Absence of fear of dying predicts new organ failure: Results of a multicenter prospective observational cohort study

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Abstract

Rationale: Intensity of anxiety at admission in intensive care unit (ICU) is associated with subsequent deterioration.

Objective: The primary aim of this study was to assess predictive value of stressful fears and feelings to predict new organ failure within the first seven days after ICU admission.

Methods: We conducted a prospective three-center cohort study of non-comatose patients without delirium or invasive mechanical ventilation. A twelve-item questionnaire was developed to assess stressful fears and feelings. Illness severity was assessed using SAPS-II and SOFA scores. Intensity of chronic and acute anxiety was assessed with the 'Trait' and 'State' forms of the State-Trait Anxiety Inventory (STAI). Patients were followed-up for seven days.

Results: From April 2014 to December 2017, 373 patients (median age, 63y.o. [49-74]; 159 [40.7%] women; SAPS-II 28 [19-37]) were included. Feeling of vulnerability and fear of dying was reported in 209 (54.4%) and 178 (46.4%) patients, respectively. STAI was equal or above 40 in 192 (51.5%) patients. Ninety-four (25.2%) patients developed a new organ failure. Feeling of vulnerability (OR=1.96, 95%CI:1.12-3.43], p=0.01) and absence of fear of dying (OR=2.38, 95%CI:1.37-4.17], p=0.002) were associated with occurrence of a new organ failure after adjustment on STAI ≥40, SAPS-II and SOFA.

Conclusion: Absence of fear of dying is associated with occurrence of new organ failure within the seven post-ICU admission days. We hypothesize that fear of dying might be protective for subsequent deterioration by mobilizing patient's homeostatic resources.

Trial registration: NCT02355626

Introduction

Hospitalization in intensive care unit (ICU) is a stressful event for critically ill patients. The acute behavioral response is characterized by emotions such as anxiety or fears and their study could provide new physiological markers to improve prognosis. Anxiety is a major behavioral component of the response to stress and has an early prognostic value in critically ill patients(1). A more precise characterisation of the behavioral response could provide new personalized markers for prognostication(2). Indeed, anxiety is mainly regulated by the amygdala, which is connected with the neuroendocrine and autonomic centers. On one hand, the amygdala integrates exteroceptive and interoceptive stress signals; on the other hand, it modulates the behavior, neuroendocrine and autonomic responses, in order to maintain the homeostasis (3). In a prospective multicenter study, we found that half of the patients who reported moderate to severe anxiety at ICU admission presented more frequently a new organ failure independently of severity of critical illness. To further characterize the behavioral response to stress to improve its prognosis value, we focused on the fears shown by patients upon ICU admission. There are evidences suggesting that fears could also predict subsequent worsening. For

instance, we previously found that a qualitative assessment was informative in patients with Guillain-Barré syndrome (GBS). The uncertainty as how the disease would progress was the most stressful fear and was associated with subsequent failure in GBS patients(4). It is therefore conceivable that particular psychological patterns are identifiable among critically ill patients, of which some might be associated with short-term outcome. Interestingly, the incidence and prognosis value of fears and feeling have never been assessed in the general population of critically ill patients and no questionnaire has been developed for this purpose, so far. In a cohort of our previously published work we evaluated the prevalence of fears and feelings upon ICU admission.

This study aimed at determining whether fears and feelings was predictive of the occurrence of death or new organ failure within the first seven days following ICU admission (1).

Material And Methods

Study design

This prospective observational cohort study was conducted between April 2014 and December 2017 in the medico-surgical ICUs of the Raymond Poincaré university hospital (Garches, France), the Sud-Essonne hospital (Etampes, France) and the tertiary oncologic Hospital of the Gustave Roussy Institute (Villejuif, France). The study was registered prior to the inclusion of the first patient (ClinicalTrials.gov, NCT02355626) and the report follows the STROBE Checklist instructions for observational studies(5).

Main objective

The main objective was to assess whether the patients' fears and feeling at time of ICU admission was associated with death of new organ failure within the seven days after ICU admission.

Study population

Consecutive adults admitted to the participating ICUs and breathing spontaneously were enrolled into the study. Patients were excluded if they had delirium or impaired consciousness, assessed by the Confusion Assessment in ICU (CAM-ICU) score, negative Richmond Assessment Sedation Scale (RASS) value or Glasgow Coma Score (GCS) value below 15; were referred for a suicide attempt; had a history of impaired cognition; or were non-French speakers. The present study was approved by the ethical committee of St Germain-en-Laye. It was also approved by the Advisory Committee for Data Processing in Health Research (CCTIRS) with a waiver for written informed consent. According to the French regulation only verbal and written information were required. The study has been conducted in accordance with the French regulation and the Helsinky declaration.

Anxiety assessment and ICU fear questionnaire

We conducted an interview with each patient within 12 hours of ICU admission, in which fears were qualitatively assessed using a dedicated ICU fear questionnaire as well as anxiety through the STAI.

In a preliminary step, we asked experienced 11 ICU-physician, nine nurses and two psychologists to list the most frequent fears that patients may report or encounter during their stay in ICU. Based on their responses, we then designed the “ICU fear questionnaire” in which consists of 9 questions: 1) “Do you believe your condition to be severe?”, 2) “Are you afraid of being intubated?”, 3) “Do you feel vulnerable?”, 4) “Are you afraid of becoming disabled?”, 5) “Are you afraid of dying?”, 6) “Are you afraid of abandoning your close friends/loved ones?”, 7) “Are you afraid of your environment?”, 8) “Do you believe that information regarding your condition is being withheld?” 9) “Are you afraid of being abandoned?”. Similarly to the STAI scoring, possible answers ranged from “very much so”, “moderately so”, “somewhat” to “not at all”. Finally, the use (or withdrawal) of any drug that may affect mental status or cognitive function was recorded. We finally asked patients whether the interview had been a source of anxiety.

As described elsewhere, the STAI-state was used to assess the level of anxiety and the STAI-trait to assess chronic anxiety. The score for both formularies ranges from 20 to 80, with a score above 40 indicating anxiety of at least moderate intensity(6, 7).

Data collected upon inclusion

At inclusion, we systematically collected demographic characteristics, marital and professional status, psychotropic drug consumption (i.e. antidepressant, anxiolytics), comorbidities (assessed using the Knaus(8), and Mc Cabe(9) categories), direct admission from home, reason for ICU admission, vital signs, CAM-ICU(10), RASS(11), and GCS(12). Severity of illness was assessed using the SAPS-II(13) and SOFA(14) scores. Routine laboratory tests were recorded. The need for non-invasive mechanical ventilation (NIV), renal replacement therapy, vasopressors, and blood transfusion were also recorded.

Follow-up data

Follow-up in the ICU lasted 7 days. Were recorded daily 1) Anxiety, dyspnea, pain, hunger and thirst, estimated by VAS; 2) Vital signs, the SOFA score, the CAM-ICU, GCS and RASS (when appropriate); 3) The use of mechanical ventilation (MV), renal replacement therapy and blood transfusion; 4) The administration of vasopressors, sedative or psychotropic drugs; 5) The need for unplanned surgery or coronary angiography; 6) routine laboratory tests; 7) Re-admission to the ICU. The lengths of MV, of ICU and hospital stay were also collected up to 90 days.

Outcomes

The primary outcome was the occurrence of death or any new organ failure over the first 7 days following ICU admission. As described elsewhere(1), new respiratory failure was defined as the use of MV without being admitted for respiratory failure and in patient with a respiratory SOFA of 0 at admission; circulatory failure as the use of norepinephrine or epinephrine as vasopressors (*i.e.* SOFA>2) with a cardiovascular SOFA of 0 at admission; renal failure as the need for hemodialysis or a renal SOFA>2 without being admitted for renal failure and a renal SOFA of 0 at admission; hepatic or hematologic failure were defined by a hepatic or hematologic SOFA score >2 and a hepatic or hematologic SOFA of 0 at admission.

Neurological failure was defined by delirium evaluated with CAM-ICU or coma defined by GCS≤8. Secondary outcomes were the duration of MV, hospital and ICU length of stay and mortality.

Risk of bias and confounding factors

In order to minimize bias, the ICU staff remained blinded to the results of the assessment of discomfort, STAI questionnaires and “ICU fear questionnaire”. The STAI-State questionnaire was completed during a standardized nurse- or physician-driven interview of the patient. Although the STAI-State is usually a self-administered questionnaire, we considered that an interview with a nurse or a physician would be more appropriate for critically ill patients. Indeed, tiredness and the potential rapid degradation of their critical illness could preclude them from properly fulfilling the questionnaires.

Investigators were trained to ask questions distinctly, in a neutral tone and to repeat the question if necessary. Patients were asked to answer spontaneously. The tests were systematically performed in a predefined order: 1) STAI-State, 2) STAI-Trait and 3) “ICU fear questionnaire”.

Statistical analysis

Quantitative variables were expressed as mean with standard deviation or median with interquartile ranges and compared using the *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were expressed as numbers and percentages and compared using the Pearson χ^2 test or Fisher's exact test, as appropriate. Associations between baseline characteristics and the occurrence of death or any new organ failure within 7 days of ICU admission (dependent variable) were assessed by calculations of crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI) in binary logistic regression models. No missing value was found for these variables. Variable selection was performed stepwise, whereby candidate variables entered the model at a level of $p<0.20$ in univariable analysis and were retained only in the final multivariable model if they remained associated at $p<0.05$ with the dependent variable. Covariates were assessed for potential collinearity and interaction effects. Three models were derived, without STAI-state≥40, with STAI-state≥40 (“Anxiety Model”) and with items from ICU-fear questionnaire (“Anxiety, fears and feelings Model”). We subsequently compared the discriminative ability of the 3 models based of their c-statistics (*i.e.* the area under the receiver operating characteristic curve) and 95% CIs. We also calculated the net reclassification index (NRI) and the integrated discrimination improvement (IDI, (15). Finally, we conducted a sensitivity analysis in which the STAI score was not dichotomized (<40 vs. ≥40) but considered as a continuous variable. All tests were two-sided, at $p<0.05$ significance level and were carried out using SAS 9.4 (SAS Institute, Inc, Cary, NC).

Results

Study population

Among the 1315 spontaneously breathing patients admitted to participating ICUs between April 2014 and December 2017, 408 patients met the inclusion criteria, of which 35 were excluded (Figure 1). A total of

373 patients were eligible for the main analysis. Median age was 63 (48-74) years and 152 (40.8%) patients were female (Table 1). Twenty-three (6.2%) patients were usually treated with antidepressants and 36 (9.7%) with anxiolytics (Table 1). Patients were admitted predominantly on medical grounds and primarily for acute respiratory failure (118, 31.6%). On day 1, NIV or high-flow nasal oxygen (HFNO) was required in 77/373 (20.6%) patients.

Table 1
Demographic and clinical and biological characteristics on ICU admission

	All (n=373)	Primary endpoint met (n=94)	Primary endpoint not met (n=279)	P
Age (Years), Median (IQR)	63 (48-74)	65 (58-76)	61 (46-73)	0.01
Female Gender n (%)	152 (40.8)	38 (40.4)	114 (40.9)	0.94
Married/living with a partner n (%)	209 (56.0)	52 (55.3)	157 (56.3)	0.82
Active professionals n (%)	158 (42.4)	31 (33.0)	127 (45.5)	0.02
Psychotropic usage n (%)	48 (12.9)	18 (19.1)	30 (10.8)	0.02
Antidepressants n (%)	24 (7.2)	7 (7.4)	16 (5.7)	0.49
Anxiolytics n (%)	38 (11.5)	15 (16.0)	21 (7.5)	0.01
Knaus score C or D n (%)	145 (38.9)	35 (37.2)	110 (39.4)	0.71
Mc Cabe score = 2 n (%)	38 (10.2)	12 (12.8)	26 (9.3)	0.34
Admission from home n (%)	116 (31.1)	28 (29.8)	88 (31.5)	0.75
Cause of ICU admission n (%)				0.70
Acute respiratory failure	118 (31.6)	32 (34.0)	86 (30.8)	
Sepsis	72 (19.3)	22 (23.4)	50 (17.9)	
Surgery	35 (9.4)	8 (8.5)	27 (9.7)	
Acute renal failure	18 (4.8)	5 (5.3)	13 (4.7)	
Cardiac insufficiency	12 (3.2)	3 (3.2)	9 (3.2)	
Other	118 (31.1)	24 (25.5)	94 (33.7)	
Inclusion				
SAPS-II Median (IQR)	27 (19-37)	33 (24-42)	26.0 (18.0-34.0)	<0.001

Abbreviations: STAI-State: State Trait Anxiety Inventory State questionnaire (from 20 to 80). IQR: Interquartile range; ICU: Intensive Care Unit; SOFA: Sequential Organ dysfunction Assessment, SAPS-II: Simplified Acute Physiology Score. HFNC: High Flow nasal cannula (HFNC) oxygen therapy

	All (n=373)	Primary endpoint met (n=94)	Primary endpoint not met (n=279)	P
SOFA Median (IQR)	1 (0-3)	2 (0-4)	1 (0-2)	<0.001
Patients without organ failure at admission n (%)	231 (61.9)	41 (43.6)	190 (68.1)	<0.001
Plasma lactate level (mmol/L) Median (IQR)	1.5 (1.0-2.3)	1.7 (1.2-2.5)	1.4 (0.9-2.3)	0.07
Plasma creatinine level (mg/dL) Median (IQR)	79 (61-123)	95 (62-163)	76 (61-107)	0.01
Platelet count (G/L) Median (IQR)	220 (155-291)	215 (125-298)	221 (167-287)	0.48
Non-invasive mechanical ventilation or HFNC, n (%)	77 (20.6)	26 (27.7)	51 (18.3)	0.05
Vasopressive agent, n (%)	18 (4.8)	12 (12.8)	6 (2.2)	0.0002
Renal replacement therapy, n (%)	15 (4.0)	6 (6.4)	9 (3.2)	0.22
Abbreviations: STAI-State: State Trait Anxiety Inventory State questionnaire (from 20 to 80). IQR: Interquartile range; ICU: Intensive Care Unit; SOFA: Sequential Organ dysfunction Assessment, SAPS-II: Simplified Acute Physiology Score. HFNC: High Flow nasal cannula (HFNC) oxygen therapy				

Fears, feelings and discomfort upon admission

As shown in Table 2, 192 (51.5%) patients reported mild to severe anxiety, defined as a STAI-State ≥ 40. About two-thirds of patients perceived their condition as being serious (n=255, 68.4%), declared to fear intubation (n=238, 63.8%), to feel vulnerable (n=203, 54.4%), or to fear becoming disabled (n=197, 52.8%). Almost half of patients declared to be afraid of dying (n=172, 46.1%). The ICU fear questionnaire was considered stressful by 43 patients (11.6%) patients. Patients who felt vulnerable or feared to die were more frequently women, had a pre-existing anxiety and were treated with anxiolytics but also more frequently had a pre-existing disease according to the Knaus category (supplementary table 1, (8)).

Table 2
Characteristics of anxiety and fears on ICU admission

	n = 373	Primary endpoint met (n=94)	Primary endpoint not met (n=279)	p
STAI-State (20 to 80), Median (IQR)	40 (31-51)	43 (32-53)	39 (30-50)	0.08
STAI-State >40, n (%)	192 (51.5)	58 (61.7)	134 (48.0)	0.02
Answers to the ICU fear questionnaire				
Believe to be in a serious condition, n (%)	255 (68.4)	69 (73.4)	186 (66.7)	0.22
Afraid of being intubated, n (%)	238 (63.8)	62 (66.0)	176 (63.1)	0.62
Believe to be vulnerable, n (%)	203(54.4)	62 (66.0)	141 (50.5)	0.009
Afraid of becoming disabled, n (%)	197 (52.8)	54 (57.4)	143 (51.3)	0.30
Afraid of dying, n (%)	172 (46.1)	34 (36.2)	138 (49.5)	0.02
Afraid of abandoning close friends/loved ones, n (%)	134(35.9)	31 (33.0)	103 (36.9)	0.49
Afraid of the environment, n (%)	80(21.4)	26 (27.7)	54 (19.4)	0.09
Believe that information is being withheld, n (%)	74 (19.8)	19 (20.2)	55 (19.7)	0.92
Afraid of being abandoned, n (%)	68 (18.2)	16 (17.0)	52 (18.6)	0.73
Abbreviations: STAI: State Trait Anxiety Inventory (from 20 to 80) – State questionnaire and Trait questionnaire; IQR: interquartile range. ♯				

Fears, feelings and outcome

Ninety-four (25.2%) patients met the criteria for the primary outcome. A total of 16 (4.3%) patients died. The type of new organ failure was neurological, respiratory, and cardiovascular in 54 (57.4%), 30 (31.9%), and 11 (11.7%) patients, respectively. Fifty-five (14.3%) required to be intubated and 25/383 (6.5%) renal replacement. Compared with patients without deterioration, those with new organ failure were more likely to have a feeling of vulnerability (66.0% *versus* 50.5%, p=0.009) and were less likely to be afraid of dying (36.2% *versus* 49.5%, p=0.02; Table 2). Also, the proportion of patients with STAI-state ≥ 40 differed between patients meeting or not the primary endpoint (61.7% *versus* 48.0%, p=0.02).

As expected, the model integrating intensity of anxiety (*i.e.* STAI _state ≥ 40) had a greater predictive value for bad outcome than the model without taking into account only the critical illness severity scores (Figure 2). In a pre-planned multivariable analysis, a STAI score ≥ 40, feeling of vulnerability and absence of fear to die were independently associated with death or new organ failure, after adjustment on SAPS-II and SOFA (Table 3). The “anxiety, fears and feelings” model had significantly higher discriminative ability than the “anxiety” model only taking into account the level of anxiety (Table 3 and Figure 2; c-statistics 0.73 versus 0.69; $p = 0.03$)). Compared with the reference model, the “anxiety, fears and feelings” model was also associated with a greater NRI and IDI (Table 3). The existence of organ failure at admission did not significantly modify the association between (1) fear of dying and the occurrence of death or new organ failure (p for interaction = 0.78), and (2) between feeling of vulnerability and the occurrence of death or new organ failure (p for interaction = 0.48). Absence of fear of dying and feeling of vulnerability remained independently associated with the death and new organ failure in a sensitivity analysis in which STAI score was considered as a continuous variable (data not shown).

Table 3
Multivariate analysis of factors associated with occurrence of new organ failure

	OR (95% CI)	p#
	Final logistic regression model after stepwise selection (‘new’ model)	
STAI-State score ≥40	2.08 (1.18-3.66)	0.01
Absence of fear of dying	2.38 (1.37-4.17)	0.002
Feeling of vulnerability	1.96 (1.12-3.43)	0.02
SAPS II (per 1 point increase)	1.03 (1.01-1.05)	0.01
SOFA score (per 1 point increase)	1.23 (1.06-1.42)	0.006

OR: Odds Ratio; 95% CI confidence interval; STAI: State Trait Anxiety Inventory (from 20 to 80) – State questionnaire and Trait questionnaire; SOFA: Sequential organ dysfunction assessment score. The multivariate analysis included the 373 patients.

Discussion

With help of the original ICU-fear questionnaire specifically developed for our aims to assess the rate and prognosis value of fears and feelings at time of ICU admission, our study discloses two salient findings. First, feeling of vulnerability and absence of fear of dying were independently associated with new organ failure within the first seven days after ICU admission. Second, feelings of being vulnerable or in serious condition and fears to be intubated or become disabled were reported by about two-third of conscious patients admitted in ICU. Taking these qualitative aspects of anxiety into account led to an improved prediction of new organ failure or death compared with a previously published model including intensity of anxiety and critical illness severity. These findings suggest that both quantitative and qualitative

assessments of anxiety are feasible, not stressful and informative for ICU physicians, enabling to apprehend patient's psychological stress, determine anxiogenic factors and anticipate short outcome.

Anxiety and fears are warning signs designed to protect us from danger, alike pain(16). They are regulated by the limbic system, which integrates internal and external stimuli and modulates the behavioral, neuroendocrine and autonomic responses. Thus, they are the psychological expression of a highly integrated system aiming at maintaining homeostasis or its resetting into allostasis(17). By contrast with feeling of vulnerability, the relationships between absence of fear of dying and subsequent deterioration may seem paradoxical. A lack of fear of dying may be considered protective as it reduces the allostatic burden by reducing the psychological stress. Conversely, a lack of fear of dying may reflect a misperception of danger, impairing the mental and somatic response to stress. This misperception could result from impaired pathways mediating interoceptive signals, their integration by the amygdala or both. We were unable to determine whether the absence of fear to die was adaptive or maladaptive in our patients. By the way, the concept of the Bayesian-Laplacian brain could account for our results(18). According to this theory, the brain is a prediction machine, meaning that it uses predictive processing of exteroceptive and interoceptive sensory input for making decision. It has to be noted that fear of death has been shown to be associated with decreased 28 days mortality in acute myocardial infarction (19). However, the most likely explanation is that cardiac patients who express fear of death will receive more attention from the health care professional.

Our study allows to identify a psychological pattern that is easily assessable, common and may be useful to anticipate the course of critical illness. It prompts ICU physicians and nurses to question and take into account patient's anxiety and fears; given that this assessment was reported as being stressful by few patients. However, the outcome of patients reporting that the questionnaire was stressful did not differ from the remaining population. This finding suggests that critically ill patients are aware of their condition and are keen to express their feelings and fears. The present study has some practical relevance as it might help caregivers alleviate the anxiety of ICU patients. Indeed, a pharmacological treatment of anxiety alone might not be appropriate, as patients would foremost need information about their clinical status, its treatment and its prognosis but also to be reassured about their affective environment. Our results provide a strong incentive to extend this qualitative evaluation method, From the ICU-fear questionnaire, ICU teams might develop their own questionnaire with integrating other items, notably patients' socio-cultural determinants as well as archaic fears.

Study limitations

Our findings concern the specific population of moderately-severe critically ill patients. However, approximately half of our population had persisting organ failure, developed new organ failures or required major interventions, indicating the potential severity of the selected patients and the relevance of their admission in ICU. Our findings warrant to assess anxiety and fears and their prognosis value in more severe critically ill patients, notable in those requiring invasively mechanically ventilated patients. However, these patients very often require sedation at least the first days, precluding their interview (20).

Conclusion

The present multicenter observational study showed that moderate to severe anxiety, feeling of vulnerability and no fear of dying at ICU admission were independently associated with subsequent clinical deterioration in ICU patients with moderate critical illness. This psychological pattern could either reflect a misperception or a maladapted integration of warning signals. These findings suggest that quantitative and qualitative assessment of anxiety should be better taken into account in patient care in the ICU as fears are both frequent and stressful. Further studies should be undertaken to address the mechanisms linking anxiety with critical illness worsening and to assess specific interventions.

Declarations

- Ethics approval and consent to participate

The present study was approved by the ethical committee of St Germain-en-Laye. It was also approved by the Advisory Committee for Data Processing in Health Research (CCTIRS) with a waiver for written informed consent. According to the French regulation only verbal and written information were required.

- Consent for publication

All authors have read the paper and gave their consent for its publication.

- Availability of data and material

Pr Tarek Sharshar and Dr Aurélien Mazeraud had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

- Competing interests

The authors do not state any conflict of interest

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- Authors' contributions

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Figures

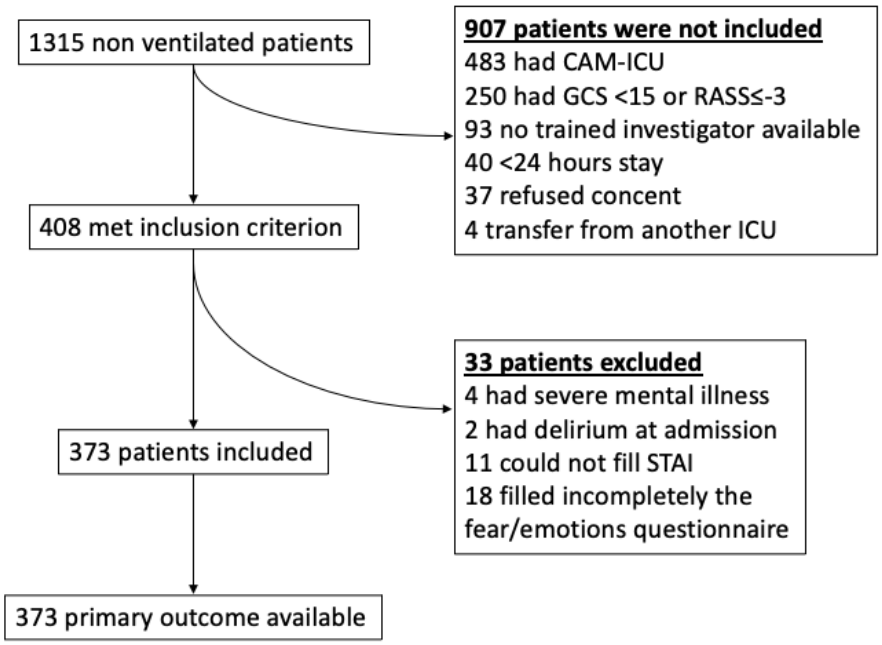

Figure 1

CAM-ICU: Confusion Assessment Method for Intensive Care Unit, GCS: Glasgow coma score; STAI: State Trait Anxiety Inventory

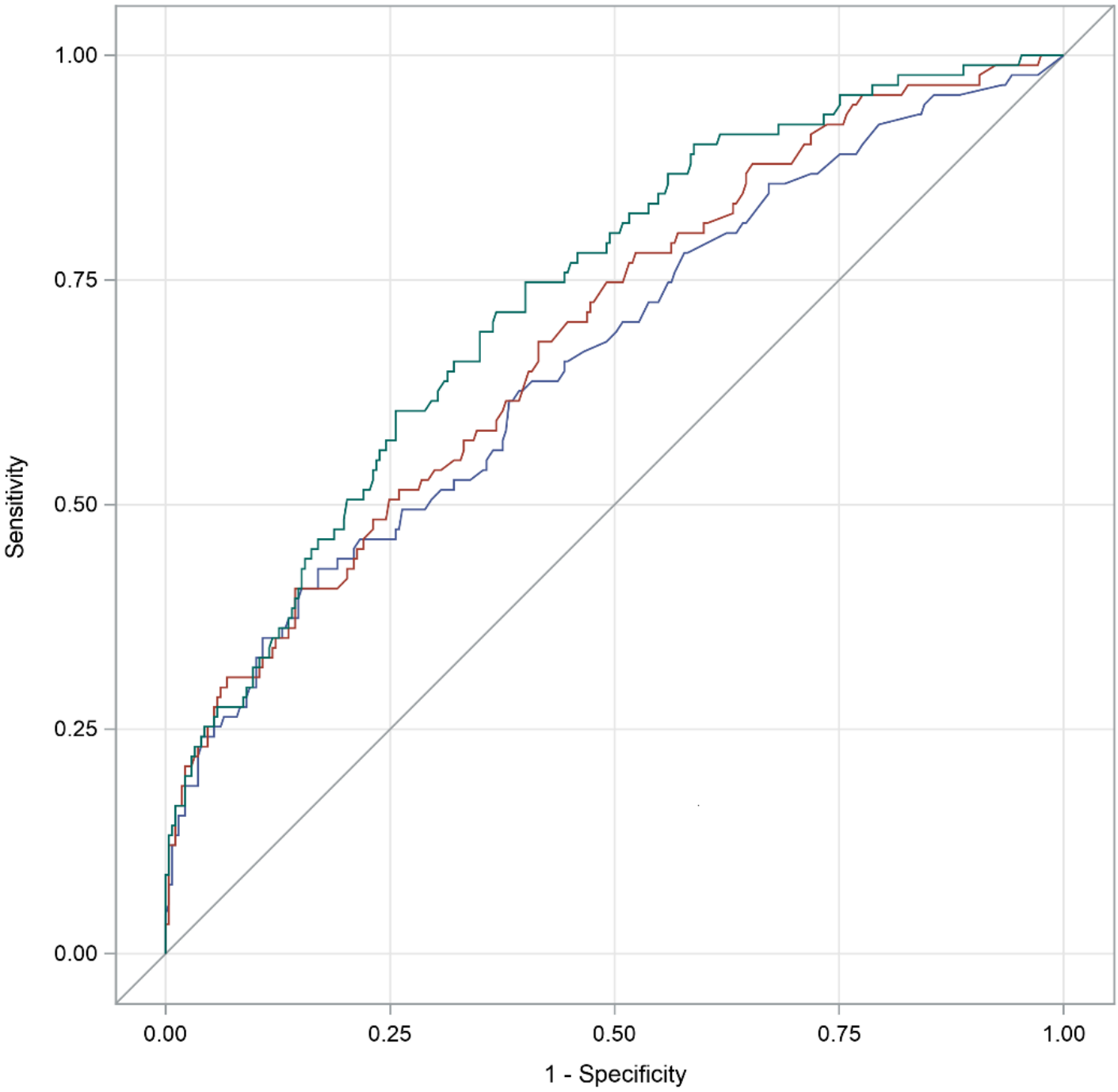

Figure 2

Comparison of ROC curves for prediction of new organ failure or death. Blue curve: Baseline model including only critical illness severity scores, i.e. SAPSII and SOFA (AUC: 0.66); Red curve: 'Reference' model including STAI-state ≥ 40, SAPSII and SOFA (AUC: 0.69); Green curve: 'New' model including feeling of vulnerability, absence of fear of dying, STAI-state ≥40, SAPSII and SOFA (UC: 0.73). The 'reference' model has been previously proposed for prediction of new organ failure and death(1). The c-statistic of the 'new' model was significantly higher than the one of the 'reference' model: 0.73 [95%CI:0.67-0.79] versus 0.69 [95%CI:0.63-0.75]; p=0.03. The net reclassification index (NRI) was of 25% [95%CI: 10%-39%], p=0.0009; with 11% events and 14% non-events correctly reclassified with the 'new'

model, respectively. The integrated discrimination improvement was of 0.03 [95%CI 0.01-0.05), p=0.0007. Abbreviations: AUC: area under the curve; ROC: Receiver operating characteristic ; ICU: Intensive Care Unit; SAPS-II: Simplified Acute Physiology Score, SOFA: Sequential Organ dysfunction Assessment and State Trait Anxiety Inventory State questionnaire (from 20 to 80)

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