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ORIGINAL ARTICLE

Long-term mortality and quality of life after trauma: an ancillary study from the prospective multicenter trial FROG-ICU

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Abstract

Introduction The long-term outcomes of intensive care unit (ICU) patients are known to be worse than those of the general population, but they are poorly known in severe trauma patients. We conducted an ancillary examination of the FROG-ICU study to identify risk factors and biomarkers associated with the poorer long-term outcomes and mortality in trauma ICU patients.

Methods Mortality, quality of life (QoL) and stress level scores were obtained 1 year after discharge from ICU. Blood samples were collected at ICU admission and discharge for measurement of inflammatory and cardiovascular biomarkers.

Results ICU trauma patients had a significantly lower 1-year mortality than non-trauma patients (7% vs. 23%, $p < 0.001$), but had worse stress levels scores (19 vs. 13, $p = 0.041$). No difference was found regarding physical and mental QoL scores (33 vs. 31, $p = 0.19$ and 30 vs. 28, $p = 0.42$). Patients with better QoL scores had lower tracheotomy rates (11% vs. 30%, $p = 0.01$). Worse stress level scores are associated with poor QoL scores and vice versa. Some study biomarkers were significantly higher in those ICU trauma patients who had worse QoL scores at 1 year after discharge.

Discussion Our study suggests that quality of life 1 year after an ICU stay is poor and is similar in both trauma and non-trauma patients, but ICU trauma patients are at greater risk of developing post-traumatic stress disorder-related symptoms. Tracheotomy and high levels of inflammatory biomarkers could be associated with impaired quality of life.

Keywords Severe trauma · Quality of life · Post-traumatic stress disorder · Biomarker · Intensive care unit

Introduction

Trauma is one of the main causes of morbidity and mortality in the general population and the leading cause of mortality in young adults [1]. The assessment and care of severe

FROG-ICU investigators are listed in the acknowledgements section.

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trauma patients has evolved during the last decade, with a average 3% mortality rate reported by reference centers [2]. However, the long-term outcomes of these patients are unknown.

Evaluations of long-term outcomes after intensive care unit (ICU) admission report worse survival rates and quality of life (QoL) compared to the general population [3, 4]. Post-intensive care syndrome (PICS) describes the disabilities that remain after surviving critical illness, which are categorized as physical and cognitive impairments, and mental health difficulties [5].

For severe trauma patients, who are often young and active, the burden of PICS is likely to be greater than that of other ICU patients; indeed, it probably produces a socio-economic loss for society. However, prospective assessments are still required to measure the extent of these effects [6].

The objective of the French and euROpean Outcome reGistery in Intensive Care Units (FROG-ICU) study was to identify risk factors and biomarkers associated with poor long-term outcomes and mortality after an ICU stay [7, 8]. We conducted an ancillary study focused on ICU trauma patients since their long-term outcomes have been investigated less often.

Materials and methods

Study design

The FROG-ICU was a prospective, observational, multicenter cohort study designed to assess the incidence of and identify the risk factors for mortality during the year after ICU discharge. Twenty-one medical, surgical, or mixed ICUs in 14 hospitals in France and Belgium participated in the original study. The organization of the ICUs is described elsewhere [9], and details of the study's materials and methods have also been previously published [7, 8]. Briefly, all consecutive patients admitted to a participating ICU during the recruitment period were included when the following inclusion criteria were met: invasive mechanical ventilation support for at least 24 h and/or treatment with a positive inotropic agent for more than 24 h. Patients with severe head injury at admission (Glasgow Coma Scale < 8) were non-included. The goal of these criteria was to select patients with homogenous severity and exclude those without respiratory or circulatory failure and those whose capacity to complete questionnaires at 1 year was may have been limited. All trauma patients included in the FROG-ICU were enrolled in our ancillary study.

The FROG-ICU was conducted in France and Belgium in accordance with the Good Clinical Practice guidelines of Helsinki and was validated by local ethics committees (Comité de Protection des Personnes: Île de France IV, IRB no. 00003835; Commission d'éthique biomédicale hospitalo-facultaire de l'hôpital de Louvain, IRB no. B403201213352). The study was registered on clinicaltrials.gov (NCT01367093).

Study objectives

The primary objective of our study was to assess the mortality and QoL of ICU trauma patients in the year following an ICU stay. Our secondary objectives were to identify the risk factors and biomarkers associated with poor QoL.

Data collection

Details on the data collection methods used in the FROG-ICU have been previously published [7, 8]. We collected patient demographics at ICU admission, Charlson score, ICU severity scores, and routine laboratory results. We also collected respiratory, renal, and cardiovascular variables and details of treatments undertaken during each patient's ICU stay. Our data included the length of ICU stay, the duration of mechanical ventilation and Sequential Organ Failure Assessment (SOFA) scores; this information was originally obtained on the ICU discharge day. Blood and urine samples were collected at both admission and discharge and were used to measure the following biomarkers in a centralized laboratory: pro-brain natriuretic peptide (proBNP), BNP, adrenomedullin (bio-ADM), hyper-sensitive troponin (hs-TnI), soluble ST2, cystatin-C, neutrophil gelatinase-associated lipocalin (NGAL), and interleukin-6 (IL-6).

We followed all patients who survived to be discharged from the ICU, except for the severely disabled (Glasgow Outcome Scale < 4 at discharge). Information regarding vital status, QoL and stress levels was collected at 3, 6, and 12 months after leaving hospital. The Short Form-36 (SF-36) and the Impact of Event Scale-Revised (IES-R) were used to assess the patients' QoL and stress levels, respectively.

The SF-36 survey is a standardized, patient-reported questionnaire that accounts for both physical and mental health. The IES-R allows for subjective assessment of stressors perceived during a traumatic event. An IES-R score higher than 30 suggests the presence of post-traumatic stress disorder (PTSD) [10].

Statistical analysis

The results are expressed as median (interquartile range, IQR) or count (percentage) as appropriate. Any marginal association between single variables and 1-year mortality, poor QoL, and stress levels was assessed using the Wilcoxon rank-sum and the Chi-squared tests for quantitative and qualitative variables, respectively.

A univariate multiple logistic regression was used to determine a set of variables independently associated with poor QoL and stress levels. All statistical analyses were performed using version 3.1.1 or above of R statistical software (The R Foundation for Statistical Computing, Vienna, Austria) by a team of statisticians working in conjunction with the FROG-ICU investigators.

Results

The FROG-ICU study included 2087 patients. Of these, 1570 were followed for 1 year after discharge. Four hundred and forty-one patients responded to a request to complete and submit the SF-36 and IES-R forms at 3 months, including 157 ICU trauma patients. One hundred and forty-three of these were completed the 1-year follow-up after discharge.

Demographics

The ICU trauma patients were younger (47 years vs. 64 years, $p < 0.001$), had fewer pre-existing diseases (Charlson score 0 vs. 3, $p < 0.001$), and had lower ICU severity scores (SOFA 6 vs. 7, $p = 0.015$) than non-trauma patients. The ICU length of stay was longer in trauma patients, but in-ICU mortality rate was lower (Table 1).

One-year mortality and QoL

Sixty-four and 42 ICU trauma patients completed the SF-36 and IES-R forms at 1 year, respectively. ICU trauma patients had significantly lower 1-year mortality rates than non-trauma patients (7% vs. 23%, $p < 0.001$). The IES-R scores were 9 in ICU trauma patients and 13 in non-trauma patients ($p = 0.041$). Physical (33 vs. 31, $p = 0.19$) and mental (30 vs. 28, $p = 0.42$) QoL scores were similar in ICU trauma and non-trauma patients. However, the QoL scores of the ICU patients were lower than those of the general population (French median SF-36 score = 70). These results are summarized in Table 2.

QoL and stress level risk factors

Next, we assessed the risk factors for poor QoL by separating ICU trauma patients according to the median SF-36 score calculated in for cohort, which was 49. Patients with an SF-36 score above 49 were younger (38 years vs. 57 years, $p = 0.0006$), had fewer pre-existing conditions

Table 1 Comparison of ICU trauma and non-trauma patient demographics

	Non-trauma ($n = 1930$)	ICU trauma ($n = 157$)	p
ICU LOS, days (IQR)	12 (7–20)	13 (8–24)	**0.0015**
ICU mortality, *n* (%)	438 (23)	14 (9)	**0.001**
Age, years (IQR)	64 (52–75)	47 (33–64)	**0.0001**
Male, *n* (%)	1240 (64)	121 (77)	**0.0012**
Charlson score (IQR)	3 (1–5)	0 (0–2)	**0.0001**
Alcohol consumption, *n* (%)	332 (17)	33 (21)	0.23
Smoking, *n* (%)	529 (28)	41 (26)	0.71
SOFA score (IQR)	7 (4–10)	6 (4–8)	**0.015**

Bold values indicate a statistically significant difference, with $p < 0.05$

ICU intensive care unit, *IQR* interquartile range, *LOS* length of stay, *SOFA* sequential organ failure assessment

Table 2 Comparison of the 1-year mortality, quality of life, and stress level scores between ICU trauma and non-trauma patients

	Non-trauma ($n = 1930$)	ICU trauma ($n = 157$)	p
One-year mortality, *n* (%)[a]	324 (23)	9 (7)	**0.001**
SF36-PCS (IQR)[b]	33 (25–49)	31 (23–40)	0.19
SF36-MCS (IQR)[b]	30 (26–44)	28 (24–47)	0.42
IES-R (IQR)[c]	13 (4–26)	19 (8–34)	**0.041**

Bold values indicate a statistically significant difference, with $p < 0.05$

SF36-PCS short form 36—physical component score, *SF36-MCS* short form 36—mental component score, *IQR* interquartile range, *IES-R* impact of event scale—revised

[a]1427 non-trauma patients, 143 ICU trauma patients

[b]377 non-trauma patients, 64 ICU trauma patients

[c]399 non-trauma patients, 42 ICU trauma patients

(Charlson score: 0 vs. 2, $p = 0.014$), and had lower tracheotomy rates (11% vs. 30%, $p = 0.01$) (Table 3).

We assessed the risk factors for higher stress levels using an IES-R score cut-off value of 30 to separate our cohort; we found no differences between the two groups.

We also compared ICU trauma patients QoL scores in terms of stress levels and reciprocally.

Patients with an SF-36 score below 49 had worse IES-R scores (31 vs. 10, $p = 0.0078$) and patients with IES-R scores higher than 30 had worse SF-36 scores (34 vs. 60, $p = 0.025$) (Table 4).

Biomarkers

Generally, the plasma concentrations of the study biomarkers were significantly lower in ICU trauma patients than in non-trauma patients. At ICU discharge, soluble ST2, bio-ADM, and cystatin-C levels were higher in patients with an SF-36 score of less than 49 : 98 µg/L (IQR: 66–111) vs. 83 µg/L (IQR: 48–89), $p = 0.037$; 26 mmol/L (IQR: 21–30) vs. 19 nmol/L (IQR: 11–26), $p = 0.05$ and 10 µg/L (IQR: 80–120) vs. 80 µg/L (IQR: 70–100), $p = 0.047$, respectively. ProBNP levels were higher in the patients with an IES-R > 30 [113 ng/L (IQR: 52–236)] than in those with an IES-R < 30 (34 ng/L [IQR: 11–181], $p = 0.02$).

Table 3 Risk factors for a poor quality of life in ICU trauma patients

	SF-36 ≥ 49 ($n = 32$)	SF-36 < 49 ($n = 32$)	p
Age, years (IQR)	38 (22–52)	57 (47–69)	**0.0006**
Male, *n* (%)	25 (78)	22 (69)	0.4
Charlson score (IQR)	0 (0–1)	2 (0–3)	**0.014**
SOFA score (IQR)	5 (4–6)	5 (3–5)	0.39
ICU LOS, days (IQR)	14 (9–21)	12 (10–29)	0.53
Tracheotomy, *n* (%)	14 (11)	7 (30)	**0.012**
Renal replacement therapy, *n* (%)	6 (5)	0 (0)	0.29
Catecholamine, *n* (%)	100 (78)	16 (70)	0.41
RBC transfusion, *n* (%)	63 (49)	10 (44)	0.64
Plasma transfusion, *n* (%)	33 (26)	5 (22)	0.7
IES-R (IQR)	10 (5–21)	31 (16–41)	**0.0078**
IES-R > 30, *n* (%)	4 (18)	10 (50)	**0.029**

Bold values indicate a statistically significant difference, with $p < 0.05$

SF-36 short form 36, *ICU* intensive care unit, *IQR* Interquartiles range, *LOS* length of stay, *SOFA* sequential organ failure assessment, *RBC* red blood cell, *IES-R* impact of event scale—revised

Table 4 Risk factors for higher stress levels in ICU trauma patients

	IES-R < 30 ($n = 28$)	IES-R ≥ 30 ($n = 14$)	p
Age, years (IQR)	41 (24–52)	47 (21–55)	0.98
Male, *n* (%)	21 (75)	10 (71)	0.8
Charlson score (IQR)	0 (0–1)	0.5 (0–2)	0.36
SOFA score (IQR)	5 (4–6)	5 (3–5)	0.63
ICU LOS, days (IQR)	15 (11–20)	13 (9–17)	0.26
Tracheotomy, *n* (%)	4 (14)	1 (7)	0.65
Renal replacement therapy, *n* (%)	1 (4)	0 (0)	0.65
Catecholamine, *n* (%)	21 (75)	10 (71)	1
RBC transfusion, *n* (%)	13 (46)	9 (64)	0.34
Plasma transfusion, *n* (%)	33 (26)	5 (22)	0.7
SF-36 (IQR)	60 (47–69)	34 (30–49)	**0.025**
SF-36 < 49, *n* (%)	10 (36)	11 (78)	**0.0088**

Bold values indicate a statistically significant difference, with $p < 0.05$

IES-R impact of event scale—revised, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *SOFA* sequential organ failure assessment, *RBC* red blood cell, *SF-36* short form 36

Discussion

This study showed that ICU trauma patients had better survival rates 1 year after discharge compared to non-trauma patients in a general ICU population; the 1-year post-ICU mortality rate was 7% in our trauma patients. Possible explanations for this finding are the young age [11] and low severity scores at ICU admission of our trauma patients. These results are consistent with previous studies [2, 12]. We also found that ICU trauma survivors had a poor QoL 1-year after ICU discharge and were likely to develop PTSD-related symptoms [13, 14]. In ICU trauma patients, we observed that worse QoL scores were associated with higher stress levels and reciprocally, that higher stress levels were accompanied by worse QoL scores.

Our study was the first to investigate the association between ICU management and the long-term outcomes of trauma survivors. We found an association between tracheotomy and QoL, and this is a critical finding because a debate persists about the benefit of tracheotomy in ICUs [15, 16]. While tracheotomy does not improve survival odds, it may increase comfort in patients being weaned from prolonged mechanical ventilation [17]. However, other studies have failed to confirm these benefits [18], and rare but serious complications have also been documented in the literature [19, 20]. Our investigations should be replicated in future studies because confounding factors may have interfered with our findings.

The FROG-ICU study was designed to identify associations between biomarkers and clinical outcomes. Our investigation assessed the role of inflammatory (IL-6) and cardiovascular risk biomarkers (BNP, proBNP, ST2, ADM, and cystatin-C). In adults with chronic illness, higher concentrations of inflammatory biomarkers have been associated with worse QoL scores [21–23]. In addition, previous studies have reported that soldiers suffering from PTSD have higher concentrations of inflammatory biomarkers than their healthy control counterparts [24]. From these results, trauma could be said to influence the levels of these particular biomarkers. More specifically, high levels of cardiovascular risk biomarkers have been associated with worse QoL in some specific populations, although data are scarce [25]. Our study shows that at ICU discharge, biomarker profiles differed in relation to patient stress levels and QoL scores. These preliminary results are of major interest because such biological profiles could facilitate better estimation of long-term outcomes in severe trauma patients.

Our study has several limitations. First, the low number of patients that were included precludes definitive conclusions. With respect to this issue, we did not perform regression analysis. Second, variables that may impact QoL and stress levels, such as treatments, physiotherapy, recovery centers, nursing, injury type and site, were not considered, nor were variables that may impact biomarker concentrations in ICU patients such as hemodilution, distribution volume variations, and pharmacokinetic alterations. Third, we did not assess the Injury Severity Score (ISS) in our patients, because FROG-ICU was not originally designed to assess trauma patients in particular. Hence, no adjustment on ISS was feasible for poor QoL and stress level risk factors. However, it is noted that our trauma patients required ICU admission, norepinephrine or mechanical ventilation support for the first 24 h, and a prolonged ICU stay (13 (8–24) days). In addition, the cohort's average SOFA score and mortality rate were high, (6 and 9%, respectively), suggesting that most of these patients were severely injured. Finally, we excluded patients with impaired neurological function to obtain an adequate rate of compliance to the questionnaire at 1 year. Thus, our inclusion criteria excluded patients with severe brain injury whose long-term outcome have been reported elsewhere [26, 27].

Conclusion

In conclusion, our study suggests that QoL for ICU trauma patients 1 year after discharge is poor but similar to that of non-trauma patients. ICU trauma patients are at higher risk of developing PTSD-related symptoms, and worse stress level scores are associated with poor QoL scores and vice versa. Within the limitations of our study, recourse to tracheotomy could be associated with an impaired QoL. High levels of inflammatory and cardiovascular biomarkers are associated with poor QoL and stress levels. Our results deserve to be strengthened by a large-scale, trauma-focused, prospective study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate The study was conducted in France and Belgium in accordance with Good Clinical Practice (Declaration of Helsinki 2002) and Ethical Committee approvals (Comité de Protection des Personnes—Ile de France IV, IRB no. 00003835 and Commission d'éthique biomédicale hospitalo-facultaire de l'hôpital de Louvain, IRB no. B403201213352).

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