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ORIGINAL

Tailored multicomponent program for discomfort reduction in critically ill patients may decrease post-traumatic stress disorder in general ICU survivors at 1 year

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Abstract

Purpose: Reducing discomfort in the intensive care unit (ICU) should have a positive effect on long-term outcomes. This study assessed whether a tailored multicomponent program for discomfort reduction was effective in reducing post-traumatic stress disorder (PTSD) symptoms at 1 year in general ICU survivors.

Methods: This study is a prospective observational comparative effectiveness cohort study involving 30 ICUs. It was an extension of the IPREA3 study, a cluster-randomized controlled trial designed to assess the efficacy of a tailored multicomponent program to reduce discomfort in critically ill patients. The program included assessment of ICU-related self-perceived discomforts, immediate and monthly feedback to the healthcare team, and site-specific tailored interventions. The exposure was the implementation of this program. The eligible patients were exposed versus unexposed general adult ICU survivors. The prevalence of substantial PTSD symptoms at 1 year was assessed based on the Impact of Event Scale–Revised (IES-R).

Results: Of the 1537 ICU survivors included in the study, 475 unexposed patients and 344 exposed patients had follow-up data at 1 year: 57 (12.0%) and 21 (6.1%) presented with PTSD at 1 year, respectively ($p = 0.004$). Considering the clustering and after adjusting for age, gender, McCabe classification, and ICU-related self-perceived overall discomfort score, exposed patients were significantly less likely than unexposed patients to have substantial PTSD symptoms at 1 year ($p = 0.015$).

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Conclusions: Implementation of a tailored multicomponent program in the ICU that has proved to be effective for reducing self-perceived discomfort in general adult ICU survivors also reduced the prevalence of substantial PTSD symptoms at 1 year.

Trial registration: ClinicalTrials.gov identifier NCT02762409.

Keywords: Critical care, Post-traumatic stress disorder, Discomfort, Tailored program, Patient-reported outcome, ICU

Introduction

Critically ill patients in intensive care units (ICUs) are exposed to stressful conditions and experience discomfort from multiple sources [1–6], such as the environment or related to care provided in the ICU, depending on the care organizations and patient health status. This discomfort may have short-term and long-term consequences for survivors of critical illness [7], such as various degrees of anxiety and/or depression [8–10] or post-traumatic stress disorder (PTSD) [11–15], which may affect patients' quality of life [16–19], slow down the recovery process [20], and lead to increasing healthcare utilization and considerable associated costs [21]. PTSD has been the most investigated post-ICU psychiatric morbidity, with a primary focus on preexisting risk factors [22, 23] and early detection methods after the patient was discharged from the ICU [24]. This contrasts with the fact that little is known about risk factors or predisposing conditions related with the ICU stay on which intensivists could act. Among the various factors incriminated as risk factors for PTSD, to date at our knowledge, benzodiazepine administration, delirium, post-ICU memories of frightening ICU experiences [25], and other psychological factors such as stress, agitation, fear, panic, mood, loss of control, and inability to express needs [26] can be considered as ICU-related risk factors for developing post-ICU PTSD, and the only tested interventions involving ICU professionals were those involving the implementation of an ICU diary [27, 28], implementation of a self-help rehabilitation manual [29], or a nurse-led ICU follow-up clinic [30], with differing results in terms of reduction in PTSD symptoms.

Little is known about how confrontation with a life-threatening critical illness, the repetitive physical and psychological stressors, sometimes induced by invasive procedures, and the consequences thereof affects the generation of early memories of frightening ICU experiences or delusional memories that could induce late PTSD. Based on a conceptual model addressing the identification, prevention, and management of post-ICU PTSD, leading intensivists to act on modifiable rather than non-modifiable factors [31], it seems logical that the aim of preventing painful or frightening experiences (possibly intensified in a context of global discomfort caused by multiple sources or symptoms, sometimes distressing) based on a multidisciplinary approach including intensivists and psychiatrists, rather than only detecting these memories at the ICU discharge, should guide strategies for preventing post-ICU PTSD symptoms.

Take-home message

After carrying out the cluster-randomized controlled IPREA3 study demonstrating that a tailored multicomponent program based on assessment of self-perceived discomfort, feedback to the healthcare teams, and tailored site-targeted measures was effective in reducing self-perceived overall discomfort, we performed a 1-year follow-up of ICU survivors included in the IPREA3 study to assess psychiatric morbidity at 1 year. Our tailored multicomponent program was also associated with lower rates of post-traumatic stress disorder at 1 year. Based on this positive long-term result, this study confirms the need to implement a new strategy for reducing discomfort in the ICU utilizing such programs.

We hypothesized that reducing discomfort in the intensive care unit (ICU) could reduce the occurrence of post-ICU PTSD symptoms. The implementation of a program for discomfort reduction previously proved to be effective, based on the results of a cluster-randomized controlled trial, in reducing perceived overall discomfort during ICU stay in general adult survivors of critical illness. To our knowledge, no study has assessed the long-term beneficial consequences of this kind of program with respect to psychiatric morbidity, especially PTSD.

The aim of this study was thus to assess the effect of the implementation of a tailored multicomponent program for discomfort reduction on substantial PTSD symptoms at 1 year in general adult ICU survivors.

Methods

The AQVAR study (*Améliorer la Qualité de Vie Après un séjour en Réanimation*, Improving quality of life after an ICU stay) was a prospective cohort study including patients exposed and unexposed to a tailored multicomponent program for discomfort reduction in the ICU. The AQVAR study was an extension of the IPREA3 study, a cluster-randomized controlled trial designed to assess the efficacy of the program for reducing self-perceived discomfort in critically ill patients [32, 33]. The AQVAR study included general adult ICU survivors

(previously included in the IPREA3 study) with a 1-year follow-up after the ICU discharge. The AQVAR study was not scheduled when we enrolled ICU survivors in the IPREA3 study, and required specific funding and legal authorization. It was approved by the French Institutional Review Board of Tours, France, and is reported using the recommendations of the STROBE statement (Fig. 1) [34].

ICUs and patients

Of the 34 ICUs that participated in the IPREA3 study [32], 30 agreed to participate in the AQVAR study. The ICUs were medical, surgical, or mixed medical-surgical adult ICUs, located at academic tertiary care hospitals or community hospitals. All patients aged 18 years or older who survived an ICU stay of three calendar days or more and had been included in the IPREA3 study were eligible for inclusion in the AQVAR study.

The exclusion criteria included the following: death prior to the 1-year follow-up after the index ICU hospitalization, patients under trusteeship, patients with cognitive incapacity, and patients who did not understand French sufficiently to complete the questionnaires exploring psychiatric morbidity. All participants provided oral informed consent.

Exposure: definition of the tailored multicomponent program

The exposed group was composed of patients hospitalized in an ICU that had implemented the tailored multicomponent program for discomfort reduction for at least 5 months, and the unexposed group was composed of patients hospitalized in an ICU that had never implemented this program. The generation of these two groups was derived from the study design of the IPREA3 study, described elsewhere [32] (Fig. 1). The tailored multicomponent program has been described in detail elsewhere [32, 33]. Briefly, experts and nursing managers in the ICU constituting the steering committee of the IPREA3 study formulated guidelines regarding concise recommendations to prevent each discomfort item of a French 16-item questionnaire on ICU-related self-perceived discomfort (IPREA questionnaire) as reminders to the healthcare teams. The entire program for discomfort reduction was locally coordinated by a physician–nurse duo to act as site champions. The program targeted all members of the healthcare teams and focused on continuous identification of self-perceived discomfort items, barrier identification, reinforcement of multidisciplinary teamwork, local adaptation, and use of site champions. Our philosophy was to encourage the participating ICUs to adopt the same methodology by launching such a tailored multicomponent program in their ICU, and not to duplicate externally designed measures that may have been inadequate or not useful for a given ICU. The following steps were performed during the program: discomfort assessment on the day of ICU discharge by the bedside nurse (or the assistant nurse) with the IPREA questionnaire [35]; immediate feedback to the bedside nurse (or the assistant nurse) after the end of IPREA administration, including the overall discomfort score and three concise electronic reminder messages based on the types of reported discomfort with the highest scores; monthly feedback to the ICU healthcare team that included the cumulative discomfort scores from the ICU and their relative ranking compared to other ICUs in which the program was implemented; and tailored site-targeted interventions to reduce discomfort based on this monthly feedback.

Data collection

In each participating ICU, a trained research assistant was designated to collect IES-R and Hospital Anxiety and Depression Scale items in eligible ICU survivors at 1 year post-ICU discharge (± 30 days), either by phone or after mailing the questionnaires, according to patient preference; the research assistant was available to provide any necessary help in understanding the questionnaires. The patient life situation (patient at home or patient hospitalized) was also collected at 1 year. The data related to the ICU stay were collected during the IPREA3 study.

PTSD symptoms were assessed using the Impact of Event Scale–Revised (IES-R), which seems to be sensitive to a general construct of traumatic stress, including for patients with lower symptom levels [36]. The IES-R is a self-reported questionnaire consisting of 22 items, each rated on a five-point scale from 0 (not at all) to 4 (extremely). The IES-R yields a total score ranging from 0 to 88, with higher scores indicating increased probability of having PTSD related to the event (i.e. the index ICU hospitalization). To define the prevalence of substantial PTSD symptoms, we used a mean cutoff score of 1.5 equivalent to a total score of 33, as this cutoff was found to provide the best diagnostic accuracy from the first psychometric validation study conducted in male Vietnam veterans [37].

We assessed anxiety and depression symptoms at 1 year using the Hospital Anxiety and Depression Scale (HADS) [38]. The HADS anxiety and depression subscales both include seven items, each rated on a four-point scale from 0 to 3, yielding anxiety and depression scores of 0 to 21, with higher scores indicating increased probability of having anxiety or depression. Patients with a score ≥ 8 on either subscale were considered symptomatic with general anxiety or depressive symptoms [8, 10]. The HADS was developed to detect

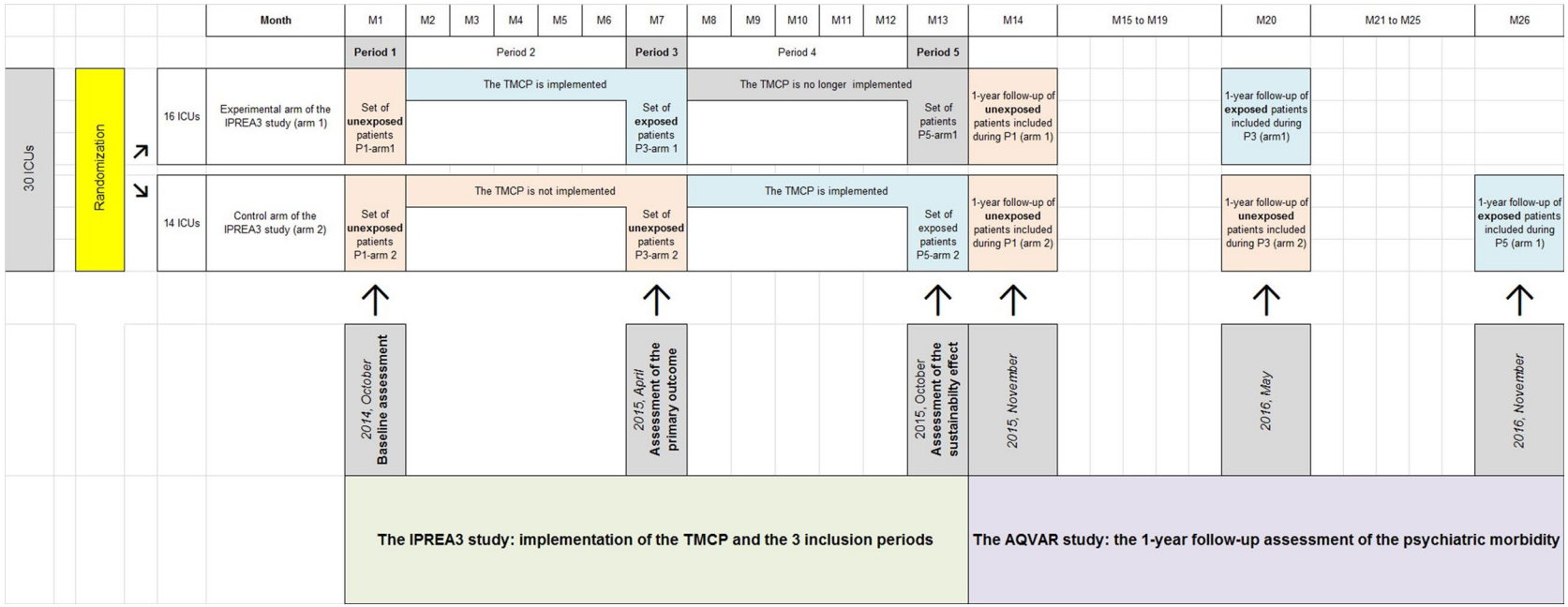

Fig. 1 Study design. Assessment of primary outcome of psychiatric morbidity at 1 year after ICU discharge was conducted in November 2015, May 2016, and November 2016, involving five sets of patients, which included three sets of unexposed patients and two sets of exposed patients. No 1-year follow-up was conducted for patients included in the IPREA3 study during period 5 and randomized to arm 1 (experimental arm) because they were hospitalized in an ICU that had already implemented the TMCP, even if the TMCP was no longer applied; these patients could not be considered as exposed or unexposed patients. *ICU* intensive care unit, *TMCP* tailored multicomponent program

psychiatric symptoms in general medical patients [39]. The data related to the ICU stay included the following: SAPS II score, reason for ICU admission (medical vs. surgical), McCabe classification [40], number of days with mechanical ventilation, number of days in the ICU, and self-perceived overall discomfort assessed the day of ICU discharge using the French 16-item IPREA questionnaire on ICU-related self-perceived discomfort [35]. This questionnaire contains the following 16 discomfort items: (1) noise; (2) excess light; (3) discomfort related to sleeping in a bed other than the one at home; (4) sleep deprivation; (5) thirst; (6) hunger; (7) feeling of cold; (8) feeling of heat; (9) pain; (10) being restricted by perfusion lines, tubes, or connections to monitoring devices; (11) no respect for intimacy; (12) anxiety; (13) isolation; (14) limited visiting hours; (15) absence of a phone; and (16) lack of information. Each discomfort item score varied from 0 (no perceived discomfort) to 10 (maximum discomfort), leading to the calculation of the overall discomfort score related to the entire ICU stay as the mean of each discomfort item score multiplied by 10, yielding a score ranging from 0 to 100 (no overall discomfort to maximum overall discomfort). We also collected the numbers of each invasive procedure that occurred throughout the entire ICU stay from among the following ten: arterial catheter insertion, central venous catheter insertion, bronchoscopy, digestive endoscopy, transesophageal echocardiography, chest drain withdrawal, chest drain insertion, external electric shock, lumbar puncture, and intra-hospital transport. The density of invasive procedures related to the ICU stay was calculated as the sum of the number of these invasive procedures that occurred during the ICU stay.

Statistical analysis

Comparisons between patients assessed at 1-year follow-up after ICU discharge and non-assessed patients were performed on baseline characteristics at ICU admission and during the ICU stay using the Student *t* test or Mann–Whitney test for continuous variables (according to the variable distribution), and χ^2 test or Fisher's exact test for qualitative variables. Comparisons between exposed and unexposed groups were performed using the same procedure. The proportions of patients with detected PTSD and anxiety and depression symptomatology were provided for the whole sample and per group. The effect of the program on the PTSD score derived from the IES-R using the cutoff of 33 was assessed using a chi2 test. Adjustment on confounding variables was performed through two different logistic models based on data clustering as follows: model 1 based on adjustment of the five variables linked to the 1-year PTSD from univariate analysis with $p < 0.05$ (gender, age, McCabe classification, overall discomfort score, and group); model 2 based on adjustment of eight potential main known confounding factors for substantial PTSD symptoms (gender, age, reason for ICU admission, SAPS II, number of days in the ICU stay, density of invasive procedures while in the ICU, overall discomfort score, and group).

The IES-R and HADS scores are presented as medians with interquartile ranges (IQR), and the results with respect to comparisons between exposed and unexposed patients are presented using odds ratios (OR) and their 95% confidence intervals (CI).

A sensitivity analysis was also performed, with the cutoff score of 35 derived from the IES-R questionnaire, to define substantial PTSD symptoms using the same procedure.

A post hoc analysis was also performed with multiple imputations for the IES-R score from six predictive variables (gender, age, reason for ICU admission, SAPS II, group, and centre) allowing to present pooled results. The effect of calendar time at inclusion (ICU discharge in April vs. October) on the IES-score was also tested.

All statistical analyses were performed with SPSS version 20.0 software (IBM Corp., Armonk, NY, USA).

Results

ICUs and patients

Among the 30 participating ICUs in the AQVAR study (11 surgical, 5 medical, and 14 mixed, representing a total of 429 beds; 19 of them located at academic tertiary care hospitals and 11 at community hospitals), 14 ICUs and 16 ICUs had been randomized to arm 1 and arm 2 of the IPREA1 study, respectively. This study followed unexposed patients hospitalized in the ICUs randomized to arm 1 of the IPREA3 study in October 2014 and patients hospitalized in the ICU randomized to arm 2 of the IPREA study in October 2014 and April 2015. The included patients exposed to the tailored multicomponent program were hospitalized in the ICUs randomized to arm 1 of the IPREA study in April 2015 and arm 2 of the IPREA study in October 2015 (Fig. 1). A total of 1537 ICU survivors were included, 655 of whom were exposed to the program applied by the ICU healthcare team for more than 5 months, and 882 who were not exposed to the program (i.e. never applied by the ICU healthcare team). Of the 1537 included ICU survivors, 244 (15.8%) died before the 1-year follow-up assessment (73 before hospital discharge after the index ICU hospitalization, and 171 after hospital discharge), 213 (13.8%) were lost to follow-up, 166 (10.8%) declined to participate, 70 (4.6%) lacked the cognitive capacity to answer self-reported questionnaires, and 25 (1.6%) had

mail undelivered. A total of 344 exposed and 475 unexposed patients were contacted 1 year after their ICU discharge. All of the details are provided in the flow chart (Fig. 2). Assessed patients who were contacted at 1 year did not differ from the patients who were not assessed at 1 year in terms of gender ratio, overall discomfort score, or number of days in the ICU. The number of patients admitted to the ICU for a medical reason was greater and SAPS II scores were higher among patients who were not assessed at 1 year compared with those assessed at 1 year, in both groups (exposed vs. unexposed). Non-assessed patients were older than assessed patients only in the unexposed group (Electronic Supplementary Material 1). Because of missing IES-R or HADS questionnaires, 342 and 469 ICU survivors were analyzed in the exposed and unexposed groups, respectively. Key clinical and demographic characteristics at ICU admission were balanced between exposed and unexposed groups, with the exception of reason for admission and McCabe classification (Table 1). The percentage of patients hospitalized after surgery, as well as the percentage of patients with the lowest McCabe classification scores (non-fatal disease), was higher in the exposed group than in the unexposed group. The median (and IQR) overall discomfort score for ICU-related self-perceived discomfort measured at the end of the ICU stay was lower in the exposed group than in the unexposed group [13 (7–22) vs. 21 (12–29), respectively].

Prevalence of psychiatric morbidity at 1 year after ICU discharge

Of the 811 patients analyzed in our study with complete follow-up data (IES-R and HADS) at 1 year, 78 patients presented with substantial PTSD symptoms (9.6% of the whole cohort) derived from the IES-R; 229 (28%) and 196 (24%) patients presented with substantial anxiety and depression symptoms, respectively, derived from the HADS.

The IES-R total score was higher in the unexposed group compared with the exposed group [9 (IQR 3–20) vs. 7 (IQR 3–15), $p = 0.003$]. Using the cutoff of 33 for the total score derived from the IES-R, patients who were not exposed to the program presented more substantial PTSD symptoms than patients who were exposed to the program: 57 of 469 (12.2%) vs. 21 of 341 (6.1%) [$p = 0.004$; OR (95% CI): 2.12 (1.26–3.56), respectively] (Table 2). Considering the clustering, the OR was 1.87 [95% CI (1.21–2.91); $p = 0.005$] (Table 3).

Scores for anxiety and depression symptoms did not differ between exposed and non-exposed groups. We also found no difference between groups concerning the proportion of patients with anxiety symptoms but a difference concerning the proportion of patients with depression symptoms (Table 2).

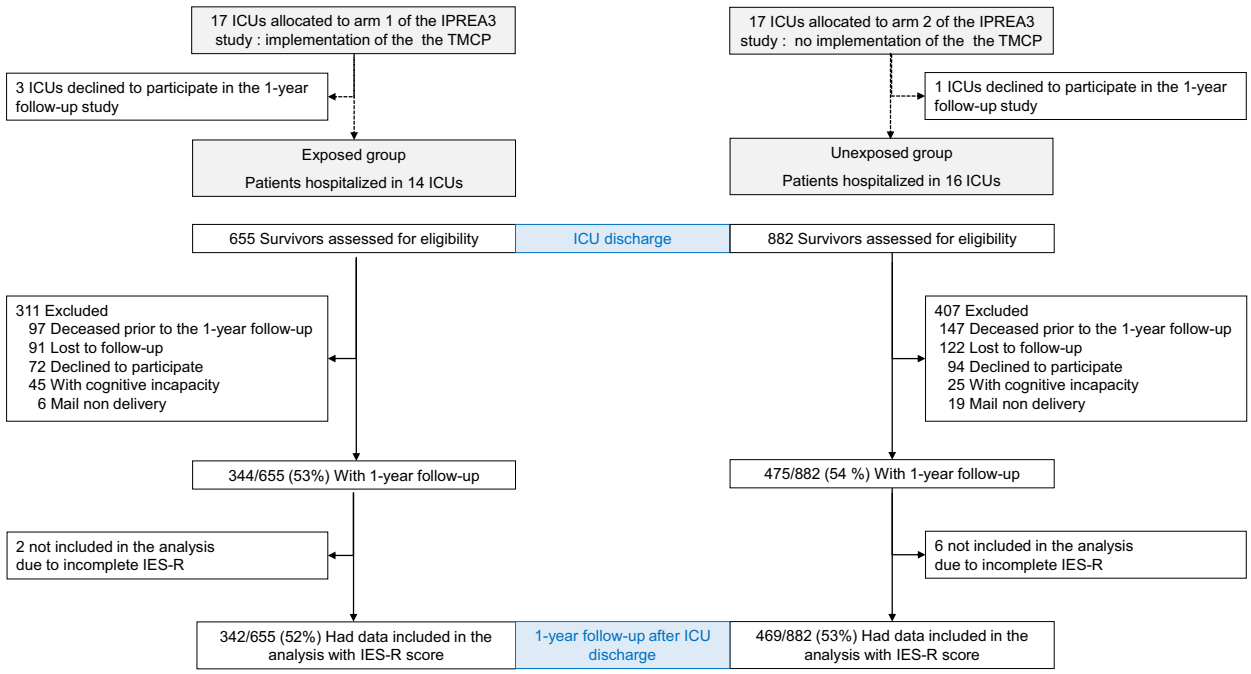

Fig. 2 CONSORT-style flow diagram of patient screening, eligibility, and enrollment in the cohort. *ICU* intensive care unit, *TMCP* tailored multicomponent program, *IES-R* Impact of Event Scale–Revised

Table 1 Baseline characteristics of exposed and unexposed patients at ICU admission and during the ICU stay

	Unexposed ($n=475$)	Exposed ($n=344$)	*P* value
Age, year, mean (SD)	62 (15)	63 (15)	0.076
Male gender, *n* (%)	308 (65%)	232 (67%)	0.438
SAPS II score[a], mean (SD)	34.3 (16.2)	34.4 (15.2)	0.946
Reason for ICU admission, *n* (%)			0.043
Medical	195 (42%)	120 (35%)	
Surgical	264 (58%)	219 (65%)	
McCabe classification, *n* (%)			0.001
Nonfatal disease	320 (67%)	271 (79%)	
Ultimately or rapidly fatal disease	155 (33%)	73 (21%)	
Days of mechanical ventilation, median (IQR)	1 (0–2)	1 (0–2)	0.362
Invasive procedures during ICU stay, *n* (%)			
Arterial catheter	191 (40%)	123 (36%)	0.196
Central venous catheter	160 (34%)	102 (30%)	0.214
Bronchoscopy	45 (9.5%)	25 (7.5%)	0.265
Digestive endoscopy	15 (3.2%)	10 (2.9%)	0.835
Transesophageal echocardiography	16 (3.4%)	11 (3.2%)	0.893
Chest drain withdrawal	115 (24%)	90 (26%)	0.524
Chest drain insertion	37 (7.8%)	29 (8.4%)	0.740
External electric shock	6 (1.3%)	4 (1.2%)	0.897
Lumbar puncture	9 (1.9%)	5 (1.5%)	0.631
Intra-hospital transport	147 (31%)	91 (26%)	0.162
Invasive procedure density[b], median (IQR)	2 (0–3)	2 (0–3)	0.892
Days in ICU, median (IQR)	4 (2–6)	4 (2–7)	0.932
Self-perceived overall discomfort score[c], median (IQR)	21 (12–29)	13 (7–22)	< 10–3

ICU intensive care unit, *SAPS* Simplified Acute Physiology Score

[a] SAPS II score may range from 0 to 156, with higher scores indicating more severe illness

[b] Calculated as the sum of each invasive procedure (among the 10 listed invasive procedures) performed during the ICU stay

[c] Calculated as the mean of the 16 item scores included in the IPREA questionnaire multiplied by 10, yielding a score ranging from 0 to 100 (minimum to maximum overall discomfort)

Effect of the tailored multicomponent program on PTSD at 1 year

Two multivariate models were built, considering adjustment for confounding variables and taking into account the clustering: model 1 based on adjustment for the five variables linked to the 1-year PTSD from univariate analysis with $p<0.05$ (gender, age, McCabe classification, overall discomfort score, and group); model 2 based on adjustment for eight potential main known confounding factors for substantial PTSD symptoms (gender, age, reason for ICU admission, SAPS II, number of days in the ICU, density of invasive procedures while in the ICU, overall discomfort score, and group). These two models provided similar findings: the unexposed group was associated with a higher prevalence of PTSD at 1 year compared with the exposed group (OR [95% CI]: 1.79 [1.12–2.85], $p=0.015$, and 1.82 [1.14–2.89], $p=0.012$, respectively) (Table 3). In comparison with patients without post-ICU PTSD, patients with post-ICU PTSD were younger, were more often women, reported a higher overall discomfort score at the end of the ICU stay, and presented concomitantly at 1 year with higher scores for anxiety and depression symptoms (Table 4). Using multiple imputations for the IES-R score to take into account missing data, the pooled results showed a higher risk of presenting substantial PTSD symptoms in the unexposed group than in the exposed group (pooled OR [95% CI]: 1.55 [1.03–2.33], $p=0.035$). A calendar time effect was found: patients who were discharged from the ICU in April more often presented substantial PTSD symptoms at 1 year than patients discharged from the ICU in October, regardless of the group (OR [95% CI]: 1.13 [1.02–1.98], $p=0.033$).

Table 2 Post-traumatic stress disorder (PTSD) and substantial anxiety and depression symptoms at 1 year after ICU discharge

	Unexposed (*n* = 475)	Exposed (*n* = 344)	*P* value
PTSD			
IES-R total score[a], median (IQR)	**9 (3–20)**	**7 (3–15)**	0.003
Absence of PTSD[b], *n* (%)	412 (88%)	321 (94%)	0.004
Presence of PTSD, *n* (%)	**57 (12%)**	**21 (6%)**	
Anxiety symptoms			
HADS anxiety score[c], median (IQR)	5 (3-8)	5 (3-8)	0.488
No substantial anxiety symptoms[d], *n* (%)	329 (70%)	245 (72%)	0.702
Probable anxiety symptoms[d], *n* (%)	79 (17%)	58 (17%)	
Confirmed anxiety symptoms[d], *n* (%)	63 (13%)	39 (11%°	
Depression symptoms			
HADS depression score[c], median (IQR)	4 (1–8)	4 (1–7)	0.764
No substantial depression symptoms[d], *n* (%)	347 (74%)	260 (76%)	0.022
Probable depression symptoms[d], *n* (%)	72 (15%)	32 (9%)	
Confirmed depression symptoms[d], *n* (%)	52 (11%)	50 (15%)	

ICU intensive care unit, *IES-R* Impact of Event Scale–Revised, HADS Hospital Anxiety and Depression Scale

[a] IES-R score is a self-reported questionnaire consisting of 22 items, each rated on a five-point scale from 0 to 4, and may range from 0 to 88, with higher scores indicating increased probability of having PTSD

[b] PTSD was diagnosed using the mean cutoff score of 1.5 equivalent to a total score of 33

[c] The anxiety and depression subscales of HADS both include seven items, each rated on a four-point scale from 0 to 3, and may range from 0 to 21, with higher scores indicating increased probability of having anxiety or depression, respectively

[d] Patients with a score ≥ 8 on each subscale are considered as having substantial symptoms: patients with a score ranging from 8 to 10 presenting with probable symptoms and patients with a score ≥ 11 presenting with confirmed symptoms

Table 3 Effect of the tailored multicomponent program for discomfort reduction on the PTSD at 1 year

	OR [95% CI][a]	*P* value
Without adjustment	1.87 [1.21–2.91]	0.005
With adjustment		
Model 1[b]	1.79 [1.12–2.85]	0.015
Model 2[c]	1.82 [1.14–2.89]	0.012

PTSD post-traumatic stress disorder, *OR* odds ratio, *CI* confidence interval

[a] Risk for PTSD: unexposed patients (patients hospitalized in an ICU that had never implemented the program) compared with exposed patients (patients hospitalized in an ICU that had implemented the program for at least 5 months), taking into account data clustering

[b] Model 1: adjustment for 5 variables linked to the 1-year PTSD from the univariate analysis with < 0.05 (gender, age, McCabe classification, overall discomfort score derived from the IPREA questionnaire, and group) and taking into account data clustering

[c] Model 2: adjustment for 8 potential main known confounding covariates (gender, age, reason for ICU admission, SAPS II, number of days in the ICU, density of invasive procedures while in the ICU, overall discomfort score derived from the IPREA questionnaire, and group) and taking into account data clustering. The density of invasive procedures was calculated as the sum of the number of invasive procedures that occurred during the ICU stay among the following 10 procedures: arterial catheter, central venous catheter, bronchoscopy, digestive endoscopy, transesophageal echocardiography, chest drain withdrawal, chest drain insertion, external electric shock, lumbar puncture, and intra-hospital transport

Discussion

In this prospective cohort study involving general adult critically ill patients surviving an ICU hospitalization of 3 days or more, we found that the prevalence of substantial PTSD symptoms, assessed 1 year after ICU discharge, was lower in patients hospitalized in an ICU that had implemented a specific tailored multicomponent program for discomfort reduction (proved to be effective in reducing ICU-related self-perceived discomfort) for more than 5 months than in patients hospitalized in an ICU that had never implemented such a program.

The AQVAR study, an extension of the IPREA3 study [32, 33], was designed to investigate the potential long-term beneficial effects of our tailored multicomponent program for discomfort reduction in ICU survivors from a cohort of patients who were previously included in the IPREA3 study. The previously obtained positive results for our program were based only on the reduction of self-perceived discomfort reported on the day of discharge from the ICU using the French 16-item questionnaire, which allows the calculation of an overall discomfort score. Although the AQVAR study was not based on a randomized design as was the IPREA3 study, it provides additional reasons to use our program, as we found an interesting result at the 1-year follow-up involving a not infrequent post-ICU morbidity, PTSD, assessed using the

Table 4 Comparison between patients without PTSD and patients with PTSD

	No PTSD ($n=733$)	PTSD ($n=78$)	*P* value
Group			**0.004**
Exposed, *n* (%)	321 (44%)	21 (27%)	
Unexposed, *n* (%)	412 (56%)	57 (73%)	
Age, years, mean (SD)	**63 (14)**	**53 (16)**	**$<10^{-3}$**
Male gender, *n* (%)	**495 (68%)**	**40 (51%)**	**0.004**
SAPS II score[a], mean (SD)	34.5 (15.6)	33 (18.7)	0.432
Reason for ICU admission, *n* (%)			0.177
Medical	286 (40.0)	24 (32.0)	
Surgical	429 (60.0)	51 (68.0)	
McCabe classification, *n* (%)			**0.028**
Nonfatal disease	**537 (73%)**	**48 (62%)**	
Ultimately or rapidly fatal disease	**196 (27%)**	**30 (38%)**	
Days of mechanical ventilation, median (IQR)	1 (0–3)	1 (0–2)	0.724
Invasive procedures during ICU stay[b], median (IQR)	2 (0–3)	2 (1–4)	0.375
Days in ICU, median (IQR)	4 (2–6)	4 (3–7)	0.103
Self-perceived overall discomfort score[c], median (IQR)	**17 (9–25)**	**24 (11–35)**	**0.008**
HADS depression score[d]	**5 (3–7)**	**11 (8–14)**	**$<10^{-3}$**
HADS anxiety score[d]	**3 (1–7)**	**10 (6–13)**	**$<10^{-3}$**

Bold type highlights statistically significant differences between group values

PTSD post-traumatic stress disorder, *ICU* intensive care unit, *SAPS* Simplified Acute Physiology Score, *HADS* Hospital Anxiety and Depression Scale

[a] SAPS II score may range from 0 to 156, with higher scores indicating more severe illness

[b] The density of invasive procedures was calculated as the sum of the number of invasive procedures that occurred during the ICU stay among the following 10 procedures: arterial catheter, central venous catheter, bronchoscopy, digestive endoscopy, transesophageal echocardiography, chest drain withdrawal, chest drain insertion, external electric shock, lumbar puncture, intra-hospital transport

[c] Calculated as the mean of the 16 item scores included in the IPREA questionnaire multiplied by 10, yielding a score ranging from 0 to 100 (minimum to maximum overall discomfort)

[d] The HADS anxiety and depression subscales both include seven items, each rated on a 4-point scale from 0 to 3, and may range from 0 to 21, with higher scores indicating increased probability of having anxiety or depression, respectively

IES-R questionnaire, a validated tool widely employed by many authors.

The AQVAR study was also designed to quantify the prevalence of other substantial symptoms defining psychiatric morbidity: anxiety and depression symptoms in adult general ICU survivors 1 year after ICU discharge. In contrast with other studies [8–11, 40–42], the AQVAR study included a very large cohort of ICU survivors at ICU discharge, which enabled more than 800 patients with complete follow-up data at 1 year to be included. With respect to substantial post-ICU anxiety and depression symptoms, we found concordant estimates of the prevalence of this psychiatric morbidity [8–10]. Concerning PTSD, we found a lower prevalence in both groups compared with most previous studies. The relatively low density of invasive procedures during the ICU stay in our study population, likely due to the inclusion of general unselected ICU survivors (and not only selected patients with more severe conditions such as acute respiratory distress syndrome requiring invasive mechanical ventilation over a period of several days), could explain this difference. Initially, when post-ICU PTSD was recognized by pioneers, the prevalence of this pathology was often reported with higher (and more variable) rates than the present studies involving critically ill patients, probably because of the absence of adequate methods for diagnosing PTSD [43]. Indeed, more than 10 years ago, reviews about PTSD in ICU survivors reported a range of prevalence of PTSD in ICU survivors as large as 5–64% when diagnosed by self-report measures [41]. The main interest of these studies was to alert intensivists to this post-ICU psychiatric morbidity [43]. Davydow et al. conducted another systematic review based on 15 studies selected with more stringent criteria and found a median prevalence of post-ICU PTSD of about 20%, which differed slightly according to the method of diagnosis: 22% when PTSD was based on questionnaire-ascertained "clinically significant" symptoms and 19% when PTSD was diagnosed by clinicians [11]. Over the last decade, the growing interest in PTSD among ICU survivors has led to a high number of publications in this field. A recent meta-analysis of PTSD in ICU survivors found a prevalence of "clinically important" PTSD symptoms of 20% [25]. However, in a recent study involving veterans and

civilians hospitalized in the ICU, Patel et al. found a 10% prevalence of PTSD over a 1-year follow-up after ICU discharge, a result very similar to ours [22].

A meta-analysis recently conducted by Parker et al. found only one pre-ICU risk factor, comorbid psychopathology, and two in-ICU risk factors, exposure to benzodiazepines and post-ICU memories of frightening experiences [25]. Identification of this pre-ICU risk factor was confirmed by Patel et al. [22], who reported both preexisting depression and preexisting PTSD as risk factors for developing ICU-anchored PTSD. However, the true causal relationship between each of these presently identified risk factors for PTSD remains a matter of debate, making it difficult to define a clear strategy for the prevention of post-ICU PTSD. Indeed, it was suggested that patients with preexisting psychopathology are at greater risk of receiving higher doses of sedatives than patients without psychiatric history prior to ICU admission. We may also hypothesize that patients with preexisting psychopathology may more often suffer from early memories of frightening ICU experiences. It makes sense to attempt to modify the strategy of care in the ICU in order to limit or suppress potentially frightening ICU experiences for all critically ill patients, from the day of admission throughout the entire stay until discharge, independently of prior psychopathology that could be unknown to the healthcare teams at admission.

Our study suggests an impact of our program on the prevalence of substantial PTSD symptoms after an ICU stay and raises the question of how our tailored multicomponent program has had such positive effect. It is even more difficult to answer this question, because the measures for discomfort reduction used in the 30 ICUs participating in the AQVAR study were numerous, were dependent on the specific context of a given ICU (environment, care organization, patient case mix), and targeted all the discomfort items contained in the IPREA questionnaire. As predicted, the overall discomfort score (measured at the end of the ICU stay) was higher in patients who would present 1 year later with substantial PTSD symptoms in comparison with patients without such symptoms. However, this association does not mean a causal link between the efficacy of our program applied during the ICU stay (to reduce self-perceived overall discomfort as reported at the end of the ICU stay) and post-ICU morbidity. Interestingly, substantial PTSD symptoms at 1 year were lower in the exposed versus the unexposed patients, even after a model adjustment took into account the self-perceived overall discomfort score; this could reflect the simple fact that being hospitalized in an ICU where the healthcare team is trained (with the help of local champions) to collectively reduce all possible types of discomfort that may occur in the ICU is sufficient to improve long-term outcome, or at least reduce the risk of substantial PTSD symptoms. These additional data about the long-term impact of our tailored multicomponent program should prompt intensivists, first, to apply such a program, and secondly to refine this program, as our program is inherently evolutionary based on the decisions of each healthcare facility and not previously predetermined by experts. More attention could, in fact, be given by the healthcare teams to reach this new goal and prevent the occurrence of substantial PTSD symptoms. Considering the theoretically negative effect of being confronted by imminent death or being defenseless against the development of ICU-anchored PTSD, for example, the multicomponent program could be conducted using precise measures aimed at increasing patients' reassurance and communication of information by the healthcare members throughout the ICU stay, but especially from the day of admission during which organ failure or decompensation of chronic disease must be treated. Further studies involving patients with prior psychiatric history hospitalized in the ICU are also essential and could influence specific care or recommendations to be applied during the ICU stay for such patients (particularly regarding the use of sedatives or other medications, or non-pharmacologic treatments, etc.), which necessitates an acknowledgment by the healthcare teams of the preexisting psychopathologic status soon after ICU admission.

Our study has many strengths, as outlined earlier, especially the first assessment of an original intervention for application during an ICU stay, with PTSD as the outcome criteria, but it also has several limitations. First, our study was not designed to demonstrate that the implementation of our tailored multicomponent program would reduce post-ICU PTSD, when we enrolled general ICU survivors in the IPREA3 study. However, we found a lower prevalence of post-ICU PTSD in the exposed group versus the unexposed group, and this difference persisted after adjustment for potential confounding factors, justifying the need for a confirmatory study using a randomized design. Indeed, secondary data sources provide a low-cost means for addressing the research issue. However, some answers can be obtained in a relatively short time frame, thanks to data obtained from large cohorts of patients with follow-up over long time periods, which produces a more representative view of routine clinical care. The proportion of assessed patients with complete follow-up data at 1 year was slightly over 50% and, although comparable to that of many studies on post-ICU PTSD, raises the question of the generalization of our results. However, the data imputation process for the IES-R score to take into account missing data for non-assessed patients showed similar

conclusions, reinforcing the robustness of our findings. One major limitation is the absence of prospectively collected data regarding prior psychiatric morbidity before ICU hospitalization. In most studies, the inclusion was performed on the day of admission to the ICU, with the critical illness making it difficult to collect precise previous psychopathological status without risk of bias due to contamination by current psychological distress or early ICU-related acute stress phenomena. Another limitation is related to the diagnostic method used to determine substantial PTSD symptoms. We measured anxiety, depression, and PTSD symptoms using validated and recommended questionnaires rather than clinical diagnostic interviews; like many authors, we used the IES-R questionnaire, which was adapted to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. In the meantime, the interim two-decade revision, the DSM-V, replaced the previous definition of PTSD according to DSM-IV. The selection of the appropriate cutoff used to determine substantial PTSD symptoms in general critically ill patients could be also a matter of debate. However, when we compare the continuous total score derived from the IES-R, we still found a significant difference between exposed and unexposed patients. We also performed the same analysis using the higher cutoff of 35 for the interpretation of the total IES-R score recommended by many authors [15], and the comparison was unchanged, with lower prevalence of post-ICU PTSD in both groups. Regardless of the cutoff, the prevalence of PTSD was low in comparison with previous studies, which leads to questions regarding the representativeness of our sample of general medical and surgical ICU survivors. Our methodology did not permit assessment of the course of PTSD symptoms at several follow-up points after ICU discharge, but only allowed the assessment of the prevalence of substantial PTSD symptoms at 1 year. Due to the variable onset of post-ICU PTSD, ranging from 1 month to several years, and the different possible courses (continuous, recurring, or remitting), it was not possible to determine the true long-term prevalence of post-ICU PTSD in our cohort. However, the main objective of our study was not to describe the influence of our program on the course of potential post-ICU PTSD, but to compare the impact of a program between two patient groups, using relatively easy-to-collect data from a validated questionnaire, leading to a simple surrogate marker of this psychiatric morbidity in a large cohort. All these limitations should be taken into account for designing further studies that are needed to confirm the efficacy of our program, which should include randomized design, several follow-up points, measures to increase responses rates, use of an actualized diagnostic tool adapted to the DSM-V such as the PCL-5, and attempts to prospectively collect precise data regarding the psychopathological status, especially any prior history of PTSD. Such further studies could also benefit from a refinement of our program based on new recommendations aimed at reducing frightening experiences in the ICU.

In conclusion, a tailored multicomponent program for discomfort reduction in the ICU may significantly reduce the prevalence of substantial PTSD symptoms assessed 1 year after ICU discharge. The dissemination of such a program should be actively promoted across ICUs, which would pave the way for a new strategy in care management.

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest

Dr. Kalfon has received consulting fees from Philips Healthcare and General Electric Healthcare. On behalf of all remaining authors, the corresponding author states that the remaining authors have no conflict of interest.

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