ICU professionals' knowledge invites and empowers ICU patients and their families to be more involved in conversations around the care of their family members and helps to manage their expectations for long-term recovery, facilitating an individualized, preparatory approach instead of a reactionary one.

As far as we are aware, only Oeyen et al. have developed a practically usable prediction model for the general ICU population's long-term QoL [16]. Although our overall conclusions are similar, the major difference between the studies is the inclusion of patients who died in the year after admission, an approach that was rejected due to our focus on the increasing number of patients who survive their ICU stay and the manner of their survivorship. After all, when survival is apparent, data on the long-term health outcomes of survivors are incredibly important. This study also had more planned surgical patients and incorporated more physiological patient characteristics within the first 24 h of admission. The authors consider this study to be an elaboration, with a focus on the manner of survivorship and a proposed method of prediction model visualisation.

Past implementation of prediction modelling in ICU practice has been impeded by doubts about model accuracy [16,44]. Medical professionals familiar with prediction modelling might think the PREPARE model performance inferior to the predictive performance measurements of other oft used prediction models in ICU practice (SAPS III aROC: 0.86 [12], APACHE IV aROC: 0.88 [11] predict patients' chance to die in hospital). Any prediction for long-term health can only ever be used as a supplement to ICU professionals' knowledge and experience. Considering the difficulty of predicting a long-term PROM such as QoL, we deem the current achieved model performance based only on variables available within the first 24 h of admission to be a substantive step in the right direction. All the same, the CIs of the PREPARE model predictions are still fairly wide, and it predicts better for larger QoL differences than smaller ones. In order to use the prediction model in clinical practice, the model performance and accuracy should be improved upon. For instance, by more detailed patient data from the EHR, instead of only data from the first 24 h. Moreover, the applicability of the PREPARE prediction is conditional on 1-year survival. As has been noted in literature before, clinicians cannot always reliably predict survival [8]. At this time, therefore, we foresee optimal use of the prediction model to be in conversations between physicians and family members, who can explain the current limitations to the PREPARE model while still using the prediction to start and improve the quality of the discussions and prepare patients and family members for post-ICU recovery.

Though the aim was to develop the best possible prediction model rather than identify and explain associations, this study found, like other studies detailing the prediction of physical long-term ICU health outcomes, that among the predictors the pre-ICU QoL is by far the most important predictor for long-term QoL (used as the sole predictor a-R^2 = 51.1%) [16,21,45-49]. Being admitted to the ICU in a good state improves the changes of being discharged with good outcomes. Previous research into the importance of pre-ICU QoL for post-ICU QoL has

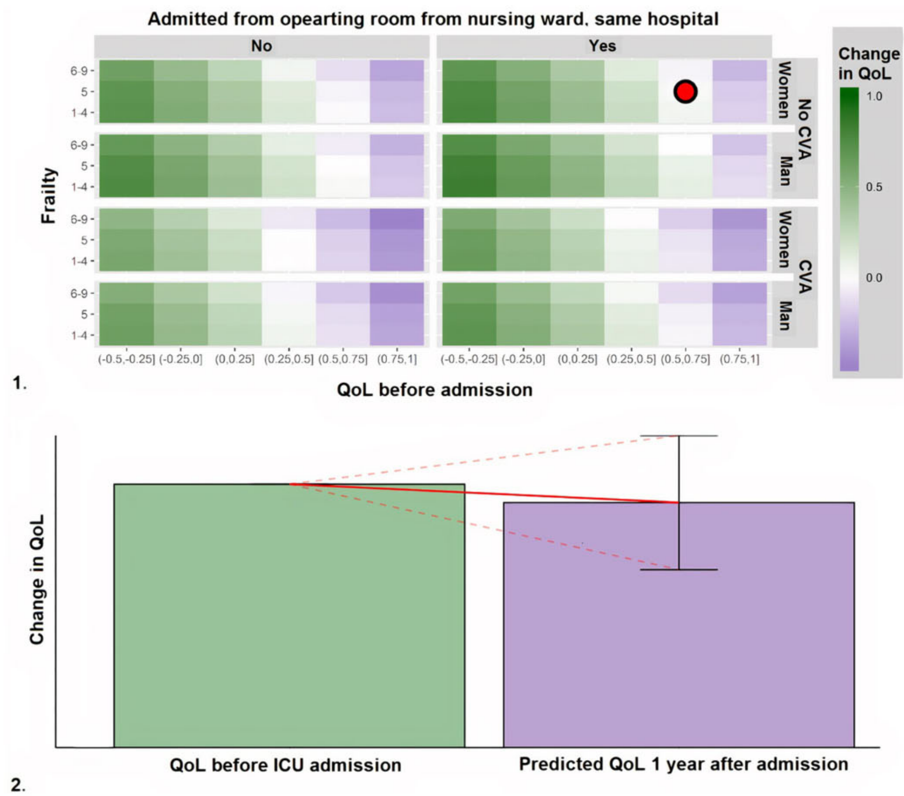

Fig. 2. Risk table visualising the PREPARE model.

*The PREPARE model has five predictors and is described by the following formula: Change in QoL 1 year after ICU admission = 0.63 + Baseline QoL score * −0.77 + Planned surgery admission * 0.07 + Male sex * 0.05 + Frailty score * −0.02 + CVA (present at admission) * −0.14*

1. The red dot points to the predicted change in QoL (Δ = −0.08, 95% CI: −0.43 − 0.26) after one year for a fictional female patient who is frail (Frailty score = 6), had a baseline QoL score of 0.84 and who was admitted after a planned surgery with no CVA present.

2. Case example: A 74-year-old woman, still living at home, is admitted for a planned operation to her knee. The operation leaves her with some complications which prolong her stay for several days. Fortunately, the complications appear to pass, and after 5 days on the ICU things are looking good. In the second of two family conversations in the ICU, the physician sits down with the family. As part of the conversation, the physician talks to the family about the long-term health situation of the patient, who before admission had an EQ-5D utility score of 0.85. The model predicts a change of −0.08, meaning her predicted score one year after admission is 0.75, lower than the Dutch national average for her age category. The physician discusses this slight deterioration in general terms, reminding the family of the uncertainty in the prediction, and uses the schematic image to discuss with the family several likely general scenarios regarding the patient's future quality of life, depending on the rest of her ICU and hospital stay. A conversation around the weeks of rehabilitation ahead and what the patient would consider a satisfying quality of life ensues. Eventually, the physician notes that while the patient will likely be able to go home this time, it is worthwhile to consider what a potential future admission would mean for her. The family clarify what they know of the situation at the moment, and discuss among themselves their understanding of the patient's limits.

Using the PREPARE model has ensured that the physician, who might normally not have started speaking about the long-term health situation, has given the family a visual reminder of the days ahead. This has provided the family with food for thought regarding the future. It has reminded them that they have a choice about how to proceed with possible future ICU care and has engaged them in discussions about what care should and shouldn't be considered. Using the prediction in the conversation has provided the physician with information about the patient that they can use to inform further treatment decision making.

shown that a majority of ICU-survivors regained their pre-ICU QoL [48]. Conversations about pre-ICU health status are already an important part of many ICU physicians' manner of providing care. Supplementing these conversations with a more standardized set of questions and more long-term data will increase their quality.

Inviting patients and families to talk about both the opportunities and the disadvantages of an ICU admission in a frank manner is important to prepare them for recovery [5,9,10]. This study is new evidence supporting the importance of pre-ICU health in ICU decision making. Moreover, while age is generally one of the most crucial factors considered when performing triage [50,51], this study shows that while it was associated with the outcome in the full model, the results show that baseline QoL and frailty score are more important predictors of long-term QoL than age, which is supported by literature [21,52]. However, this may be explained by the narrowness of the age range of the study population, or the fact that the majority of study population had a planned admission.

This is a large prospective cohort study based on ICU patients' past and long-term health. Though second of its kind, it demonstrates the possibility of achieving an acceptable predictive performance combined with a reduction of the number of predictors needed, compared to its predecessor in purpose [16], thereby possibly providing physicians and families with a tool to enhance the quality of their conversations on the ICU.

This study has some limitations. There is a possible survival bias in the relatively healthier ICU patient group that agreed to participate in the MONITOR-IC study, and by extension, are included in the prediction model. Over one third of the eligible MONITOR-IC patients was lost to follow-up or failed to fill in the questionnaire one year after ICU admission, and, with their outcome data missing, were excluded from the analysis. The possible reason for the loss-to-follow-up might go two ways. It might be due to a loss of study engagement after a complete recovery, but it could also be due to a worsening of health outcomes. This could have caused our results to reflect a too-healthy ICU population. More than two thirds of the included patients were admitted due to planned surgery (e.g. cardiac surgery, oncology surgery, neurosurgery). Generally, these patients are more prepared for an ICU stay and have better outcomes. Even though the prediction model is for ICU survivors only, this sample may be slightly better off than the general ICU survivor population. This could have caused the predictions to be overoptimistic and may affect the generalizability of the PREPARE model. An external validation procedure with data from more centers and with a larger proportion of medical ICU patients is needed to assess and further improve model accuracy. Also, our aim of developing a static prediction model usable within the 24-h of admission has necessarily caused us to not include variables possibly associated with the outcome that can be measured post-ICU, such as ICU-acquired weakness and symptoms of anxiety and depression at discharge. Moreover, though proxies filling in the questionnaire when patients were unable to might have introduced a small underestimation of their QoL scores [53], though the literature on this is not consistent [54], we believe that excluding these patients would have led to bias as well [55]. The fact that some patients and proxies took some days to fill in the questionnaire might have introduced some recall bias. We consider the choice to use only ICU survivor data to be best considering the aim, though we realize that it is not always clear who will survive long-term. However, we still believe that the conversations around the information the model provides will be a valuable contribution to the improved ICU care of today, with its shifting focus towards the manner of survivorship.

In order to further model implementation, the next step is an external validation procedure with more multicenter long term outcome data with a larger proportion of medical ICU patients to assess and further improve model accuracy.

5. Conclusions

This study shows the development of the PREPARE model, a prediction model for ICU survivors' change in QoL one year after ICU admission that may be usable in clinical practice in the future due to the small number of predictors available on the first day of admission. Though the explained variance of 55.3%, as supported by internal validation, marks the model as a potential helpful future complement to ICU professionals' knowledge and expertise to improve the quality of conversations with patients and their families, there is a need for more long term outcome data with a larger proportion of medical ICU patients to assess and further improve model accuracy. In the future, conversations using long-term QoL information could be integrated in ICU care to better inform ICU decision making and to aid ICU survivors in managing their long-term health expectations.

Funding

This work was supported by Zorginstituut Nederland (2018026879). Zorginstituut Nederland was not involved in the design of the study, nor with the data collection, analysis, interpretation or writing of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.04.019.

References

[1] Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9.
[2] Kerckhoffs MC, Soliman IW, Wolters AE, Kok L, van der Schaaf M, van Dijk D. Long-term outcomes of ICU treatment. Ned Tijdschr Geneeskd. 2016;160:A9653.
[3] Feetham L. The long road to recovery after the ICU. Lancet Respir Med. 2018;6(3):180–1.
[4] Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA. 2020;323:1545–6.
[5] Curtis JR, Kross EK, Stapleton RD. The importance of addressing advance care planning and decisions about do-not-resuscitate orders during novel coronavirus 2019 (COVID-19). JAMA. 2020;323:1771–2.
[6] Kerckhoffs MC, Kosasi FFL, Soliman IW, van Delden JJM, Cremer OL, de Lange DW, et al. Determinants of self-reported unacceptable outcome of intensive care treatment 1 year after discharge. Intensive Care Med. 2019;45(6):806–14.
[7] Soliman IW, Cremer OL, de Lange DW, Slooter AJC, van Delden J, van Dijk D, et al. The ability of intensive care unit physicians to estimate long-term prognosis in survivors of critical illness. J Crit Care. 2018;43:148–55.
[8] Frick S, Uehlinger DE, Zuercher Zenklusen RM. Medical futility: predicting outcome of intensive care unit patients by nurses and doctors–a prospective comparative study. Crit Care Med. 2003;31(2):456–61.
[9] Bell SK, Roche SD, Mueller A, Dente E, O'Reilly K, Sarnoff Lee B, et al. Speaking up about care concerns in the ICU: patient and family experiences, attitudes and perceived barriers. BMJ Qual Saf. 2018;27(11):928–36.
[10] Fisher KA, Smith KM, Gallagher TH, Huang JC, Borton JC, Mazor KM. We want to know: patient comfort speaking up about breakdowns in care and patient experience. BMJ Qual Saf. 2019;28(3):190–7.
[11] 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(5):1297–310.
[12] Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3–from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. Intensive Care Med. 2005;31(10):1336–44.
[13] Brinkman S, Abu-Hanna A, de Jonge E, de Keizer NF. Prediction of long-term mortality in ICU patients: model validation and assessing the effect of using in-hospital versus long-term mortality on benchmarking. Intensive Care Med. 2013;39(11):1925–31.
[14] Carson SS, Kahn JM, Hough CL, Seeley EJ, White DB, Douglas IS, et al. A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. Crit Care Med. 2012;40(4):1171–6.
[15] 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(9):1718–26.
[16] Oeyen S, Vermeulen K, Benoit D, Annemans L, Decruyenaere J. Development of a prediction model for long-term quality of life in critically ill patients. J Crit Care. 2018;43:133–8.
[17] Geense W, Zegers M, Vermeulen H, van den Boogaard M, van der Hoeven J. MONITOR-IC study, a mixed methods prospective multicentre controlled cohort study assessing 5-year outcomes of ICU survivors and related healthcare costs: a study protocol. BMJ Open. 2017;7(11):e018006.
[18] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, 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.
[19] Ware Jr JE, 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.
[20] Versteegh M, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value Health. 2016;19(4):343–52.
[21] Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38(12):2386–400.
[22] Turnbull AE, Rabiee A, Davis WE, Nasser MF, Venna VR, Lolitha R, et al. Outcome measurement in ICU survivorship research from 1970 to 2013: a scoping review of 425 publications. Crit Care Med. 2016;44(7):1267–77.
[23] McPeake J, Shaw M, Iwashyna TJ, Daniel M, Devine H, Jarvie L, et al. Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE). Early evaluation of a complex intervention. PLoS One. 2017;12(11):e0188028.
[24] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
[25] Steyerberg EW. Clinical prediction models: a practical approach to development, validation and updating. Springer; 2019.
[26] Rojas JC, Carey KA, Edelson DP, Venable LR, Howell MD, Churpek MM. Predicting intensive care unit readmission with machine learning using electronic health record data. Ann Am Thorac Soc. 2018;15(7):846–53.
[27] 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(8):1105–22.
[28] Ferrand N, Zaouter C, Chastel B, Faye K, Fleureau C, Roze H, et al. Health related quality of life and predictive factors six months after intensive care unit discharge. Anaesth Crit Care Pain Med. 2019;38(2):137–41.
[29] Shmueli G. To explain or to predict? editor , In: Petrone S, editor. Statistical science. 25: Institute of Mathematical Statistics; 2010. p. 289–310.

[30] Akaike H, Petrov BN, Csaki F. Second international symposium on information theory. Budapest: Akadémiai Kiadó; 1973.
[31] Thomas Lumley based on Fortran code by Alan Miller. leaps: regression subset selection. R package version 3.1 https://CRAN.R-project.org/package=leaps. ed2020.
[32] Harrell Jr FE, Lee KL, Mark DB. Tutorial in biostatistics: multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Statistics in medicine. 15: John Wiley & Sons, Ltd; 1996. p. 361–87.
[33] Wickham Hadley, Bryan Jennifer. readxl: read excel files. R package version 1.3.1 https://CRAN.R-project.org/package=readxl. ed2019.
[34] Wickham Hadley, Henry Lionel. tidyr: tidy messy data. R package version 1.0.2 https://CRAN.R-project.org/package=tidyr. ed2020.
[35] Wickham Hadley, Miller Evan. haven: import and export 'SPSS'. 'Stata' and 'SAS' files. R package version 2.2.0 https://CRAN.R-project.org/package=haven. ed2019.
[36] Zeileis Achim, Hothorn Thorsten. Diagnostic checking in regression relationships. R New; 2002.
[37] R Core Team. foreign: read data stored by 'Minitab', 'S', 'SAS', 'SPSS', 'Stata', 'Systat', 'Weka', 'dBase'. R package version 0.8–75 https://CRAN.R-project.org/package=foreign.
[38] Mahmoudian Mehrad. varhandle: functions for robust variable handling. R package version 2.0.5 https://CRAN.R-project.org/package=varhandle. ed2020.
[39] Dragulescu Adrian, Arendt Cole. xlsx: Read, Write, Format Excel 2007 amd Excel 97/2000/XP/2003 Files. R package version 0.6.2 https://CRAN.R-project.org/package=xlsx. ed2020.
[40] Venables WN, Ripley BD. Modern applied statistics with S. 4th ed.. New York: Springer; 2002.
[41] Wickham H. ggplot2: Elegant graphics for data analysis. New York: Springer-Verlag; 2016.
[42] Wickham H. The split-apply-combine strategy for data analysis. J Stat Softw. 2011; 40:1–29.
[43] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 2015;350:g7594.
[44] Veerbeek JM, Kwakkel G, van Wegen EE, Ket JC, Heymans MW. Early prediction of outcome of activities of daily living after stroke: a systematic review. Stroke. 2011; 42(5):1482–8.
[45] Cuthbertson BH, Wunsch H. Long-term outcomes after critical illness. The best predictor of the future is the past. Am J Respir Crit Care Med. 2016;194(2):132–4.
[46] Hofhuis JG, Spronk PE, van Stel HF, Schrijvers AJ, Bakker J. Quality of life before intensive care unit admission is a predictor of survival. Crit Care. 2007;11(4):R78.
[47] Pietilainen L, Hastbacka J, Backlund M, Parviainen I, Pettila V, Reinikainen M. Premorbid functional status as a predictor of 1-year mortality and functional status in intensive care patients aged 80 years or older. Intensive Care Med. 2018;44(8): 1221–9.
[48] Wehler M, Martus P, Geise A, Bost A, Mueller A, Hahn EG, et al. Changes in quality of life after medical intensive care. Intensive Care Med. 2001;27(1):154–9.
[49] Geense WW, Zegers M, Peters MAA, Ewalds E, Simons KS, Vermeulen H, et al. New physical, mental, and cognitive problems 1-year post-ICU: a prospective multicenter study. Am J Respir Crit Care Med. 2021 online ahead of print.
[50] Kuriyama A, Ikegami T, Nakayama T. Impact of age on the discriminative ability of an emergency triage system: a cohort study. Acta Anaesthesiol Scand. 2019;63(6): 781–8.
[51] Gopalan PD, Pershad S. Decision-making in ICU - a systematic review of factors considered important by ICU clinician decision makers with regard to ICU triage decisions. J Crit Care. 2019;50:99–110.
[52] Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020;5:e444–51.
[53] Hofhuis J, Hautvast JLA, Schrijvers AJP, Bakker J. Quality of life on admission to the intensive care: can we query the relatives? Intensive Care Med. 2003;29(6):974–9.
[54] Badia X, Diaz-Prieto A, Gorriz MT, Herdman M, Torrado H, Farrero E, et al. Using the EuroQol-5D to measure changes in quality of life 12 months after discharge from an intensive care unit. Intensive Care Med. 2001;27(12):1901–7.
[55] Geense WW, van den Boogaard M, Peters MAA, Simons KS, Ewalds E, Vermeulen H, et al. Physical, mental, and cognitive health status of ICU survivors before ICU admission: a cohort study. Crit Care Med. 2020;48:1271–9.