Title page

Clinical impact of chronic substance abuse in a Norwegian ICU-population

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Short title: Substance use disorders in ICU-patients
This work was carried out at the Oslo University hospital, Ullevaal and the Diakonhjemmet Hospital, Oslo, Norway.

Word count:
Abstract: 248 words
Manuscript: 3180 words

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Conflicts of interests
Regarding possible conflicts of interest, Professor Dag Jacobsen and Dr. Fridtjof Heyerdahl are shareholders in "Orphan Diagnostics", developing diagnostic strips for the use in methanol & ethylene glycol poisonings. Dr. Fridtjof Heyerdahl is founder and shareholder in Epiguard (transportation systems for patients with contagious diseases). None of these are considered to be of relevance for the current work. We have no other conflicts of interest to disclose.

Abstract

Background: The clinical impact of chronic substance abuse of alcohol and drugs – referred to as substance use disorders (SUD) – is often overlooked in the intensive care (ICU) setting. The aims of the present study were to identify patients with SUD – regardless of cause of admission - in a mixed Norwegian ICU-population, and to compare patients with and without SUD with regard to clinical characteristics and mortality.

Methods: Cross-sectional prospective study of a mixed medical and surgical ICU-population aged ≥18 years in Oslo, Norway. Data were collected consecutively, using a questionnaire including the AUDIT-C test, medical records and toxicology results. Patients classified with SUD were divided into the subgroups alcohol use disorders (AUD) and drug use disorders (DUD).

Results: Overall, 222 (26%) of the 861 patients included were classified with SUD; 137 (16%) with AUD and 85 (10%) with DUD. 130/222 (59%) of the SUD-patients had substance abuse-related cause of ICU-admission. Compared to non-SUD patients, DUD-patients were younger (median age 42 vs. 65 years) and had lower SAPS II scores (41 vs 46), while AUD-patients had higher SOFA scores (8.0 vs 7.3). Overall, age-adjusted logistic regression analysis showed similar hospital mortality for SUD-patients and non-SUD patients, but AUD was associated with increased mortality among medical patients and in patients with sepsis (OR 1.7 (95%CI 1.0-2.8), and OR 2.6 (95%CI 1.1-6.2)).

Conclusion: One in four ICU-patients had SUD regardless of cause of admission. Alcohol use disorder was associated with increased mortality in medical patients and in patients with sepsis.

Introduction

Acute substance abuse is a common cause of admission to intensive care units (ICUs) [1-5]. Furthermore, chronic substance abuse of alcohol or drugs – collectively referred to as substance use disorders (SUD) – is associated with a wide range of detrimental health effects predisposing the patients to other types of critical illness such as sepsis and respiratory infections[6-10].

Early recognition of SUD in ICU-patients may have important therapeutic and prognostic implications[7]. However, due to lack of routine screening, critical care providers often fail to identify patients with SUD, possibly delaying important clinical interventions[6, 11, 12]. Thus, a more systematical identification of ICU-patients with SUD may improve outcomes for these critically ill patients[5, 13].

Reported prevalence of SUD in ICU-populations are in the range of 14-39%[4, 14, 15], but differences in inclusion criteria, case-mix and patterns of abuse complicate the generalizability of these data. Furthermore, the majority of studies addressing the clinical impact of SUD in ICU-patients concern patients with alcohol use disorders (AUD), while ICU-patients with drug use disorders (DUD) have been less described.

The present study is based on cross-sectional data of a mixed medical and surgical ICU-population in Oslo, Norway, collected with the overall purpose of evaluating the impact of acute and chronic substance abuse of alcohol and drugs on the ICU-population. As previously published[1], substance abuse was direct or indirect cause of ICU-admission for 20% of the patients, of which the majority were due to *acute* substance abuse. In the present study we wanted to gain more knowledge regarding the clinical impact of *chronic* substance abuse, independent of the reason for ICU-admission. As such, the aims of the present study were to identify patients with SUD of alcohol or drugs – *regardless of cause of admission* – and to compare the clinical characteristics and mortality of patients with and without SUD.

Methods

Design and setting

Cross-sectional data were obtained from a prospective observational cohort study of ICU-patients admitted to ICUs at the Oslo University Hospital Ullevaal and the Diakonhjemmet Hospital between February 3, 2014 and February 2, 2015[16]. We included patients ≥18 years with at least one of the following inclusion criteria: (1) Intubation regardless of length of stay **and/or** (2) ICU length of stay ≥24 hours *and* dysfunction of ≥ two organ systems as defined in *appendix 1*. In order to avoid individuals being represented multiple times, *only* the first admission of each patient during the study period was registered. As such, 861 patients were included (Figure 1).

Data collection and classification

Data were collected consecutively using a standardized registration form, including information from a questionnaire regarding prior alcohol and drug use, the patient`s medical records and toxicology results. The questionnaire was answered by the patient or next of kin and included the Alcohol screening test Audit-C[17] and the initial question of the Drug Use screening test DUDIT[18]. Main agents of abuse, frequency of use and route of administration (intravenous, per oral or inhalation) were registered. Substance abuse-related admissions (abbreviated SARA) were defined as ICU-admissions associated with acute or chronic abuse of alcohol or drugs[1] (*appendix 2*). Preadmission and clinical variables were registered as described in *appendix 3.* Outcome measures were ICU-mortality and total hospital mortality**.**

Substance Use Disorder (SUD)

The term substance use disorder (SUD) was used when referring to patients with long term, excessive use of alcohol and/ or drugs, fulfilling ≥1 of the following criteria:

A. Documented alcohol (AUD) or drug use disorder (DUD) in the medical record and/or questionnaire. For the AUDIT-C test a cut off level of ≥ 8 points (range 0 -12) was chosen, as it has been found to correspond to severe alcohol misuse and an increased risk of ICU-admission[19, 20]. Patients with drug use more than 2-3 times a week and all patients with intravenous drug abuse were classified with drug use disorder (DUD).
B. Documented medical condition causally related to chronic substance abuse of alcohol or drugs. Defined according to the ICD-10 criteria, these included hepatic encephalopathy, esophageal varices, alcoholic gastritis, alcoholic hepatitis, alcoholic liver failure, alcohol related seizures, alcohol withdrawal and heroin nephropathy.

Based on main agent of abuse, patients classified with SUD were divided into the subgroups 1) alcohol use disorders (AUD) and 2) drug use disorders (DUD). For patients with combined drug and alcohol abuse, the patients were classified based on which agent of abuse was considered the most important.

Identification of patients with SUD

The evaluation of whether a patient had SUD or not, was made by a small group of study personnel consisting of physicians and nurses on the wards. Regular consensus meetings were held in order to reduce interrater variability. Patients where collateral information (from medical records and/or next of kin) strongly indicated current substance abuse were classified as SUD despite discrepancy with the information given in the questionnaire. Patients with manifest complications of chronic substance abuse were classified as SUD regardless of current alcohol or drug consumption.

Of the 670 (78%) patients included by consent, the questionnaire regarding prior alcohol and drug use was completed for 620 (93%) (Figure 1); by the patient in 271 (44%) cases and by next of kin in 349 (56%) cases. 16 patients were classified with AUD despite an AUDIT C score < 8. Of these, 7 patients had secondary complications of chronic substance abuse, while for 9 patients there was a discrepancy between the AUDIT C score and collateral information. In 6 cases AUD was confirmed by next of kin, although AUDIT C scores were not obtained due to incomplete questionnaires. For the 241 patients

included without questionnaires, evaluation of SUD was based on information from medical records and laboratory results alone.

Ethics

Ethics approval was granted by the Norwegian Regional Ethics Committee (REK), case number 2012/12601. Informed consent was given by the patient or next of kin. Exceptions were made for patients (1) unable to give their consent themselves and without next of kin who could be asked, (2) admitted with acute poisoning and (3) who died during ICU treatment.

Sample size

The total number of patients was expected to be in the range of 800-1000 during the study period of 1 year. For percentage data, a sample size of 800 gives a 95% confidence interval length of less than 3.5 percentage points for any presented proportion. This precision was considered to be sufficient for the purposes of the study. For subgroup analysis (e.g. mortality) the length of the confidence interval will be longer.

Statistics

IBM SPSS® version 26.0 for Windows (Armonk, NY, USA) was used for statistical analysis. Continuous variables were expressed as median and inter-quartile range or mean and range. In order to assess precision, 95% confidence intervals were presented where appropriate. When appropriate, the data was stratified for gender and type of admission (medical vs. surgical). Logistic regression analysis was used to adjust for confounding variables when comparing mortality in subgroups. Variables included in the regression analysis were chosen for clinical relevance, independency and whether they contributed in the multivariate analysis.

Results:

Prevalence of SUD

Of the 861 patients included, 222 (26%) were classified with substance use disorders (SUD): 137 (16%) with alcohol use disorders (AUD) and 85 (10%) with drug use disorders (DUD) (Figure 2 and Table 1). Of the 222 patients with SUD, 130 (59%) had substance abuse related cause of ICU-admission (SARA), while 92/222 (41%) had *non*-substance abuse-related cause of admission. In addition, 38(6%) of the 639 patients *not* classified with SUD (non-SUD patients) had SARA (Table 1) Overall, 260/861 (30%) of the study population had either SARA and/or SUD (Figure 2.)

The prevalence of SUD was twice as high in male as in female patients (176/567, 31% (95%CI 27-35%) vs 46/294, 16% (95%CI 12-20%). Of the 567 males, 106 (19%) had AUD and 70 (12%) had DUD. Of the 294 females 31 (11%) had AUD while 15 (5%) had DUD. Males aged 30-59 years had the highest prevalence of SUD (94/197, 48%). The prevalence of SUD was similar in medical and surgical patients (143/537, 27% (95%CI 23-30%) vs 79/324, 24% (95%CI 20-29%). Median AUDIT C scores for AUD-patients was 10 (IQR 8-11) (Table 1). Of the 85 patients classified with DUD, 58(68 %) were prior or current intravenous drug abusers.

Preadmission characteristics and cause of admission

Compared to non-SUD patients, SUD-patients were younger (median age 55 vs 65 years (95%CI 53-58 vs 95%CI 63-67 years)), and had higher proportion of males (176/222, 79% (95%CI 74-84%) vs 391/639, 61% (95%CI 58-65%)) and current smokers (161/222, 73% (95%CI 66-78%) vs 143/639, 22% (95%CI 19-26%)) (Table 1). When compared to non-SUD patients, DUD-patients were significantly younger (median age 42 vs 65 years (95%CI 33-53 vs 95%CI 63-67 years)) and had lower Charlson comorbidity index (mean 1.3 vs 2.4 (95%CI 0.9-1.7 vs 95%CI 2.3-2.5)), while there were no such differences between AUD-patients and non-SUD patients.

Poisoning (40/65, 62%), gastrointestinal disease (27/81, 33%) and trauma (58/191, 30%) had the highest prevalence of SUD. Overall, 59/85 (69%) of the DUD-patients had substance abuse-related ICU-

admissions (SARA) (Table 1), of which 56/59 (95%) were due to *acute* substance abuse. Correspondingly, 71/137 (52%) of AUD-patients had SARA (Table 1). However, while 32/35 (91%) SARA-admissions in surgical AUD-patients were associated with *acute* substance abuse, 26/36 (72%) of SARA-admissions in medical AUD-patients were caused by complications of *chronic* substance abuse.

Severity of illness, complications and treatment

Overall, severity of illness was similar for SUD and non-SUD patients (Table 1). However, DUD- patients had lower SAPS II scores (mean 41 vs 46 (95%CI 38-44 vs 95%CI 45-47), and AUD-patients had higher SOFA scores on admission when compared to non-SUD patients (mean 8.0 vs 7.3 (95%CI 7.5-8.5 vs. 95%CI 7.2-7.4)). In medical patients, AUD-patients had a higher proportion of patients with increased SOFA scores after 48 hours (SOFAΔ48) than non-SUD patients (32/61, 52% (95%CI 40-65%) vs 84/276, 30% (95%CI 25-36%). There was no such difference in SOFAΔ48 between surgical AUD-patients and non-SUD patients.

DUD-patients had shorter duration of mechanical ventilation than non-SUD patients (median days 1 vs 3 (95%CI 1-2 days vs 95%KI 2.5-4 days, respectively) Table 1). AUD-patients had longer duration of mechanical ventilation than non-SUD patients, but this difference was not statistically significant (median days 4.5 vs 3 (95%CI 3-6 vs 95%CI 2.5-4 days)). Among patients with sepsis, pulmonary infection was the most common source of infection among non-SUD patients and patients with AUD (70/168, 42% and 10/25, 40% respectively), while soft tissue infection and endocarditis were most common among sepsis patients with DUD (10/17, 59%). Acute liver failure was more common in AUD-patients than in non-SUD patients (23/137, 17% (95%CI 11-24%) vs 24/639, 4% (95%CI 2-5%).

Mortality

Overall, logistic regression analysis showed no difference in mortality between SUD and non-SUD patients (OR 0.8(95%CI 0.6-1.1), Table 2). DUD-patients had lower mortality than non-SUD patients (OR 0.4, (95%CI 0.2-0.8)), but this difference disappeared when adjusting for age (OR 0.9 (95%CI 0.5-

1.6). AUD-patients had age-adjusted mortality similar to that of non-SUD patients (OR 1.1 (95%CI 0.8-1.7)), but AUD was associated with higher age-adjusted mortality in medical patients and in patients with sepsis (OR 1.7 (95%CI 1.0-2.8) and OR 2.6 (95%CI 1.1-6.2), Table 2). Comparison of 30-day mortality for SUD and non-SUD patients showed similar trends as for hospital mortality (Table 1).

Discussion

In the present study, one in four ICU-patients, and almost half of males aged 30-59, had an underlying substance use disorder (SUD). In addition, previously published data has shown that 20% of the study population had substance abuse-related cause of ICU-admission (SARA)[1]. When combined, these findings show that 30% of the ICU-patients had SARA and/or SUD. This demonstrates that substance abuse of alcohol and drugs is not only a common predisposing factor for ICU-admission, but also an important comorbidity factor among ICU-patients both with and without substance abuse-related causes of ICU-admission. Although overall mortality was similar for SUD and non-SUD patients, subgroup analysis showed diverging trends for AUD and DUD-patients, reflecting the heterogeneity of patients with SUD.

Prevalence of SUD

In the present study 19% of the males and 11% of the females were classified with AUD. This is more than twice as high as the estimated prevalence of AUD in the general Norwegian population, which is 8% for males and 3% for females[21]. The 10% prevalence of DUD in the present study is many times higher than the estimated prevalence of 0.9% in Oslo[21]. This demonstrates that patients with SUD are significantly overrepresented among patients in need of intensive care, in line with previous findings[14, 19].

Few ICU-studies have addressed the prevalence of SUD due to both alcohol and drugs. The 26% prevalence of SUD in the present study is higher than the 19% in a US ICU-study[14] and lower than the 39% described by de Wit et al in a US study of mechanically ventilated medical patients[15]. Variations in inclusion criteria (in our study ICU-patients with established organ dysfunction), case-mix and patterns of abuse may have contributed to these differences. Since most prior studies of SUD in ICU-patients have described patients with alcohol use disorders (AUD)[13, 22], distinguishing between patients with mainly AUD and mainly drug use disorders (DUD) may be of interest when comparing studies. In the present study, 16% of all patients were classified with AUD. This proportion is higher than a US study[10],

but markedly lower than in studies from Finland[23] and Scotland[22]. Since both these countries have a much higher alcohol consumption than Norway[24] we consider differences in drinking patterns an explanatory factor.

Characteristics of patients with substance use disorders

In line with previous studies, patients with SUD differed from the mixed medical/surgical ICU-population in being younger, with a higher fraction of males, and more likely to be admitted due to poisoning, trauma and gastrointestinal disease[14, 23, 25]. Nonetheless, preadmission and clinical characteristics differed significantly between patients with AUD and DUD, reflecting the heterogeneity of patients with SUD. Although severity of illness overall was similar for SUD and non-SUD patients, DUD-patients had significantly lower SAPS II scores. This may explain why DUD-patients had shorter duration of mechanical ventilation when compared to non-SUD patients.

Mortality

When evaluating the impact on SUD on hospital mortality, subgroup analysis showed diverging trends for AUD and DUD-patients. DUD-patients had lower hospital mortality than non-SUD patients, most likely explained by the high proportion of patients admitted due to acute substance abuse (such as poisoning) associated with low hospital mortality[1, 26]. However, DUD-patients were markedly younger than AUD and non-SUD patients, and the difference in mortality disappeared when adjusting for age.

The higher mortality among AUD patients with sepsis is in line with previous findings showing that AUD is a known risk factor for mortality in ICU-patients with sepsis[10]. Impaired immune function associated with chronic alcohol consumption is likely an important contributory factor [6, 7].

Regarding the comparatively high mortality of patients with AUD in medical but not in surgical patients, we consider that the higher proportion of patients with complications of chronic substance abuse was of importance, these being known risk factors of mortality in AUD-patients [25]. Furthermore, more medical than surgical AUD-patients had an increase in SOFA scores the first 48 hours, an unfavorable development associated with increased mortality[27].

Methodological considerations

In the present study we included patients who either received mechanical ventilation, and/or had length of stay >24 hours combined with organ dysfunction of at least two organ systems. The main reason for this choice of inclusion criteria was to study the impact of substance abuse on the more resource demanding ICU-patients, and avoid confounding results from "lighter" ICU-patients with a need for observation rather than real organ dysfunction.

Although several screening methods may aid the identification of patients with problematic alcohol use[7, 12, 28], there appears to be limited use of these assessment tools in the ICU[11, 12]. In the present study we used the AUDIT-C test in identifying AUD-patients, a validated screening tool recommended for emergency settings[17] with good corroboration between patient and proxy reports[29]. In the present study more of than half of the questionnaires were answered by next of kin. For the AUDIT-C test (scores 0-12), a cut-off score of 4 points is commonly used in screening for alcohol misuse[30]. However, several recent studies have defined risk-zones to select patients with different degrees of alcohol misuse[19, 31-33]. Thus, in order to select patients with a high probability of AUD, we chose a cut-off score of ≥ 8 for the present study.

Strengths and limitations

The patient cohort in the present study is relatively large and contains ICU-patients with a variety of diagnoses. Data were collected consecutively and included a comprehensive data set, including data from validated screening tools. The use of a questionnaire contributed to important supplementary information regarding the patient's prior alcohol and drug use.

The inclusion criteria helped select ICU-patients with a high severity of illness. However, it may also represent a limitation since cases of intoxications, particularly due to substances with short elimination half-lives, may have been missed. Furthermore, the higher prevalence of substance abuse in larger cities – such as Oslo – when compared to more rural areas[21], and the high proportion of trauma patients in our study population, represent possible selection bias affecting the generalizability of our

results. As to bias due to confounding, logistic regression analysis was used. As to potential information bias, alcohol and drug consumption may have been under-reported for some patients. Another weakness is possible subjective bias in the decision-making process on whether patients were classified with substance use disorder or not. Thus, in order to reduce interrater variability the registrations were made by a small number of study personnel. Questionnaire information was not obtained for one fifth of the patients, mainly due to limited communication and interaction with critically ill patients or lack of next of kin who could provide supplementary information. For these patients, biomarkers might have been useful but were not used due to limited laboratory resources.

Clinical implications

Our findings indicate that patients with SUD have significantly increased risk of ICU-admission when compared to the general population. Considering that substance abuse represents a potentially modifiable risk factor for critical illness, SUD should be acknowledged as a comorbid condition that deserves attention similar to that given to other chronic conditions in ICU-patients. Hospital admission may represent a window of opportunity, as it may result in referral to follow-up[34-38].

More than 40% of SUD-patients had *non*-substance abuse-related cause ICU-admission, demonstrating the importance of screening ICU-patients for substance abuse *regardless* of cause of admission. The high response rate of the questionnaire used in the present study suggests that implementation of routine screening for alcohol and drug abuse is feasible.

Due to the heterogeneity of patients with SUD, further subgroup analysis such as stratified analysis within diagnostic categories would have been of interest. This was not possible in the present study due to limited sample size, but should be a topic for future studies concerning substance abuse in intensive care patients.

Conclusions

- Alcohol use disorder was associated with increased hospital mortality in medical patients and in patients with sepsis.
- One in four ICU-patients and almost half of male ICU-patients age 30-59 had underlying substance use disorders (SUD).
- More than 40% of SUD-patients had *non*-substance abuse-related cause of ICU-admission demonstrating the importance of screening for substance abuse r*egardless* of cause of admission.

List of abbreviations

SUD – substance use disorder

AUD – alcohol use disorder

DUD – drug use disorder

SARA – substance abuse-related cause of ICU-admission

ICU – intensive care unit

LOS- length of stay

OR – odds ratio

IQR – interquartile range

95%CI – 95% confidence interval

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the Norwegian Regional Ethics Committee (REK), case number 2012/12601. Se ethics section in the manuscript for further details.

Consent for publication

Not applicable

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

Regarding possible conflicts of interest, Professor Dag Jacobsen and Dr. Fridtjof Heyerdahl are shareholders in “Orphan Diagnostics”, developing diagnostic strips for the use in methanol & ethylene glycol poisonings. Dr. Fridtjof Heyerdahl is founder and shareholder in Epiguard (transportation systems for patients with contagious diseases). None of these are considered to be of relevance for the current work. We have no other conflicts of interest to disclose.

Funding

Not applicable.

Author`s contributions

KHT contributed substantially to the conception and design of the study, and was in charge of the inclusion process and the acquisition of data. Furthermore, she performed the statistical analysis in cooperation with LS and was the main writer of the manuscript. DJ and FH contributed substantially to the conception and design of the study and were major contributors in the writing of the manuscript. MB, GTD, CLH, GØA and LMH contributed with the acquisition of data including inclusion of patients

and completion of the registration form. In addition, MB played a vital role in the practical organization and implementation of the inclusion process while CLH also contributed significantly in the writing of the manuscript. LS contributed with the statistical analysis and interpretation of the data, as well as revision of the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

The authors wish to thank the nurses and medical staff at the ICUs at the Oslo University Hospital Ullevaal and the Diakonhjemmet Hospital for their cooperation and assistance with the inclusion of patients during the study period.

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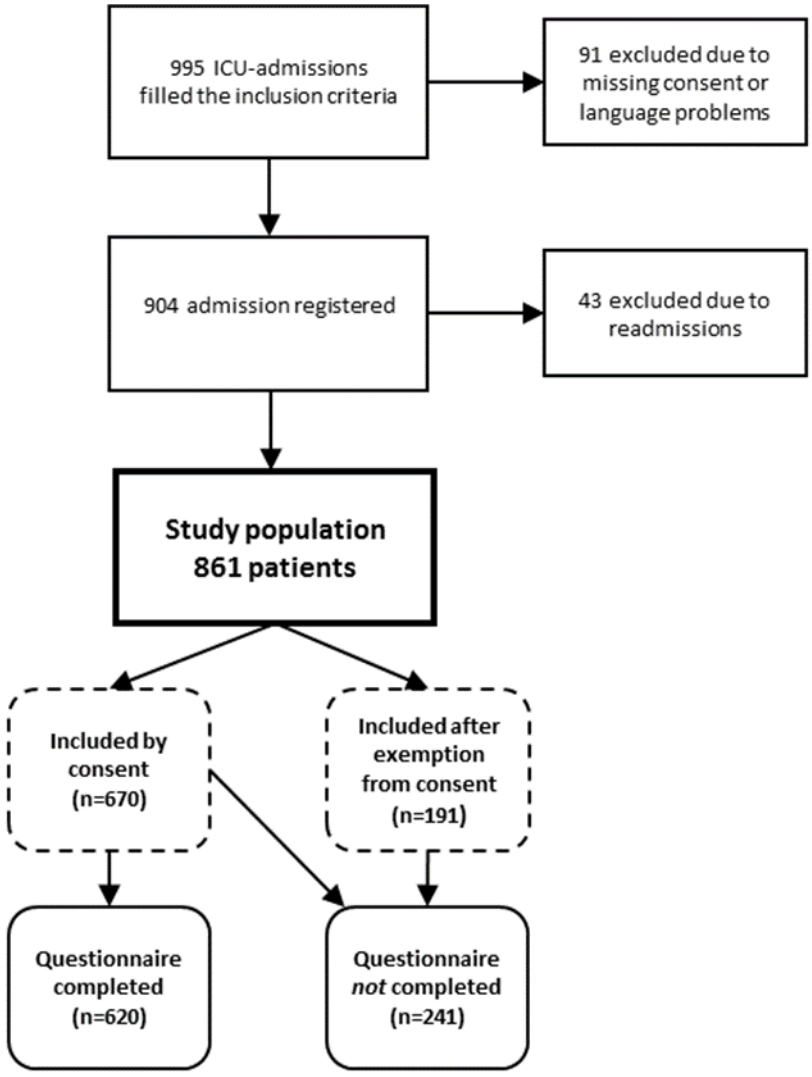

Figure 1. Flowchart of the inclusion process

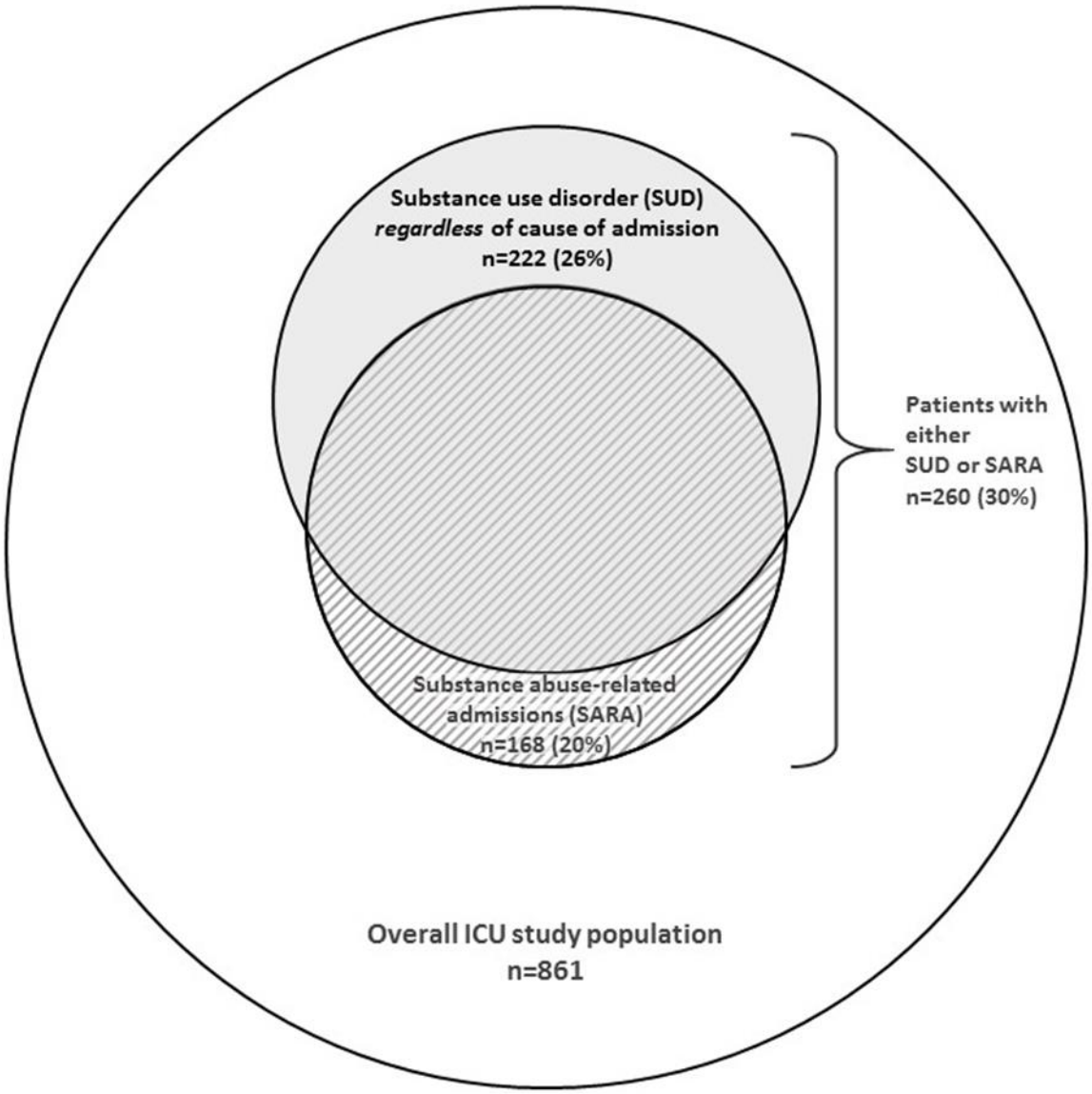

Figure 2. Patients with chronic substance abuse (SUD) and patients with substance abuse-related admission (SARA) in the ICU-population

Table 1.Comparison of SUD and non-SUD patients, overall and in subgroups

	SUD PATIENTS (n=222)			**NON-SUD PATIENTS** (n=639)
	SUD, total	**Subgroups**		
	(n=222)	**AUD** (n=137)	**DUD** (n=85)	
Baseline characteristics				
Age, median (IQR)	55(43-66)	63 (55-70)	42 (34-51)	65 (51-75)
Males n (%)	176 (79%)	106 (77%)	70 (82%)	391 (61%)
Charlson comorbidity score, mean ± SD	2.0 ± 2.0	2.3± 2.0	1.3 ±1.8	2.4 ± 2.3
Current smoker n (%)	161 (73%)	94 (69%)	67 (79%)	143 (22%)
Type of admission				
Medical n (%)	143 (64%)	81 (59%)	62 (73%)	394 (62%)
Surgical n (%)	79 (36%)	56 (41%)	23 (27%)	245 (38%)
AUDIT-C score, median (IQR)	9 (5-11)	10 (8-11)	5 (1-8)	2 (1-4)
Main diagnose n (%)				
Trauma	58 (26%)	38 (28%)	20 (24%)	133 (21%)
Cardiovascular disease	30 (14%)	24 (18%)	6 (7%)	150 (24%)
Sepsis	26 (12%)	13 (10%)	13 (15%)	90 (14%)
Respiratory disease	12 (5%)	10 (7%)	2 (2%)	76 (12%)
Gastrointestinal disease	27 (12%)	23 (17%)	4 (5%)	54 (9%)
Neurologic disease	18 (8%)	13 (10%)	5 (6%)	55 (9%)
Poisoning	40 (18%)	10 (7%)	30 (35%)	25 (4%)
Cancer	2 (1%)	2 (2%)	0	21 (3%)
Other	9 (4%)	4 (3%)	5 (6%)	35 (6%)
Cause of admission n(%)				
Substance abuse-related cause of ICU-admission (SARA)	130(59%)	71 (52%)	59 (69%)	38 (6%)
_*acute* substance abuse	98 (44%)	42 (31%)	56 (66%)	38 (6%)
_complication of *chronic* substance abuse	32 (14%)	29 (21%)	3 (3%)	0
Severity of illness/treatment				
SAPS II score, mean ± SD	46 ± 19	49 ± 20	41 ± 17	46 ± 18
Sofa score admission, mean ± SD	7.5 ± 3.6	8.0 ± 3.3	6.7 ± 4.0	7.3 ± 3.3
Increase in SOFA after 48 h (SOFA Δ48), n (% of pat. with LOS ≥48 hrs.)	52/150 (35%)	43/105 (41%)	9/45 (20%)	145/483 (30%)
Length of stay (LOS), median days (IQR)	4.6 (1.5-9.9)	6.1 (2.1-12.6)	2.3 (1.1-6.1)	4.4 (2.1 – 9.8)
Mechanical ventilation (MV), n (%)	169 (76%)	105 (77%)	64 (75%)	463 (73%)
Time of MV, median days (IQR)	3 (1-8.5)	4.5 (1-10.5)	1 (0.5-4)	3 (1-8)
Renal replacement therapy n (%)	34 (15%)	18 (13%)	16 (19%)	71 (11%)
Complications n (%)				
Sepsis (diagnose or complication)	42 (19%)	25 (18%)	17 (20%)	168 (26%)
Acute liver failure n (%)	26 (12%)	23 (17%)	3 (4%)	24 (4%)
Acute kidney injury (AKIN 1-3) n (%)	80 (36%)	50 (37%)	30 (35%)	248 (39%)
Mortality n (%)				
ICU mortality n (%)	43 (19%)	31 (23%)	12 (14%)	162 (25%)
Hospital mortality n (%)	63 (28%)	48 (35%)	15 (18%)	216 (34%)
30-day mortality n (%)	64 (29%)	49 (36%)	15 (18%)	221 (35%)

Table 2. Comparison of hospital mortality for SUD and non-SUD patients (reference category), absolute mortality and logistic regression analysis

	Overall population (N=861)	**Medical patients** (n=537)	**Surgical patients** (n=324)	**Patients with sepsis** (main diagnosis or complication) (n=210)
Hospital mortality n (%)				
Non-SUD patients	216/639 (34%)	145/394(37%)	71/245 (29%)	50/168 (30%
SUD, total	63/222 (28%)	48/143(34%)	15/79 (19%)	16/42 (38%)
- Alcohol use disorder (AUD)	48/137 (35%)	37/81 (46%)	11/56 (20%)	13/25 (52%)
- Drug use disorder (DUD)	15/85 (18%)	11/62 (18%)	4/23 (17%)	3/17 (18%)
Hospital mortality, crude (Odds ratio and 95% C.I.)				
Non-SUD (reference category)	1	1	1	1
SUD, total	0.8 (0.6-1.1)	0.9 (0.6-1.3)	0.6 (0.3-1.1)	1.5 (0.7-2.9)
- Alcohol use disorder (AUD)	1.1 (0.7-1.6)	1.4 (0.9-2.3)	0.6 (0.3-1.2)	2.6 (1.1-6.0)
- Drug use disorder (DUD)	0.4 (0.2-0.8)	0.4 (0.2-0.7)	0.5 (0.2-1.6)	0.5 (0.1-1.8)
Hospital mortality adjusted for age (Odds ratio and 95% C.I.)				
Non-SUD (reference category)	1	1	1	1
SUD, total	1.1 (0.7-1.5)	1.3 (0.9-2.1)	0.7 (0.3-1.2)	1.9 (0.9-4.0)
- Alcohol use disorder (AUD)	1.1 (0.8-1.7)	1.7 (1.0-2.8)	0.6 (0.3-1.2)	2.6 (1.1-6.2)
- Drug use disorder (DUD)	0.9 (0.5-1.6)	0.8 (0.4-1.7)	1.1 (0.3-3.5)	0.9 (0.2-3.4)