Posttraumatic stress symptoms, sense of coherence and pain after intensive care treatment and the effect of early nurse-led follow-up consultations

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1 ACKNOWLEDGEMENTS

2 ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ASA	The American Society of Anesthesiologists Physical Status Classification
AUDIT-C	Alcohol Use Disorders Identification Test Consumption
BPI-SF	Brief Pain Inventory-Short Form
CAM-ICU	Confusion Assessment Method for Intensive Care Unit
CBT	Cognitive Behavioural Therapy
CCN	Critical Care Nurse
CG	Control Group
CI	Confidence Interval
CRF	Case Report Form
DTS	Davidson Trauma Score
HRQL	Health Related Quality of Life
IASP	International Association for the Study of Pain
IPAT	Intensive Care Psychological Assessment Tool
ICU	Intensive Care Unit
IES	Impact of Event Scale
IES-R	Impact of Event Scale-Revised
IG	Intervention Group
LMM	Linear Mixed Model
LOH	Length of Hospital
LOS	Length of Stay
NLC	Nurse Led Consultation
NRS	Numeric Rating Scale
NTNU	The Norwegian University of Science and Technology
OG	Observation Group
OUH	Oslo University Hospital
OUHU	Oslo University Hospital Ullevål
OUHR	Oslo University Hospital Rikshospitalet
PICS	Post Intensive Care Syndrome
PROMs	Person Reported Outcomes Measured
PSEQ	Pain Self Efficacy Questionnaire
PTS	Post Traumatic Stress
PTSS-10-I-A	Post-Traumatic Stress Scale 10 items Intensive part A
PTSS-10-I-B	Post-Traumatic Stress Scale 10 items Intensive part B
PTSD	Post Traumatic Stress Disorder
RASS	Richmond Agitation and Sedation Scale
RCT	Randomized Controlled Trial
REK	Regional Etisk komite
VAS	Visual Analogue Scale
SPSS	Statistical Package for the Social Sciences
SAPS II	The New Simplified Acute Physiology Score II
SD	Standard Deviation
SOC	Sense of Coherence
SOC-C	Sense of Coherence Comprehensibility
SOC MA	Sense of Coherence Manageability
SOC ME	Sense of Coherence Meaningfulness

SOFA	The Sequential Organ Failure Assessment
SOMCT	The Short Orientation-Memory-Concentration Test
WHO	World Health Organization

3 LIST OF PAPERS

Paper I

Valsø Å, Rustøen T, Skogstad L, Schou-Bredal I, Ekeberg Ø, Småstuen M, Myhren H, Sunde K, Tøien K.

Post-traumatic stress symptoms and sense of coherence in proximity to intensive care unit discharge

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Paper II

Valsø Å, Rustøen T, Småstuen MC, Ekeberg Ø, Skogstad L, Schou-Bredal I, Myhren H, Sunde K, Tøien K.

Effect of nurse-led consultations on post-traumatic stress and sense of coherence in discharged ICU patients with clinically relevant post-traumatic stress symptoms - a randomized controlled trial

Crit Care Med 2020 Vol. 48 Issue 12 Page 1218-1225

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Paper III

Valsø Å, Rustøen T, Småstuen MC, Puntillo K, Skogstad L, Schou-Bredal I, Sunde K, Tøien K.

Occurrence and characteristics of pain after ICU discharge: A longitudinal study

Nurs Crit Care 2021 Page 1-10

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4 SUMMARY

Mental and physical symptoms such as posttraumatic stress (PTS) symptoms and pain is common after treatment of critically ill patients in the intensive care unit (ICU). This can further develop to posttraumatic stress disorder (PTSD) and chronic pain and represent a severe health burden leading to reduced health related quality of life. Early identification of patients with the potential of developing PTSD is therefore important to be able to prevent or treat it. In addition, more knowledge about possible associations between PTS symptoms, pain, and sense of coherence (SOC, coping skills) after ICU discharge in a large general ICU sample is needed. We therefore aimed to measure the effect of nurse-led consultations in a pragmatic non-blinded randomized controlled trial (RCT) on reducing PTS symptoms and increase SOC the following year after ICU discharge in ICU patients with clinically relevant PTS symptoms (paper II). Furthermore, we intended to describe the occurrence of PTS symptoms at the hospital ward after ICU discharge, and investigate possible associations between PTS symptoms, SOC, pain as well as demographic and clinical variables in a large sample of discharged ICU patients (paper I). In paper III we investigated occurrence of pain at the hospital ward and the following year and associated variables in the same cohort of discharged ICU patients.

Adult discharged ICU patients from five ICUs at Oslo University Hospital between 2014 and 2016 were included and screened for PTS symptoms at the hospital ward within a week after ICU-discharge (baseline). SOC and pain were simultaneously measured and all three scales were reevaluated after three, six and 12 months. Patients with clinically relevant PTS symptoms were randomized to the intervention group (IG, up to three nurse-led consultations within two months) or the control group (CG, receiving standard care only).

Patients without clinically relevant PTS symptoms were included in the observation group (OG, also receiving standard care), and these patients were also available for papers I and III.

In total, 523 patients were included and screened for PTS symptoms and available for papers I and III, and 224 patients were randomized to IG (111) and CG (113), respectively (paper II). There was a significant association between more PTS symptoms and lower SOC, higher pain interference with function, more delusional memories from the ICU, lower age and not being a trauma patient early after ICU discharge (paper I). Among patients with clinically relevant PTS symptoms early after ICU discharge, there was no significant difference in level of PTS symptoms or in total SOC score between IG and CG at three, six and 12 months after ICU discharge (paper II). However, PTS symptoms decreased, and SOC increased in both groups during the follow-up year (paper II). In total, 68% of discharged ICU patients reported worst pain intensity early after ICU discharge (paper III). At three, six- and 12-months follow-up, half of the patients still reported worst pain intensity. A statistically significant association was found between higher worst pain intensity and more PTS symptoms, female gender, shorter ICU length of stay (LOS), and more traumatic experiences from the ICU, during the follow-up year. For higher pain interference there was a similar statistically significant association, except for shorter ICU LOS. In addition, lower age and not being admitted with a primary medical diagnosis were also associated with higher pain interference (paper III).

In conclusion, nurse-led consultations compared with standard care did not reveal any significant effect on PTS symptoms or SOC after ICU discharge in patients with clinically relevant PTS symptoms. Several discharged ICU patients experience PTS symptoms and pain in the following year after ICU discharge, although it seems to decline over time.

5 SAMMENDRAG

Mentale og fysiske problemer som posttraumatisk stress (PTS) symptomer og smerte er vanlig etter behandling av kritisk syke pasienter på intensivavdelingen. Dette kan videre utvikle seg til post traumatisk stress lidelse (PTSD), med eller uten kronisk smerte, som kan føre til stor helse belastning, og redusert helserelatert livskvalitet for pasienten. Tidlig identifisering av pasienter med risiko for utvikling av PTSD er derfor viktig for å kunne forebygge og behandle denne lidelsen. I tillegg er det behov for mer kunnskap om mulige sammenhenger mellom PTS symptomer, smerte og mestringsfølelse etter utskrivelse fra intensiv i et stort utvalg av kirurgiske og medisinske intensivpasienter. Vi ønsket derfor gjennom en randomisert studie, å måle effekten av sykepleierledede konsultasjoner, for å redusere PTS symptomer og øke mestringfølelsen det påfølgende året etter utskrivelse fra intensivavdelingen, blant intensivpasienter med klinisk relevante PTS symptomer (artikkel II). Videre ønsket vi å beskrive forekomsten av PTS symptomer på sengepost etter utskrivelse fra intensivavdelingen, samt kartlegge mulige assosiasjoner mellom PTS symptomer, mestringsfølelse, smerte, og demografiske og kliniske variabler blant et stor utvalgt av utskrevede intensivpasienter (artikkel I). I artikkel III undersøkte vi forekomsten av smerte på sengepost og det påfølgende året etter utskrivelse og assosierte variabler i den samme, store kohorten av utskrevede intensivpasienter.

Voksne intensivpasienter fra fem forskjellige intensivavdelinger ved Oslo universitetssykehus i perioden 2014 - 2016 ble inkludert og screenet for PTS symptomer på sengepost innen en uke etter utskrivelse fra intensivavdelingen. Mestringsfølelse og smerte ble også målt samtidig, og alle spørreskjemaene ble sendt ut igjen etter tre, seks og tolv måneder. Pasientene med klinisk relevante PTS symptomer på sengepost ble randomisert til enten intervensjonsgruppen (IG, opptil tre konsultasjoner med en intensivsykepleier innen to

måneder etter utskrivelse fra intensiv) eller kontrollgruppen (KG, standard behandling) (artikkel II). Pasientene som ikke hadde klinisk, relevante PTS symptomer på sengepost ble inkludert i en observasjonsgruppe (OG), fikk standard behandling og inngikk i artikkel I og III (i tillegg til de som var randomisert til IG eller KG fra artikkel II).

Totalt 523 pasienter ble inkludert i henholdsvis IG (111), KG (113), og OG (299). Lavere mestringsfølelse, større grad av smertepåvirkning, mer deliriske minner, lavere alder og det å ikke være traumepasient var signifikant assosiert med høyere nivå av PTS symptomer på sengeposten (artikkel I). Blant pasientene med klinisk relevante PTS symptomer fra sengeposten ble det ikke funnet noen forskjell i PTS symptomer og mestringsfølelse mellom IG og KG etter tre, seks og 12 måneder (artikkel II). Imidlertid sank PTS symptomer og mestringsfølelsen økte i begge gruppene gjennom oppfølgingsåret (artikkel II). Etter utskrivelse fra intensivavdelingen rapporterte 68 % av de 523 inkluderte pasientene fortsatt maksimal smerteintensitet på sengeposten, og etter tre, seks og 12 måneder ble fortsatt maksimal smerteintensitet rapportert blant halvparten av pasientene (artikkel III). Det ble funnet en signifikant assosiasjon mellom høyere smerteintensitet, mer PTS symptomer, kjønn (kvinne), kortere intensivopphold, og mere traumatiske minner fra intensivoppholdet. Disse variablene, bortsett fra kortere intensivopphold, var også signifikant assosiert med høyere smertepåvirkning. I tillegg var yngre alder og det å ikke ha en indremedisinsk diagnose signifikant assosiert med høyere smerte-påvirkning (artikkel III).

Vi fant altså ingen effekt av sykepleierledede konsultasjoner sammenlignet med standard behandling på PTS symptomer eller mestringsfølelse hos pasienter med klinisk relevante PTS symptomer etter intensivbehandling. Mange intensivpasienter opplever fortsatt PTS symptomer og smerte året etter intensivbehandling, men symptomene ser ut til å reduseres over tid.

6 INTRODUCTION

Critically ill or injured patients have different degree of life-threatening conditions. They are treated in intensive care units (ICUs) with the goal to treat and stabilize their critical conditions, to maintain vital organ perfusion and save their lives (1, 2). ICU treatment can be demanding and very challenging, and different complications from several organ systems frequently occur. As a critical care nurse (CCN) with more than 10 years of clinical experience from the ICU, I have treated and seen many sick patients fighting for their lives. They have been connected to different medical and technical equipment; some in coma and some awake, with or without pain, breathing problems, hallucinations, delirium, frightening memories, lack of memory, among others. Consequently, several of these patients are anxious and concerned for their and their families future, both during the ICU stay and in the recovery period after ICU discharge. My role as a CCN is to work close with the patients and their relatives, and to give continuous professional care and organ support required, including mental and interpersonal care and support, all as part of a multidisciplinary treatment team.

Working close with these vulnerable patients has over the years made me reflect on how these patients are doing after their ICU discharge. We see critically ill patients coming and going, in all kinds of conditions, but how they manage their life situation after leaving the ICU is usually an unexplored field for the CCNs. How are they doing physically and especially mentally? We are aware of the post ICU syndrome (PICS) and challenging physical and psychological sequels after ICU treatment, such as posttraumatic stress (PTS) symptoms and PTS disorder (PTSD), depression, anxiety, reduced health-related quality of life and pain (3, 4). Many patients have traumatic memories from the ICU or memories of hallucinations and nightmares, some have no memories about what happened during their critical illness (5). However, how these conditions are affecting quality of life, economy, and social situation

within the family, with friends and the society in general, is easy to forget in a busy ICU weekday. I have wondered how CCNs might help these patients to process traumatic memories, cope in the new situation and reduce mental symptoms.

Thus, this thesis focuses on the challenging period after ICU discharge, with special attention towards PTS symptoms, sense of coherence (SOC) (coping) and pain the following year after ICU discharge. Can I, as a dedicated CNN, contribute to increase understanding of these problems, explore associations with symptoms and outcome, and evaluate if nurse-led consultations (NLCs) after ICU discharge can improve outcome for patients at risk for developing PTSD?

7 BACKGROUND

7.1 Intensive care unit

The intensive care unit (ICU) is a specialized hospital unit where critically ill/injured patients are treated by a qualified inter-professional team. The aim is to observe, diagnose, give care, treat, and stabilize the patients and prevent further deterioration in vital organs (1, 2, 6, 7). Specially trained healthcare professionals such as critical care nurses (CCNs), intensive care physician, physiotherapists and pharmacists is a part of the staff at ICUs (6). In addition, depending on internal logistics or type of hospital/ICU, the staff generally have close cooperation with different surgeons, internists, and other medical specialists depending on the diagnoses and type of ICU patients. Psychologists, psychiatrists, or psychiatric nurses are also frequently consulted in the ICU. Different ICUs can be differently organized based on type of ICU patients, from general patient groups consisting of both medical and surgical ICU patients to more specialized units focusing on specific sub-groups like trauma, neurosurgical, gastrosurgical, thoracic surgical or medical ICU patients. They can also be divided into adult and pediatric/neonatal ICUs (6).

The multidisciplinary health professionals working in the ICUs are specially educated and trained to work with critically ill patients providing organ support using sophisticated monitoring equipment (1, 2, 6). Worldwide, approximately five million patients are yearly admitted to ICUs (7), included approximately 15.000 to Norwegian ICUs (2). Number of ICU beds and volume of admissions vary around the world (8, 9). ICU bed capacity have been reported to be highest in Germany, Austria and United Sates (33.9, 28.9 and 25.8 per 100 000 inhabitants, respectively), while Norway is one off the countries with lower capacity (8.5 per 100 000) (10). The ICUs at Oslo University Hospital have between 9-16 ICU beds, with different daily capacities depending on several different circumstances.

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7.2 ICU treatment

There is a magnitude of sophisticated equipment in the ICU. Mechanical ventilators to assist breathing through endotracheal or tracheostomy tubes are commonly used since respiratory failure is a frequent problem (1). In Norway, approximately 60% of the ICU patients are treated with mechanical ventilation (2). In addition, different monitors for cardiac and respiratory monitoring and more general monitoring of other body functions (like temperature), as well as several infusions from intra- or central venous lines, different feeding tubes, drains/catheters and suction and syringe pumps are frequently in use. Complex drugs to treat or prevent different conditions are required, and to induce or maintain medical coma in patients treated with mechanical ventilation different sedatives and analgesics are needed. Sedation and analgesics predispose for partial or total loss of memory and reduce stress, pain, agitation-related harm and anxiety, and increase comfort (11, 12). However, the downside of deep sedation is increased ICU length of stay (LOS) and more delirium, which are associated with increased ICU- and hospital mortality (13). Over the years, lighter level of sedation has been recommended where possible, reducing length of mechanical ventilation and LOS, as well as decreased incidence of delirium and cognitive dysfunction (11, 12). In addition, use of sedatives like benzodiazepines, duration of sedation and treatment with mechanical ventilation in the ICU are all also risk factors for development of posttraumatic stress (PTS) symptoms (14). Assessment-driven protocol-based approach using validated tools for pain and sedation, where pain is treated first (analgosedation), is recommended (11). In the different ICUs at Oslo University Hospital (OUH), less use of sedation and daily mobilization have become a high priority the recent years.

7.3 ICU patients

ICU patients are critically ill or injured patients, with manifest, acute and threatening failure in one or several vital organs, particularly lungs, cardiovascular system, and kidneys (1, 7). The patients are normally continuously connected to different monitoring equipment based on their diagnosis and illness severity, and experience total dependence on health care professionals, specialized equipment and ongoing medication through different intravenous lines or feeding tubes (1). Stressful experiences of pain, fear, anxiety, nightmares, hallucinations, and sleep disturbances have previously been reported among ICU patients (15-18). Not being able to speak, ask questions or express feelings due to the endotracheal tubes, heavy sedation or other medical reasons, puts the patient into a very vulnerable situation (19), which easily can progress to stress, panic and frustration (19). On the other hand, to be less sedated, and be more alert and aware of the scope of the illness severity during ICU treatment, might also be stressful and difficult to handle for some patients. Experiences of pain are common for both medical and surgical patients, and can be related to bed rest (20), daily procedures and activities (21, 22), and to the underlying illness, or surgery and/or trauma (23). Insufficient pain management might lead to severe consequences such as psychosis, fatigue, delayed mobilization, inactivity, and agitation (20, 24, 25). All these complications will further negatively influence on the patient´s illness severity, and additional complications may occur and increase morbidity and ICU LOS. Usually, ICU LOS varies between days to weeks, and sometimes months, of course depending on several factors like diagnosis, comorbidity, treatment, injury/illness progression and those factors already mentioned above. ICU LOS is also associated with PTS symptoms after ICU discharge (26, 27), as already mentioned. Patient comorbidity and personal resources prior to ICU admission varies also substantially.

ICU patients treated at the different ICUs at OUH represent a heterogeneous population with both medical and surgical patients with different diagnoses (trauma,

complications to surgery, chronic diseases), and with all kinds of illness severity. This illness severity can be scored by different, frequently used ICU scores such as the Simplified Acute Physiology Score (SAPS II), which calculates severity of illness the first 24 hours of the ICU stay (28). In addition, the Sequential organ failure assessment (SOFA) score is in daily use to measure the severity and course of organ failures during the ICU treatment (29).

7.4 Critical care nurses

In Norway, most nurses working in the ICUs are specially trained critical care nurses (CCNs). They carry out direct hands-on care for injured or critically ill patients at specialised units, and are trained to handle and assess different technical equipment, medical interventions and lifesaving treatment in emergencies (30). In contrast to CCNs in many other countries, the CCNs in Norway are responsible for all bedside care to the ICU patients (6). Thus, they are constantly bedside focusing on the optimal evidence-based care and procedures for the critically ill patients including administration of medication, infusion pumps, mechanical ventilation, continuous renal replacement therapy (if used), among others, as well as mobilization together with the physiotherapist. The CCNs work closely together with the intensive care physician and have daily bedside rounds where the patient's needs and individual treatment are planned through a day-to-day aim of treatment. All CCNs have special knowledge and training in communication with patients and their families in crisis, and the close bedside connection, based on continuity whenever possible, provides a special relation with patients and families (31). Indeed, CCNs must have detailed information, knowledge and understanding about the patient's condition, treatment, and prognosis, and of course also about all procedures and routines in the ICUs. In general, the ICUs nurse-staffing is better compared to other hospital units due to the complexity and severity of the patients,

and the use of advanced medical equipment that are unique for the ICUs. The ICUs at OUH operate with a patient-to-nurse ratio between 1:1.2 and 1:1.6.

7.5 After ICU discharge

When ICU patients are ready for ICU discharge, they are normally transferred to a hospital ward or to a local hospital ICU. In some circumstances they can also be transferred directly to a rehabilitation centre or even home. Noteworthy, patients discharged from ICU to a ward might still be severely ill, but they are no longer dependent on sophisticated ICU equipment or on continuous nursing from a CCN. Some ICU patients with dismal prognosis can also be discharged to palliative care at the ward.

Due to illness severity, with or without different sedation, analgesics or even psychopharmacological drugs or previous delirium, many patients struggle with fragmentary memories or loss of memories from the ICU treatment (18, 32). Recall of unpleasant memories of pain, helplessness, and frightening and delusional experiences from their ICU stay are for many patients a significant burden to deal with after ICU discharge (17, 18, 33, 34). Such ICU memories can be both from real or unreal experiences (5).

Over the years the numbers of ICU survivors increase. At the same time, experiences of long lasting physical, cognitive and mental health disabilities after ICU treatment is frequently present (4, 35, 36), and established with the preferred definition of post-intensive care syndrome (PICS) (4). PICS include mental and physical disabilities such as posttraumatic stress disorder (PTSD), anxiety (37, 38), depression (35), reduced health-related quality of life (39), and chronic pain (24, 40, 41).

7.6 Post-traumatic stress symptoms

After ICU discharge, when patients are recovering after severe illness, several reactions including re-experiencing, avoidance and hyperarousal are normal human's responses to their traumatic experiences from the ICU. These reactions might extinguish over days or weeks after the traumatic event (42). However, if the reactions persist for more than one month, and make significant impact on daily life, occupational, social or other functions, PTSD may be apparent (43). According to The Diagnostic and Statistical Manual of Mental Disorders, the criteria for the diagnosis of PTSD have recently been revised. The current definition of PTSD (for adults) in the 5th Edition (43) includes the following criteria;

- exposure to one or more actual or threatened traumatic injury/death (directly experiencing or witnessing in person).

- followed by symptoms associated with the trauma or threatened traumatic injury/death (e.g., recurrent distressing dreams, dissociative reaction flashbacks, intrusive distressing memories)

- frequent avoidance and attempting to avoid stimuli associated with the trauma (e.g. memories of the place/people associated to the event)

- negative alterations in mood/cognition (e.g. negative emotional state) and increased arousal related to the traumatic event (e.g., guilt, shame).

- marked change in arousal related to the traumatic event (e.g., irritable behaver, problem with concentration, sleep disturbance).

The prevalence on experiences of PTS symptoms has been reported to be between 5-63% in critically ill survivors (14, 37, 38). This large difference in prevalence might partly be explained due to different assessment methods, different times when PTS symptoms were registered (from seven days to eight years after ICU discharge), and different cut-off scores to define clinical relevant PTS symptoms (14, 37, 38). Of note, PTS symptoms and PTSD is also

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present in the general population. Worldwide, PTSD has been reported to be more frequent in in Asia, Africa and Latin-America and lower in Europe (43). The lifetime prevalence of PTSD in Norway was reported to be 2.6% in 2013 (44), compared to 7-8 % in USA (45) and Australia (46).

Reported PTS symptoms after ICU discharge have gained increasing recognition the last years (14). Patients with ongoing PTS symptoms after ICU discharge are in severe risk for developing PTSD. PTSD is a debilitating illness, and the persistence of symptoms might increase the risk for other mental health problems such as depression (47), thereby having substantial negative effects on health-related quality of life (HRQOL) (37). In addition, it will also affect close relatives and be costly for the society (42). Thus, early screening to identify patients with clinical relevant PTS symptoms after ICU discharge have been recommended to early identify patients in needs of interventions to prevent development of PTSD (48).

PTSD symptoms and PTS symptoms are synonyms and have both previously been used in the literature to describe symptoms of PTSD in patients discharged from ICU. In this thesis, the symptoms will generally be addressed as PTS symptoms, as the patients were not diagnosed for PTSD and the symptoms were measured within the first month after ICU discharge.

7.6.1 Measurement of posttraumatic stress symptoms after ICU discharge

Both validated self-reported questionnaires and semi structured psychiatric interviews have been used to measure the prevalence of PTS symptoms after ICU discharge (14, 37, 38). The most used self-reported questionnaires are Impact of Event Scale (IES), Impact of Event Scale-revised (IES-R), and Posttraumatic Stress Scale 10 (PTSS-10). However, validated self-reported questionnaires used early after ICU discharge cannot conclusively diagnose PTSD, even though the questionnaires have an acceptable sensitivity and specificity detecting PTS

symptoms in long-term survivors of ICU patients (49, 50). PTSS-10 have been used in the present studies and will be further presented in the Methods section.

7.6.2 Factors associated with PTS symptoms after ICU discharge

The most consistent reported associations with PTS symptoms after ICU discharge are shown to be early memories of frightening experiences such as hallucinations, nightmares and/or paranoid delusions from the ICU stay (14, 17, 27, 34, 37, 51-54). In addition, both pre- (37, 55-58) and post-ICU psychopathology (anxiety, depressive disorder, substance abuse) (17, 54, 59, 60), use of benzodiazepines (14, 37), and duration of sedation (14) have been associated with PTS symptoms. No associations between PTS symptoms and diagnoses prior to ICU admission (26, 49, 53-55, 57) or ICU delirium (61, 62) have been displayed in previous studies. However, only a few studies have investigated associations between ICU delirium and PTS symptoms.

There are several factors reported associated with PTS symptoms after ICU discharge. However, there are no clear association between gender or age and PTS symptoms (14, 37), and associations with ICU LOS (26, 27), severity of illness (63) and use and duration of mechanical ventilation (26, 49) have only been found in a few studies. Unfortunately, some of these studies had small samples (14, 37), thereby reducing validity. In addition, prior to 2013 (when the studies presented in this thesis were initially planned), we were lacking high quality studies of possible associations between PTS symptoms and other factors such as pain and coping in a large mixed ICU sample.

7.6.3 Methods for preventing PTS symptoms

Previously, several different methods have been used in attempts to prevent PTS symptoms in different patient groups. One of the most used methods is *trauma focused*

Cognitive Behavioural Therapy (CBT) including a combination of psycho-educative technique, exposure therapy, cognitive restructuring, coping with anxiety, restrictive thoughts, avoidant and dysfunctional behaviour (64, 65). In a Cochrane Database Systematic Review from 2013 this method was shown to be effective in reducing PTS symptoms after three months in a general adult population with PTS symptoms (66). In patients with mild traumatic brain injury, it reduced PTS symptoms already after two weeks in two other studies (67, 68). Another example is the *narrative method*, based on helping the patients to process their traumatic experiences (69). Through construction of a narrative from the ICU stay, fragmentary memories from the ICU can be integrated in their own life history (70). Due to this, ICU diaries have been used to help patients construct an illness narrative after their critical illness (70, 71). Further, previous qualitative follow-up studies have reported that *receiving information about what happened during the ICU stay*, and the opportunity to talk face-to face about *experiences and memories from the ICU*, are also important for the patients (71-76). Finally, a combination of cognitive and narrative methods seems useful for coping with traumatic experiences (77) and was already in 2006 recommended as a method to reduce development of PTSD (78). Unfortunately, we are still lacking high quality studies investigating these method-combinations in patients after ICU discharge.

Nurse led follow-up consultations

Prior to 2013, only two studies had investigated the effects of nurse led follow-up consultations (NLCs) with intention to promote recovery and reduce PTS symptoms in adult general ICU patients after ICU discharge (79, 80). None of these studies found any effect of the NLCs. The first study was a randomized controlled trial (RCT) from the UK, randomizing 286 patients to two NLCs three and nine months after ICU discharge vs controls. The NLCs were based on a structured case review, where the patient's ICU experiences were discussed.

Assessments of requirement for specialist medical referral, and screening for psychological morbidity related to admission to the ICU, were used. PTS symptoms were measured at six and 12 months after ICU discharge using Davidson Trauma Score (DTS) (79). The other study, a Swedish before-and-after observational study including 259 adult patients, included a nurse-visit on the ward within a week after ICU discharge, followed by an interdisciplinary follow-up consultation (nurse and a physician-led) at three, six and twelve months after ICU discharge. These consultations included re-stating ICU care and treatment as well as identifying and discussing nightmares and delusional memories. PTS symptoms were measured after 14 months with IES (80). However, in both studies the first NLC was performed after three months (79, 80), which is a major limitation since many patients already had developed PTSD.

Identification of the right patients

Indeed, more and better studies to early identify the patients in need for follow-up after ICU treatment are recommended (79, 80). In addition, early screening to identify patients in need for follow-up has been shown to be effective when investigating interventions with aims to reduce psychological distress after traumatic events (81, 82). Obviously, more knowledge about screening of PTS symptoms, effective methods, and the optimal timing of interventions is warranted (79, 80, 83).

In summary, based on the evidence available prior to the present studies were planned, clinical follow-up after ICU discharge varied in structure, content and outcome measured (84). Scandinavian countries and the UK offered various individual follow-up consultations in outpatient clinics and rehabilitation programs, either nurse-led or multidisciplinary (85, 86). Programs with clear goals and programme assessment, with active involvement from patients and families were recommended in Scandinavia (85). However, no national or international

guidelines or standard protocols for follow-up clinics focusing on PTS symptoms were

established (84-86).

7.7 Sense of coherence

7.7.1 The theory of salutogenesis

Since ICU patients are exposed to stress, this alone carries a high risk for PTS

symptoms after ICU discharge. Aron Antonovsky (1923-1994) developed the theory of

salutogenesis in 1979 (87), focusing on factors that can maintain and develop positive health

outcomes under difficult circumstances. This is a slightly different focus than traditional

medical science, were pathogenesis is important in order to understand the development and

causes for diseases (88).

7.7.2 Sense of coherence

The key concept in the theory of salutogenesis is SOC, explaining peoples' ability to

endure stressful life events and still stay healthy (89). The coherence between the individual,

the group and the environment affects the development of SOC (90). In patients with a strong

SOC, aspects of behavioural, cognitive and emotional resistance are integrated, which can

protect an individual from negative effects of adversity and stress (91). In addition, low SOC

seems to reflect low coping ability to stress (92). SOC has three core components;

- comprehensibility (SOC C, make sense of adversity). SOC C represents to what extent

  the person perceives stimuli and information in life to be clear, structured and coherent

  and make cognitive sense (90).

- manageability (SOC MA, resources to meet the challenges). SOC MA represents the

  person's trust in own resources to manage and control the demands in life events (90).

- meaningfulness (SOC ME, challenges worth engagement). SOC ME represents the motivation element and include the ability to make sense of life events emotionally and cognitively (90).

Antonovsky developed two questionnaires (SOC-29 and SOC-13) including these three dimensions (89, 90). Higher scores indicate stronger SOC, and a strong SOC will help to perceive a situation as understandable, manageable, and meaningful. SOC has been shown to be relatively stable by the end of young adulthood (93). However, it can be affected negatively or positively by major life events, like critical illness (90). SOC-13 is used in the present study and will be further explained in the Methods section.

7.7.3 Factors associated with SOC

Previous research has described low SOC (reflecting low coping-ability) to be significantly associated with PTS symptoms in trauma patients and after an accidental injury (92, 94-96). However, more knowledge about SOC and possible associations to PTS symptoms in former ICU patients might be important in the development of interventions for patients who are struggling with PTS symptoms. Further, strong SOC is positively associated with HRQOL in patients after ICU discharge (97), in women with systematic lupus erythematosus (98), as well as in the general Finnish population (99). In the general population, strong SOC is reported to be associated with good mental health (100), stronger subjective state of health (99), reduction in mortality, cardiovascular diseases (101), and cancer (101, 102), and reported to be stable over time in adults (93). In acute trauma patients, factors like higher prevalence of hazardous alcohol consumption, illicit drug abuse, smoking and lower values on socioeconomic variables have previously been associated with lower SOC (103). More knowledge about variables possibly associated with SOC in former ICU patients might lead to a wider understanding of these patients' coping skills.

7.7.4 Follow–up with intention to increase SOC

Even though previous studies have found associations between higher SOC and lower level of PTS symptoms, (92, 94-96) no previous studies had evaluated the effect of NLCs to improve SOC in discharged ICU patients. In a previous RCT, investigating patients suffering from mental health problems, significantly higher SOC and SOC-MA were present in the intervention group compared to controls one week after group-therapy based on the salutogenic treatment principles (104). According to a previous qualitative study in patients discharged from ICU (71), sense of disorientation, lack of temporal coherent, and lack of causal coherence was a challenge for the patients after ICU discharge. Focus on constructing a coherent story about what happened during the ICU stay was important for the patients to understand their critical illness and transfer it into a meaningful and also beneficial event (71). Thus, to construct an illness narrative into a coherent story of the ICU treatment might increase SOC and further lead to endure future stressful life events.

7.8 Acute and chronic pain

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (105). Pain experience is subjective, influenced by psychological, biological, and social factors that to varying degrees might lead to negative effects on psychological, social, and functional well-being. It is important to understand that pain is not the same phenomena as nociception and might be present without activity in sensory neurons (105). Everyone is learning about pain through their life experiences, and same pain stimuli can be described differently between two persons (105). However, individual-reported pain experience should be respected, and those who are not able

to verbally articulate their pain (e.g., due to mechanical ventilators, heavy sedation, critical illness) may still be in need for pain-relieving treatment (106).

Pain could be divided into acute or chronic pain. Acute pain is defined as pain that can arise from cutaneous (e.g., from skin), visceral structures (e.g., from organs in abdomen or chest) or be deep somatic (e.g., from bone, muscle) (24). Definition of chronic pain is pain associated with emotional distress, daily life activities, and or social participation, and exceeding an average healing period of three months (107, 108). Chronic pain has been estimated to be present in approximately 20% of the general population worldwide (108), whereas a Norwegian study from 2012 reported a higher number of 31% in pain lasting more than six months (109). Chronic pain is certainly a severe and common health problem (108-110) with large socio-economic costs (111).

7.8.1 Documentation of pain

Valid and reliable tools and assessment methods are important to identify and measure pain. The patient's self-reported pain is the gold standard of assessing pain, and one method for measuring pain intensity is the Numeric Rating Scale (NRS) from 0-10, were 0 is no pain and 10 refer to worst pain imagined. NRS is valid and feasible and can be administrated verbally or visually (12). A criterion for using the NRS oral scale is that the patients are cognitive and verbally able to express pain on a scale (112). The self-reported questionnaire Brief Pain Inventory short form (BPI-SF), measures pain intensity, pain interference with daily life, pain location and pain treatment and relief, where pain rates on the NRS scale from 0-10 (113, 114). BPI have previously been used to measure pain in different patient groups including ICU survivors (115, 116). Detection of physiological symptoms, and behavior related to pain, is important to be aware of in patients not being able to express pain verbally

(11, 12). The BPI-SF was used in the present studies and will be further presented in the Methods section.

7.8.2 Occurrence of acute and chronic pain after ICU treatment

Several previous studies have investigated pain in seriously injured or critically ill patients during the ICU stay, and the reported pain might be related to diagnosis, as well as to therapeutic and diagnostic procedures (20, 22). Moderate to severe acute pain have been reported in between 40-60% of patients treated at medical and surgical hospital wards, however, it is unclear whether these patients have been treated in an ICU prior to the ward (117, 118). A previous study with only 33 ICU patients reported moderate to severe worst pain intensity within two weeks after ICU discharge (119). We are certainly lacking studies investigating acute pain in a large sample of patients at the ward early after ICU discharge. Obviously, transfer from ICUs to hospital wards results in less pain monitoring due to lower nurse-patient ratios and therefore less continuity in preventing, detecting, and treating pain. Moreover, if acute pain persists with reduced focus due to a busy ward, these patients might be at risk for developing chronic pain (120). Two previous studies have reported chronic pain to be present in 44-49% of medical and surgical patients six months after ICU discharge (40, 121). In addition, 36% among trauma patients 24 months after ICU discharge (122), 44% in stroke patients in rehabilitation centres (123), and 10-50% in post-operative patients in the period following acute surgery had all chronic pain (41). BPI-SF were used to measure pain in three of these studies (40, 122, 123), and Pain Self Efficacy Questionnaire (PSEQ) in one study (121).

Only one previous study has reported about pain sites in former ICU patients. By using BPI-SF, they reported shoulder as the most common site in 22% of the patients at six months after ICU treatment (40). Of notice, chronic shoulder pain has been reported in 12 to

15% in the Dutch general population (124) and in the UK (125). Indeed, we are lacking good quality longitudinal studies investigating pain interference with daily life and pain intensity using BPI-SF in larger samples of recently discharged general ICU patients.

7.8.3 Factors associated with pain after ICU treatment

Few previous studies have investigated factors associated with persistent pain in ICU survivors. Reported factors have been sepsis, increasing age (40), longer treatment with mechanical ventilation, and longer ICU LOS (121). Some of these studies are rather small, and samples vary between 99-323 patients. An association between lower SOC and acute pain was found in patients after laparoscopic cholecystectomy (126). Other studies investigating chronic post-operative pain have reported pre-operative anxiety (127), intensity or extent of acute postoperative pain, pain prior to surgery (128), genetic factors, neuropathic pain, ongoing inflammation, lack of perceived social and solicitous support and response (41), and coronary artery bypass surgery (129) as possible risk factors of persistent postoperative pain.

There is a lack of studies investigating patients' ability to cope with stress and pain among discharged ICU patients. More knowledge about ICU patients pain experiences and factors associated with pain shortly after ICU discharge at the hospital ward, and during the following year, can be important to learn more and hopefully prevent chronic pain in ICU survivors.

8 AIMS AND RESEARCH QUESTIONS

Paper I

To examine the occurrence of PTS symptoms in general ICU patients early after ICU discharge and to assess possible associations between PTS symptoms and SOC, ICU memory, pain, and demographic and clinical characteristics.

Paper II

To investigate the effect of NLCs on reducing PTS symptoms and increasing SOC in discharged ICU patients with clinically relevant PTS symptoms and to identify variables associated with symptoms 12 months later.

Paper III

To describe pain intensity, interference with function and location in patients up to one year after ICU discharge. To identify demographic and clinical variables and associations with worst pain intensity and interference.

9 METHODS

9.1 Study design and setting

Paper II, the main study, is a pragmatic non-blinded RCT (clinicaltrails.gov identification NCT02077244). Papers I and III are predefined sub-studies from the main study. These are therefore descriptive and observational studies with cross sectional (paper I) or longitudinal (paper III) design, based on the same patients eligible for the RCT. Thus, in the following Methods section, the main methodology for the three different papers is mainly presented together. Table 1 gives a detailed and structured overview over the three papers.

Table 1. Thesis overview

	Paper I	Paper II	Paper III
Paper title	Post-traumatic stress symptoms and sense of coherence in proximity to intensive care unit discharge	Effect of nurse-led consultations on post-traumatic stress and sense of coherence in discharged ICU patients with clinically relevant post-traumatic stress symptoms - a randomized controlled trial	Occurrence and characteristics of pain after ICU discharge: A longitudinal study
Objectives	To examine the occurrence of PTS symptoms in general ICU patients early after ICU discharge and to assess possible associations between PTS symptoms and SOC, ICU memory, pain, and demographic and clinical characteristics.	To investigate the effect of nurse-led consultations on reducing PTS symptoms and increasing SOC in discharged ICU patients with clinically relevant PTS symptoms, and to identify variables associated with symptoms 12 months later.	To describe worst pain intensity, interference with function and location in patients up to 12 months after ICU discharge. To identify demographic and clinical variables and their association with worst pain intensity and pain interference.
Study design	Prospective cross-sectional study	A pragmatic non-blinded RCT	Longitudinal descriptive secondary study
Patient samples	All included patients eligible for the RCT (n=523)	Patients with PTSS-10-I-B≥25 (n=224)	All included patients eligible for the RCT (n=523)
Data collection	Self-reported questionnaires (PTSS-10-I, SOC-13, BPI-SF), patient records, and the local intensive care registry.		
Time points for data collection/ questionnaires	Baseline	Baseline, 3, 6 and 12 months	Baseline, 3, 6 and 12 months
Intervention	Standard care	Standard care and up to three individually nurse led consultations within two months after ICU discharge	Some with standard care and some with up to three individually nurse led consultations within two months after ICU discharge
Statistical analysis	Descriptive statistics. Multivariate linear regression analysis	Descriptive statistics. Linear mixed model analysis for repeated measures with unstructured correlation matrix. Multivariate linear regression analysis.	Descriptive statistics. Multivariate linear mixed model analysis for repeated measures

Abbreviations: ICU; intensive care unit, PTS symptoms; Post-traumatic stress symptoms, SOC; sense of coherence, PTSS-10-I; Post Traumatic Stress Scale-10 Intensive Part B, SOC-13; Sense of coherence-13, RCT; randomized controlled trial, BPI-SF; Brief Pain Inventory Short Form.

All patients were continuously included between March 2014 and December 2016 from five medical and surgical ICUs at two locations at OUH. OUH Rikshospitalet (OUHR), a national hospital for transplant surgery and a regional hospital for different patient groups, and OUH Ullevål (OUHU), a trauma referral center for Eastern and Southern Norway, a regional hospital for different patient groups in the same area and a local hospital for parts of Oslo. The five ICUs at OUH have between nine and 16 beds, as previously explained.

In the following chapters, I will explain the methodology for the RCT (paper II) in more detail. As the main aim was to evaluate the effect of NLCs on PTS symptoms the following year after ICU discharge, all patients were aimed to be screened for PTS symptoms at the hospital ward within a week after ICU discharge to be able to identify the right patients for the intervention. The Post Traumatic Stress Scale-10- Intensive part B (PTSS-10-I-B) was used to identify patients with clinically relevant symptoms (see below).

9.2 The Post Traumatic Stress Scale

The PTSS-10 was developed in 1989 by Weisaeth to assess the level of PTS symptoms, and consist of 10 items (50, 130). PTSS-10 was revised to Post-traumatic Stress Scale-10-Intensive (PTSS-10-1) in 1999 by Stoll et al. who added four questions about traumatic memories from the ICU. PTSS-10-I-B is a questionnaire including the 10 original items using a scale from 1 to 7 (total score 10-70) (50, 130). PTSS-10-I-A consists of these four "yes/no" items about memories from the ICU (severe nightmares/hallucinations, feelings of anxiety or panic, pain, troubles to breath/feelings of suffocation)(50).

The sum score from PTSS-10-1-A is from four to eight (no=1, yes=2) and it was translated into Norwegian using an accepted forward-backward translation procedure (131). PTSS-10-I-B has answering options from 1 to 7, where 1 is "never", 3 "sometimes", 5

"moderate, half of the days" and 7 "always", with a total score range from 10 to70 (130).

Higher scores indicate more PTS symptoms. PTSS-10- I-B has been used in different patient

populations showing validity (50, 130, 132, 133) and high specificity and sensitivity in

predicting PTSD (50, 130). Previous studies investigating PTS symptoms in ICU survivors

have defined clinically relevant PTS symptoms with a cut-off score of PTSS-10-I-B varying

from 20 to 35 (62, 134-136). Cronbach's alpha measured at baseline in the current study was

0.88 (PTSS-10-I-B).

Fig.1 Screening and randomization
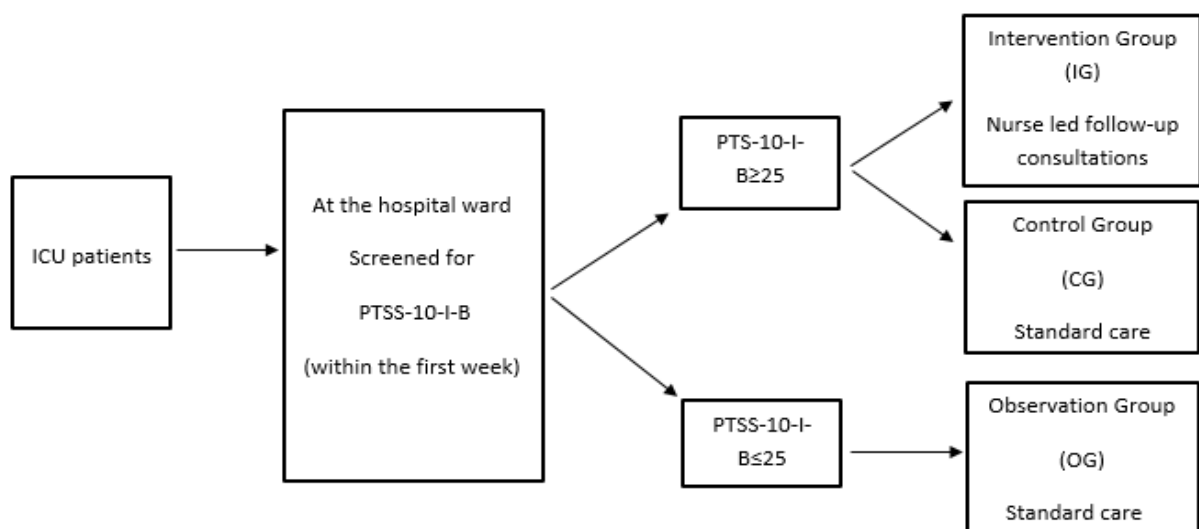
Abbreviations: ICU; intensive care unit, PTSS-10-I-B; Posttraumatic Stress Scale-10- Intensive part B.

9.3 Sample size calculation

A power calculation for the primary outcome in the RCT based on the PTSS-10-I-B

score (paper II), was calculated based on findings from a similar study using the same

questionnaire (134). Noteworthy, their results lacked report of the standard deviation (SD)

which made it a bit challenging. Our first sample size calculation was performed with a

calculated SD of 30 to reveal a statistically significant difference between IG and CG of 10 in PTSS-10-I-B score at 12 months. With this calculation, allowing 20% dropouts, 247 patients with a score like or above cut-off were needed. However, due to uncertainty with the SD estimate, a new statistician was allocated to the project during the recruitment period and a recalculation with a SD of 15 reduced the sample size (alpha 5% and beta 20%) to 134 patients. This intervention led to termination of further inclusions with the already included 224 patients. Of note, the first statistician later confirmed the findings from the second calculation.

9.4 Pilot test

In 2013 a pilot test in 16 discharged ICU patients was performed to evaluate the inclusion procedure, screening process and to get experience with the NLCs. The Short Orientation-Memory-Concentration Test (SOMCT) (137) was used prior to inclusion to avoid inclusion of patients with seriously reduced cognitive function. In the pilot study, we used a PTSS-10-I-B cut-off score of ≥ 35 to identify patients with high levels of PTS symptoms. Thus, patients with a score ≥ 35 were offered three individual NLCs, within two months after ICU discharge, based on a semi-structured guide. Thereafter, we collected feedback from the patients, and based on these, in addition to our own experiences, a few adjustments in the study design were undertaken. First, SOMCT for assessment of cognitive function were omitted to reduce the potential patient burden. Instead, we collected information about the patients' cognitive function and presence of delirium or other important complications from the ICU stay from primary nurses prior to inclusion. Second, the cut off value for clinically significant PTS symptoms was reduced to PTSS-10-1-B ≥ 25, to also include patients with moderate level of PTS symptoms, in agreement with another relevant study (136). Third, the semi-structured guide for the NLCs was slightly changed. We needed to emphasize that the

intention of the NLC was directed towards the patients' experiences from their current ICU stay to avoid them from focusing on past experiences and problems. Finally, we realized that all technical ICU equipment used needed to be better explained.

9.5 Study procedures and samples

After screening at the hospital ward as early as possible after ICU discharge, we ended up with two different main groups depending on their PTSS-10-1-B score. Those with a score ≥ 25 were included in the RCT and randomized into IG and CG, stratified by the two locations OUHU and OUHR (paper II). If the score was < 25, the patients could not be included in the RCT but kept in an observation group (OG) (Figure 1, Table 1). All patients from IG, CG and OG were included in the descriptive and observational sub-studies in paper I and III (Figure 1, table 1). Inclusion criteria were adult ICU patients, treated for more than 24 hours in the ICU, and being able to read and understand Norwegian. Exclusion criteria were severe psychiatric disorder, severe brain injury, being moderately or severely cognitively impaired, being admitted to ICU due to self-inflicted injuries (suicidal attempts) or poor Norwegian language skills. Data collections were performed at baseline (papers I, II, III), and 3, 6 and 12 months after ICU discharge (papers II and III) (Table 1).

9.5.1 Paper II

All patients with a PTSS-10-I- B score ≥ 25 were randomly assigned to an intervention (IG) or a control group (CG) in a 1:1 ratio using computer-generated block randomization provided by the Norwegian University of Science and Technology (NTNU) (Web CRF NTNU). Inclusion of patients were to be performed within the first week after ICU discharge by CNNs who were familiar with the ICUs and the patient group. They gave all patients the same information prior to inclusion and screening, using an inclusion guide. If a patient was

not able to read or write when answering the baseline questionnaires, the CCN helped with

completion of the questionnaires without affecting the patients´ answers (138). For follow up,

all included patients received questionnaires again at three, six and twelve months by mail,

which should be returned in a pre-paid envelope. A reminder was sent by mail in the presence

of no answer. Two telephone numbers from the study group were included in all information

letters following the questionnaires at baseline, three, six and twelve months to enable the

patients to call about any questions concerning the questionnaires and/or the trial. In the

presence of any health-related questions, patients were encouraged to contact their general

practitioner. In special cases, relevant questions related to ICU treatment could also be

discussed with the intensivist from the project group.

9.5.2 Nurse led follow-up consultations vs standard care

All patients in IG were offered standard care plus three individual semi-structured

NLCs (45-60 minutes), with the few adjustments based on the pilot test. The first consultation

was a face-to-face meeting between the CCN and the patient at the hospital ward within the

first week after ICU discharge. Later, the second and third NLCs were obtained after one and

two months either at the hospital (face-to-face) or by phone depending on the patient´s

situation and preference. The CCNs prepared for the first NLC by reading the patient's

medical record from the ICU stay, as well as information from the patient's self-reported

symptom profiles in PTSS-10-I A and B.

A semi-structured guide for the three NLCs were developed by the study group,

including a psychiatrist and a psychotraumatologist. The semi-structured guide was inspired

by previous intervention guides for consultations with physically injured patients (66, 67) and

for emergency reception patients (139). Elements from cognitive behavior therapy focusing

on the patient's individual challenges with restrictive thoughts, cognitive restructuring,

avoidant, and dysfunctional behavior were used (66, 140). These elements were combined with Antonovsky's theory about salutogenesis with the core concept sense of coherence (90), and a narrative method (69, 70). The CCNs initiated the NLC by encouraging the patient to tell a narrative history of what they remembered from their hospital admission, ICU stay, treatment, and ICU discharge, in addition to possible frightening memories, hallucinations, nightmares and traumatic experiences. A voluntary visit to the ICU where the patient was treated was offered, and individually adjusted for each patient. Information about the ICU stay and treatment were given to the patients, also focusing on clarifications on possible misunderstandings from their ICU treatment. This was done as an exposure to what might have been experienced as a frightening place to process traumatic memories, and as an aid to construct narratives about what happened during their ICU stay (141).

Patients in CG and OG did only receive standard care. Standard care included early mobilization and physical therapy. In some cases, the patients were offered physical therapy or physical rehabilitation, if required, after hospital discharge. Mentally disturbed patients at the ICU or at the hospital ward were offered psychiatric consultations from a Liaison team (psychiatric nurse, psychologist, or a psychiatrist). Of note, physical restraints are generally not used at OUH.

Finally, after one year, when all data was collected and the trial completed, all patients in CG were offered one NLC, to clarify questions, uncertainties, or different needs. However, only eight (7%) of these CG patients received it.

9.5.3 Training of critical care nurses for the intervention

Two CCNs from each ICU were selected for the NLCs. These CCNs were recommended from the ICU chair, had good communication skills and broad ICU experience. They received a specialized and focused four-hour training program from the study group,

focusing on cognitive methods, crisis reactions, and about how to construct a coherent story from the ICU stay. The training included intervention performance and case simulation in communication with a patient with PTS symptoms. In addition, local meetings with the included CCNs were organized every third month during the inclusion period to share experiences and for continuous guidance.

9.5.4 Paper I

With the aim to examine occurrence of PTS symptoms in ICU patients early after ICU discharge and to assess associations between PTS symptoms and SOC, ICU memory, pain and demographic and clinical characteristics, PTS symptoms and SOC were measured at the ward within the first week after ICU discharge using PTSS-10-1-B and SOC-13. Only these baseline values were further analyzed, and no interventions other than standard care had been undertaken in the included patients.

9.5.5 Paper III

With the aim to describe pain intensity, interference with function and location in patients up to one year after ICU discharge, all patients screened early after ICU discharge were included in the study. Pain intensity, -interference, and -location were measured using the BPI-SF at the hospital ward (baseline) and 3, 6, and 12 months after ICU discharge, also to identify demographic and clinical variables and associations with worst pain intensity and interference.

9.6 Data Collection

Demographic and clinical data were collected from the self-reported questionnaires, patient records, and the local intensive care registry. Data from the questionnaires were

scanned into Statistical Package for Social Sciences (SPSS) data files. All clinical data from each patient were documented in a case report form (CRF) in File maker and exported into a SPSS file. In addition to the already described PTSS-10-1 part A and B, several other scoring tools were used, which are described below.

9.6.1 Local intensive care registry

The New Simplified Acute Physiology Score II (SAPS II) was used to measure illness severity in the first 24 h in the ICU with a scale from 0 to 163. The SAPS II score is calculated based on 17 variables, including 12 physiological variables such as oxygenation and vital signs, some severe underlying diseases (acquired immune deficiency syndrome (AIDS)), hematologic malignancy and metastatic cancer), age and type of admittance diagnose. Higher score indicate higher illness severity and higher risk of hospital mortality (28). The highest SAPS score was chosen in cases were the patient had more ICU admissions during the same hospital stay.

9.6.2 Patient records

The American Society of Anesthesiologists Physical Status Classification (ASA) score is a measure of a patient's physical co-morbidities prior to anaesthetic procedures. In the present studies, the ASA score was used to measure the patient's physical health status and comorbidity prior to hospital admission, calculated based on data from the patient's medical record. The categories are graded from Class 1 (a normal healthy patient) to 5 (moribund patient who is not expected to survive for 24 h, with or without surgery). The calculated ASA score did not consider age, since age is only included in the Norwegian ASA calculation and not in the internationally used ASA calculation (142, 143).

All types of analgesics, sedatives and psychotropic drugs from the ICU stay were collected, and categorized into benzodiazepines, opioids, dexmedetomidine, clonidine, antipsychotics, and/or regional analgesics. ICU LOS, total hospital stays, and medical diagnoses (i.e. the hospital admission cause) were obtained from the medical record. The study group first created a variable with 11 diagnostic groups describing cause of hospital admission: trauma (not violence trauma), violence trauma, acute surgery, elective surgery, organ transplantation, hematological (leukemia), cancer, sepsis, neurological disease, cardiac arrest, and internal medicine. Due to very few patients in some diagnostic groups, we ended up recoding into six final categories: trauma, acute surgery, elective surgery, organ transplantation, cancer, and internal medicine. In cases when several diagnoses were reported, the primary admittance diagnosis was used.

9.6.3 Patient-reported background characteristics

In the questionnaires, the patients had to answer one question about work situation, with eleven answering options, at baseline. This variable was further recoded into five categories: working (full-time and part time), sick leave, disability pension, retired and other (student, military service, homemaker). Answering options for civil status was married/cohabitant, unmarried, widower/widow and divorce. These categories were recoded into a new variable: married/cohabitant "yes/no".

The patients' highest level of education was answered by selecting one of six categories: primary/secondary school ≤10 years, high school 1-2 years, high school three years, university/college up to four years, and university/college more than four years. These six categories were finally recoded into three categories: primary school, high school, and university/college.

9.6.4 Patients-reported questions developed by the study group

Five questions about use of hypnotics, anxiolytics, antidepressants, and analgesics, with or without prescription, prior to hospital admission were developed by the study group. The following answering options were "not at all", "sometimes but not daily", "one tablet daily", "two-three tablets daily", or "four tablets or more daily". These were measured at baseline and recoded into "yes/no".

Five "yes/no" questions about mental health problems prior to admission were based on previous questions describing mental health problems in emergency reception patients (139): "Have you had psychological problems without consulting a physician", "consulted the physician/family doctor because of psychological problems", "been treated by a psychologist/psychiatrist because of psychological problems", "been in contact with a district psychiatric center", or "have been admitted to a mental hospital". These five questions were measured at baseline and recoded into previous psychiatric problems "yes/no".

In addition, we added nine "yes/no" questions about experiences of a traumatic or important events during the year prior to ICU admission; "death in close family", "married or cohabitant", "divorced", "child birth", "seriously residential and economic problems", "new job", "dismissal from work", "retired", or "other important events". These questions were measured at baseline and further recoded into "important event" "yes/no".

9.6.5 Patient-reported measures of alcohol consumption

Alcohol consumption was measured at baseline using a modified version of Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) (144, 145) with three items:

1) How often do you have a drink containing alcohol?

2) How many standard drinks containing alcohol do you have on a typical day?

3) How often do you have six or more drinks on a single occasion?

The range for the sum score is from 0 to 12, where a sum score of ≥3 in females and ≥4 in males indicates hazardous drinking (144). Finally, this sum score was dichotomized into hazardous drinker "yes/no" (145).

9.6.6 Sense of coherence

Sense of Coherence Scale 13 (SOC-13) (25) was used to measure SOC (coping ability) at baseline and 3, 6 and 12 months after ICU discharge. SOC-13 includes 13 items and is developed from the original Orientation to Life Questionnaire with 29 items (SOC-29). The 13 items have scales from 1 to 7 with five different endpoints. Thirteen items are reversed before a sum score for all items is calculated with a total range from 13–91, where higher score indicates stronger SOC (89). SOC-13 includes three components: comprehensibility (SOC-C, five items), manageability (SOC-MA, four items) and meaningfulness (SOC-ME, four items). SOC-13 is translated into Norwegian and has previously shown to be valid in patients with mental health problems (104), after ICU treatment in trauma patients (94) and satisfactory validity and reliability in individuals worldwide (146). Cronbach's alpha measured at baseline was 0.83 (total SOC score).

9.6.7 Pain

BPI short form (SF) was used to measure the patients' self-reported pain at baseline, as well as 3, 6 and 12 months after ICU discharge. The first question is about pain in the preceeding 24 h ("yes/no"), and if "yes" they are asked to indicate pain intensity, whether pain interfere with daily living and function, pain relief, and pain location (113, 114). A numeric rating scale (NRS) from 0 ("no pain") to 10 ("pain as bad as you can imagine") is used to rate worst pain, least pain, average pain during the last 24 hours and current pain. In paper I, worst pain was divided into moderate (4 to 6) and severe (7 to 10) on the NRS scale

(147), and in paper III worst pain was divided into mild (1 to 3), moderate (4 to 5) and severe (6-10) pain (115). Marks on a body map were used to report pain locations. Pain interference includes seven items about how much pain interferes with daily life ("general daily activity", "mood", "walking ability", "normal work", "relations with others", "sleep", "enjoyment of life") and was answered using NRS from 0 (does not interfere) to 10 (completely interferes). These seven items were computed into one mean value reflecting pain interference. The questionnaire has previously been translated into Norwegian and has been shown to have well-established reliability in cancer patients, sensitivity in longitudinal cancer studies (148, 149) and validation in different groups of patients (including ICU survivors) with acute and chronic pain (115, 116, 150).

9.6.8 Memory from the ICU stay

The ICU Memory Tool consists of 14 items, including memories and amnesia from ICU admission, ICU stay, and if the patient had talked to nurse, physician, family, or friend, about their ICU stay ("yes/no") (86, 151). Questions were measured at baseline, and 3, 6 and 12 months after ICU discharge and consist of different memories from the ICU stay, including 21 specific single memories ("yes/no"). These have later been recoded into three different categories; "factual", "delusional memories" and "memories of feelings" (151). The ICU memory tool has previously shown high validity in ICU patients (54).

Table 2. Patient reported outcomes at baseline, 3, 6 and 12 months after ICU discharge

Instrument (self-reported)	Sub scales	Item scales	Total scoring range	Number of items	Paper
PTSS-10-I-B		1-7	10-70	10	I, II, III
SOC-13	Total score	1-7	13-91	13	I, II, III
	Comprehensibility		5-35	5	II, III
	Manageability	1-7	4-28	4	II, III
	Meaningfulness	1-7	4-28	4	II, III
BPI-SF		0-10	0-150	15	I, II, III

Abbreviations: PTSS-10-I-B; Post Traumatic Stress Scale 10 Intensive part B, SOC-13; Sense of coherence scale 13, BPI-SF; Brief Pain Inventory Short Form.

9.7 Data management

All data registered in the CRF were double-checked for errors and subsequently corrected before they were imported into a SPSS file. The SPSS file was checked for correct scanning of the questionnaires by choosing the first, second, third and so on in piles of 10 questionnaires, from all the four measurement time points (10%, baseline, 3, 6 and 12 months). Items not answered were defined as missing, and only available data were used in the statistical analyses.

9.8 Statistics

All statistical analyses were performed using IBM SPSS statistics version 21 in paper I and II, and version 25 in paper III (IBM Corp., Armonk, NY, USA). Data collected

from the questionnaires were reported according to the guideline for each of the

instruments. Descriptive statistics for continuous variables are presented as mean and

SD if normally distributed, and median and range in non-normally distributed data. Table 3

provides an overview over the statistical tests used in papers I – III.

Table 3. Statistical tests used in paper I, II and III

Statistical test	Paper I	Paper II	Paper III
Descriptive statistics for categorical variables Number (n) and percent (%)	X	X	X
Correlation analysis	X	X	X
Univariate Linear regression analysis with Beta, 95% CI and p-value. Associations between dependent and independent variables	X	X	X
Pearson chi-squared test (for dichotomous variables) (n, % and p-value) compared (categorical variables) between IG and CG.		X	
Independent sample t-test (for continuous variables) compared between IG and CG		X	
Multivariate linear regression analysis Beta, 95% CI and p-value	X	X	X
Multivariate linear mixed model analysis for repeated measured. Regression coefficients (B) with 95% CI, estimated marginal means and p-values		X	X

Abbreviations: CI; Confidence Interval, IG; Intervention Group, CG; Control Group.

9.8.1 Papers I and III

In paper I and III, a linear regression analysis was used in three steps and controlled

for gender and age in all steps. In step 1, a univariate analysis was performed, and each

selected independent demographic and clinical variable was investigated for associations with

the dependent outcomes PTS symptoms in paper I, and pain intensity and interference in

paper III. All the covariates in papers I and III were selected based on previous literature and

clinical considerations. In step 2, a multivariate linear regression model was performed, and

all independent variables with $p \leq 0.1$ for each dependent variable in step 1 were divided into

three blocks consisting of background characteristics, ICU-related- and ward-related

variables. In step 3, all included variables with $p \leq 0.1$ from step 2 were included in a multivariate analysis.

In paper I, a multivariate linear regression analysis was used, and in paper III a multivariate linear mixed model analysis for repeated measures was used. The multivariate linear mixed model analysis in paper III was fitted with an unstructured covariance matrix and selected covariates were entered as fixed effects. All the independent variables in paper 1 were correlated < 0.7 using Pearson's correlation coefficient. Significance level was set at $p < 0.05$.

9.8.2 Paper II

The independent sample t test and the Pearson chi-square test were used at baseline to compare clinical and demographic variables in IG and CG to assess their representativeness of data. Gender, age, and variables with statistically significant differences between the two groups at baseline were adjusted for in the final linear mixed model analyses for repeated measures (LMM). Possible differences at baseline between the responders to follow up (patients with baseline data and at least one available follow up measurement) and patients lost for follow up (only baseline data) were examined in the dependent variables PTSS-10-I-B, total SOC, as well as the independent variables like pain, previous psychiatric problems, SAPS II, ASA, and ICU and hospital LOS.

To investigate differences between IG and CG in PTS symptoms, total SOC score and SOC score in the three dimensions at three, six and 12 months, LMM analyses were performed. All subjects with baseline data and at least one available follow-up measurement were included, and the analyses were performed according to the intention-to-treat principle. An unstructured correlation matrix was used in LMM when analyzing for differences in PTSS-10-I-B, total SOC score, and the three SOC dimensions SOC-C, SOC-MA, SOC-ME.

Covariates were entered as fixed effects, and group vs time and group vs gender interactions were modelled. In addition, the LMM analyses were stratified by gender. Results were presented as point estimates of regression coefficient or mean with 95% CI, all tests were two-sided and a p-value < 0.05 was considered statistically significant.

In addition, a multivariate linear regression analysis for the whole sample was performed to identify variables associated with the main outcome PTSS-10-I-B score at 12 months. Factors (40 independent variables) at baseline were investigated for associations with PTSS-10-I-B at 12 months in three steps (like in papers I and III). Gender, age, and variables with $p \leq 0.1$, were included in the multivariate linear regression analysis. Co-linearity between the independent variables were checked in the multiple regression analysis with no correlations < 0.7, and significance level was considered at $p < 0.05$.

9.9 Ethics

The RCT (paper II) and the predefined sub-studies (papers I and III) are registered in Clinicaltrials.gov with identifier NCT02077244, approved by the Regional Committees for Medical and Health Research Ethics (REK) (2012/1715) and the Data Inspectorate at the hospital. The RCT was performed according to ethical standards of WMA Declaration of Helsinki-Ethical Principles of Medical Research (152). All patients included were given a study number used in the data file. The data code list was only available for the main investigators and the study nurses. Prior to inclusion, the patients received information about the study and the right to decline participation or to withdraw from the study (at any time during the year without any reason). This information was given both orally and in written form. The patients' written consents and the patient data were stored separately from the identifiable personal patient information, in a separate closed cupboard and on a secured data platform.

10 RESULTS

10.1 Recruitment

Among 3162 discharged ICU patients treated >24 hours in the five ICUs, 776 were eligible for the study (Figure 2). Since 253 patients (33 %) refused participation, we ended up with 523 patients receiving questionnaires (OG:299, IG:111, CG:113) at baseline (Figure 2). The baseline questionnaires were collected median four days after ICU discharge (range 0-48 days). These 523 patients could be included in paper I, and later also in paper III. In the following year, 381 (73%), 353 (67%), and 327 (63%) responded to the questionnaires at three, six and twelve months, respectively. Among the 523 included patients, 224 (43%) had a PTSS-10-I-B score ≥ 25 and were included in the RCT (paper II). Of these, 111 and 113 were randomized to IG and CG, respectively (Figure 2).

Fig 2. Flow diagram of patient recruitment in paper I, II and III
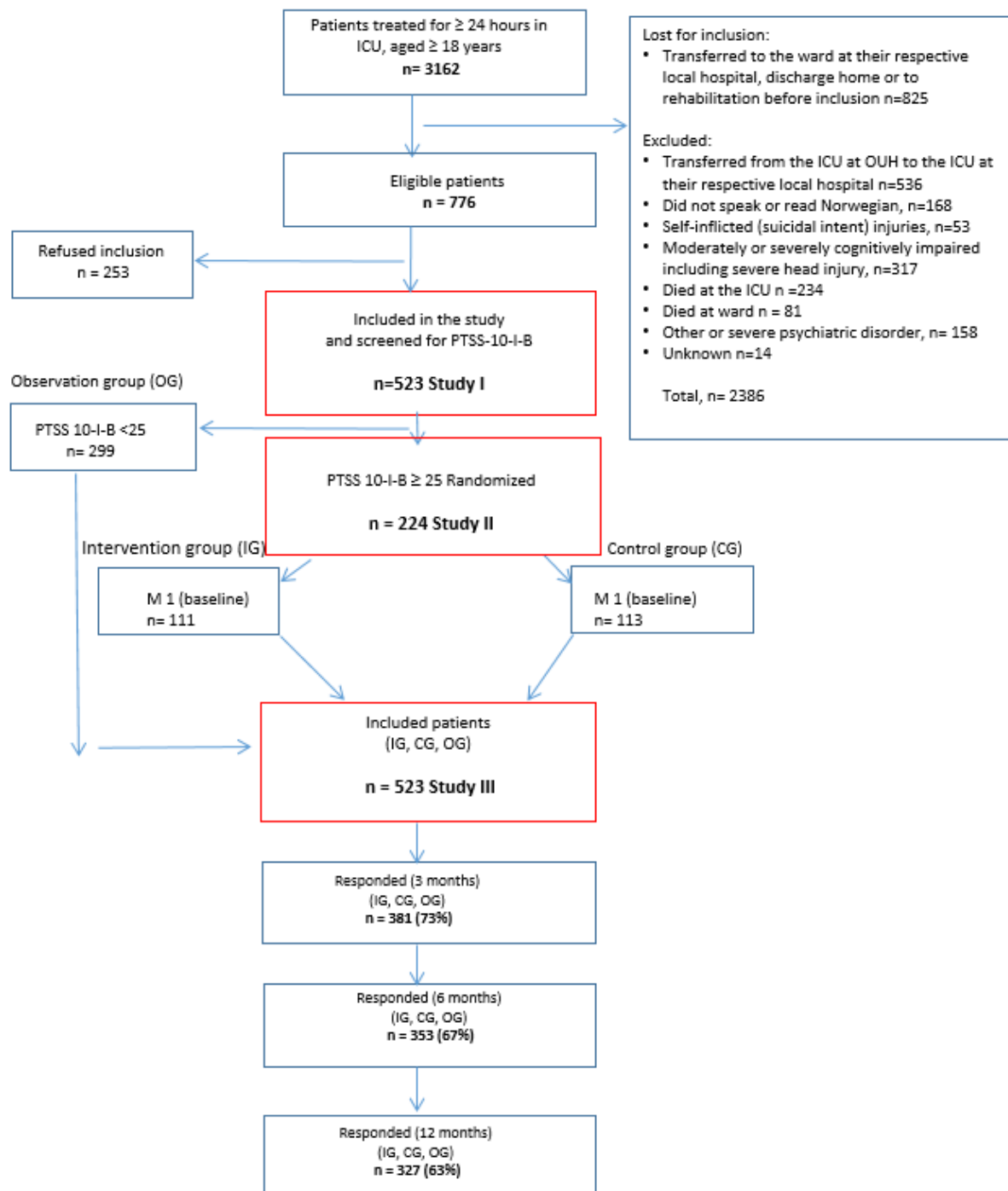
Abbreviations: ICU; Intensive care unit, OUH; Oslo University Hospital, PTSS-10-I; Post-Traumatic Stress Scale 10 Intensive part B, IG; Intervention group, CG; Control group, OG; Observation group.

10.2 Background characteristics of the total sample

Of the 523 included patients, 279 (53%) were male, median age 57 years (range 18–94 years), and 280 (54%) had received mechanical ventilation during their ICU stay (Table 4). Median ICU LOS and total OUH stay were three days (range 1–83) and 20 days (range 3–217 days), respectively, and median ASA- and SAPS II scores 2 (range 1–4) and 24 (range 0–78), respectively. Elective (23%) and acute (20%) surgery were the largest primary admission causes, followed by trauma (18%) and organ transplantations (10%). Previous psychiatric problems and heavy/hazardous drinking were reported in 20% and 40% of all patients, respectively (table 4).

Table 4. Demographic and clinical characteristics of the total sample of discharged ICU patients included in papers I and III, and differences between the two groups among patients randomized to intervention or control in the RCT (paper II)

| | | Paper I and III n=523 | | Paper II n=224 | | | | |
| | | | | IG | | CG | | |
		n	*%*	*n*	*%*	*n*	*%*	P-value
Gender	Male	279	53·3	50	45	55	49	0.503
	Female	244	46·7	62	55	57	51	
Level of education[1]	Primary school	64	12·2	13	12	14	13	
	Secondary school	200	38·2	47	43	46	42	
	University/college	248	48·1	50	46	50	46	0.976
Work situation[1]	Working	229	45·4	39	36	46	42	0.495
	Sick leave	33	6·5	11	10	13	13	
	Disability pension	52	10·3	20	19	15	14	
	Retired	146	29·0	26	24	19	17	
	Other	44	8·7	12	11	17	16	
Civil status[1]	Married/cohabitant	321	61·8	70	63	64	57	0.367
	Caring for children<18y.	107	20·9	24	22	31	28	0.294
Diagnosis	Trauma (reference category)	93	17·8	18	16	18	16	
	Acute surgery	103	19·7	22	20	26	23	0.515
	Elective surgery	118	22·6	28	25	30	27	0.760
	Organ transplant	54	10·3	16	14	11	10	0.305
	Cancer	97	18·5	23	21	15	13	0.154
	Internal medicine	58	11·1	5	5	12	11	0.077
ICU Memory tool: Factual[1]		469	89·7	99	88	103	92	0.369
ICU Memory tool: Feelings[1]		414	79·2	94	84	99	88	0.333
ICU Memory tool: Delusional[1]		234	44·4	59	53	66	59	0.346
Benzodiazepines in ICU		250	47·9					
Opioids in ICU		488	93·3					
Antipsychotics in ICU		60	11·5					
Dexmedetomidine in ICU		105	20·2					
Clonidine in ICU		37	7·1					
Regional analgesic in ICU		286	54·8					
Medication use at home[1]	Hypnotics	154	30·9					
	Anxiolytic/antidepressant	116	22·2					
	Analgesics without prescription	250	55·3					
	Analgesics with prescription	252	54·5					
Mechanical ventilation		280	53·5	62	55	61	55	0.893
Heavy/hazardous drinking[1*]		203	39·5					
Psychiatric problems[1*]		102	19·5					
Important events [1]		173	33·1					

Table 4 (continued)

		Paper I and III n=523		Paper II n=224				
				IG		CG		
		Median	Range	Mean	SD	Mean	SD	P
Total score PTSS-10-I-B				38	10	36	9	0.107
PTSS-10-I-A		5	4-8					
Total score SOC 13		68·9	12·5	61	13	63	12	0.173
Age, years		57	18–94	53	16	50	18	0.090
Worst pain last 24 hr				7	2	6	33	0.031
Length of stay in ICU		3	1–83	7	9	7	9	0.764
Length of stay in OUH		20	3–217	29	26	27	26	0.646
ASA		2	1-4	2.4	0.9	2.2	0.9	0.042
SAPS II		24	0-78	25	12	23	13	0.152

Abbreviations: ICU; intensive care unit, IG; intervention group, CG; control group, OUH; Oslo University Hospital, ASA; American Society of Anesthesiologists Physical Status Classification; SAPS II, New Simplified Acute Physiology Score, PTSS-10-I-B; Post Traumatic Stress Scale-10-Intensive part B, SOC 13; Sense of Coherence 13-Item Scale, Other; student, military service, homemaker, Important event; in the past year before hospital admission, Length of stay; days, y; years.*; before hospital admission, [1]Self-reported.

10.3 Paper I

Among the 523 included patients, 165 (32%) had a PTSS-10-I-B score ≥ 29 and 358 (68%) < 29. The patients had a moderate to strong mean SOC-13 score of 69 (SD 12.5) (not tabulated) and 44% reported delusional memories from their ICU stay (table 4). Presence of pain during the last 24 hours (at the hospital ward) was reported in 65% of the patients, with mean worst pain intensity and pain interference of 5.9 (SD 2.7) and 4.5 (SD 2.7), respectively.

In the multivariate linear regression analysis there was a significant association between higher PTS symptoms and lower SOC-13 score (B= -0.39 (p<0.001) [CI -0.48 to -0.31]), higher pain interference with function (B= 1.22 (p<0.001) [CI 0.87 to 1.57]), more delusional memories from the ICU (B= 5.11 (p<0.001) [CI 3.31 to 6.92]) and lower age (B= -0.06 (p=0.033) [CI -0.11 to -0.01]). Patients admitted to hospital due to trauma had significantly lower PTS symptoms than the other diagnostic groups (B= -2.70 (p=0.024) [CI -5.04 to -0.36]).

10.4. Paper II

There were no major differences in demographics between patients in IG vs CG, except for more patients in IG had "worst pain the last 24 hours" and a higher ASA score (table 4). Mean age of the 224 included patients was 52 ± 17 years, and 53% were females (Table 4). Mean PTSS-10-1-B score at baseline was 38 ± 10 vs 36 ± 9 in IG vs CG, respectively (p=0.107) and mean SOC-13 score was 61 ± 13 vs 63 ± 12 (p=0.173), respectively (Table 4).

In total, 14 (13%), 35 (32%) and 53 (48%) patients completed one, two or three NLCs, respectively. In other words, 80% of the patients in IG received at least two NLCs. Nine patients (8%) did not receive the intervention due to delirium or rejection. Eighteen (16%) patients in IG visited the ICU as a part of the intervention.

There was no significant difference in level of PTS symptoms or in total SOC score or in any of the SOC dimensions between IG and CG at three, six and 12 months after ICU discharge (Table 5 and 6). No significant differences in the mean PTSS 10-1-B score during the year among patients receiving one, two or three NLCs were found.

Of note, PTSS-10-1-B score was reduced (p<0.001) (Table 5 and 6) and SOC-C score increased (p<0.008) in both IG and CG during the follow up year. In addition, the time trajectories for IG and CG were significantly different (p=0.034) for SOC-ME, indicating that the time trajectories for the groups revealed different patterns during the year.

Some gender differences were present between IG and CG. There was a significant difference in the gender-group interaction related to all SOC dimensions (Table 10), and a group vs gender interaction for the PTSS-10-1-B score (p<0.001). However, no differences in total PTSS-10-1-B scores between IG and CG during the year were found in the LMM analysis when stratified by gender, but a significant different time trajectory between males and females was present (Figure 3). Whereas it was quite stable during the year for females in

IG vs CG, (Figure 3), males in IG had a significant higher mean score at baseline vs CG (PTSS-10-I-B 41 [CI 38 to 44] vs 34 [CI 31 to 36]) with a decrease in IG to three months (similar to CG at three months). Thereafter, no significant differences between IG and CG were present, although the patterns over time seemed different (Figure 3). In total 88, CG and 83 IG patients were included in the LMM analysis, and six different variables (PTSS-10-I, SOC-13, SAPS II, ASA, ICU LOS, and worst pain last 24 hours) were checked for differences between the patients included and those lost for follow-up. However, only SOC-13 score was significantly different with lower scores in patients lost for follow-up vs those included in the LMM analysis (mean 58 ± 14 vs 63 ± 12, p=0.015).

The multivariate linear regression analysis, evaluating baseline variables' associations with PTS symptoms at 12 months in the whole patient sample (IG and CG), showed that low total SOC score (B = -0.2 [CI -0.4 to -0.0]), worst pain intensity last 24 hours (B = 1.0 [CI 0.2 to 1.9]), and previous psychiatric problems (B = 6.3 [CI 0.9 to 11.8]) were significantly associated with more PTS symptoms. Delusional ICU memories, on the other hand, were not associated with more PTS symptoms at 12 months.

Table 5. Overall test of fixed effect of nurse led consultations (group) and selected possible predictive factors (independent variables) on PTS symptoms and SOC during 12 months of follow-up

	PTS symptoms	SOC
Covariates	p-value	p-value
Group	0.538	0.471
Gender	0.160	1.000
Prehospital ASA	0.828	0.426
Worst pain last 24 hours	<0.001	0.111
Time	<0.001	0.117
Age	0.030	0.011
Time*group	0.785	0.058

Abbreviations: PTS; Posttraumatic stress, SOC; Sense of coherence, ASA; American Society of Anaesthesiologists Physical Status Classification, Time*group; Interaction between time and group

Table 6. Estimated mean values for PTS symptoms and SOC for each time point*

PTS symptoms		
	Intervention group	Control group
	Mean (95% CI)	Mean (95% CI)
Baseline	39 (37-41)	37 (35-39)
3 months	32 (28-35)	32 (29-35)
6 months	31 (28-34)	30 (27-33)
12 months	31 (28-34)	29 (26-33)
SOC		
	Mean (95% CI)	Mean (95% CI)
Baseline	61 (58-63)	62 (60-65)
3 months	63 (60-66)	61 (58-65)
6 months	62 (59-66)	65 (61-68)
12 months	62 (59-65)	65 (62-68)

Abbreviations: PTS; Posttraumatic stress, SOC; Sense of coherence. CI; Confidence interval (no overlap in CI indicates significant difference)

*: estimated with linear mixed model, adjusted for independent variables

Fig 3. Time trajectory in PTS symptoms score between males and females during 12 months of follow-up
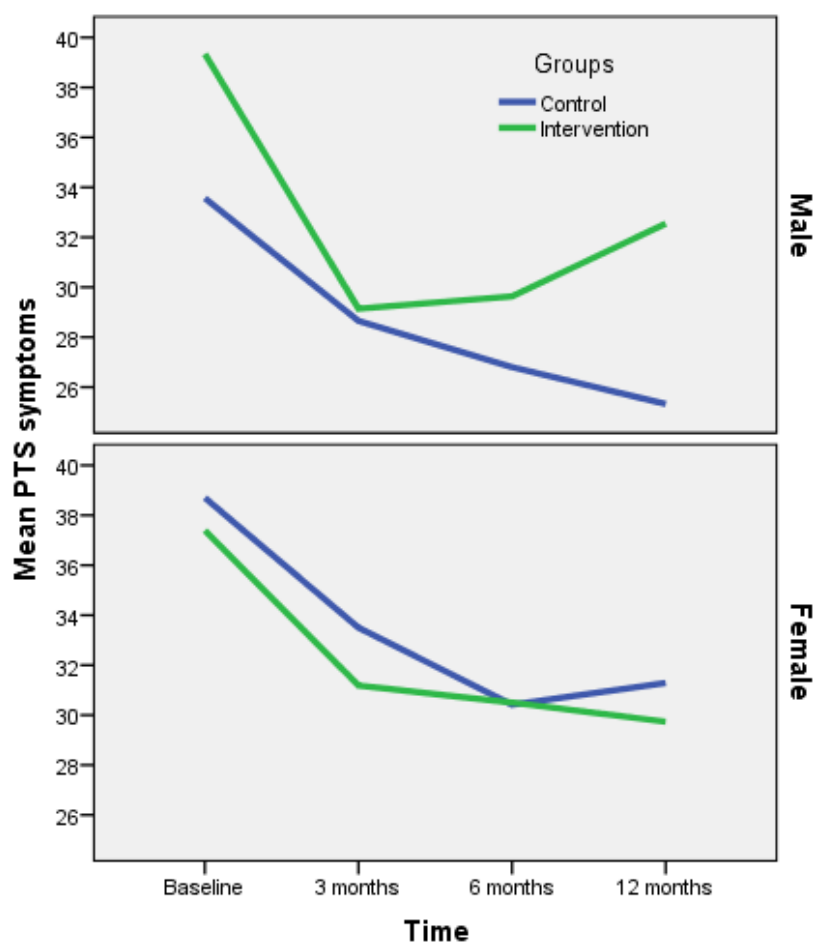
10.5 Paper III

Since there was no effect of the NLCs on PTS symptoms, SOC, or pain intensity, IG and CG were merged when evaluating pain intensity, interference with function and location in patients after ICU discharge. In addition, also patients with PTSS 10-1-B score < 25 (OG) could be included, thereby ending up with 523 patients (Figure 2).

The main findings were that 68% of the discharged ICU patients reported worst pain intensity (NRS > 0) median four days after ICU discharge at the hospital ward. In total, 79% of these patients reported pain as moderate to severe intensity (range 4-10). In the follow-up

period, 56%, 50% and 51% still reported worst pain intensity (NRS > 0) at three, six and 12 months, respectively. However, estimated mean values for worst pain intensity and pain interference (adjusted for independent variables) declined during the year from 5.5 [CI 4.6-6.5] to 3.8 [CI 2.8-4.8] and 4.5 [CI 3.7-5.3] to 2.9 [CI 2.1-3.7], respectively.

Abdominal pain (43%) was the most frequent pain location of the 523 patients. Noteworthy, 86% of these 43% had gastrointestinal disease or abdominal surgery, and elective (23%) and acute (20%) surgery (most frequently gastrointestinal surgery) were the largest primary admission causes. Mean number of reported pain sites at the ward were three (SD 4.3, range 0 to 30).

In the LMM analyses, a statistically significant association was found between higher worst pain intensity and the following variables during the year of follow-up: sum score of PTSS-10-I-B ≥ 25) (B= 0.57 [95% CI 0.08 to 1.07]), female gender (B 0.57 [95% CI 0.15 to 0.99]) shorter ICU LOS (B -0.04 [95% CI -0.06 to -0.01]), and higher sum score of PTSS-10-I-A (traumatic experiences from the ICU) (B 0.19 [95% CI 0.02 to 0.36]) (Table 7).

For higher pain interference there was a similar statistically significant association with the sum score of PTSS-10-I-B ≥25 (B= 1.48 [95% CI 1.08 to 1.87]), female gender (B= 0.45 [95% CI 0.07 to 0.82]) and higher sum score of PTSS-10-I-A (B 0.18 [95% CI 0.04 to 0.33]), but not for shorter ICU LOS. In addition, lower age (B= -0.01[95% CI -0.02 to -0.00]) and being admitted with a primary medical diagnosis (B= -0.79 [95% CI -1.47 to -011]) were also associated with higher pain interference (Table 7).

Table 7. Estimated regression coefficient for fixed effects of worst pain intensity and pain interference during 12 months of follow up*

Variables		Worst pain intensity (n=400)			Pain interference (n=462)		
		Fixed effects			Fixed effects		
		B	95% CI	P value	B	95% CI	p-value
Baseline		1.71	1.28 to 2.15	<.001	1.57	1.20 to 1.93	<.001
3 months		-0.10	-0.47 to 0.26	.570	0.33	-0.01 to 0.67	.060
6 months		0.31	-0.81 to 1.43	.585	-0.01	-028 to 0.26	.945
12 months	(Reference)						
PTSS-10-I-B	PTSS<25 (Reference)						
	PTSS≥25	0.57	0.08 to 1.07	.023	1.48	1.08 to 1.87	<.001
Gender	Male (Reference)						
	Female	0.57	0.15 to 0.99	.008	0.45	0.07 to 0.82	.020
Age		-0.00	-0.01 to 0.01	.856	-0.01	-0.02 to 0.00	.037
Diagnosis in ICU	Elective surgery (Reference)						
	Trauma	-0.11	-0.74 to 0.52	.737	0.54	0.02 to 1.11	.060
	Acute surgery	-0.44	-1.07 to 0.18	.164	0.09	-0.47 to 0.64	.761
	Organ transplant	-0.09	-0.85 to 0.66	.807	-0.07	-0.75 to 0.61	.848
	Cancer	-0.56	-1.22 to 0.11	.101	-0.15	-0.73 to 0.44	.628
	Internal medicine	-0.60	-1.43 to 0.23	.155	-0.79	-1.47 to -0.11	.022
PTSS-10-I-A		0.19	0.02 to 0.36	.029	0.18	0.04 to 0.33	.015
ICU LOS		-0.04	-0.06 to -0.01	.001			
Total Score SOC 13		-0.01	-0.03 to 0.01	.155			
ICU Memory	Factual Memories	-0.65	-1.40 to 0.10	.090			

Abbreviations: Male = 1, Female = 2, No = 0, Yes = 1, PTSS-10-I-B <25=0, PTSS-10-I-B≥25=1, Elective surgery=0, Trauma, Acute surgery, Organ transplant, Cancer and Intern medicine=1, PTSS-10-I-B; Post Traumatic Stress Scale-10-I part B, ICU; intensive care unit, PTSS-10-I-A; Post Traumatic Stress Scale-10-I part A, ICU LOS;,Intensive care unit length of stay, days, SOC 13; Sense of Coherence 13-Item Scale.
*Adjusted for selected independent variables

11 DISCUSSION

The discussion is divided into two main parts. In part I will discuss different aspects of methodological considerations with focus on the validity of the results. This is followed by a general discussion around the main findings. Due to the study design with one RCT and predefined sub studies from the same main sample of ICU patients, the three papers are discussed together.

11.1 Methodological considerations

11.1.1 Internal and external validity

The validity of a study is divided into internal and external validity (153). Internal validity holds the question to what degree outcomes can be inferred from investigated factors or is caused by uncontrolled external factors (154). Bias (systematical errors) and random errors (statistical errors) are two main errors that could influence the quality of the evidence and reduce internal validity (153, 155). External validity is whether the results and conclusions of a study could be applied in other samples, in other settings and/or in other times (153). However, internal validity is a prerequisite for external validity (153).

11.1.2. Study design

The overall goal of choosing a study design is to optimize the internal validity of the study. A well-conducted RCT, where randomization and blinding are keys to internal validity (153), is the gold standard and the most powerful form of evidence evaluating cause-effect relationships between intervention and outcomes (156, 157). The main study in this thesis (paper II) has an RCT design, and the predefined sub-studies are both descriptive

observational studies from the same patient cohort, with a cross-sectional (paper I) and longitudinal (paper III) design. In the following sections I will first discuss limitations and strengths of these studies, focusing primarily on the RCT design.

Lack of Blinding

Obviously, both the CNNs performing the NLCs and the patients knew who received NLCs and who did not. Lack of blinded procedure might have led to bias such as change in manner and behavior related to patient's expectations related to their allocated group (IG or CG) (156, 157). Patients in IG might have reported less symptoms during the follow up period as they believed the intervention had effect (156), and patients in CG might have taken initiative to get help from family, friend or other health professionals since they were informed about the study design and realized that they did not receive any intervention. There was a non-significant trend towards more patients in CG vs IG (40% vs 28%, respectively, p=0.057) that had talked to a physician at the hospital ward about their ICU stay. The latter might have led to contamination bias which occurs when patients not randomized to an intervention virtually receive similar treatment as those randomized to intervention (155). Health care workers might also in general be influenced by lack of blinding, and give more care and attention to patients receiving an intervention (156). However, inclusion in the study was performed at the hospital ward blinded to the responsible nurses, and they were not informed about group allocation after randomization.

Randomization

Patients with a PTSS 10-I-B score ≥25 were randomly assigned to IG and CG by a computer-generated block randomization with stratification between OUHU and OUHR as previously described. This was performed to prevent selection bias by distributing possible confounding factors affecting outcome randomly between groups (153, 156, 157), and to

make balance in the number of patients from the two sites assigned to each of the groups (153, 156). The randomization in itself does not guarantee for bias between patient characteristics in the groups (156). However, when looking at the several clinical and demographic variables at baseline, including gender and age, only two variables (ASA score and worst pain last 24 hours) were significantly different between IG and CG. This indicate that the randomization was successful. Of note, the variables ASA score and worst pain last 24 hours were further adjusted for in the final LMM analysis in paper II.

Intention to treat

The responsible nurses at the different hospital wards assessed eligible patient´s condition before each patient could be introduced to the study. Despite this, nine included patients still had to be excluded after randomization due to delirium or refusal. To prevent attrition bias (systematical differences between IG and CG after randomization), all randomized patients were analyzed in the group they were assigned to, according to the intention-to-treat principle (153). The intention-to-treat principle prevents to overestimate clinical effectiveness of an intervention (158), and is a strength of RCTs.

Pilot test

As already described, a pilot test was performed to get experience and information from the NLCs, and based on the feedback a few changes and improvements in the NLCs were undertaken prior to study initiation. This strengthens the quality of the RCT, since a pilot test is important to assess feasibility, and to improve design and the intervention of a study (159).

Cross sectional and longitudinal design

The cross-sectional design in paper I includes data collection measured simultaneously from only one single time point (baseline, at the hospital ward within the first week after ICU discharge). It is not possible with this design to predict outcome or to draw any casual conclusions (160, 161). However, with the cross-sectional design it was suitable to measure PTS symptoms and possible associations with clinical and demographic variables at baseline. The longitudinal design in paper III consists of several measurement time points (baseline, 3, 6 and 12 months), and possible changes in pain intensity, interference with function and location in patients during the year was therefore possible to identify.

11.1.3 Study sample and generalizability

All included patients in papers I, II and III were from a single center study, which can be a criticism to representativeness and generalizability of study interpretation. Lack of external validity occurs when the characteristics of a sample is misrepresentative, due to attrition or challenge with recruitment, and therefore disable the results to be generalizable to the original population (160). However, the study sample came from five different ICUs with mixed patient groups, including both medical, different surgical and trauma patients, thereby being representative for other general ICU samples. Of note, 825 patients were missed for screening due to different reasons; some were transferred to the ward at their respective local hospital, and others were discharged home or to rehabilitation units before inclusion was feasible. More resources to continuously include patients earlier might have improved this number. However, the size of the total sample of 523 discharged ICU patients is large and strengthens the quality of the study. It is unclear whether the 825 missed patients are different from the eligible patients or how they would have affected the results.

11.1.4 Sample size calculation

To ensure that we had enough statistical power to detect a possible true difference between an intervention- and control-group, taking false-positive and false-negative errors into account, a sample size calculation for the primary outcome (PTS symptoms, based on the PTSS-10-1-B score) prior to initiation of the RCT was performed. Originally, we anticipated a large SD which was later corrected (as previously described in the method part), thus we included a larger number of patients than needed given the corrected estimates of anticipated differences and variation in data. In addition, the dropout rate was 24%, which was similar to the estimated 20% in the sample size calculation. Thus, the study was sufficiently powered, and the large sample size strengthened the validity of the statistical conclusion of the RCT.

Refused inclusion

Of the eligible patients, 253 (33 %) refused inclusion in the study. This refusion number is slightly higher compared to other RCTs including patients after ICU discharge (14-28%) (79, 162, 163). The most relevant reason for the present high number of refusals could be the fact that inclusion was very early after ICU discharge, with several patients still experiencing reduced capacity and lack of energy due to their illness severity. To facilitate inclusion all patients were helped in completing the questionnaires. Most of the inclusions were undertaken by me and the project chair (KT), who knew the study and patient group well and were able to answer questions from the patients. In addition, some trained ICU nurses with clinical ICU experience assisted in the inclusion. Again, it is unclear how these 253 patients refusing inclusion would have affected the results.

Compliance and dropouts

The response rates at three, six and 12 months follow-up among the 523 included discharged ICU patients declined slightly during the year, with 73%, 67% and 63% attending, respectively. The response rates, both in the total sample of 523 patients and those 224 included in the RCT (paper II) were similar to response rates reported in previous RCTs investigating PTS symptoms in ICU patients between six to twelve months after ICU discharge (61-79%) (79, 163, 164). Too many questionnaires or not enough reminders for answering the questionnaires might have influenced compliance and dropouts. Other possible factors impacting on the response rates might be worsening in the patient's general condition, special circumstances or hospital readmissions. On the other side, lack of blinding could also affect compliance because patients knowing they are getting an intervention might be more motivated to answer questionnaires/attend follow-up. However, the number of patients lost for follow-up were similar between IG and CG (20 and 21, respectively) from the RCT (paper II). Thus, the groups were still balanced, strengthening the interpretation of the study. An additional factor related to the CG group, was that they were offered one follow-up consultation after data collection was completed (after 12 months) as a compensation for not receiving NLCs.

Noteworthy, if patients lost for follow-up differ from those remaining in a study it could lead to observed differences and the results would no longer be attributable to the independent variables. It is therefore important to evaluate symptoms in non-responders as well and compare those with the responding patients. The patients lost for follow-up in the RCT (paper II, i.e those who only answered baseline questionnaires), had significantly lower SOC compared to patients included in the LMM analysis (the only variable with significant differences among seven investigated variables). Thus, it is assumable that these non-

responders lost for follow-up were not random, since patients with low SOC have low coping ability influencing significantly on the ability in answering questionnaires.

11.1.5 Data collection and psychometric properties of selected instruments

Well known and previously described person-reported outcomes measures (PROMs) like PTSS-10-I (A and B), SOC-13, and BPI used in papers I-III were selected based on the aims of the studies. The main benefit of using PROMs is that the patients directly report their own symptoms. However, a threat to data validity might be influence from family, friends, or others during completion of the questionnaires. In the present studies, this might have affected the results from three, six and 12 months (mainly done at home).

The validity of an instrument describes if the instrument is measuring what it is intended to measure (165). When evaluating the effect of an intervention, it is important to know whether the instruments used for outcome measures are sensitive enough to detect both possible differences between the groups and changes over time (e.g. reduction in PTS symptoms during the year). Although we intended that the eligible patients should complete their questionnaires within the first week after ICU discharge, and the median time of completion of those included was four days, it was a large range between 0-48 days, certainly limiting validity. Differences in PTS symptoms and SOC between patients at baseline could be due to this large time interval between ICU discharge and completion of questionnaires. However, the sample is heterogeneous, including patients with different causes, conditions and treatment, and some of the patients might also have been readmitted to the ICU. It was therefore necessary to give the patients more time in completion of the baseline questionnaires to increase the number of inlcuded patients. But indeed, this is a clear limitation in the present study.

Finally, new documentation programs (Metavision and Dips) were implemented at OUH during the inclusion period, and this might have influenced on the documentation rate. This could be one possible reason for the large proportion of missing Confusion Assessment Method for Intensive Care Unit (CAM ICU) (166) scores collected from Metavison. Delirium measured with CAM-ICU has previously been described to be associated with PTS symptoms (167). The missing data on CAM-ICU hindered the further investigation of this association and is also a clear limitation of the present studies.

11.1.6 Outcome measures

Posttraumatic stress symptoms

Posttraumatic stress symptoms were measured with PTSS-10-I-B (referred to as PTSS-10 in paper I). An instrument´s reliability is the ability to consistently measure the phenomenon of interest (168). Internal consistency describes if all items in the scale measure the same concept and statistically assessed by testing how closely related a set of items in an instrument is (168). Cronbach's alpha is the most common test score to measure such internal consistency (165, 168). With a score of 1, the inter-correlation is perfect, but scores between 0.70 to 0.95 are reported to be acceptable (165). The Cronbach's alpha for PTSS-10-I-B for the 523 included patients at baseline was 0.88 (paper I), which indicates that the internal consistency was acceptable. Further, PTSS-10-I-B seems to be sensitive for changes since a reduction in PTS symptoms was found during the year (paper II), in similar with findings from Milton et al (169).

Sense of Coherence

SOC-13 was used to measure patients' ability to cope with stress. SOC-13 is the short version of SOC-29 and is therefore more suitable for hospitalized patients with reduced

capacity or lack of energy. The Cronbach's alpha for SOC-13 for the 523 included patients at baseline was 0.83, which indicate high internal consistency. The SOC level increased during the year, indicating that also SOC-13 was sensitive for changes over time.

Pain

BPI was used to measure pain. The first item in the BPI scale is a "yes/no"-question about presence of current pain. Of note, some of the patients answered "no" to this item, but still completed the items following about pain location, worst pain intensity and pain interference. Thus, in the data analysis these patients were reported as having pain, as this better seemed to reflect the actual pain situation. Noteworthy, we did not collect data exploring if the reported pain was directly related to the disease leading to hospitalization, or if the patients had pain prior to hospital admission. This is obviously a clear limitation.

In paper III the prevalence of pain was reported using the worst pain intensity variable (NRS>0). The number of patients answering about pain intensity seemed to be lower compared to those answering on pain interference (76% vs 88%, respectively). This is different from a previous Norwegian study validating pain with BPI in cancer patients, where they found a higher number of patients not reporting pain interference compared to pain intensity (114). However, in paper III we only used one (worst pain intensity) of four possible answers on worst pain intensity the last 24 hours, and this might be an explanation for lower numbers in pain intensity compared to pain interference.

11.1.7 Data analysis

Linear regression analysis

Selection of covariates from previous empirical evidence, clinical considerations and statistical assessments were performed to adjust for potential confounders in paper I and III,

and in the linear regression analysis in paper II. The selected covariates in all three papers were divided into three blocks as already described in the Statistics part of Methods; "background prior to ICU admission", "during ICU treatment", and "after ICU discharge" to reduce the number of covariates in the multivariate linear regression analysis. Some strengths and limitations in the selection of covariates in the present studies will be further be discussed below.

The patients were asked at baseline whether they had previously been treated in an ICU. However, this variable was not possible to use in the further data analysis, due to a high rate of missing data. This might be a limitation because reported PTS symptoms and memories from ICU in some patients might be related to earlier ICU stays (170). In addition, the present study did not control for number of surgeries, mobilization, or actual pain management at the hospital ward, which further limits the scientific interpretation of all three papers.

Linear mixed model analyses

In longitudinal studies (papers II and III), the same patient is assessed at several time points which leads to statistical dependencies (differences within individuals are considered smaller than differences between individuals) that needed to be accounted for. On the other hand, this type of design enables a better estimation within and between patient variance, which increases the precision of regression coefficients when using linear mixed models for repeated measures. Unlike traditional approaches such as ANOVA, which are based on assumption of the outcome being normally distributed and the measurements being evenly distributed in time, LMM does not require the dependent being normally distributed. Further, when the model is fitted with unstructured covariance matrix, there are very few assumptions which need to be fulfilled. In addition, the LMM does not require a full data set with complete

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data unlike ANOVA, so no imputation of missing values was necessary. Thus, we consider the performed statistical analyses using LMM for repeated measures in papers II and III robust (171). Patients with baseline data and at least one available follow-up measurement were included in the analyses from papers II and III, which reduced the negative impact of patients lost for follow-up and attrition that would likely lead to selection bias. In paper II, 83 of 111 (75%) patients in IG and 88 of 113 (78%) in CG were included in the LMM analysis.

The results were presented as fixed effects, an overall assessment of the strength of the associations between a selected covariate and the outcome variables (PTSS and SOC) considering the whole follow-up (papers II and III). Time and group were modelled as fixed factors and the results were expressed as regression coefficients (B) with 95% CI. We used unstructured covariance matrix so no constrains were imposed on the time variable at baseline, three, six and 12 months, which strengthens the study. Given the fact that we had enough statistical power, we were able to fit LMM models with unstructured covariance matrix.

11.2 Main findings

The objectives leading up to all papers in this thesis, was to document PTS symptoms, SOC and pain the following year after ICU discharge, and to evaluate if well planned and structured NLCs among patients at high risk for maintaining PTS symptoms and developing PTSD could reduce PTS symptoms and increase SOC. The main findings were the following:

1. There was a significant association between more PTS symptoms and lower SOC-13 score, higher pain interference with function, more delusional memories from the ICU, lower age and not being a trauma patient early after ICU discharge (paper I).

2. Among patients with clinically relevant PTS symptoms early after ICU discharge randomized to NLCs or control (IG or CG), there was no significant difference in level

of PTS symptoms or in total SOC score or in any of the SOC dimensions between IG and CG at three, six and 12 months after ICU discharge. However, PTS symptoms decreased, and SOC increased in both groups during the follow-up year (paper II).

3. In total, 68% of discharged ICU patients reported worst pain intensity (NRS > 0) early after ICU discharge. At three, six- and 12-months follow-up, 56%, 50% and 51%, respectively, still reported worst pain intensity (NRS > 0). A statistically significant association was found between higher worst pain intensity and more PTS symptoms, female gender, shorter ICU LOS, and more traumatic experiences from the ICU, during the follow-up year. For higher pain interference there was a similar statistically significant association, except for shorter ICU LOS. In addition, lower age and being admitted with a primary medical diagnosis were also associated with higher pain interference (paper III)

The main findings from all three papers will be discussed together, and I will first focus on a discussion around why the NLC intervention did not affect PTS symptoms or SOC (paper II).

11.2.1 Lack of effects from the NLCs

In planning and preparation of the present RCT in 2013 we were aware of limitations and challenges from two previous studies on follow-up after ICU discharge (79, 80). Of these two studies, there was on RCT (79), but neither this or the other study screened patients to identify those with clinically relevant PTS symptoms (79, 80). It was a clear aim to take advantage of this knowledge to improve methodology and design of the study and the content of the NLCs. Still, no effects of the NLCs in reducing PTS symptoms or improving SOC compared to controls were found, making the present findings comparable to previous and recent studies (79, 80, 162-164, 172). There are many possible explanations why the NLCs we used failed,

and the following main topics are considered being the most plausible explanations requiring further discussion.

Screening of PTS symptoms

High level of PTS symptoms may occur in ICU patients the first months after ICU discharge (43), and could further develop into PTSD (173). Consequently, early screening to identify those patients with clinically relevant PTS symptoms prior to interventions with an aim to reduce PTS symptoms have previously been recommended (48, 79, 80, 172, 174-176). It was therefore important to screen patients within the first week after ICU discharge. However, only PTSS-10-I-B was used in the screening process when selecting patients with moderate to severe PTS symptoms for inclusion in the RCT (paper II). It could be speculated if also using PTSS-10-I-A (four question about traumatic experiences from the ICU), in addition to PTSS-10-I-B, could have further improved identification of the targeted patients with clinically relevant PTS symptoms in need for interventions. Wade et al found similar results in an RCT from 2019 (163), where they screened patients in the ICU or following ICU discharge using the Intensive Care Psychological Assessment tool (IPAT) (177).

Another important question is which PTSS-10-I-B cut-off score to use? Previously, scores ≥ 35 (135, 178), ≥ 29 (169), measured within one week after ICU discharge, and >20 (136), measured one week after weaning from mechanical ventilation, have been used. In the present RCT (paper II), we ended up using a cut-off score of ≥ 25 after adjustments based on the pilot study to include patients with clinically relevant PTS symptoms (patients with moderate to high PTS symptoms). Perhaps this cut-off score was too low, however, Milton et al showed in a prospective cohort study with a cut off score of ≥ 29 (the same as we used in paper I) measured one week after ICU discharge, that a score above this predicted clinically significant PTS symptoms after three months with a sensitivity of 91% and specificity of 86% (169). Jubran et al. identified in a prospective longitudinal study measuring PTSS-10 score

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one week after weaning from mechanical ventilation, that a score > 20 diagnosed patients with PTSD after three months with an area under the receiver-operating characteristic curve of 0.91(136). This indicates that the chosen similar cut-off score could be regarded as satisfactory and appropriate. Indeed, more research to detect the most appropriate instrument and optimal cut-off score for identifying patients with clinically relevant PTS symptoms is needed.

Content of the NLCs

Another very relevant explanation for failed effects of the intervention is related to the content of the NLCs. First, it is recommended that a post ICU follow-up model should be based on individual risk factors for long term physical, cognitive and psychological disabilities (179, 180), because PTS symptoms and PTSD are complex and involves individual risk factors (35, 179). Although the current NLCs were individually adjusted by focusing on the patients' individual ICU stay and the self-reported symptoms profiles in PTSS-10-I (A and B), they should probably have been more individually adjusted tailored towards specific symptoms, needs and resources. However, this would require way more resources and independent consultations than we had available.

Moreover, the families/next of kin were not included in the NLCs. Inclusion of them could also have improved the quality, because families have previously been shown to be a significant factor in patients self-management and ability to cope with stress in daily life (87). Many relatives are providing significant amount of care for patients after hospital discharge and also supporting in constructing memories and stories from the ICU stay, which is important for the patients (181). On the other hand, being related to an ICU patient can be a burden that might lead to stress and PICS (180), and maladaptive coping strategies (such as accusatory, exclusionary and uncooperative behavior towards the medical staff) both during

and after ICU discharge (182). In conclusion, follow-up including both patients and relatives have been recommended, although the effects of such follow-up programs have not in detail been described (180, 183).

According to a systematic review (37) and a meta-analysis (170), early post-ICU memories like frightening and psychotic experiences as well as having a prior mental disorder are the most important factors associated with PTS symptoms after ICU discharge. In 10 of 12 studies included in the meta-analysis by Parker et al from 2015, significant associations between PTS symptoms and frightening memories (hallucinations, delirious memories) were found (170). In paper II, low SOC, previous psychological problems and pain were associated with increased PTS symptoms at 12 months after ICU discharge. However, delusional memories from the ICU stay were only associated with PTS symptoms at baseline (paper I) and not after 12 months (paper II). It could be speculated if the patients at all were in need for NLCs focusing on creating a narrative history from the ICU and/or from traumatic memories from the ICU stay, thereby diluting possible effects of the NLCs.

Another issue that should be addressed is the SOC level at baseline prior to randomization. Compared to the Rapit trial in general ICU patients (172), the present SOC level was moderate to high, and higher scores indicate stronger SOC and lower level of PTS symptoms (92, 94-96, 184). In addition, a low SOC was associated with more PTS symptoms both at baseline and during the following year. Noteworthy, the SOC level had a slight increase in both IG and CG during the year independent of the intervention, and it could be speculated if the increased SOC level during the year caused the reduction in PTS symptoms. SOC is relatively stable in young adulthood, but it can be negatively or positively affected (90, 185). This is supported by the idea of Antonovsky's salutogenic model (90), and two previous studies investigating coping in different patient groups (patients on haemodialysis and patients with chronic heart diseases) found a significant positive correlation between

strong SOC and self-management (186, 187). Patients with stronger SOC were able to cope with symptoms, complications, and the resulting negative influence on daily life (186, 187). Thus, patients with stronger SOC, as in the present study, can possibly manage problems related to their PTS symptoms after ICU discharge on their own thereby not being in need for NLCs.

Elements of CBT and narrative method were used in the present NLCs. According to two recent meta-analyses, CBT and exposure-based therapy seem to be two of the most effective treatments to reduce PTS symptoms in patients after trauma (188, 189). CBT aim to reduce dysfunctional thoughts from the trauma and to correct or replace those thoughts with more adaptive and rational cognitions (188). With the present NLCs, the CCNs intended to give information and help the patients to construct information of what happened to them at the ICU. The aim was to reduce stress and increase rational cognitions. However, the CCNs performing the consultations are not psychologists or were not previously familiar with this methodology, which assumable reduced the quality and intentions limiting scientific interpretations.

Moreover, a visit to the ICU, which was part of the intervention in the present study, has previously been recommended as a possibility for the patients to fill in the memory gap and to get information from the ICU staff to construct a narrative for strengthening of their SOC (190). In addition, an ICU visit is an exposure of the place that many former ICU patients might have experienced as frightening, and the visit should help the patient to process traumatic memories. Exposure therapy is used to learn that nothing bad or frightening will happen when patients are confronted by the place related to their injury or disease. The aim is to reduce or eliminate avoidance of feared situations (188). However, only 16% of the patients in IG visited the ICU. In addition to this very low number, only one visit might not be enough to handle their negative associations. This has been previously described as a common

problem, and the main reason might be because of avoidance (191). More research is indeed required to evaluate effects of ICU visits on PTS symptoms or other related symptoms.

Follow-up times and number of consultations

The NLCs were offered maximal three times, and 80% of the patients in IG received it more than two times. Only 48% of the IG patients participated in all three NLCs. Unfortunately, we did not document their reasons for not participating, but it might be due to their condition, readmissions to ICUs, other hospitals or other institutions, or because they felt they were not in need for several NLCs. Only two to three NLCs during a two-month period after ICU discharge might not be potent enough to reduce PTS symptoms or increase SOC. On the other hand, no differences were found between the patients who participated in one, two or three NLCs, respectively, which again might confirm that the content of the NLCs were not potent enough. If several, and more potent interventions delivered with shorter duration between each consultation over a longer time period could improve PTS symptoms and SOC is left unanswered. In comparison, CBT which have showed promising results, consist of a minimum of eight to 12 weekly sessions (188), indicating that more research is required related to this aspect.

Regarding the duration of the intervention period, two previous meta-analyses (179, 192) evaluated associations between follow-up interventions delivered between one to six months after ICU discharge and improvements in PTS symptoms (179, 192). Although the data are related with uncertainties, they concluded that duration of interventions did not seem to improve long term outcome. Both meta-analyses included studies with varying interventions and different types of health-care providers (including NLCs), and different number of consultations (one to five consultations, including telephone calls) (179, 192). In different patient groups or populations, however, some results have been promising. With a

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similar intervention including consultations, performed five to 16 times over a period of four to nine months, benefit in increasing SOC in patients with mental or chronic diseases have been shown (104, 185, 193).

Finally, another interesting qualitative study, investigating 12 males 30 years after an avalanche, emphasized that three coping states ("comfortable life", "a challenging life" or "a damaged life") seemed to be important for the participants balancing their life situation after the avalanche (194). The participants with the coping state "a comfortable life" had a higher degree of using adopting coping strategies to manage life compared to the other two groups, and those with "a damaged life" used more maladaptive coping strategies. This finding confirmed that the patient's individual coping strategies affected daily life even 30 years after a traumatic life-threatening condition. Thus, these findings might also be relevant for long-term outcome in discharged ICU patients after critical disease or injury, and that targeted and tailored interventions to reduce PTS symptoms and increase SOC, over a longer time period, should be evaluated in future studies.

Training and education of the intervention nurses

The 10 CCNs performing the NLCs had all broad clinical experience from ICUs. However, they did not have any formal therapeutic education in using CBT, and only four hours of training by a psychiatrist and a psychotraumatologist was probably not enough to gain enough experience and understanding of the magnitude of the NLCs. In addition, some CCNs had more NLCs than others, and this might have led to different quality of the NLCs. On the other hand, they had all broad experience from communication and interpersonal contact with ICU patients and their relatives. In addition, knowledge about the complexity of the ICU culture, equipment, procedures, and all the different patient groups, should have made them well suited for providing a coherent story from the ICU stay to the respective patients.

11.2.2 PTS symptoms and SOC during the year after ICU discharge

Among the 523 patients included in paper I, using a cut-off-score of PTSS-10-1-B $\geq$ 29, the occurrence of PTS symptoms at the hospital ward within a week after ICU discharge was 32%. In the RCT (paper II), with a cut-off score$\geq$25, occurrence of PTS symptoms among the 224 included patients was 43%. Thus, this explains the difference in reported PTS symptoms at baseline in paper I vs paper II. We demonstrated in paper II that PTS symptoms declined during the year independent of the intervention. In a meta-analysis from 2015, Parker et al reported a similar decline during the first year after ICU discharge, with a PTS prevalence between 4-62% between one and 12 months. However, use of clinical assessment tools, cut-off scores, and time points used varied widely in the studies included, making direct comparisons difficult (170).

A statistically significant association between higher PTS symptoms and lower SOC were found both at baseline (paper I and II) and after 12 months (paper II). These findings are important, because I am not aware of previous studies that have investigated this association in such a large and mixed sample of ICU patients. In smaller samples, however, this association has been documented in injured patients (92, 94-96). In addition, in a meta-analysis from 2019 with individuals after general traumatic or stressful life events, a similar association was documented (184). More focus on individual coping skills and the association with PTS symptoms might make it easier to identify patients in need for follow-up, and to develop more individually customized and tailored treatments as early as possible after ICU discharge. Although not directly comparable to ICU patients, Braun-Lewensohn et al reported in a study investigating religious adolescents from the Gaza Strip, that stressful events which could be successfully managed might lead to recovery of the SOC level and a better long term outcome (195).

11.2.3 Pain and associations with PTS symptoms

In paper III, as many as 68% of the 523 included patients reported to have pain at the hospital ward early after ICU discharge. Estimated means of worst pain intensity and pain interference were high at baseline at the hospital ward but later declined during the year. However, among all patients that were followed during the year after ICU discharge, approximately half of the patients still had pain after three, six and 12 months. As already stated, we did not collect data on chronic pain prior to hospital admission which certainly is a limitation. However, the present results are comparable to previous studies reporting long term pain-specific outcomes using BPI in general ICU samples (150, 196), and in patients with sepsis (197). Chronic pain has been reported in 14-77 % of discharged general ICU patients (198, 199), and in a study on surgical patients 57% reported pain up to eight years after ICU discharge (200). Certainly, pain after ICU discharge is a serious problem deserving more attention, both regarding awareness, documentation, and treatment, but also to prevent development of chronic pain. Multimodal drug management, initiated already at the ICU and properly adopted to the individual patient's needs, have been pointed out as an important measure to prevent pain (201, 202). Finally, higher prevalence of opioid use disorder has also been reported in chronic pain patients with PTSD compared to patients without PTSD (203). These findings might also include patients developing PTSD after ICU discharge.

Pain at the hospital ward after ICU discharge was associated with higher level of PTS symptoms, as documented in paper I. In addition, in paper III both pain interference and pain intensity were associated with PTS symptoms during the following year. Moreover, a significant association between increased worst pain intensity/pain interference and traumatic ICU memories (PTSS-10-1-A) at the hospital ward were found during the 12 months follow-up. Again, these findings are important because we are lacking studies exploring associations

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between PTS symptoms and pain in large ICU samples (198). In specific patient groups with a natural development of pain, such as trauma patients, chronic pain has been reported between 40-73% of the patients (204, 205). However, the relationship between psychological stress like PTS symptoms and pain is complex and bidirectional and makes the causality difficult to explain or understand (204). Studies have reported that patients diagnosed with PTSD have more severe pain compared to patients without PTSD (205).

Further, more severe pain in patients with PTSD have been explained by the mutual maintenance model, which is an underlying positive feedback loop between pain and PTSD (206). The mutual maintenance model assumes that patients with PTSD have more pain because they see stimuli as danger, use avoidance as a coping strategy and further reduce their activity levels (206, 207). The mutual maintenance model might also be a potential explanation for the association between PTS symptoms and pain among those patients included in the present studies. Unfortunately, we did not collect data or have any information about mobilization or activity level at the hospital ward or during the follow-up year among the included patients.

The finding of an association between shorter ICU-LOS and more severe worst pain intensity also deserves attention (208). This has not previously been documented in discharged ICU patients (40, 150), but any conclusion should be looked at with caution. However, it could be speculated that a longer ICU stay gives more time to know and understand each patient better, including better time to plan individual needs and more correct pain management, in addition to improved handover to the ward. In the busy daily dynamic ICU weekday, with patients coming in and out, we might lose information and status on important mental or physical aspects as well as pain. If not handled adequately in the ICU, the patients might suffer from these conditions in a longer run affecting long-term outcome.

Significant associations between traumatic ICU memories and both worst pain intensity and pain interference were found in paper III. According to a previous qualitative study in discharged ICU patients, Berntzen et al reported that half of the patients expressed unpleasant delusional memories following mechanical ventilation (209). They were struggling with memories, discomfort, rarely pain, and to "not getting a grip of the reality" (209). It is therefore important for healthcare professionals to take into account that pain is a subjective experience also influenced by several psychological factors from an ICU stay (210).

11.2.4 Impact of age and gender

Lower age was significantly associated with more PTS symptoms at baseline (paper I) and greater pain interference during the follow-up year (paper III) among the 523 included patients. However, lower age was not associated with PTS symptoms after 12 months among the 224 patients included in the RCT (paper II). Previous studies have shown conflicting results regarding this association, with nine out of 16 studies in a meta-analysis from 2015 showing no association (170). In the other seven studies, lower age were associated with more PTS symptoms (170).

We did not find that gender was associated with PTS symptoms, neither in the whole sample of 523 patients at baseline (paper I) or among the 224 patients included in the RCT during the following year (paper II). This finding is comparable to results from the previously mentioned meta-analysis from 2015, finding no association between PTS symptoms and gender in 13 out of 18 studies (170). However, in the general population it has been documented that females are twice as often diagnosed with PTSD than males (211). A combination of gender roles, genetic predisposition and hormonal influences have been described as possible factors (211). One interesting finding among the 224 patients included in the RCT (paper II), was that the PTS symptoms in men declined in both groups between baseline and three months. In addition, a different pattern in PTS symptoms between males in

IG and CG at three to six months were found, although this mainly could be attributed to the relatively high level of PTS symptoms at baseline in IG. I am not aware of other studies in ICU patients showing this pattern in gender. However, a Norwegian 30-years follow-up study from 2019 documented that trained male military personnel exposed to natural disasters had a reduction of PTS symptoms after one year, but the level of PTS symptoms further persisted and even increased at 30 years (212). Indeed, we do not know if this has anything to do with gender, since only males were followed in that study, and since increased PTS symptoms over time have been reported in both ICU patient and trauma patients after ICU stay (26, 213). However, more research investigating PTS symptoms in general ICU patients over a longer time-period is warranted.

Female gender was associated with higher pain interference after 12 months (paper III). This finding is in accordance with two recent studies showing that female gender was a risk factor for chronic pain one year after ICU discharge (202), and in chronic pain patients in the general population in Europe (110). Both biological and psychosocial differences between males and females have been explained as factors for a higher risk of pain in the female gender (214).

11.3 Limitations

Although limitations already have been discussed, there are a few more general limitations that should be mentioned. Too long inclusion time, from 4-48 days, after ICU discharge is a limitation to the study, but as already stated this increased significantly the number of included patients. It could, however, have affected the results. Moreover, too many questionnaires at baseline and at three, six and 12 months might have imposed a burden for the patients. However, assistance to complete the baseline questionnaire was offered to all included patients. In addition, the inclusion of patients after organ transplantation might be a

limitation as well, as this group might be very different from other patients. Obviously, patients not being able to speak or read Norwegian were excluded from the study, and no registration of cultural and religious differences were registered. This is also a limitation, affecting generalizability of the results.

It is possible that some of the included patients were readmitted to the ICUs at their local hospitals, and thereby could have been further transferred to local rehabilitation facilities. These data were unfortunately not collected. Follow-up service to patients and families after ICU discharge were offered from 33 Norwegian ICUs in 2013, and of those, 20 offered follow-up consultations in combination with ICU diaries (215). If some of the patients included in the RCT (paper II) were offered local rehabilitation programs during the follow-up period, this is certainly a possible confounder and a limitation to the studies.

12 CONCLUSIONS

Paper I

There was a significant association between more PTS symptoms and lower SOC, higher pain interference with function, more delusional memories, lower age early and not being a trauma patient after ICU discharge at the hospital ward among general ICU patients. A wider focus on possible risk factors associated with more PTS symptoms might lead to increased knowledge about the patients in need of interventions preventing development of PTSD.

Paper II

Among patients with moderate to severe PTS symptoms early after ICU discharge randomized to NLCs (IG) or control (CG), there was no significant difference in level of PTS symptoms or in total SOC score or in any of the SOC dimensions between IG and CG at

three, six and 12 months after ICU discharge. However, PTS symptoms decreased and SOC increased in both groups during the follow-up year.

Paper III

In total, 68% of discharged ICU patients reported worst pain intensity early after ICU discharge. Approximately half of the patients still reported worst pain intensity at three, six and 12 months follow-up after ICU discharge. A statistically significant association was found between higher worst pain intensity and more PTS symptoms, female gender, shorter ICU LOS, and more traumatic experiences from the ICU, during the follow-up year. For higher pain interference there was a similar statistically significant association, except for shorter ICU LOS. In addition, lower age and being admitted with a primary medical diagnosis were also associated with higher pain interference.

12.1. Clinical implications and future perspectives

The present findings highlight that we need to focus more on discharged ICU patients at risk of developing PTS symptoms and struggling to cope with their PTS symptoms. These symptoms are already present at the ward early after ICU discharge, and in many patients, they are still present influencing on their quality of life 12 months later. With early screening, we might detect those patients with clinically relevant PTS symptoms, but if NLCs will help them to cope with stress, increase their SOC and reduce PTS symptoms could not be documented with the NLC design provided in the present thesis. The NLCs should definitively be more individually adjusted to help these vulnerable patients. Individually adjusted interventions focusing on patients´ ability to cope with stress deserves to be investigated in further studies. Screening with SOC-13 to identify patients with low coping skills might be important to find patients in need of interventions to reduce PTS symptoms.

Additional studies should investigate possible risk factors during the ICU stay and if it is causal relationship between the ICU stay and PTS symptoms after ICU discharge (175). Finally, if proceeding with more studies using NLCs, they should probably be offered more frequently and over a longer time. This, however, requires more resources, is time demanding and logistically challenging, but it certainly deserves more future studies.

The present results might also help health professionals to pay more attention to patient's ability to cope with stress. A wider focus, including pain early after ICU discharge and presence of previous psychiatric problems, should be taken into account when individual adjusted interventions are developed to prevent PTS symptoms after ICU discharge. Information about the high occurrence of pain and probable risk factors for female gender, high level of PTS symptoms, traumatic ICU memories from ICU, younger age, and shorter ICU stay, is important knowledge for both healthcare-workers at the ICU and at the hospital ward to prevent development of chronic pain. More focus on pain and pain management in patient handover from the ICU to the hospital ward is definitively warranted.

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RESEARCH

Post-traumatic stress symptoms and sense of coherence in proximity to intensive care unit discharge

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Abstract

Background: Post-traumatic stress (PTS) symptoms following intensive care unit (ICU) treatment can lead to post-traumatic stress disorder and represent a severe health burden. In trauma patients, a strong sense of coherence (SOC) is associated with fewer PTS symptoms. However, this association has not been investigated in a general ICU sample.

Aims and objectives: To examine the occurrence of PTS symptoms in general ICU patients early after ICU discharge and to assess possible associations between PTS symptoms and SOC, ICU memory, pain, and demographic and clinical characteristics.

Design: This was a cross-sectional study.

Methods: Adult patients aged ≥18 years admitted for ≥24 hours to five ICUs between 2014 and 2016 were recruited. PTS symptoms and SOC were measured at the ward within the first week after discharge from the ICU using the Posttraumatic Stress Scale-10 and Sense of Coherence Scale-13. Multiple linear regression analysis was used to identify associations between PTS symptoms and SOC and the selected independent variables.

Results: A total of 523 patients were included (17.8% trauma patients; median age 57 years [range 18-94]; 53.3% male). The prevalence of clinically significant PTS symptoms was 32%. After adjustments for gender and age, lower SOC (P < 0.001), more ICU delusional memories (P < 0.001), greater pain interference (P < 0.001), not

being a trauma patient (*P* = 0.02), and younger age (*P* = 0.03) were significantly associated with more PTS symptoms.

Conclusions: One third of patients experienced clinically relevant PTS symptoms early after discharge from the ICU. In the present study, SOC, delusional memory, pain interference, younger age, and not being a trauma patient were factors associated with more PTS symptoms.

Relevance to clinical practice: Early individual follow up after ICU discharge focusing on pain relief and delusional memory may reduce PTS symptoms, with a potential of improving rehabilitation.

KEYWORDS

intensive care unit, post-traumatic stress symptoms, sense of coherence

1 | INTRODUCTION

Many intensive care unit (ICU) patients experience a significant threat to life and physical integrity. This may lead to psychological problems, such as post-traumatic stress (PTS) symptoms after ICU discharge,[1] and have been reported in 4 to 62% of ICU patients.[1] If the PTS symptoms persist for more than 1 month, making a significant impact on social, occupational, or other areas of functioning, PTS disorder (PTSD) may be evident.[2]

Previous studies have focused on risk factors for PTS symptoms after ICU treatment. In a meta-analysis, Parker et al found that more PTS symptoms were associated with early memories of frightening ICU experiences (paranoid delusions, nightmares, and hallucinations). They also described that pre-ICU psychopathology was associated with PTS symptoms.[1] Increased pain at hospital discharge in traumatic orthopaedic patients has been shown to correlate with PTSD.[3] In addition, it has been shown that trauma patients with PTS symptoms are at risk of "self-medication" with alcohol[4] and that alcohol use can reduce recovery from PTSD in female crime victims.[5] However, to our knowledge, we are lacking studies on mixed ICU patients that explore PTS symptoms at the ward shortly after ICU discharge in relation to both pain and alcohol use.

Because it is impossible to eliminate all stress related to an ICU stay, factors associated with the coping of stressful experiences is an important and unexplored area. Sense of coherence (SOC) might be such a factor.[6] Antonovsky created the concept of SOC[7] from the philosophy on salutogenesis (health-promoting factors) to explain people's maintenance or improvement on a continuous scale of illness and health. This theory explains why some people become ill after stress, whereas others cope with the experience and remain healthy. Core concepts are manageability, comprehensiveness, and meaningfulness.[8] An association between PTS symptoms and low SOC has been described in patients after accidental injury,[9] paramedics,[10] and in trauma patients after ICU discharge (1-18 months),[11-13] but we are lacking studies focusing on early PTS symptoms and SOC in large samples of general ICU patients.

WHAT IS KNOWN ABOUT THIS TOPIC

- ICU survivors suffer from PTS symptoms, and strong SOC is associated with fewer PTS symptoms in trauma patients.
- Few studies have focused on PTS symptoms and SOC and clinical characteristic in a large general sample in the ward shortly after ICU discharge.

WHAT THIS PAPER ADDS

- The present study has shown that there is an association between PTS symptoms shortly after ICU discharge and SOC, delusional ICU memories, and pain interference in daily life.

Some studies have measured PTS symptoms in general ICU patients at the ward after ICU discharge.[14-16] However, an early intervention during hospitalization may be effective to prevent acute psychological stress and prevent the development of PTSD after critical illness.[17] In addition, screening of PTS symptoms could make it possible to identify patients in need of further follow up for the prevention of sustained PTS symptoms and the development of PTSD.[18,19] Thus, the aims of the present study were to estimate the prevalence of PTS symptoms at the ward shortly after ICU discharge (within the first week) in a general ICU sample and to identify associations between PTS symptoms, SOC, ICU memory, pain interference with daily life, and demographic and clinical characteristics.

2 | METHODS

The present study is a pre-planned sub-study, presenting baseline data (before randomization) from a not-yet published randomized

controlled trial (NCT02077244) investigating the effects of an intervention aimed at reducing PTS symptoms and improving psychological health in patients recently discharged from the ICU.

2.1 | Patient settings

Adult patients aged ≥18 years admitted to one of five ICUs (medical and surgical) at Oslo University Hospital (OUH) in Norway for ≥24 hours were included consecutively from March 2014 to December 2016. OUH is a regional hospital for Eastern and Southern Norway and is the trauma referral centre for the same region and national hospital for transplant surgery. There is no systematic psychological follow up, but patients with obvious psychiatric disorders or those suffering from extreme situations are offered early consultations and follow up from psychiatrists/psychologists.

Within the first week after ICU discharge (defined as "shortly after ICU discharge"), patients received oral and written study information, including a questionnaire, from a member in the study group and signed a written consent before inclusion. Patients with self-inflicted (suicidal intent) injuries, unable to read/understand Norwegian, severe brain injury, too cognitively impaired, terminal disease, severe psychiatric disorder, or those who had already been transferred to a local hospital were excluded.

2.2 | Data collection

Demographic and clinical data were collected from patient records, the local intensive care registry, and the study questionnaire. Educational level, work situation, living status, information about previous psychiatric problems, alcohol habits, and medication were self-reported by the patients. If a patient needed assistance with the questionnaire, a study nurse offered guidance.

Illness severity was reported using the New Simplified Acute Physiology Score (SAPS II) on a scale from 1 to 163.[20] Information about diagnosis, treatment, and length of treatment was collected from patients' records. The American Society of Anaesthesiologists Physical Status Classification (ASA) score, measuring physical health status and comorbidity in five categories graded from Class 1 (a normally healthy patient) to 5 (moribund patient), was calculated based on information from the patient's record.

All patients were asked five "yes" or "no" questions to identify psychiatric problems before hospital admission.[21] Six self-reported questions about the use of hypnotics, anxiolytics, antidepressants, and analgesics (yes/no) were also included. Anxiolytics or antidepressant drugs were categorized into one group. All patients were asked whether they had experienced any important event (yes/no) in the past year before present hospital admission.

2.3 | PTS symptoms

PTS symptoms were measured using the Posttraumatic Stress Scale-10 (PTSS-10), comprising 10 items with a scale ranging from 1 (never) to 7 (always). The sum of these scores gives a total range of 10 to 70, with a higher score indicating greater stress.[22] The reliability and validity of PTSS-10 have been tested in different patient populations.[22-24] To discriminate between cases and non-cases, PTSS-10 has been shown to have high specificity and sensitivity.[22] Screening cut-off value for discriminating between cases and non-cases for PTSS-10 was >29 points.[14] Cronbach's alpha in the present study was 0.88.

2.4 | Sense of coherence

SOC was measured using the Sense of Coherence Scale 13 (SOC-13).[7] SOC-13 comprises 13 items and is scored on a scale from 1 to 7, giving a scoring range of 13 to 91. The higher the score, the stronger the SOC. SOC-13 has been used after ICU treatment in trauma patients[11] and in other populations, with satisfactory reliability and validity.[25,26] Cronbach's alpha in the present study was 0.83.

2.5 | Pain

The brief pain inventory (BPI) was used to identify the presence of pain in the preceding 24 hours (yes/no), the worst pain intensity, and whether pain interfered with daily living.[27,28] Worst pain intensity was rated using a numeric rating scale (NRS) from 0 (no pain) to 10 (pain as bad as you can imagine). For pain interference, seven items about how much pain interferes with daily activities (general activity, mood, working ability, normal work, relations with other, sleep, enjoyment of life) were answered using an NRS from 0 (does not interfere) to 10 (completely interferes) and computed into one pain interference scale. A score of 4 to 6 was considered moderate and 7 to 10 severe on the NRS scale.[29] Reliability and validity of BPI have been demonstrated in different groups of patients experiencing acute pain.[30] Only pain interference was used for analyses in the present study.

2.6 | Memory of the ICU stay

The ICU Memory Tool, with 14 items, was used to assess memory of the ICU stay.[31,32] This questionnaire consists of three parts, but we only measured memory of the ICU stay. It comprises 21 specific memories, grouped into three different categories: memory of factual events, feelings, and delusional memory, and each were recoded to indicate the presence or absence of memory (yes/no). This tool has been shown to have favourable reliability and validity.[33]

2.7 | Alcohol consumption

To measure alcohol consumption, a modified version of the 10-question Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire containing three items was used[34,35]: (a) How often do you have a drink containing alcohol? (b) How many standard drinks containing alcohol do you usually consume? (c) How often do you have six or more drinks on a single occasion? In a range from 0 to 12, a score of ≥4 in males and ≥3 in females is considered to indicate hazardous drinking.[35] These questions were finally dichotomized into a yes/no hazardous drinker question.[34]

2.8 | Statistics

All analyses were performed using IBM SPSS statistics 21 (IBM Corp., Armonk, New York). In the descriptive analysis, data are presented with mean and SD for normally distributed data and median and range for non-normally distributed data. Categorical data are presented as numbers and percentages.

Univariate analysis was performed using linear regression analysis, and each demographic and clinical variable was investigated for its association with the dependent variable (PTSS-10 score) as follows:

Step 1: univariate analysis of all independent variables.

Step 2: all independent variables with $P < 0.1$ from Step 1 were divided into three blocks: background before ICU admission, demographic and clinical characteristics during ICU treatment, and clinical and demographic characteristic after ICU discharge.

Step 3: included variables with $P < 0.1$ from Step 2 in a multivariate linear regression analysis; a total of 29 independent variables were investigated.

Gender and age were controlled for in all steps. Pearson's correlation coefficient between the independent variables showed that all correlations were <0.7. Significance level was set at $P < 0.05$.

2.9 | Ethics

The Regional Ethics committee and Data Inspectorate approved the study (REK number: 2012/1715). The questionnaire might have imposed a burden for the patients to answer. Patient conditions were therefore assessed by the nurses in charge at the wards before inclusion to ensure that too sick or inadequate patients were not answering the questionnaires.

3 | RESULTS

In the recruitment period, 3162 patients aged ≥18 years were treated for ≥24 hours in the five recruiting ICUs. A total of 2386 patients were excluded for different reasons. Some patients were lost before inclusion as a result of transferral directly from our ICU to the ICU at a local hospital, transferral to local hospitals, or being discharged home before they were approached by the research team. Among 776 eligible patients, 253 refused inclusions, resulting in 523 included patients (Figure 1). With some individual differences because of patient's condition, 75% of the questionnaires were collected within 8 days after ICU discharge (median 4 days, range 0-48).

3.1 | Demographic and clinical characteristics of the sample

Median age was 57 years (range 18-94 years); 53% were male, with a median ASA score of 2 (range 1-4) and SAPS II score of 24 (range 0-78), and 54% had been mechanically ventilated. Elective and acute surgery was present in 23% and 20% of the patients, respectively. Median length of ICU stay was 3 days (range 1-83), and median stay
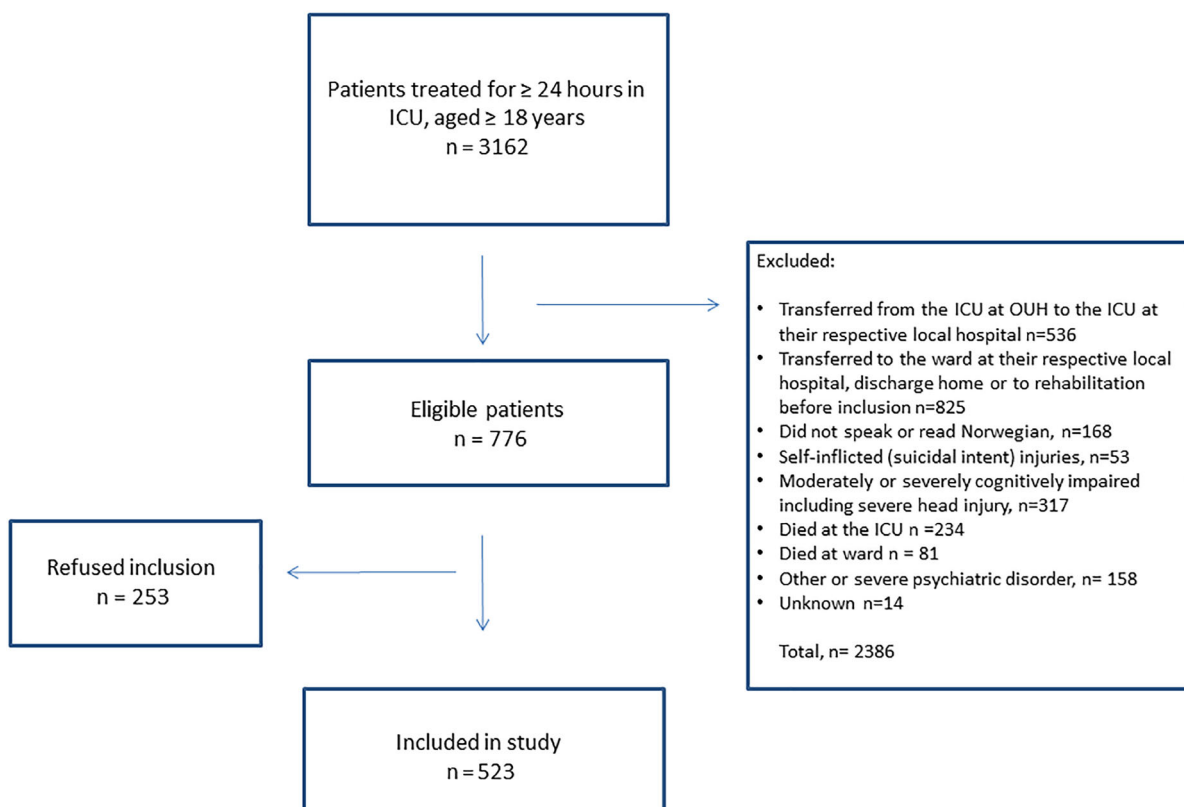

FIGURE 1 Flow diagram of patient recruitment. ICU, intensive care unit; OUH, Oslo University Hospital

TABLE 1 Demographic and clinical characteristics, Post-traumatic stress, and sense of coherence of the total sample (n = 523)

	n	%
Gender		
Male	279	53.3
Female	244	46.7
Level of education[a]		
Primary school	64	12.2
Secondary school	200	38.2
University/college	248	48.1
Work situation[a]		
Working	229	45.4
Sick leave	33	6.5
Disability pension	52	10.3
Retired	146	29.0
Other (student, military service, homemaker)	44	8.7
Civil status[a]		
Married/cohabitant	321	61.8
Caring for children aged <18 years	107	20.9
Diagnosis		
Trauma	93	17.8
Acute surgery	103	19.7
Elective surgery	118	22.6
Organ transplant	54	10.3
Cancer	97	18.5
Internal medicine	58	11.1
Prevalence of PTSS-10 >29[a]	165	31.5
ICU memory tool: Factual[a]	469	89.7
ICU memory tool: Feelings[a]	414	79.2
ICU memory tool: Delusional[a]	234	44.4
Benzodiazepines in ICU	250	47.9
Opioids in ICU	488	93.3
Antipsychotics in ICU	60	11.5
Dexmedetomidine in ICU	105	20.2
Clonidine in ICU	37	7.1
Regional analgesic in ICU	286	54.8
Medication use at home[a]		
Hypnotics	154	30.9
Anxiolytic/antidepressant	116	22.2
Analgesics without prescription	250	55.3
Analgesics with prescription	252	54.5
Mechanical ventilator treatment	280	53.5
Patient with heavy/hazardous drinking before hospital stay[a]	203	39.5
Previous psychiatric problems[a]	102	19.5
Important events (in the past year) before hospital admission[a]	173	33.1

(Continues)

TABLE 1 (Continued)

	n	%
	Median	Range
Age, years	57	18-94
LOS in ICU, days	3	1-83
LOS in OUH, days	20	3-217
ASA score	2	1-4
SAPS II score	24	0-78
Total PTSS-10[a]	22	10-70
	Mean	SD
Total SOC-13 score[a]	68.9	12.5
BPI total pain inference[a]	4.5	2.7

Abbreviations: ASA, American Society of Anesthesiologists Physical Status Classification; BPI, brief pain inventory; ICU, intensive care unit; OUH, Oslo University Hospital; LOS, length of stay; PTSS-10, Post Traumatic Stress Scale-10; SAPS II, New Simplified Acute Physiology Score; SOC 13, Sense of Coherence 13-Item Scale.
[a]Self-reported.

at OUH was 20 days (range 3-217 days) (Table 1). Of all patients, 40% reported heavy/hazardous drinking, and 20% reported previous psychiatric problems.

3.2 | PTS symptoms, SOC, pain, and ICU memory

The median PTSS-10 score was 22 (range 10-70), and prevalence of clinically significant PTS symptoms (PTSS-10 score > 29) was 32%. The mean SOC-13 score was 69 (SD 12.5), reflecting a moderate to strong SOC. Of the patients, 65% reported pain in the past 24 hours, with a mean worst pain intensity of 5.9 (SD 2.7). Mean score for total pain interference was 4.5 (SD 2.7). Delusional memories of the ICU stay were present in 44% of the patients (Table 1).

3.3 | Relationships between PTS symptoms, SOC, and demographic and clinical characteristics

In the multivariate regression analysis, after adjustment for gender and age, a low SOC-13 score was strongly associated with a higher PTSS-10 score. A 1-point decrease in SOC-13 increased the PTSS-10 score by 0.39 points. Trauma patients were the only diagnostic subgroup with a significantly different PTSS-10 score, being 2.7 points lower than the other subgroups. Pain interference, delusional memories, and age were significantly associated with PTS symptoms. A 1-point increase in the pain interference score increased the PTSS-10 score by 1.2 points. Patients with delusional memories had a mean PTSS-10 score that was 5.1 points higher than those without delusional memories. Previous psychiatric problems and heavy/hazardous drinking before hospital stay were not associated with the PTSS-10 score (Table 2).

TABLE 2 Results of linear regression analysis of selected variables on post-traumatic stress (n = 523)

Characteristic	Univariate analysis			Multivariate analysis		
	B	95% CI	P-value	B	95% CI	P-value
Gender	3.43	1.31, 5.55	0.002			
Age	−0.15	−0.15, 0.03	<0.001	−0.06	−0.11, −0.01	0.033
Diagnosis						
Elective surgery (reference category)						
Trauma	−3.58	−6.92, −2.25	0.035	−2.70	−5.04, −0.36	0.024
Acute surgery	−0.67	−3.92, 2.57	0.683			
Organ transplant	−0.40	−4.35, 3.55	0.841			
Cancer	−3.613	6.908, 0.317	0.032			
Internal medicine	−7.15	−11.02, −3.27	<0.001			
Work situation[a]						
Work (reference category)						
Unemployed	−1.01	−7.95, 5.94	0.776			
Disability pension	3.30	−0.28, 6.87	0.071			
Sick leave	0.04	−4.39, 4.46	0.987			
Retired	−3.74	−6.22, −1.26	0.003			
Other (eg, student, military service, homemaker)	8.02	4.12, 11.91	<0.001			
Total score SOC 13[a]	−0.55	−0.63, −0.48	<0.001	0.39	−0.48, −0.31	<0.001
Important events last year before hospital admission[a]	4.30	2.01, 6.45	<0.001			
ICU memory tool: Delusional[a]	7.00	4.96, 9.05	<0.001	5.11	3.31, 6.92	<0.001
ICU memory tool: Feelings[a]	4.56	1.99, 7.13	0.001			
BPI total pain inference[a]	2.11	1.74, 2.47	<0.001	1.22	0.87, 1.57	<0.001
SAPS II	−0.10	−0.19, −0.01	0.023			
LOS in OUH	5.30	0.00, 0.00	0.045			
Benzodiazepines in ICU	47.8	2.68, 6.87	<0.001			
Opioids in ICU	3.91	1.81, 0.07	0.079			
Dexmedetomidine in ICU	4.23	1.60, 6.87	0.002			
Clonidine in ICU	7.56	3.46, 11.66	<0.001			
Antipsychotics in ICU	2.83	−05.0, 6.16	0.095			
Previous psychiatric problems[a]	10.79	8.25, 13.30	<0.001			
Medication before hospital admission[a]						
Hypnotics	4.52	2.21, 6.83	<0.001			
Anxiolytics/antidepressants	4.19	2.39, 7.45	<0.001			
Analgesics with prescription	3.81	1.59, 6.07	0.001			

Note: Male = 1, Female = 2. No = 0, Yes = 1. R^2 = 46.5% (adjusted R^2 = 50.2%).
Abbreviations: B, unstandardized coefficient; BPI, brief pain inventory; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; OUH, Oslo University Hospital; SAPS II, New Simplified Acute Physiology Score; SOC 13, Sense of Coherence 13-Item Scale.
[a]Self-reported.

4 | DISCUSSION

Our main finding is that 32% of the patients reported clinically relevant PTS symptoms in the ward early after ICU discharge. In addition, a high PTSS-10 score was significantly associated with a low SOC-13 score, not being a trauma patient, having a delusional ICU memory, pain interference with daily life, and younger age.

4.1 | Prevalence of PTS symptoms after the ICU stay

Only a few studies have measured PTS symptoms in general ICU patients at the ward shortly after ICU discharge. Milton et al[14] found a prevalence of 15% of clinically significant PTS symptoms at 3 months after assessing PTS symptoms within the first week after ICU discharge using the PTSS-10-1 Part B (sensitivity of 91% and specificity of 86% in predicting PTS symptoms). Twigg et al[15] using the Impact of

Event Scale (IES), and Wu et al[16] using the IES Revised, reported 23% and 10% of PTS symptoms, respectively. Myhren et al[36] found a prevalence of 25% using IES, measured 4-6 weeks after ICU discharge in their home environment. The prevalence of 32% in the present study was higher than previously reported, but some had lower patient samples. Milton et al,[14] Wu et al,[16] Myhren et al[36] and Twigg et al[15] used high cut-off scores to indicate severe symptoms. However, in a meta-analysis, Parker et al[1] found a pooled prevalence of clinically significant PTS symptoms of 24% using different tools, conducted at least 1 to 6 months after ICU discharge in the home environment. Despite all variations, we still believe the results are comparable, and early screening for PTS symptoms after ICU discharge could make it easier to identify patients in need of further follow up for the prevention of sustained PTS symptoms and development of PTSD.[18,19] Twigg et al[15] found that PTS symptoms measured with PTSS-14 at 4-14 days and 2 and 3 months after ICU discharge showed good validity in detecting symptoms of PTSD in ICU survivors.

4.2 | Relationships between PTS symptoms, SOC, pain, ICU memory, and demographic and clinical characteristics

A low SOC was associated with a higher PTSS-10 score in the present study in accordance with Antonovsky's SOC theory[7] and previous studies in different populations.[9-13] We strongly believe this highlights the need for further research on the association between general ICU patients and their ability to cope with stress.

We found that 65% of the patients reported severe pain (mean NRS 6) shortly after ICU discharge. This is similar to a follow-up study in orthopaedic patients[3] reporting an average pain intensity (BPI of 6.3 [SD 2.4]), with 44% of the patients having severe pain in the past 24 hours (NRS ≥ 7) before hospital discharge. Furthermore, a higher pain interference score in the ward was associated with a higher PTSS-10 score. Archer et al[3] found, in orthopaedic patients, using the Clinical-Administered PTSD Scale and Mississippi PTSD Scale significant correlations between pain and PTSD at hospital discharge and after 1 year. To the best of our knowledge, our study is the first to measure pain in a general ICU population in the ward shortly after ICU discharge, and the amount of patients reporting pain and the association between pain and PTS symptoms/PTSD warrant further research.

Furthermore, we found a significant association between delusional memories and PTS symptoms, highlighting the negative consequences of memories of delirious experiences. However, our results differ from those of Toien et al,[37] who found that factual but not delusional memories were one of the strongest predictors of PTS symptoms in trauma ICU patients. In the present study, in a more general ICU sample, we found no such association between PTS symptoms and factual memories, consistent with previous findings.[36,38,39]

Our finding—that trauma patients had a significantly lower PTSS-10 score than other ICU patients— differs from previous studies.[40-42] Our trauma patients receive daily, systematic, goal-directed care through an interdisciplinary treatment strategy, and the most severely injured patients are offered follow up at a trauma outpatient clinic. We might assume that this specialized care might help to prevent the development of PTS symptoms.

Previous studies[19,43] have shown that younger age is associated with more PTS symptoms, which was confirmed in the present study. We might speculate that younger ICU patients may suffer more as a result of the fear of losing working capacity, financial uncertainties, and the effects on family responsibilities.

In our sample, heavy/hazardous drinking was reported by 40% of the patients, higher than previous reports of 9 to 24% using different AUDIT scores.[44-46] We used the AUDIT-C cut off score with cut-off ≥3 in women and ≥4 in men, and because of differences in the cut-off values used, our results might be comparable.[45] According to Bush et al,[35] a score ≥8 on the AUDIT has similar sensitivity as a score ≥4 on the AUDIT-C, which might indicate quite a high alcohol consumption in our ICU sample. However, alcohol consumption (AUDIT-C ≥ 4) was not associated with PTS symptoms, similar to previous findings.[42,44] Finally, we reported a previous psychological disorder in 20% of the patients, and this was associated with PTS symptoms in the univariate regression analysis but did not reach significance in the multivariate analysis. Parker et al[1] found that the majority of studies reported an association between previous psychopathology and PTS symptoms after an ICU stay. SOC might have confounded this association, although SOC correlated <0.7 with previous psychiatric disorder.

5 | LIMITATIONS

Our study has several limitations. First, we do not know whether included patients had PTS symptoms before ICU admittance. Second, patients were included shortly after ICU discharge, and some of these patients might still have been too sick. It is plausible to assume that some might have refused participation because of a bad general condition or that those who were lost before inclusion might be very different from those included. Furthermore, the questionnaire could have imposed a burden for the patients as it had to be answered shortly after ICU discharge, which could have influenced response rates and their answers. Third, we only used self-reported assessment to define significant PTS symptoms, and a diagnostic interview might have given a different prevalence. PTSS-10 and PTSS-14 have both shown good validity in detecting symptoms of PTSD in ICU survivors according to the DSM IV criteria.[15,47] We chose to use PTSS-10 to reduce the number of items to answer for this vulnerable group of patients. Fourth, patients who refused to participate and those who were lost because of transfer to a local hospital or were discharged home before inclusion may have impacted the data. However, there is no reason to believe that patients who were transferred early to other hospitals directly were different from the other. Finally, we did not report data on delirium in the ICU (too many missing values), and this might limit data interpretation.

6 | IMPLICATIONS AND RECOMMENDATIONS FOR PRACTICE

Early screening after ICU discharge with PTSS-10 and SOC-13 might be valuable for identifying patients with PTS symptoms. This could help health care professionals be aware of patients in need of early intervention before development of PTSD. SOC-13 is easy to use and provides information about coping ability[48] for possible individually adjusted interventions.

7 | CONCLUSION

One-third of our patients experienced clinically relevant PTS symptoms after ICU discharge. In our large, general ICU sample, SOC, delusional memory, pain interference, younger age, and not being a trauma patient were factors associated with more PTS symptoms.

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II

III

RESEARCH

BACN Nursing in Critical Care   WILEY

Occurrence and characteristics of pain after ICU discharge: A longitudinal study

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Abstract

Background: Pain is a serious problem for intensive care unit (ICU) patients, but we are lacking data on pain at the hospital ward after ICU discharge.

Aims and Objectives: To describe pain intensity, -interference with function and -location in patients up to 1 year after ICU discharge. To identify demographic and clinical variables and their association with worst pain intensity and pain interference.

Design: A longitudinal descriptive secondary analysis of a randomized controlled trial on nurse-led follow-up consultations on post-traumatic stress and sense of coherence after ICU discharge.

Methods: Pain intensity, -interference, and -location were measured using Brief Pain Inventory at the hospital ward and 3, 6, and 12 months after ICU discharge. For associations, data were analysed using multivariate linear mixed models for repeated measures.

Results: Of 523 included patients, 68% reported worst pain intensity score above 0 (no pain) at the ward. Estimated means for worst pain intensity and –interference (from 0 to 10) after ICU discharge were 5.5 [CI 4.6-6.5] and 4.5 [CI 3.7-5.3], and decreased to 3.8 [CI 2.8-4.8] ($P \leq .001$) and 2.9 [CI 2.1-3.7] after 12 months ($P \leq .001$). Most common pain locations were abdomen (43%), lower lumbar back (28%), and shoulder/forearm (22%). At 12 months, post-traumatic stress (PTS) symptoms ≥25 (scale 10-70), female gender, shorter ICU stay, and more traumatic ICU memories were significantly associated with higher worst pain intensity. PTS symptoms ≥25, female gender, more traumatic ICU memories, younger age, and not having an internal medical diagnosis were significantly associated with higher pain interference.

Conclusions: Early after ICU discharge pain was present in 68% of patients. Thereafter, pain intensity and -interference declined, but pain intensity was still at a moderate level at 12 months. Health professionals should be aware of patients' pain and identify potentially vulnerable patients.

Implication for Practice: Longitudinal assessment of factors associated with pain early after ICU discharge and the following year is a first step that could improve follow-up focus and contribute to reduced development of chronic pain.

KEYWORDS

acute pain, chronic pain, critical care unit, intensive care, pain

1 | INTRODUCTION

Pain in intensive care unit (ICU) patients is common. This could be related to the diagnosis, daily activities, or from painful procedures.[1-3] Insufficient pain management can lead to inactivity and pulmonary complications, delayed mobilization, and development of chronic pain.[4] After ICU discharge to wards, patients have reduced nurse attention due to lower patient–nurse ratio, with less monitoring and focus on the patient's pain experience. Two small studies, using different pain measurement tools, described moderate to severe worst pain intensity within the two first weeks after ICU discharge.[5,6]

Chronic pain is present if it exceeds 2 to 3 months after initial pain occurrence[4] and is described to be associated with emotional distress and negatively interfere on daily life activities and social participation.[7] This contributes to reduced quality of life for discharged ICU patients.

A systematic review reported chronic pain after ICU discharge in 28% to 77% of former ICU patients.[8] Long-term outcome analysis about pain after ICU discharge has only been performed in two smaller studies,[9,10] both reported that pain interference with daily life 1 year after ICU discharge. Longer and more detailed follow-up including a large ICU sample is important to also examine how associated variables might have an impact on pain. In a systematic review, acute pain at ICU discharge, higher thoracic trauma score, surgery, pre-existing pain, organ failure, longer ventilator time or hospital stay, or sepsis were risk factors for chronic pain.[8]

Some associations between acute pain and post-traumatic stress (PTS) symptoms at the ward after ICU discharge have been described,[11] but we are lacking data on associations between chronic pain and PTS disorder (PTSD) in former ICU patients.[12] Sense of coherence (SOC), a coping concept, explains why some people suffer after stress while others remain healthy.[13] In different patient populations lower SOC and higher pain intensity has been associated with acute[14,15] and chronic pain.[16] Thus, more knowledge about pain sites and factors associated with pain intensity and pain interference after ICU discharge are warranted. In addition, data about the relationship between coping skills and pain after ICU discharge could help identifying patients at risk for development of chronic pain.

2 | AIMS

The aims of the present study were to describe worst pain intensity, −interference with function, and -location in patients early after ICU discharge and in the first year after hospital discharge. In addition, we

What is known about this topic

- Pain is common during the intensive care treatment, but pain among patients discharged from ICU is scarcely investigated.
- Only a few smaller studies have explored factors associated with pain at the hospital ward after ICU discharge, and later occurrence of chronic pain.

What this paper adds

- In this longitudinal descriptive study of a large ICU sample, 68% of the patients reported pain after ICU discharge, with 79% being moderate to severe.
- Female gender, high level of PTS symptoms, traumatic ICU-memories, shorter ICU length of stay, and lower age were associated with development of chronic pain.

intended to identify demographic and clinical variables, including PTS symptoms and SOC, and their association with worst pain intensity and -interference during the same time period.

3 | METHODS

This is a predefined longitudinal descriptive secondary analysis of a randomized controlled trial (NCT02077244) investigating effects of nurse-led follow-up consultations on PTS symptoms and SOC early after ICU discharge.[17]

Patients aged ≥18 years admitted for ≥24 hours to one of five ICUs (surgical and medical patients) at Oslo University Hospital (OUH) from March 2014 to December 2016 were included (Figure 1), with collection of follow-up data 1 year later. Patients were approached at the ward within a week after ICU discharge when they were able to complete a questionnaire. They received oral and written information about the study and the right to withdraw without any reason. If needed, patients received assistance to understand and complete the questionnaire from study group ICU nurses, trained according to a guide for inclusion and assistance to prevent bias. Patients with terminal disease, severe brain injury, cognitive impairment, severe psychiatric disorders, and self-inflicted injuries or with poor language skills were excluded.

In the RCT, patients with a Post-traumatic Stress Scale 10-Intensive part B (PTSS 10-I-B) score ≥ 25 were randomized to nurse-led follow-up consultations vs standard care. No significant differences in PTS symptoms or SOC between the two groups were found.[17] In a new multivariate linear mixed model analysis performed prior to initiation of the present study, the nurse-led follow-up consultations had also no effect on pain. Thus, we merged all included patients into one group. In addition, patients scoring <25 on PTSS 10-1-B (receiving standard care) were also included.

3.1 | Data collection

Included patients were asked to complete a questionnaire about pain, PTS symptoms, SOC, ICU memories, and use of analgesics, sedatives, anxiolytics, and antidepressants prior to admission. They were also asked about alcohol habits, previous psychological problems, and whether they had experienced any traumatic event during previous year. All included patients were sent the same questionnaire by post after 3, 6, and 12 months and asked to complete and return them in a prepaid envelope.

3.1.1 | Brief pain inventory

Worst pain intensity, −interference with function, and -location were measured using the Brief Pain Inventory (BPI) short form.[18] Pain occurrence was reported with worst pain intensity (numeric rating scale [NRS] >0). Severity of worst pain during the previous 24 hours (worst pain intensity) was rated using 0 (no pain) to 10 (pain as bad as you can imagine) on a 11-point NRS. Pain interference, with seven domains (i.e., daily activity, mood, walking ability, work, sleep, enjoyment of life, relations with others) was rated from 0 (not interfere) to 10 (completely interfere) with NRS scales. A total interference score was calculated as the mean of these seven items. Pain location was indicated using a mark on a body map. We counted number of pain locations to make the variable numbers of pain locations. Worst pain during previous 24 hours was divided into mild (1-3), moderate (4-5), and severe (6-10) pain.[19] Validity of BPI has been demonstrated in different patient groups.[19,20]

3.1.2 | Post-traumatic stress scale-10 intensive care screen

PTS symptoms were measured with PTSS-10 I-B composed of 10 items with a scale from one to seven (total score of 10-70). Higher scores indicate more symptoms.[21,22] Post-traumatic Stress scale 10 intensive part A (PTSS-10-I-A) with four additional yes/no questions about memory of traumatic ICU experiences (feeling of severe anxiety or panic, pain, nightmares/hallucinations, suffocations) was also completed.[21] It has a sum score from 4 to 8 (no = 1,

yes = 2). PTSS-10-I-B has shown validity in different patient groups.[22-24]

3.1.3 | ICU memory tool

Question 4b from the ICU memory tool consists of 21 specific memories (yes/no) and was used to measure ICU memories, recoded into three main categories: memory of factual events, feelings, and delusional memories.[25] The ICU memory tool has shown to have satisfactory validity.[26]

3.1.4 | Sense of coherence

We used SOC-13, including 13 items. Each item is rated on NRS from 1 to 7, with possible sum score from 13 to 91. Higher score indicates stronger SOC.[27] SOC-13 has been used in ICU patients,[11,17] showing acceptable reliability and validity.[28,29]

3.1.5 | Alcohol use disorders identification test-consumption

Three questions from the 10-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) were used to survey alcohol habits prior to hospital admission. Summed scores range from 0 to 12, and hazardous drinking is indicated if ≥4 in males and ≥3 in females.[30]

3.1.6 | Other independent variables

Clinical and demographic data were collected from the local intensive care registry and patient records. Simplified Acute Physiology Score (SAPS II) was used to measure severity of illness (range from 0 to 63).[31] Higher score indicates more severity. The American Society of Anaesthesiologists' Physical Status Classification (ASA) score, with five categories, from 1 being healthy to 5 being moribund not expected to survive, was used to characterize comorbidity and physical health status prior to hospitalization.[32,33]

3.1.7 | Statistical analyses

Continuous variables were described using descriptive statistics, means, and standard deviation (SD) for normally distributed data, and median and range for data with skewed distribution. Categorical data were presented as counts and percentages. Variables associated with the dependent variables worst pain intensity and pain interference, were investigated with multivariate linear mixed models for repeated measures. Covariates included in the multivariate mixed model analysis were selected based on associations with worst pain intensity and pain interference within first week after ICU discharge in three steps.

First, a univariate linear regression model for each of the outcomes and with each selected independent variable was fitted. Second, variables with a *P* value ≤ .1 were included in three different multivariate blocks consisting of background, ICU-related, and ward-related variables for each dependent variable (worst pain intensity and -interference). This analysis used multivariate linear regression models while adjusting for age and gender as previously described.[11] Third, variables from each block significantly associated with each of the two outcomes were included in the multivariate linear mixed model analyses for repeated measures adjusting for age and gender. Selected covariates were entered as fixed effects, and the model was fitted with an unstructured covariance matrix. The results were presented as Beta (B) with 95% confidence interval (CI), and estimated means with 95% CI. All patients with at least one available follow-up in addition to data obtained at the ward early after ICU discharge were included without imputing missing values.

All analyses were considered exploratory without correction for multiple testing. Data were analysed using SPSS (IBM SPSS statistics version 25). A *P*-value of <.05 was considered significant.

3.2 | Ethics

The Regional Committee for Medical and Health Research Ethics and the hospital's Data Protection Officer approved the study (NCT02077244). All patients gave written consent before inclusion.
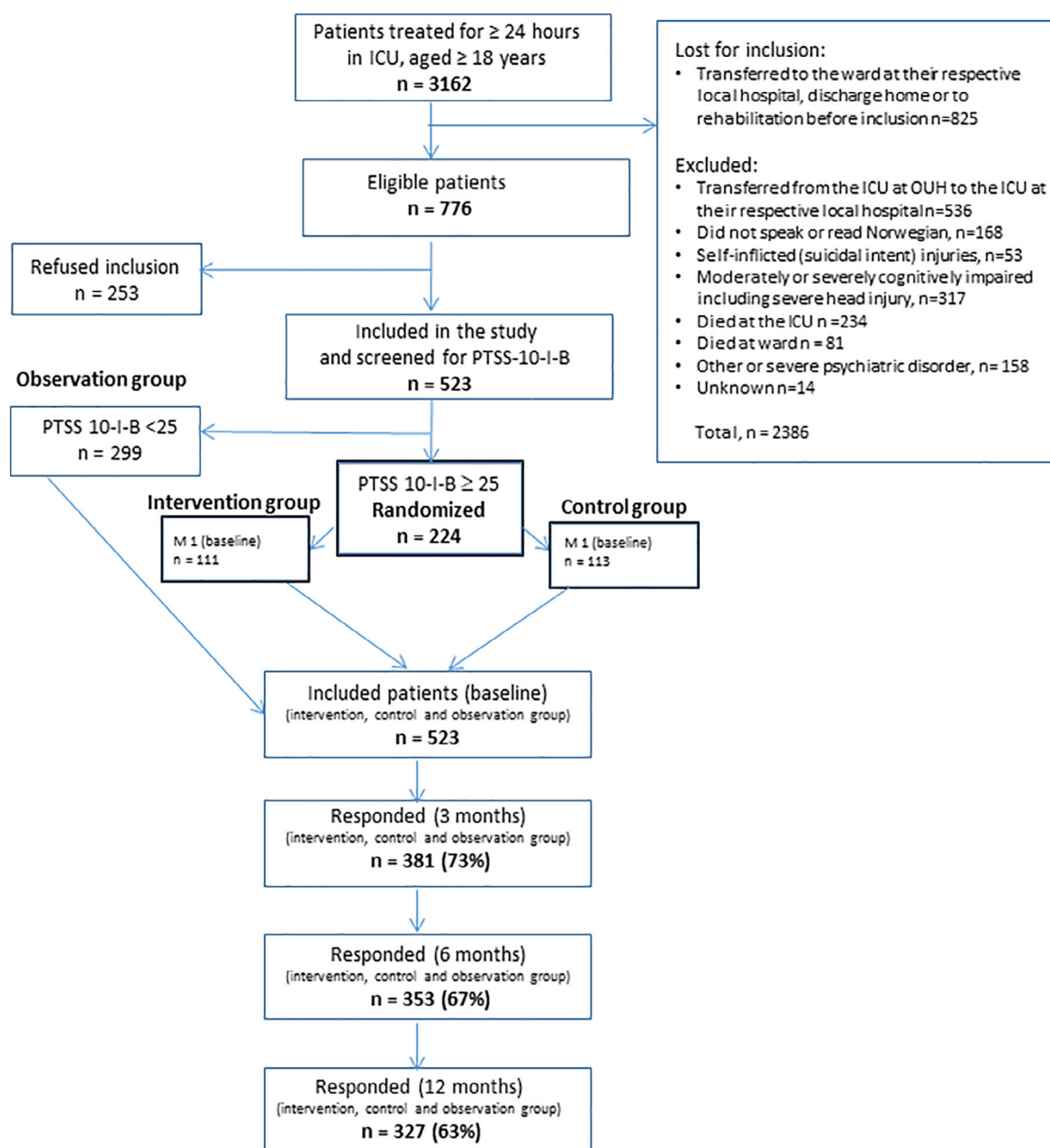

FIGURE 1 Flow diagram of patient recruitment. ICU, Intensiv care Unit; OUH, Oslo University Hospital

4 | RESULTS

We included 523 patients, and the questionnaires were completed median 4 days (range 0-48 days) after ICU discharge. Among the included patients, 53% were male, median age 57 years (range 18-94), median ICU length of stay (ICU LOS) 3 days (range 1-83 days), and 54% received mechanical ventilation. Elective major surgery (23%) was the largest patient group (Table 1).

Worst pain intensity (NRS > 0) was reported by 68% of the patients, a median of 4 days after ICU discharge, with 79% being moderate to severe (range 4-10). Estimated means for both worst pain intensity and -interference were highest early after ICU discharge and declined significantly at 12 months (Tables 2-4). In total, 213 (56%), 176 (50%), and 167 (51%) of the patients still reported worst pain intensity >0 after 3, 6, and 12 months, respectively. Observed means and SD of worst pain intensity and -interference are presented in Table S2.

Early after ICU discharge, 43% of the patients reported abdominal pain, 28% lumbar back pain, and 22% shoulder/upper arm pain (Table S1). Among 202 patients reporting abdominal pain, 173 (86%) had gastrointestinal disease or had undergone abdominal surgery. Mean number of reported pain locations was 3.0 (SD 4.3, range 0-30).

In the univariate analysis (step one), 21 independent demographic and clinical variables were investigated for significant association with worst pain intensity (13 variables) and -interference (14 variables) and further included in the multivariate linear regression (step two). In the multivariate linear mixed model analyses for repeated measures (step three), both worst pain intensity and -interference were adjusted for significant variables from step two: time, gender, PTSS 10-I-B (two groups: PTSS < 25 and PTSS ≥ 25), diagnosis, and PTSS-10-I-A (memory of traumatic experiences from the ICU) and adjusted for age (Tables 3 and 4). Variables significant only for higher worst pain intensity and adjusted for were; factual ICU memory, ICU LOS and SOC (Table 3). The following variables were statistically significantly associated with higher worst pain intensity within 12 months follow-up: sum score of PTSS-10-I-B ≥ 25 (B = 0.57 [CI 0.08-1.07]), female gender (B = 0.57 [CI 0.15-0.99]), shorter ICU LOS (B = −0.04 [CI −0.06 to −0.01]) and higher sum score of PTSS-10-I-A (B 0.19 [CI 0.02-0.36]) (Table 3). The following variables were statistically significantly associated with higher pain interference: sum score of PTSS-10-I- B ≥ 25 (B = 1.48 [CI 1.08-1.87]), female gender (B = 0.45 [CI 0.07-0.82]), lower age (B = −0.01[CI −0.02 to −0.00]), higher sum score of PTSS-10-I-A (B = 0.18 [CI 0.04-0.33]), and patients admitted with an internal medical diagnosis (B = −0.79 [CI −1.47 to −0.11]) (Table 4).

Mechanical ventilation was significantly associated to worst pain intensity in the univariate analysis (step one), but not in the multiple regression analysis (step two) and therefore not included in the final linear mixed model analyses (step three). Length of mechanical ventilation was not analysed because only 54% of the patients received it. No differences between the medical and surgical patients were found in LMV or LOS.

The following variables were either not significantly associated with worst pain intensity and -interference in the univariate linear regression

TABLE 1 Demographic and clinical characteristics (n=523)

		N	%
Gender	Male	279	53.3
	Female	244	46.7
Level of education	Primary school	64	12.2
	Secondary school	200	38.2
	University/college	248	48.1
Living status	Married/cohabitant	321	61.8
	Caring for children < 18 years	107	20.9
Diagnosis in ICU[a]	Trauma	93	17.8
	Acute surgery	103	19.7
	Elective surgery	118	22.6
	Organ transplant	54	10.3
	Cancer	97	18.5
	Internal medicine	58	11.1
Mechanical ventilator treatment		280	53.5
Heavy/hazardous drinking before hospital stay		203	39.5
Previous psychiatric problems		102	19.5
Used anxiolytics/ antidepressant before admission		116	22.2
Important events (in the past year) before hospital admission		173	33.1
		Median	**Range**
Age		57	18-94
ICU LOS[a]		3	1-83
OUH LOS[b]		20	3-217
ASA[c] score		2	1-4
SAPSII[d] score		24	0-78
Total PTSS-10-I-B[e]		22	10-70
PTSS-10-I-A [f]		5	4-8
		Mean	**SD**
Total Score SOC 13[g]		68.9	12.5

[a]ICU LOS, intensive care unit length of stay, days
[b]OUH LOS, Oslo University Hospital length of stay, days
[c]ASA, American Society of Anesthesiologists Physical Status Classification
[d]SAPS II, New Simplified Acute Physiology Score
[e]PTSS-10-I-B, Post Traumatic Stress Scale-10-I part B
[f]PTSS-10-I-A, Post Traumatic Stress Scale-10-I part A
[g]SOC 13, Sense of Coherence 13-Item Scale

model or in the block analysis: SAPS II score, ASA, heavy/hazardous drinking, medication use before hospital admission or previous psychiatric problems before hospital stay (Table 1). Therefore, they were not adjusted for in the multiple regression analysis for repeated measures. SOC and factual ICU memory were not significantly associated to worst pain intensity

TABLE 2 Mean value for worst pain intensity and pain interference for each measured point estimated with linear mixed model, adjusted for independent variables

	Within first week		3 mo		6 mo		12 mo	
	Mean	C.I	Mean	C.I	Mean	C.I	Mean	C.I
Worst pain intensity (n = 400)	5.5	4.6 to 6.5	3.7	2.7 to 4.7	4.1	2.7 to 5.6	3.8	2.8 to 4.8
Pain interference (n = 462)	4.5	3.7 to 5.3	3.2	2.4 to 4.1	2.9	2.1 to 3.7	2.9	2.1 to 3.7

Note: n, number of patients answering on pain at the hospital ward and at minimum one more time point.

TABLE 3 Estimates of fixed effects of worst pain intensity during 12 months follow-up (adjusted for independent variables) (n = 400)

		Fixed effects		
Variables at baseline		Estimate	P-value	95% Confidence interval
Time 1 (within the first week after ICU discharge)		1.71	<.001	1.28 to 2.15
Time 3 mo		−0.10	.570	−0.47 to 0.26
Time 6 mo		0.31	.585	−0.81 to 1.43
Time 12 mo	(Reference)			
PTSS-10-I-B (2 groups)	PTSS < 25 (reference)			
	PTSS ≥ 25	0.57	.023	0.08 to 1.07
Gender	Male (reference)			
	Female	0.57	.008	0.15 to 0.99
Age		−0.00	.856	−0.01 to 0.01
Diagnosis in ICU	Elective surgery (reference)			
	Trauma	−0.11	.737	−0.74 to 0.52
	Acute surgery	−0.44	.164	−1.07 to 0.18
	Organ transplant	−0.09	.807	−0.85 to 0.66
	Cancer	−0.56	.101	−1.22 to 0.11
	Internal medicine	−0.60	.155	−1.43 to 0.23
PTSS-10-I-A		0.19	.029	0.02 to 0.36
ICU LOS		−0.04	.001	−0.06 to −0.01
Total score SOC 13		−0.01	.155	−0.03 to 0.01
ICU memory	Factual memories	−0.65	.090	−1.40 to 0.10

Note: Male = 1, Female = 2. No = 0, Yes = 1, PTSS <25 = 0, PTSS≥25 = 1, Elective surgery = 0, Trauma, Acute surgery, Organ transplant, Cancer and Intern medicine = 1.
Abbreviations: ICU, intensive care unit; ICU LOS, ICU length of stay, days; PTSS-10-I-A, Post Traumatic Stress Scale-10-I part A; PTSS-10-I-B, Post Traumatic Stress Scale-10-I part B; SOC 13, Sense of Coherence 13-Item Scale.

in the multivariate linear mixed model analyses for repeated measures (Table 3). Pain interference, SOC, and factual memory did not reach statistical significance in the uni- or block analysis and were subsequently not included in the mixed model analysis.

5 | DISCUSSION

Our main findings were that 68% of patients reported pain median 4 days after ICU discharge with 79% having moderate to severe worst pain intensity. High levels of PTS symptoms, more memories of traumatic experiences from the ICU, and female gender were associated with higher worst pain intensity and -interference within 12 months.

Shorter ICU LOS was associated with worst pain intensity, and younger age was associated with higher pain interference. SOC was neither associated with worst pain intensity nor -interference.

Moderate to severe pain was reported by 79% of the patients reporting pain early after ICU discharge. Others have previously reported that up to 90% of discharged ICU patients have pain at the ward.[5] Puntillo et al reported the need for clinicians to recognize and include a better pain assessment process in the ICU to better manage patients' pain symptoms.[34] Pain management among ICU patients deserves more focus, and especially prior to discharge to the ward.[5] The reduced patient-nurse ratio at the ward with subsequent less pain monitoring might lead to reduced pain management as a consequence. Lower pain scores have been found in patients treated at a

TABLE 4 Estimates of fixed effects of pain interference during 12 months follow-up (adjusted for independent variables) (n = 462)

Variables at baseline		Fixed effects		
		Estimate	P-value	95% Confidence interval
Time 1 (within the first week after ICU discharge)		1.57	<.001	1.20 to 1.93
Time 3 mo		0.33	.060	−0.01 to 0.67
Time 6 mo		−0.01	.945	−0.28 to 0.26
Time 12 mo	(Reference)			
PTSS-10-I-B (2 groups)	PTSS < 25 (reference)			
	PTSS ≥ 25	1.48	<.001	1.08 to 1.87
Gender	Male (reference)			
	Female	0.45	.020	0.07 to 0.82
Age		−0.01	.037	−0.02 to −0.00
Diagnosis in ICU	Elective surgery (reference)			
	Trauma	0.54	.060	−0.02 to 1.11
	Acute surgery	0.09	.761	−0.47 to 0.64
	Organ transplant	−0.07	.848	−0.75 to 0.61
	Cancer	−0.15	.628	−0.73 to 0.44
	Internal medicine	−0.79	.022	−1.47 to −0.11
PTSS 10-I-A		0.18	.015	0.04 to 0.33

Note: Male = 1, Female = 2. No = 0, Yes = 1, PTSS < 25 = 0, PTSS ≥ 25 = 1, Elective surgery = 0, Trauma, Acute surgery, Organ transplant, Cancer and Intern medicine = 1.

Abbreviations: ICU, intensive care unit; PTSS-10-I-A, Post Traumatic Stress Scale-10-I part A; PTSS-10-I-B, Post Traumatic Stress Scale-10-I part B.

ward managed by an acute pain management service team, compared with a ward without pain management service.[35] This might indicate that specialized teams with anaesthesiologists and nurses trained in pain management are needed on wards to improve pain management. Such a team is available at our institution and is consulted in patients with a complex situation or with severe pain. Still, the present results might indicate that they have been underused.

Abdominal pain was reported by almost half of the patients at the hospital ward early after ICU discharge. Although 86% of these patients had gastrointestinal diseases and many had undergone abdominal surgery, the results are still disappointing. Epidural analgesia, as the central part of pain management in this patient group,[36] usually continues after transferal from ICU to the ward. Thus, ward patients would be expected to have reduced pain. It might be that most epidurals were already discontinued a median of 4 days after ICU discharge. Unfortunately, we do not have data on actual pain management for these patients.

Unlike our findings, Battle et al[37] and Langerud et al[9] showed that shoulder/upper arm were the most common pain locations in a mixed sample of ICU survivors.[9,37] However, they did not link their findings to the patient's primary diagnosis but, rather, to the patients being on bed rest, not able to move and lacking muscle tone. Also, those researchers ascertained anatomic location of the pain 3 months or later after the patients' ICU discharge.[9,37]

As expected, both mean values for worst pain intensity and pain interference declined during the 12 month follow-up period. However, worst pain intensity was still moderate after 12 months, showing

that chronic pain is of concern after ICU treatment. Two previous studies have also demonstrated that substantial pain intensity persists up to 12 months after ICU discharge.[9,38] Similar results were also found by Hayhurst et al, where moderate to severe pain was present in 31% to 35% at three and 12 months after ICU discharge.[10] Regarding pain interference over time, Langerud et al[9] found a higher score in pain interferences for all seven individual items between three and 12 months, whereas Hayhurst et al[10] found similar pain interference scores as our study at the same time points. Our results indicate that pain is affecting physical and mental functioning in daily living.

Moderate to severe PTS symptoms were associated with higher worst pain intensity and pain interference over a 12-month post-discharge period. This is in accordance with similar studies on trauma patients showing an association between PTS symptoms/PTSD and chronic pain.[39-41] In addition, we found an association between traumatic ICU memories and higher pain intensity. To our knowledge, this finding has not previously been demonstrated. This association highlights the importance of preventing traumatic experiences as well as pain during the patient's ICU stay. SOC was neither associated with worst pain intensity nor with pain interference, in contrast to previous studies reporting an association between low SOC and chronic pain in cardiac surgery patients,[16] and high SOC and lower pain intensity in patients at primary care with chronic musculoskeletal pain.[42] One explanation for the absent association in our sample could be that the SOC score increased during the year, thereby leading to better coping with pain. Subsequently, a low score in SOC at the ward would not impact on pain during the year.

Female gender was significantly associated with higher worst pain intensity and pain interference. No associations between gender and acute[5] or chronic pain[37] in mixed ICU patients have previously been found, but these studies have smaller samples compared with the present study. However, women report more chronic pain than men in the general population.[43] Younger age was significantly associated with higher pain interference, as opposed to a previous study demonstrating a significant association between increasing age and more pain.[37]

Shorter ICU LOS was also associated with higher worst pain intensity. This is a surprising finding, differing from two previous studies with mixed ICU patients showing that longer ICU LOS was associated with persistent pain.[9,37] We would expect that ICU patients with longer ICU LOS would have more complex diseases, more complications, and, subsequently, more long-term pain. The SAPS II score was lower and the ICU LOS shorter in the present study as compared with Langerud et al[9] and Battle et al,[37] respectively.

Finally, a primary internal medical diagnosis was associated with less pain interference. In a recent systematic review about persistent pain in ICU survivors, there were no differences among medical and surgical patients regarding post-discharge pain.[8] More focus on pain in handover after ICU discharge would improve and better tailor individual pain management, thereby contributing to better quality of care and less complications due to reduced or exaggerated use of pain medication. This could reduce time to hospital discharge and also the amount of chronic pain. Further research may elicit more knowledge about factors associated with post-discharge pain as a foundation for improved prevention and treatment interventions after ICU discharge.

5.1 | Limitations and strengths

The present study has several limitations and strengths. We did not ask patients about presence of any pain prior to hospital admission, and we cannot eliminate the possibility that patients' pain after ICU discharge was related to previous illness/injury. Moderate to severe chronic pain occurs in 19% of adults,[44] and 31% of Norwegians report chronic pain lasting more than 6 months.[45] Some patients were lost to follow-up, many due to early transfer to local hospitals. We do not know if they differed from included patients. Although the five ICUs and different wards use similar validated pain measurement tools (Behaviour Pain Scale, Critical Care Observation Tool, NRS in ICUs and NRS at wards), no common pain protocol exists and there might be differences in local pain management practices. Data are 4 years old because they are reanalysed as a predefined substudy from an RCT that was published last year. We do not have specific data on actual pain management or use of mobilization and physical therapy at the ward. The inclusion period lasted for 34 months. However, no systematic changes in pain management in the ICUs or at the wards were implemented during this time period, and we do not believe that the long inclusion period affected the results. Finally, only patients reading and understanding Norwegian were included, and this could limit both findings and generalizability. However, the large sample size of mixed ICU patients, and use of the BPI, a recognized and validated pain measurement tool, strengthen the present study.

5.2 | Implications and recommendations for practice

Early follow-up with focus on pain management and factors associated with pain early after ICU discharge and the following year could reduce development of chronic pain. More information on factors associated to pain/persistence of pain can help ICU nurses to improve pain management prior to ICU discharge.

6 | CONCLUSION

Seventy-nine percent of ICU patients with pain (a median of 4 days after ICU discharge) had moderate to severe pain. Although both worst pain intensity and -interference declined the following year, worst pain intensity was still moderate after 12 months. Female gender, high level of PTS symptoms, traumatic ICU memories, shorter ICU LOS, and younger age were identified as patients at risk for development of chronic pain. Future research is warranted to confirm these results and to evaluate interventions aimed to prevent acute and chronic pain after ICU stay.

AUTHOR CONTRIBUTIONS
All the authors have contributed to the manuscript. The authors ÅV, TR, MCS, LS, ISB, KS, and KT have contributed to the design and planning of the study. The first (ÅV) and last (KT) author included the patients. All authors (including KP) have contributed to the planning of the analysis, interpretation and discussing the results, and with the writing of the whole manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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