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Internet-based cognitive-behavioural writing therapy for reducing post-traumatic stress after severe sepsis in patients and their spouses (REPAIR): results of a randomised-controlled trial

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ABSTRACT

Objectives To investigate the efficacy, safety and applicability of internet-based, therapist-led partner-assisted cognitive-behavioural writing therapy (iCBT) for post-traumatic stress disorder (PTSD) symptoms after intensive care for sepsis in patients and their spouses compared with a waitlist (WL) control group.

Design Randomised-controlled, parallel group, open-label, superiority trial with concealed allocation.

Setting Internet-based intervention in Germany; location-independent via web-portal.

Participants Patients after intensive care for sepsis and their spouses of whom at least one had a presumptive PTSD diagnosis (PTSD-Checklist (PCL-5)≥33). Initially planned sample size: 98 dyads.

Interventions ICBT group: 10 writing assignments over a 5-week period; WL control group: 5-week waiting period.

Primary and secondary outcome measures Primary outcome: pre–post change in PTSD symptom severity (PCL-5). Secondary outcomes: remission of PTSD, depression, anxiety and somatisation, relationship satisfaction, health-related quality of life, premature termination of treatment. Outcomes measures were applied pre and post treatment and at 3, 6 and 12 months follow-up.

Results Twenty-five dyads representing 34 participants with a presumptive PTSD diagnosis were randomised and analysed (ITT principle). There was no evidence for a difference in PCL-5 pre–post change for iCBT compared with WL (mean difference −0.96, 95% CI (−5.88 to 3.97), p=0.703). No adverse events were reported. Participants confirmed the applicability of iCBT.

Conclusions ICBT was applied to reduce PTSD symptoms after intensive care for sepsis, for the first time addressing both patients and their spouses. It was applicable and safe in the given population. There was no evidence for the efficacy of iCBT on PTSD symptom severity. Due to the small sample size our findings remain preliminary but can guide further research, which is needed to determine if modified approaches to post-intensive care PTSD may be more effective.

Trial registration number DRKS00010676.

Strengths and limitations of this study

- This is the first study examining an intervention to reduce post-traumatic stress disorder after intensive care for both patients and their spouses.
- The internet-based intervention is tailored to the specific needs of postintensive care unit patients.
- A randomised controlled trial adhering to good clinical practice was conducted.
- Small sample size due to of challenging recruitment resulted in low statistical power.

INTRODUCTION

Experience of intensive care could affect mental health of both patients and their partners. About every fifth patient and an equal proportion of spouses develop a post-traumatic stress disorder (PTSD) as a long-term consequence of treatment in the intensive care unit (ICU).[1–4] Thus, PTSD has been considered as part of the postintensive care syndrome in ICU survivors (PICS) and their relatives (PICS-family).[5] Research on post-ICU consequences revealed that mental health of patients and their spouses following ICU experiences are interrelated and that couples seem to react as a dyadic system to a life-threatening situation.[6–9] In the context of dyadic coping research, it has been suggested to use the term 'we-disease' to describe that both, the patient and his/her partner, face the illness 'as a shared 'we-event' and a 'we-experience' rather than an individual problem of one partner requiring support from the other' (p. 595).[10] The concept of 'we-disease' also implies that the treatment of mental distress associated with the illness should always include both partners as they both suffer but also have resources and can jointly contribute to the coping

process.[6 10] Therefore, a partner-assisted intervention appears to be reasonable for treating PTSD symptoms after ICU experiences.

In the past few years, various intervention approaches have been developed to address PTSD in patients or family members that might be classified as interventions during ICU care to prevent PTSD or as interventions to treat PTSD in the long run. Preventive PTSD interventions usually consider a broad target group of ICU patients or family members at risk for post-ICU PTSD.[11–16] Contrasting, interventions addressing post-ICU PTSD are usually provided several months after ICU discharge and so far, these were designed as multitarget approaches focusing primarily on, for example, the improvement of quality of life[17] or reducing anxiety and depression.[18] In those previous intervention trials, PTSD symptom severity was considered as secondary outcome only and post-ICU patients were included irrespective of their mental health status. Based on this evidence and the research gaps revealed, it has been suggested for future trials to specifically address individuals who are at high risk for psychological distress after ICU discharge[18] and to develop targeted interventions that involve partners in the treatment, both as resource for the patient and as clients themselves.[19]

For the treatment of PTSD, clinical guidelines in general strongly recommend trauma-focused psychotherapy with cognitive-behavioural components of exposure and/or cognitive restructuring.[20 21] In the last decades, several treatment manuals of trauma-focused psychotherapy delivered via the internet have been developed, for example, internet-based cognitive-behavioural writing therapy (iCBT). The iCBT approach is usually based on a manualised, therapist-assisted treatment which is operationalised via written assignments. In general, treatment as well as the diagnostic screenings (before and after the treatment) are conducted without any face-to-face contact in a secure web portal.[22 23] ICBT was demonstrably applicable in various patient populations such as rape victims, veterans and patients with chronic somatic diseases.[24–26] Meta-analytical evidence has proven the efficacy of iCBT across these patient populations to be moderate to large (effect sizes 0.60–0.83) in PTSD symptom reduction compared with waitlist (WL) control.[24 25] Moreover, the safety of iCBT has been confirmed in numerous trials although the evidence base on negative effects is sparser than on positive.[27 28] The particular potentials of iCBT lie in providing easy access for mobility-impaired patients or patients with speech and hearing difficulties,[29] ensuring low-threshold due to visual anonymity and enabling a treatment that is independent in space and time.[26 30] These advantages render iCBT particularly suitable for patients after critical illness. Therefore, as part of research within the Center for Sepsis Control and Care (CSCC), we designed a therapist-guided partner-assisted iCBT for reducing post-traumatic stress after intensive care for sepsis in patients and their spouses. We specifically focused on sepsis because it represents a major cause of morbidity in ICU[31 32] and is known as a global burden.[33]

The primary objective of the randomised-controlled REPAIR (Reducing post-traumatic stress after severe sepsis in patients and their spouses) trial was to investigate the efficacy, safety and applicability of this newly developed iCBT compared with a WL control group. Second, considering the interrelation of mental health between patients and partners, the study aimed at examining dyadic concordance in treatment effects, that is, indirect effects of the treatment in the respective spouse of the treated participant.

MATERIALS AND METHODS

Patient and public involvement

Representatives of the self-help organisation German Sepsis Aid were asked to comment on the concept of the study and the perceived acceptability of the proposed intervention resulting in positive feedback. A representative couple participated in a preceding pilot study to check the comprehensibility of the instructions, the functionality of the treatment platform and assessment routines.[34]

Participants

Inclusion and exclusion criteria for study participation were determined a priori recruitment. We included dyads (each member ≥18 years) comprising a former patient, who was treated for sepsis on an ICU for more than 5 days and discharged from ICU more than 1 month ago, and his/her spouse (married or cohabited). Eligibility decisions were based on empirical findings proving ICU length of stay and sepsis significant risk factors for post-ICU PTSD symptoms in patients[35 36] and time since ICU discharge as predictor of PTSD symptoms in relatives.[8] A patient-spouse dyad was included if at least one of them presented a presumptive PTSD diagnosis (PTSD checklist for DSM-5 (PCL-5) ≥33)[37] with regard to the life-threating event. Reasons for exclusion on dyad-level were not having a spouse as well as acute psychosis, suicidal ideation, use of neuroleptics, not being fluent in German or ongoing psychotherapeutic treatment elsewhere of at least one dyad member.

Broad measures were taken for recruitment purposes including press releases, articles in the member journal of the German Sepsis Aid and a German health magazine. Besides, we sent study leaflets and further information to all weaning centres in Germany, early rehabilitation clinics, patient self-help groups, patient organisations and informational websites for transplanted patients in Germany, Austria and Switzerland. We established a study website and a Facebook account with study information. Furthermore, we cooperated with current and finished projects and collaborators inside and outside JUH to identify and contact former patients treated on the ICU.

Participants were screened for eligibility in a telephone interview by using the PCL-5 and completed the Life Event

Checklist for DSM-5 to ensure, that PTSD symptoms are due to the critical illness and ICU experiences.[38] Written informed consent was obtained by the patients and their spouses. In a second telephone contact, patients and their spouses with presumptive PTSD diagnosis according to PCL-5 completed the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[39] and the Structured Clinical Interview for DSM-IV[40] conducted by a trained clinical psychologist (RG). Furthermore, participants were asked to provide medical data (eg, length of intensive care, length of mechanical ventilation (if applicable) and time since ICU discharge).

Intervention

Participants allocated to the treatment condition participated in an iCBT targeted to the traumatic ICU situation. They completed two 50 min internet-based writing assignments per week over a 5-week period (ten essays in total). The number of sessions is based on findings that interventions with fewer than 10 sessions had only a moderate effect.[24] The duration of the sessions is based on the duration in face-to-face sessions. The treatment consisted of three modules: (1) resource-oriented biographical reconstruction of the participants' life (three essays), (2) in sensu trauma exposure sessions (ie, detailed description of the traumatic situation with all sensations; four essays) and (3) cognitive reconstruction (to form a new perspective on the traumatic event and to regain a sense of control; three essays). Originally, the intervention was derived from 'Interapy'[41] and was later adapted for specific target populations, such as refugees or military personnel. In REPAIR, it was tailored to traumatic ICU experiences and extended to a dyadic perspective. The intervention combines effective face-to-face treatment techniques of CBT (exposure, cognitive reconstruction) and biographical reconstruction taken from the Narrative Exposure Therapy.[42] The efficacy of this intervention has already been proven effective in reducing PTSD symptoms for various populations.[24]

After completion of each assignment, the therapist provided individual feedback and further writing instructions to the participant within one workday. Integrated in the third module, the treated participant received a supportive letter from his/her respective partner. Here, the respective partner should announce acknowledgement for the participant as well as his/her strengths and the shared future. This dyadic treatment component, that is, the interaction between the partners, was added as a new element based on discussions with experts in face-to-face couple interventions.

Participants without clinically relevant PTSD symptoms (PCL-5 <33) only completed the assessments and received psychoeducational information about mental health problems after traumatic events. Participants allocated to the WL control group also received iCBT after 5 weeks of waiting (duration of treatment), but without a supportive letter from their spouses. For details, see study protocol (online supplemental material 1).

Outcomes

Primary outcome was change in PTSD symptom severity score from baseline to the end of treatment/waiting time (about 5 weeks after randomisation) measured via the German version of PCL-5[37 43] covering the four DSM-5 symptom clusters. A cut-off of 33 was used for a presumptive PTSD diagnosis.[44] A change of 10 points or more is regarded as clinically relevant.[37]

Secondary efficacy outcomes were (A) symptoms of psychological distress, (B) relationship satisfaction, (C) health-related quality of life and (D) remission at the end of treatment/waiting time. Safety endpoints were (1) the number of suicide alerts (ie, alert which was automatically activated by specific response pattern indicating suicide ideation during assessment), (2) the number of participants with a clinically relevant PCL-5 deterioration and (3) the percentage of participants leaving the study early (during treatment phase) due to any reason. An additional secondary endpoint was dyadic concordance in treatment effects (in terms of PCL-5). Psychological distress was measured using the German version of the Brief Symptom Inventory-18 including subscales of anxiety, depression and somatisation (BSI-18).[45 46] Relationship satisfaction was assessed with the German version of the Relationship Assessment Scale (RAS).[47 48] The German version of the health questionnaire of the EuroQol-5 Dimension-5-Level group (EQ-5D-5L)[49 50] was used to measure health-related quality of life on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Remission was only considered for participants diagnosed with PTSD before treatment/waiting period via CAPS-5.[39] For those, remission was defined as being free of PTSD diagnosis after the intervention/waiting period. PTSD was diagnosed by a trained clinical psychologist (RG) as described above (for details, (online supplemental material 2). Outcomes were also measured at 3, 6 and 12 months post-treatment.[29]

Sample size

The sample size calculation was based on Student's t-test for a parametric two-group comparison, even though more complex models that address the clustering would be used for the confirmatory analysis. In accordance with a recent meta-analysis,[24] we considered effect sizes quantified by Cohen's d of 0.95 as realistic. To detect differences between the treatment groups at a two-sided significance level of 0.05 with a comparison-wise power of 0.9, a sample size of 2×34, that is, 68 patient-spouse dyads, is required for the intention-to-treat (ITT) analysis. Assuming a dropout rate of 30%, the total sample size would be 98 dyads. A higher power was chosen to address the fact that a more complex statistical analysis approach would be used.

Randomisation

Dyads of a post-ICU patient and his/her spouse were randomly assigned to either iCBT or to a WL control group (allocation ratio 1:1) with the dyad being the unit

of randomisation. Concealed allocation was performed centrally using computer-generated random numbers provided by an independent person at the Centre for Clinical Trials of the JUH and stratified by the occurrence of PTSD symptoms within the dyad of the post-ICU patient and the spouse (stratum 1: both post-ICU patient and spouse with PTSD, stratum 2: post-ICU patient with PTSD and spouse without PTSD, stratum 3: post-ICU patient without PTSD and spouse with PTSD).

Blinding

Due to the nature of the study design and intervention, blinding of therapists and participants was not possible[29] (online supplemental material 1). The clinical psychologist who conducted the CAPS-5 clinical interview was also not blinded.

Statistical methods

We relied on two populations. The dyad population included randomised participants irrespective of their presumptive PTSD diagnosis. The PTSD population only comprised participants with a presumptive PTSD diagnosis. Primary and secondary efficacy/safety outcomes were analysed in the PTSD population, while dyadic concordance is was assessed in the dyad population.

The handling of missing data was predefined in the study protocol and/or the statistical analysis plan. Based on the expected high internal consistency of the scores, we substituted missing items with the mean of the provided items of the respective participant if 10% or fewer items were missing. We applied the ITT and the per-protocol (PP) principle to both populations. In case of the PP principle, we included randomised participants (with a presumptive PTSD diagnosis) who provided pretreatment(t0) and post-treatment/waiting (t1) information. In case of the ITT principle, we considered all randomised participants (with a presumptive PTSD diagnosis). Missing score values were replaced, stratified by intervention group and type of treatment (defined according to the stratum for the randomisation), according to best-case/worst-case substitution. We denoted this data set as 'primary analysis set'. As additional sensitivity analysis that was not prespecified in the study protocol, we used multiple imputation by chained equations (MICE) using fully conditional specification[51] (for details, online supplemental material 2).

Participant characteristics (dyad population) and outcomes (PTSD population) were summarised as absolute and relative frequencies for nominal variables or as medians together with the first and third quartile (Q1, Q3) for ordinal/continuous variables. Rough group comparisons were done by Fisher's exact test or Mann-Whitney-U test. For the primary outcome PCL-5 change, we applied generalised estimating equation (GEE) modelling (independent variables: baseline PCL-5 value, treatment condition; cluster: dyad) in the primary analysis set. We performed several sensitivity analyses (ITT principle with MICE, PP principle, extension of the above defined GEE model by inclusion of further possible confounders as independent variables). For the secondary efficacy outcomes, we adapted the GEE modelling accordingly. For primary and secondary efficacy outcomes, model coefficients (adjusted mean differences or OR) with 95% CIs and p values are presented. In addition, we provide the corresponding between-group effect sizes (standardised mean differences, derived from the main analyses with GEE modelling, Cohen's *d*). For illustration, we also provide between-group effect sizes and within-group effect sizes in iCBT and WL control group for pre–post change, both as standardised mean differences (Cohen's d) based on unadjusted means applying the PP principle. For the safety outcomes, we provide absolute and relative frequencies based on the PP principle. Dyadic concordance in treatment effects (in terms of PCL-5) was assessed with Spearman correlation (together with the corresponding 95% CIs) independently from the treatment condition between post-ICU patients and his/her spouse in the dyad population according to both ITT and PP principle. We applied a two-sided significance level of 0.05 to the primary confirmatory analysis and did not correct for multiple testing otherwise as the other analyses were considered exploratory. We used R (V.3.6.0) for statistical analyses (for details, see online supplemental material 2).

RESULTS

Participants

Between February 2017 and January 2019, we received 57 enquiries from either a post-ICU patient or his/her spouse. After screening for eligibility 25 dyads were randomised, 12 to iCBT and 13 to WL (figure 1). Median age of the study participants was 55 years (Q1–Q3, 47–62).

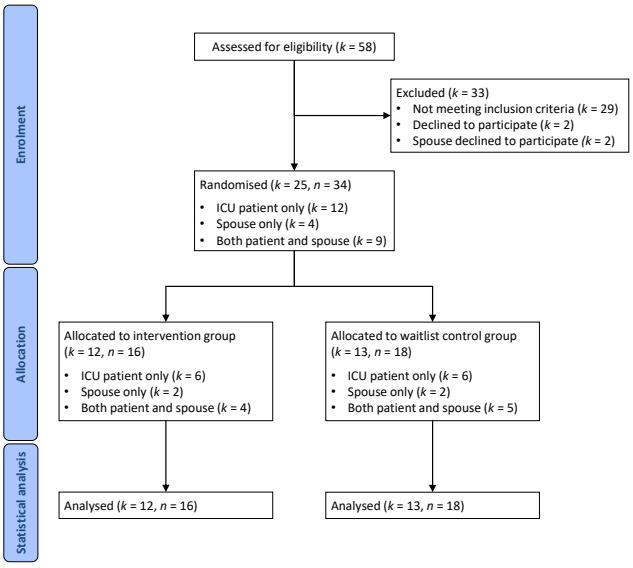

Figure 1 Flow diagram. The number of dyads (k) and the number of participants with PTSD symptoms (n) are provided. Reasons for exclusions are given. ICU, intensive care unit; PTSD, post-traumatic stress disorder.

Table 1 Characteristics of participants—overall as well as stratified by treatment group

Characteristic	Overall (N=50, k=25)	Treatment group: iCBT (N=24, k=12)	Treatment group: WL control (N=26, k=13)	P value
Male sex; n (%)	26 (52.0)	12 (50.0)	14 (53.8)	1.000
Age, in years; median (Q1, Q3)	55 (47, 62)	56 (52, 64)	54 (46, 59)	0.101
Among post-ICU patients‡				
Time since ICU treatment, in years; median (Q1, Q3)	1.8 (1.1, 3.7)	1.9 (1.2, 4.6)	1.6 (1.0, 2.0)	0.231
Duration of ICU treatment, in days; median (Q1, Q3)	21 (13, 40)	28 (12, 42)	21 (13, 28)	0.662
Mechanical ventilation				1.000
Yes; n (%)	18 (72.0)	9 (75.0)	9 (69.2)	
No; n (%)	5 (20.0)	2 (16.7)	3 (23.1)	
Not specified; n (%)	2 (8.0)	1 (8.3)	1 (7.7)	
Duration of mechanical ventilation among ventilated patients, in days; median (Q1, Q3)§	24 (16, 28)	28 (28, 35)	18 (8, 23)	0.048
College or university degree; n (%)	17 (34.0)	7 (29.2)	10 (38.5)	0.559
Pre-existing mental disorder (prior to sepsis); n (%)	16 (32.0)	9 (37.5)	7 (26.9)	0.547
Treatment of pre-existing mental disorder				
Prior to sepsis; n (%)	15 (30.0)	8 (33.3)	7 (26.9)	0.760
Post sepsis; n (%)	6 (12.0)	4 (16.7)	2 (7.7)	0.409
Presumptive PTSD diagnosis				
Post-ICU patient only; n (%)†	12 (48.0)	6 (50.0)	6 (46.2)	1.000
Spouse only; n (%)‡	4 (16.0)	2 (16.7)	2 (15.4)	1.000
Both dyad members; n (%)*	9 (36.0)	4 (33.3)	5 (38.5)	1.000
Relationship				
Duration, in years; median (Q1, Q3)*	22.2 (16.2, 32.9)	24.5 (19.1, 34.6)	21.8 (12.5, 29.4)	0.414
Marital status: married; n (%)*	21 (84.0)	10 (83.3)	11 (84.6)	1.000

The numbers are based on the dyad population. Overall, there are 25 dyads —12 dyads in the iCBT group and 13 dyads in the WL control group. Note that each dyad comprises one post-ICU patient and one spouse. The overall number of dyads (k) and the overall number of individuals (N) are provided. Characteristics are summarised as median with first and third quartile (Q1, Q3) or as absolute (n) and relative frequency (%). P values are derived from Mann-Whitney U test and Fisher's exact test, respectively, while excluding patients with missing (including non-specified) information on the respective characteristic.
*Refers to dyad.
†Refers to former ICU patient.
‡Refers to partner.
§Missing for nine patients (iCBT group: six, WL control group: three).
iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; WL, waitlist.

Thirty-four participants had a presumable PTSD diagnosis (9 dyads with affected post-ICU patient and spouse, 12 with post-ICU patient only, 4 with spouse only). Of those, 25 were initially diagnosed with PTSD in the clinical interview (iCBT: 14; WL: 11). Further characteristics of the participants are shown in table 1 (for stratification by post-ICU patient/spouse, online supplemental Table S1; for descriptive summary of the outcomes, online supplemental Table S2 and S3). Of note, one participant dropped-out directly after randomisation. For details on missing data and its impact/handling, we refer to online supplemental material 2.

Primary outcome

Individual, time-dependent PCL-5 curves are shown in figure 2. In the primary analysis set, we did not observe evidence for differences between groups in the primary outcome. The adjusted mean difference in PCL-5 score change was −0.96 (95% CI −5.88 to 3.97; p=0.703; table 2) when comparing iCBT to WL. Sensitivity analyses also showed no evidence for differences in PCL-5 change between the iCBT and the WL control group (ITT with MICE: 4.01; 95% CI −1.89 to 9.91; p=0.181; PP: 2.40; 95% CI −2.29 to 7.08; p=0.316; table 2). The corresponding between-group effect sizes varied between −0.14 (95% CI −0.81 to 0.54) and 0.48 (95% CI −0.21 to 1.16) (online supplemental table S9). The extended multivariable models revealed similar results (with a treatment group association in the multivariable models III with the PP and the ITT principle with MICE; online supplemental table S4).

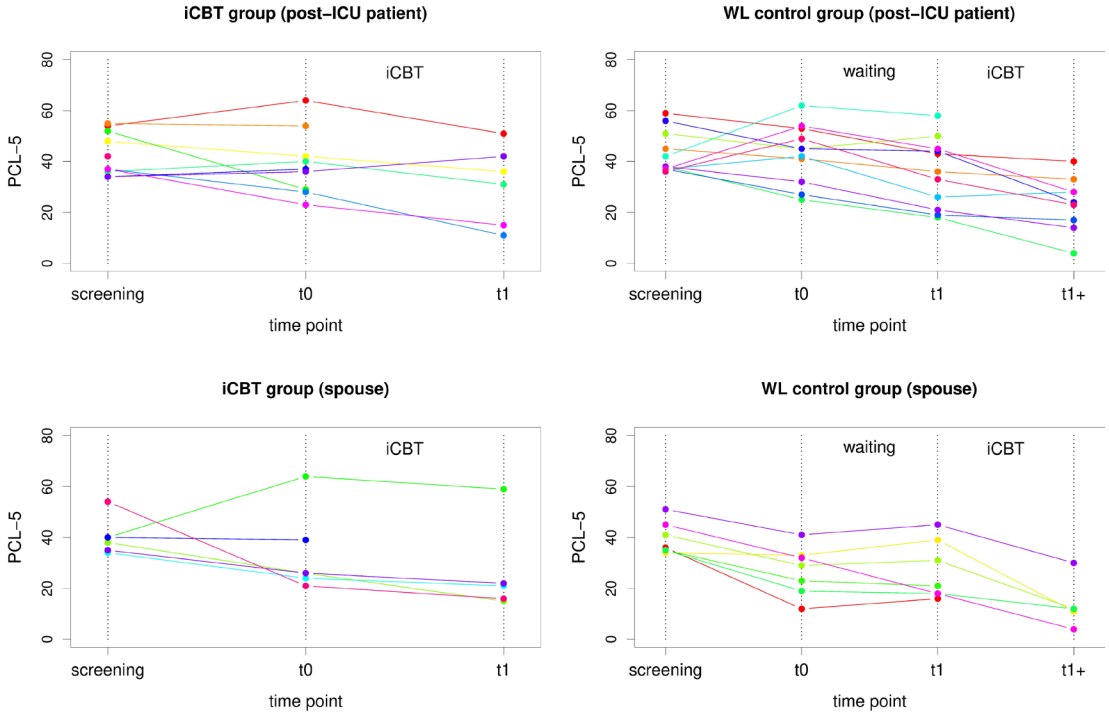

Figure 2 Observed PTSD symptoms (PCL-5 total score) in participants at trial assessments. Scores are stratified by post-ICU patient and his/her spouse as well as by treatment group (iCBT/WL control group). Pertreatment condition, dyad membership is colour-coded. Higher PCL-5 scores indicate more severe symptoms. Note that one participant (former ICU patient in iCBT group) dropped out directly after randomisation. Values are provided for several time points (including approximately time specifications): screening (t0—4 weeks); t0, start of intervention (iCBT group)/waiting (WL control group); t1 (t0 +5 weeks), end of intervention (iCBT group)/waiting (WL control group). In the WL control group, the end of intervention is at t1+ (t1 +5 weeks). iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; WL, waitlist.

Within-group effect sizes for pre–post changes in PCL-5 were similarly small in both groups (online supplemental table S10). Likewise, the proportion of participants with clinically relevant improvement in PCL-5 (ie, at least 10 points) was nearly identical in iCBT and WL control group (27.3% vs 27.8%) (online supplemental table S11).

Secondary efficacy outcomes

In the primary analysis set, we found that iCBT led to a larger RAS change than waiting (1.11; 95% CI 0.64 to 1.57; p<0.001; online supplemental table S5), with effects in favour of waiting. The corresponding between-group effect sizes for RAS change was large with −1.67 (95% CI −2.45 to −0.89); online supplemental table S9). This observation was consistent across all sensitivity analyses (online supplemental table S5). For all other secondary efficacy outcomes, we did not observe evidence for an association between score changes and iCBT in the primary analysis set (online supplemental table S6-S8) with corresponding effect sizes of 0.04 (95% CI −0.64 to 0.71) for BSI-18 and 0.25 (95% CI −0.42 to 0.93) for EQ-5D-5L (online supplemental table S9). Among patients with initial PTSD diagnosis (according to CAPS-5), remission rates were 64% after iCBT and 27% after waiting. Of note, 95% CIs for the iCBT effect for remission are wide in both ITT and, particularly, in the PP analyses; a smaller number of participants was considered in theses analyses as only participants with a presumptive PTSD diagnosis at baseline were included (online supplemental table S6).

Safety and applicability

Overall, there were five suicide alerts. All of them were clarified in immediate therapeutic contacts by telephone (see ref. [29] for a description of safety management). Three were false alarms, two were caused by reasons not related to the study and the suicidal ideations subsided quickly. During iCBT/waiting, there were no clinically relevant deteriorations in regard of the PCL-5 score. Seven participants prematurely terminated in the iCBT group and two during waiting time, respectively. All drop-outs appeared for reasons other than study or treatment participation, for example, physical deterioration, change in life circumstances (for further details on the safety endpoints, online supplemental table S10 and S11). In-depth interviews with participants after the treatment confirmed the applicability of the intervention. It was positively highlighted that iCBT met the specific needs of the patients and the spouses. In terms of feasibility, no major technical problems emerged and the internet literacy of the participants was sufficient to complete the treatment.

Dyadic concordance in treatment effects

No evidence for a correlation between the PCL-5 changes of post-ICU patients and those of his/her spouse could

Table 2 Results for PCL-5 (PTSD checklist for DSM-5) change from multivariable generalised estimating equation modelling

Variable	Mean difference (95% CI)	P value
ITT (best-case/worst-case)		
iCBT (ref.: no)	−0.96 (−5.88 to 3.97)	0.703
Baseline value (t0)	0.09 (−0.05 to 0.23)	0.225
ITT (MICE)		
iCBT(ref.: no)	4.01 (−1.89 to 9.91)	0.181
Baseline value (t0)	0.16 (−0.02 to 0.33)	0.078
PP		
iCBT(ref.: no)	2.40 (−2.29 to 7.08)	0.316
Baseline value (t0)	0.10 (−0.03 to 0.23)	0.123

Model coefficients (mean difference) together with 95% CIs and p values are provided. Positive values indicate effects in favour of iCBT. Results from both ITT approaches (best-case/worst-case as main analysis, MICE as sensitivity analysis) and the PP analysis (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were five participants in the iCBT group and none in the waitlist control group with missing information (missing PCL-5 change: 5, missing baseline value: 1; Supplemental Digital Content 1, online supplemental figures A3, A4).
iCBT, internet-based cognitive-behavioural writing therapy; ITT, intention-to-treat; MICE, multiple imputation by chained equations; PP, per-protocol; PTSD, post-traumatic stress disorder.

be observed—neither in case of only one dyad member nor in case both dyad members had a presumptive PTSD diagnosis (online supplemental table S12).

DISCUSSION

Strengths and limitations

Aim of this randomised controlled trial was to test the efficacy, safety and applicability of an iCBT for reducing PTSD symptoms in patients and their spouses. We included 25 dyads resulting in 34 treated participants. To our knowledge, this is the first study that evaluated an intervention involving both patients and spouses using a partner-assisted approach with the goal of reducing PTSD symptoms after intensive care. As a novelty, we implemented writing a supportive letter to the respective spouse as a dyadic treatment component in the iCBT.[29]

As already highlighted,[18] it is important to address individuals who are at high risk for psychological distress following critical illness and to develop interventions that should be targeted to defined subpopulations of survivors. Therefore, we sought only patients and/or spouses with clinically relevant PTSD symptoms and offered them a treatment tailored to their specific needs and their experiences during the critical illness. In addition to a self-report measure of PTSD symptom severity, we applied a clinical interview for formally diagnosing PTSD, which has been recommended as ideal but is a rare exception in clinical studies.[1]

There are, however, several important limitations that may have affected the results. First, we did not achieve the planned sample size. Despite tremendous efforts and a significant extension of the recruitment period, we experienced serious problems in recruiting participants. We can only speculate about the reasons. Although clinical research has proven the efficacy, applicability and safety of iCBT, also in the treatment of PTSD, internet-delivered psychotherapy is not yet part of routine care in the German healthcare system. So far, psychotherapy has been carried out predominantly via face to face. There might have been concerns and caveats about the practicability of the iCBT intervention[28] and the (primarily) elderly patients might be less open for such 'new' approaches. This may indicate that the newly developed treatment approach is not very desirable, at least in some age groups, and other treatment formats have to be developed and tested. Furthermore, there are no specialised post-ICU rehabilitation and outpatient ICU follow-up clinics in Germany, making it difficult to 'find' and contact patients after hospital discharge. The small sample size has resulted in a lack of statistical power. Hence, our results should be regarded as preliminary and further trials are needed to prove the efficacy of iCBT in the context of post-ICU PTSD.

Another problem emerged from missing data due to premature termination. To follow the ITT principle, we imputed missing data based on the best-case/worst-case substitution as the most rigorous method (as specified in the study protocol; online supplemental material 1). We further included sensitivity analyses applying multiple imputation and relying on the PP principle. Note that there are differences in the assumptions of these approaches reflecting common challenges in dealing with missing data. Hence, our conclusions remain fraught with uncertainty.

A further limitation concerns the selection of outcome measures. We mainly used outcome measures that depict clinically relevant symptomatology. This is not consistent with the fact that we also address spouses who do not have clinically relevant PTSD symptoms and are mentally healthy and support their partner in doing iCBT. Future studies examining dyadic interventions should also use more measures pertaining to partner well-being. Although the Impact of Event Scale-revised is recommended as core outcome measure of PTSD in post-ICU outpatient care,[52 53] we applied the PCL-5 for the assessment of PTSD symptom severity, because it is a widely used self-report questionnaire with good diagnostic accuracy, which reflects the most recent diagnostic PTSD criteria of DSM-5.[43]

With respect to the study design, it is important to consider that neither participants nor therapists were blinded. Finally, it has to be noted, that information about medical data was derived via self-report of the participants. It has to be questioned if all critical illness survivors and/or spouses were able to remember, for example,

the length or critical illness and mechanical ventilation, as well as time since ICU discharge. Therefore, it would be more reliable to use medical records for assessing this information.

Generalisability

External validity of our results is limited because we only included sepsis patients and their spouses from Germany. Since sepsis is highly frequent in ICU,[31 32] our findings might apply to a large proportion of ICU patients. Participating patients were treated in ICU about 3 weeks and most of them were mechanically ventilated. In comparison to ICU patients, both with and without sepsis,[32] we included a severely critically ill patient population. Median time after ICU discharge was 1.8 years, which is a quite long time. However, it is known that PTSD, if untreated or undertreated, might become chronic[54] and that PTSD symptoms might persist even for years after ICU discharge.[6 55] Although the iCBT manual was developed in German language, the treatment might be easily transferable in other languages, for example, English, enabling future studies with higher recruitment potential.

Interpretation

With regard to our primary outcome, we could not observe evidence that iCBT led to a larger reduction of PTSD symptom severity than waiting. This was not expected, as meta-analyses showed evidence for the efficacy of iCBT on reducing PTSD symptoms.[24 25] In particular, trauma-focused iCBT, as used in this study, was shown to produce greater effects than non-trauma-focused iCBT.[25] However, effects of the included trials were heterogeneous underpinning the need to identify patient as well as intervention characteristics which influence treatment outcome.

With regard to secondary outcomes, the comparison of remission rates in both groups (iCBT: 64%; waiting: 27%) may suggest that remission may nevertheless be an indicator of the treatment's potential effectiveness in this population. Contrary to our hypotheses, we found a relatively larger decrease of relationship satisfaction in the iCBT compared with the WL control group. There is evidence, although limited, that trauma-focused therapy is associated with higher levels of stress and is seen as demanding in terms of effort and time,[56 57] and individual stress is known to have a negative impact on relationship satisfaction.[58 59] It would be important to examine if the decrease in relationship satisfaction is a short-term "side" effect or persists over a longer time.

There was no evidence for dyadic concordance in any of the treatment effects. Beyond efficacy, participating in iCBT was safe, as no adverse events such as suicidality or clinically relevant PTSD symptom deterioration occurred that were therapy-related. Although seven participants prematurely terminated in the iCBT group, all dropouts appeared for reasons other than study or treatment participation. Compared with other iCBT studies, the dropout rate in our study (20.6%) is in the lower range, however, it should be noted that dropout rates are very heterogeneous across studies (9%–63%).[60]

Furthermore, participants confirmed the applicability of iCBT and the feasibility of the implementation and managed to reach the goals of each individual session. However, we did not formally evaluate their feedback or conducted a content analysis of their writing assignments. Based on our results, iCBT can be regarded as an applicable intervention in the particular population of post-ICU patients and their spouses.

The treatment of PTSD after traumatic ICU experiences has been subject of several randomised studies, tailored either as interventions during ICU care to prevent PTSD or as interventions to treat PTSD in the long run. Preventive interventions delivered early in ICU to reduce later PTSD symptoms of patients did not prove efficacious,[11 12 15 16] while the effectiveness of preventive approaches targeting partners' PTSD varies.[13 14] There are only few randomised controlled trials on the efficacy of treatments for reducing PTSD after ICU discharge. A nurse-led post-ICU recovery programme consisting of three consultations (one face to face, two via telephone) in the course of ten months after ICU discharge was not superior to standard care.[17] While previous treatments for post-ICU PTSD have focused exclusively on either the patient or the partner at an individual level,[11–17] dyadic approaches have received little consideration in the development of new interventions. An RCT including ICU survivors and their family members tested a telephone-based and web-based coping skills training intervention delivered by clinical psychologists against an education programme[18] with no effect on PTSD symptom reduction. In both trials,[17 18] post-ICU patients were included irrespective of their mental health status, and PTSD symptom severity was considered as secondary outcome only.

The need for ICU follow-up care to diagnose and treat PICS impairments after hospital discharge is apparent. Post-ICU patients show an increased utilisation of outpatient specialist services, including psychiatric services, higher medication intake and impaired quality of life.[61] Specialised post-ICU outpatient clinics could provide the necessary services specific to ICU survivors' healthcare needs,[5] but are however not yet established nationwide in Germany. Internet-based treatment approaches like iCBT in the follow-up of ICU patients can be particularly helpful for physically impaired patients or patients living a considerable distance from the hospital or specialised outpatient care, regardless of whether they are cared for in an ICU follow-up clinic or not.

Generally, it seems to be a difficult challenge to address the problem of post-ICU PTSD. It remains largely unknown when interventions to reduce PTSD symptoms should be initiated. The range of time after discharge from ICU in our sample was 3 –60 months. However, due to the small sample size in our study, we could not examine differences in iCBT efficacy based on the time since ICU discharge.

It seems that while some participants benefit from iCBT, others do not. In this regard, iCBT may be more appropriate as an initial intervention in a stepped pathway of care when additional treatment will be provided if the patient fails to benefit sufficiently from iCBT.[25] Moreover, predictors of treatment success should be further examined to better tailor the intervention to the participants.

CONCLUSIONS

We could not prove the efficacy of iCBT in contrast to waiting in patients and spouses after intensive care treated sepsis with a presumptive PTSD diagnosis, although such differences were observed in some sensitivity analyses. We demonstrated that iCBT is safe and applicable for both post-ICU patients and their spouses. While some participants benefited from iCBT, others did not. Hence, predictors of treatment success should be further examined. The largest limitation of the REPAIR trial was the small sample size. Therefore, our results remain preliminary. Future research could benefit by considering our findings and experiences in the planning of further tailored randomised-controlled trials. We suggest researchers informing patients early about PICS, treatment needs and trial participation, that is, before hospital discharge. Successful future studies might be designed as multicentre trials with broad support from scientific organisations and clinical institutions, for example, rehabilitation clinics or weaning centres. Promising scientific issues for future studies could be the provision of iCBT as part of a blended treatment (combining treatment modules delivered via internet and telephone or face-to-face contact) or as initial intervention in a stepped pathway of care.

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Contributors JR and CK conceived the study. CK, MB and HN developed the iCBT treatment manual. AS a priori conducted the power analysis and defined the statistical methods. MK was in charge of the statistical analysis and interpretation of the data. RG recruited patients, collected the data for the study and conducted all clinical interviews. MB and HN carried out the treatment of the participants. JR, MK and RG drafted the paper. All authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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