Substance abuse, clinical characteristics and mortality in a mixed intensive care population in Oslo: a one-year cross sectional study

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Preface

The present study was initiated by the research group at the Department of Acute Medicine at the Oslo University Hospital, Ullevaal. The research group has extensive experience in conducting clinical epidemiological studies in acute medicine, particularly concerning acute poisonings[1-3], and now wanted to utilize this experience in a study of ICU patients in Oslo.

Dr. Berit Sofie Hembre provided the initial preparations in the early stages of the study. When allowed to take responsibility for this project, I saw this as a valuable opportunity to combine my interest in intensive care medicine and toxicology to access a truly multifaceted research group. Despite several challenges along the way, this is a decision I have not regretted.

Acknowledgement

First, I want to thank my principal supervisor, professor Dag Jacobsen, for your steady guidance and support at every stage of this project. I also want to thank you for your dedication and enthusiasm for combining research and teaching. This has been very inspiring to me in my work as a clinical fellow at the University of Oslo. Likewise, I want to express my gratitude to my co-supervisor, Dr. Fridtjof Heyerdahl, for all your help and support. Your creative and sharply analytical input has been invaluable. I would also like to extend my special thanks to my other co-supervisor, professor Leiv Sandvik. In addition to providing excellent statistical counseling, you also served as a valuable mentor both personally and professionally.

The present study would not have been possible without the cooperation and assistance from the medical staff at the ICUs at the Oslo University Hospital Ullevaal and the Diakonhjemmet Hospital. I especially want to thank Dr. Marianne Bjerva. Your organizational skills and high work effort with the inclusion of patients and collection of data were indispensable. I also want to extend my gratitude to Dr. Cathrine Lund Hadley for your efforts during the data collection period and helpful contributions during the writing process. Further, I want to thank the following persons for facilitating and contributing to the inclusion of patients at the various participating ICUs; Dr. Gry Torsæter Dahl at the Diakonhjemmet hospital, Professor Geir Ø. Andersen at the Cardiac ICU, Lisa Högvall at the Neurosurgical ICU, and Dr. Nina Meidell at the Surgical ICU at the Oslo University Hospital Ullevaal. Among other helpful supporters, I would like to thank Dr. Mari Bjørnaas and the rest of the research group for their support and valuable input during the various phases of this project.

Completion of this study would not have been possible without support from my closest family and friends. I especially want to thank my parents for their unconditional support and for always encouraging me to pursue my aspirations, whether in academics or music. Last but not least, I want to thank my husband Terje and our dear children Maja and William for

their unwavering support and patience. Terje, thank you for helping me in so many ways during these years, from providing inventive technical solutions for the implementation of data to taking care of the children when I worked evenings and weekends. Your down-to-earth, humorous, and solution-oriented nature has helped to keep me grounded and focused.

Abbreviations

ICU – intensive care unit

NIR – Norwegian Intensive Care Registry

NCD – non-communicable disease

GBD – Global burden of disease

DALY – years of healthy life loss

EMCDDA – European Monitoring Center for Drugs and Addiction

SOFA – Sequential Organ Dysfunction Assessment

SAPS – Simplified Acute Physiology Score

CCI – Charlson comorbidity index

ICD-10 Criteria – International Classification of Diseases, Tenth revision

DSM diagnostic system – Diagnostic and Statistical Manual of Mental Disorders

AUDIT – Alcohol Use Disorder Identification Test

DUDIT – Drug Use Identification Test

SUD – substance use disorder

AUD – alcohol use disorder

DUD – drug use disorder

SARA – substance abuse-related cause of ICU admission

LOS- length of stay

OR – odds ratio

IQR – interquartile range

95%CI – 95% confidence interval

Summary of the thesis

Background and aims

Intensive care units (ICUs) provide advanced medical care for critically ill patients with risks for organ failure. The burden of critical illness in the developed world is high and will increase as the population ages. Efforts to improve preventive efforts and therapeutic interventions in intensive care patients must be pursued to meet this challenge. Alcohol- and drug abuse is associated with a wide range of conditions in ICU patients, representing a potentially modifiable risk factor for critical illness. Nonetheless, the impact of substance abuse on the Norwegian ICU population has not been extensively studied. The overall aim of this thesis was to provide detailed descriptive data regarding preadmission and clinical characteristics of a mixed ICU population in Oslo, with particular emphasis on the impact of substance abuse of alcohol and drugs.

Methods

The study had a prospective observational cohort design and included intensive care patients admitted to the ICUs at the Oslo University Hospital Ullevaal and the Diakonhjemmet Hospital during a one-year period from 2014 to 2015. Inclusion criteria were set to select the more resource-demanding ICU patients and were; age ≥ 18 years and 1) Intubation regardless of the length of stay and/or 2) ICU length of stay ≥ 24 hours, and dysfunction of ≥ two organ systems. Data were collected consecutively using a standardized registration form, based on information from a questionnaire, including the alcohol screening test AUDIT-C, the patient`s medical records, and toxicology results. Two aspects of substance abuse were addressed separately: 1) Substance abuse as a cause of ICU admission, referred to as Substance abuse-related admissions (SARA), 2) Chronic substance abuse – referred to as substance use disorders (SUD) – regardless of the cause of ICU-admission.

Results

Of the 861 patients included, 537 (62%) had medical admissions and 324 (38%) surgical admissions, 567 (66%) were males. Median age was 63 years, mean SAPS score was 46, and 632 (73%) received mechanical ventilation. Trauma (191, 22%), cardiovascular disease (180, 21%) and sepsis (116, 13%), were the most common diagnostic categories. Although almost

80% of the ICU patients had pre-existing chronic disease, 679 (79%) were self-reliant before admission, reflecting a relatively high level of function.

Substance abuse was associated with the cause of ICU admission (SARA) in 168 (20%) of the patients, of which the majority were associated with acute alcohol and drug abuse. More than one-third of trauma patients were under the influence of alcohol or drugs at the time of injury. Furthermore, 222 (26%) of the ICU patients had underlying substance use disorder (SUD) of alcohol or drugs, reflecting the burden of chronic substance abuse on the ICU population. Of these, 137 (16%) had alcohol use disorder (AUD), and 85 (10%) had drug use disorder (DUD). The prevalence of SUD was many times higher than the estimated prevalence of SUD in Oslo, indicating that patients with excessive alcohol and drug use are significantly overrepresented among patients in need of intensive care.

Overall, 260 (30%) of the ICU population had either SARA and/or SUD. Substance abuse-related conditions were associated with younger age and male gender, and more than half of the male patients in the age group 18-59 had SARA and/or SUD. Although most prevalent in patients admitted with trauma, poisoning, and gastrointestinal disease, patients with substance abuse were present in all diagnostic categories. Of the patients with SUD, more than 40% had a cause of ICU admission other than substance abuse.

ICU mortality was 205 (24%), and hospital mortality was 279 (32%). For both medical and surgical patients, ICU mortality and hospital mortality increased significantly with age, but elderly medical patients were more likely to die in the ward. Overall, hospital mortality was similar for patients with substance abuse when compared to patients without. Nonetheless, our results indicate that acute and chronic substance abuse had a diverging impact on hospital mortality, reflecting the heterogeneity of patients with substance abuse-related conditions. While substance abuse-related trauma was associated with lower age-adjusted mortality, alcohol use disorders were associated with higher mortality in medical patients and patients with sepsis. Among patients who died in the ICU, decisions regarding limitations of life-sustaining treatments were made in nearly 90% of the cases. Of the hospital survivors, almost 80% were discharged home or to rehabilitation. This indicates a low prevalence of futile treatment.

Conclusion

To our knowledge, this is the first study describing the impact of alcohol and drug use in a Norwegian ICU population. Overall, 30% of the patients had alcohol or drug-related cause of ICU admission or underlying chronic substance abuse independent of the cause of admission. This indicates 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. Patients with substance abuse-related conditions were present within all diagnostic categories, demonstrating the importance of screening ICU patients for substance abuse *regardless* of the cause of admission. The high response rate of the questionnaire used in the present study suggests that the implementation of routine screening for alcohol and drug abuse is feasible.

Sammendrag

Bakgrunn og formål

Intensivavdelinger tilbyr avansert medisinsk behandling til kritisk syke pasienter med risiko for organsvikt. I takt med stadige medisinske fremskritt og en aldrende befolkning forventes behovet for intensivbehandling å øke betydelig de neste tiårene. Økt innsats for å bedre forebyggende tiltak og behandlingstilbud er derfor viktig for å kunne møte denne utviklingen best mulig. Alkohol- og narkotikabruk er assosiert med en rekke sykdommer og skader hos intensivpasienter. Klinisk erfaring tyder på at slike tilstander er vanlige i norske intensiv avdelinger, men omfanget av alkohol og rusrelatert sykdom hos norske intensivpasienter er lite studert. Formålet med studien var å kartlegge tidligere helsetilstand og kliniske karakteristika hos en intensivpopulasjon i Oslo, med særlig vekt på betydningen av alkohol og narkotikabruk.

Metode

Studien er en prospektiv observasjonsstudie av intensivpasienter innlagt på intensiv-avdelingene ved Oslo Universitetssykehus Ullevål og Diakonhjemmet sykehus over en ettårsperiode fra 2014 til 2015. Inklusjonskriteriene ble valgt for å selektere de mest ressurskrevende intensivpasientene, slik at kriteriene var alder ≥ 18 år og minst ett av følgende: 1) intubasjon uavhengig av tid på intensivavdelingen og/eller 2) liggetid over 24 timer kombinert med dysfunksjon av minst to organsystemer. Data ble samlet inn fortløpende ved hjelp av et standardisert registreringsskjema basert på informasjon fra et spørreskjema om alkohol- og narkotikabruk (inkludert alkohol kartleggingsverktøyet AUDIT-C) medisinske journalsystemer og laboratorieprøver. To ulike aspekter ved alkohol og narkotikabruk ble studert: 1) Rusmiddelbruk som medvirkende årsak til intensivinnleggelse, omtalt som SARA (substance abuse-related admissions) og 2) Underliggende kronisk alkohol og narkotika-misbruk, omtalt som SUD (substance use disorders), *uavhengig* av innleggelsesårsak.

Resultater

Totalt ble 861 pasienter inkludert. Av disse hadde 537 (62%) medisinsk innleggelsesårsak og 324(38%) kirurgisk innleggelsesårsak, 567 (66%) var menn. Median alder var 63 år, gjennomsnittlig SAPS II skår var 46 og 632 (73%) av pasientene mottok respiratorbehandling.

De vanligste diagnosegruppene var traume (191,22%), kardiovaskulær sykdom (180, 21%) og sepsis (116, 13%). Til tross for at nesten 80% av pasientene hadde kjent kronisk sykdom var 679 (79%) av pasientene selvhjulpne i forkant av intensivinnleggelsen. Dette gjenspeiler et relativt høyt tidligere funksjonsnivå.

Hos 168 (20%) av pasientene var årsaken til intensivinnleggelsen direkte eller indirekte relatert til alkohol eller narkotikabruk (SARA), hovedsakelig som akutt ruspåvirkning. Mer enn en tredjedel av traumepasientene var påvirket av alkohol eller narkotika da skaden skjedde. I tillegg hadde 222 (26%) av pasientene underliggende rusbrukslidelser (SUD); 137(16%) grunnet alkohol (omtalt som alcohol use disorder, AUD) og 85 (10%) grunnet narkotika (omtalt som drug use disorder, DUD). Dette gjenspeiler byrden av kronisk rusmiddelbruk hos intensivpopulasjonen. Forekomsten av SUD er mange ganger høyere enn den estimerte forekomsten av rusbrukslidelser i Oslo. Dette indikerer at pasienter med forhøyet alkohol- eller narkotikabruk er betydelig overrepresentert blant pasienter som trenger intensivbehandling.

Totalt hadde 260 (30%) av intensivpasientene enten rusrelatert innleggelsesårsak (SARA) eller underliggende rusbrukslidelse (SUD). SARA og SUD var assosiert med yngre alder og mannlig kjønn. Blant menn i alderen 18-59 år hadde mer enn halvparten av SARA eller SUD. Selv om rusrelaterte tilstander var vanligst hos pasienter med traumer, forgiftninger og gastrointestinal sykdom, forekom pasienter med SARA og SUD i alle diagnosegrupper. Blant pasienter med underliggende rusbrukslidelse (SUD), hadde likevel 40% ikke-rusrelatert innleggelsesårsak.

205 (24%) av pasientene døde under intensivoppholdet og 279 (32%) i løpet av sykehusoppholdet. For både medisinske og kirurgiske pasienter økte intensiv- og sykehusdødeligheten betydelig med alderen, men eldre medisinske intensivpasienter døde i større grad på andre avdelinger enn intensiv. Samlet sett fant vi ingen forskjell i sykehusdødeligheten for pasienter med og uten rusrelaterte tilstander. Resultatene tyder likevel på at akutt og kronisk rusbruk har ulik innvirkning på dødeligheten. Mens rusrelatert traume var assosiert med lavere aldersjustert dødelighet, var alkoholbrukslidelser knyttet til økt dødelighet hos medisinske pasienter og hos pasienter med sepsis. Blant pasienter som døde på intensivavdeling, ble det satt begrensninger for livsforlengende behandling i nesten

90% av tilfellene. Av pasientene som overlevde sykehusoppholdet ble nesten 80% utskrevet til hjemmet eller til rehabilitering. Dette tyder på en lav forekomst av nytteløs behandling.

Konklusjon

Så vidt vi kjenner til er dette den første studien som beskriver omfanget av alkohol og narkotikarelaterte tilstander i en norsk intensivpopulasjon. Totalt hadde 30% av pasientene enten alkohol- eller narkotikarelatert årsak til innleggelse og/eller underliggende rusbrukslidelser. Dette viser at alkohol- og narkotikabruk ikke bare er en viktig predisponerende faktor for akutt kritisk sykdom, men også en viktig komorbiditetsfaktor hos intensivpasienter både med og uten rusrelatert innleggelsesårsak. Det at pasienter med rusrelaterte tilstander forekom i alle diagnosegrupper viser viktigheten av å kartlegge alkohol- og narkotikamisbruk hos alle intensivintensivpasienter uavhengig av innleggelsesårsak. Den høye svarprosenten på spørreskjemaet brukt i denne studien tyder på at innføring av en slik rutinemessig screening er gjennomførbar.

List of papers

Paper I

Acute illness, Co-morbidity and Mortality in a Norwegian Intensive Care Population

Tollisen KH, Bjerva M, Dahl GT, Meidell NK, Sandvik L, Heyerdahl F, Jacobsen D. International Journal of Anesthetics and Anesthesiology; 2019; 6:084. DOI: 10.23937/2377-4630/1410084

Paper II

Substance abuse-related admissions in a mixed Norwegian intensive care population

Tollisen KH, Bjerva M, Hadley CL, Dahl GT, Hogvall LM, Sandvik L, Heyerdahl F, Jacobsen D. Acta Anaesthesiologica Scandinavia 2020;64:329-37. DOI: 10.1111/aas.13506

Paper III

Clinical impact of chronic substance abuse in a Norwegian intensive care population

Tollisen KH, Hadley CL, Bjerva M, Dahl GT, Hogvall LM, Sandvik L, Andersen GO, Heyerdahl F, Jacobsen D. Acta Anaesthesiologica Scandinavia 2021;65:515–524. DOI: 10.1111/aas.13766

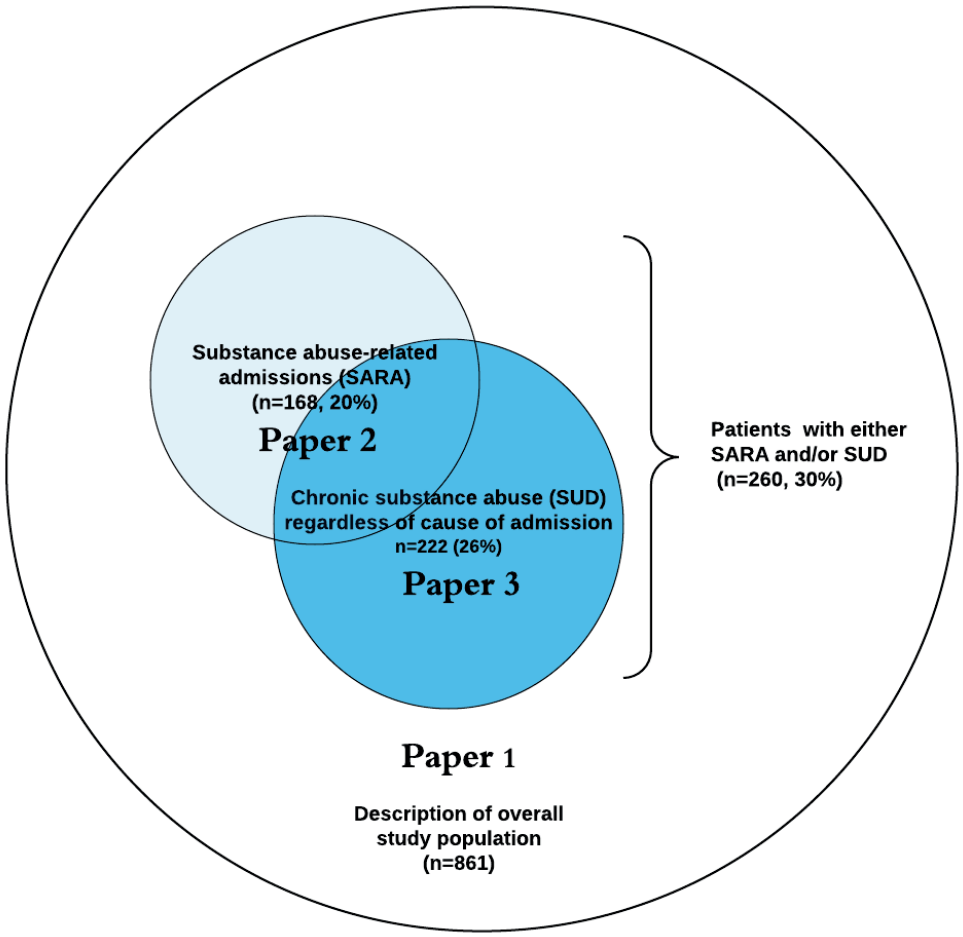

Figure 1 Overview of the topics of the papers

1. Introduction

1.1. Background and rationale

1.1.1. Global burden of disease

In the last decades, there has been a global shift from communicable, maternal, and nutritional causes of disease to non-communicable causes[4,5]. Non-communicable disease (NCD) is now the leading global cause of health loss, causing almost 70% of all deaths worldwide[5] . Overall, the three groups of risk factors that drive the most deaths and disabilities combined are a) metabolic risks caused by unhealthy diets and physical inactivity, b) environmental or occupational risks, and c) behavioral risks such as tobacco, alcohol, and drug use[6].

The global burden of disease study (GBD) is a global research program developed to quantify the burden of health loss from disease, injuries, and risk factors across countries, age, and sex[7]. Led by the Institute for Health Metrics and Evaluation, the GBD research program represents a powerful resource to understand the changing global health challenges in the 21st century[8]. Furthermore, it provides important knowledge regarding the leading causes of death and disabilities within regions that can improve health care systems and eliminate disparities[9].

1.1.2. Health consequences of alcohol and drug use

Alcohol and drug use are important contributors to the global disease burden. Alcohol is considered a component cause of more than 200 disease and injury conditions contributing to 3 million deaths each year globally[10]. Harmful use of alcohol is accountable for approximately 5% of the global burden of disease[11] and is the leading risk for premature mortality and disability in the age group 15-49 years. In order to counteract this development, the WHO executive board has developed an action plan to implement the global strategy to reduce harmful use of alcohol a public health priority[12]. Illicit drug use is considered the direct or indirect cause of over 750 000 deaths per year globally[13], particularly affecting the younger age groups. Estimates from 2017 indicate that more than 42 million years of healthy life loss (DALY) were attributable to drug use, corresponding to 1.3% of the global burden of disease[14].

Per capita consumption of alcohol and recreational drugs is an important determinant for substance abuse-related diseases and injuries in a population. Although relatively low compared to other European countries, alcohol consumption in Norway has increased by 40% during the last 20-30 years[15]. It is, therefore, reasonable to believe that the burden of alcohol-related disease has increased correspondingly. According to the EMCDDA (European Monitoring Center for Drugs and Drug Addiction), Norway has one of the highest reported rates of overdose-related deaths in Europe[16], reflecting a substantial burden of drug-related disease.

1.1.3. Increased need for intensive care treatment

The number of hospital beds per inhabitant is an important indicator of the health care system of a country. In Norway, the number of hospital beds per 1000 inhabitants was 3.6 in 2017[17]. The most advanced and resource-demanding hospital care are provided by intensive care units, treating severely ill patients with risks for organ failure. Due to the high resource use, the availability of ICU beds is limited and with large intercountry variations[18]. In Norway, the average number of ICU beds is 8 beds per 100 000 inhabitants[17,18]. In comparison, Germany has 38 ICU beds while the United Kingdom has 7 ICU beds per 100 000 inhabitants. Step-down beds provide an intermediate level of care for patients with requirements between that of the general ward and the intensive care unit[19]. High utilization of step-down units is of fundamental importance in countries with a relatively low number of ICU beds but also represents a vulnerability in times with increased demand for high-level intensive care.

Population-based studies indicate that the burden of critical illness in the developed world is higher than generally appreciated and will increase as the population ages[20-22] . In addition, the increasing prevalence of lifestyle-related comorbidities and the growing prevalence of conditions that require critical care treatment, such as high-risk surgery, will further increase the demand for critical care resources. In consequence, future demands for intensive care may exceed the availability of such treatment. From a clinical perspective, scarcity of ICU beds may lead to increasingly difficult decisions among clinical staff as to which patients should be admitted to the intensive care unit.

1.1.4. Rationale for the study

Despite the established need for more ICU beds, the expansion of critical care is challenged by high costs. Thus, in addition to evaluating how to increase critical care resources, efforts to improve preventive efforts and therapeutic interventions in intensive care patients should be addressed in order to meet this challenge.

In contrast to the global burden of disease, there is limited international epidemiological data on patients with critical illness[20,23]. Furthermore, studies indicate that the European alcohol misuse research is inadequate considering the harm it causes[24]. Alcohol and drug abuse is associated with a wide range of medical conditions found in the critically ill[25-28] , and the reported prevalence of substance abuse-related conditions in ICU populations are in the range of 14-39%[29-31]. However, few studies have addressed the proportion of both alcohol and drug-related conditions within the same ICU-population[29,30]. Although clinical experience indicates that substance abuse-related conditions are common in Norwegian ICUs, the impact of alcohol and drug abuse on the Norwegian ICU population has not been extensively studied. Since alcohol and drug use represent potentially modifiable factors for critical illness, increased knowledge about this issue is important for preventive medicine and public health.

The main rationale for conducting the present study was to increase the knowledge regarding preadmission and clinical characteristics of intensive care patients in Oslo and to what extent alcohol and drug abuse influence the ICU population. Our research group has previously performed detailed studies of patients with acute poisonings, of whom a large proportion was treated by pre-hospital services[32]. For the present study, we wanted to address the influence of alcohol and drug abuse on intensive care patients receiving high-level care since such an impact may significantly affect intensive care capacity.

In ICUs, substance abuse is associated with increased resource utilization, complication rate, and mortality[25,29,31,33]. Nonetheless, critical care providers often fail to identify patients with substance abuse-related conditions, potentially delaying important clinical interventions[25,34]. Thus, by studying patients with alcohol and drug-related conditions, we hope to contribute to a more systematic identification of ICU patients with substance abuse, which consequently could improve outcomes for these critically ill patients.

1.2. Intensive care treatment

Intensive care units (ICUs) provide advanced health care for seriously injured and ill patients. From the origin of intensive care treatment in the 1950s, in the treatment of poliomyelitis patients with respiratory failure[35], the expansion of critical care has followed the increased understanding of the pathophysiology of organ dysfunction and innovations in supportive technology. This includes advances in organ support, such as mechanical ventilation, vasopressors and dialysis, and monitoring devices. Intensive care treatment is delivered by an interdisciplinary team of medical personal including nurses and physicians, physical therapists, and pharmacists. Although the organization of ICUs varies between countries and regions, common features are high resource use, utilization of advanced medical equipment, and a specially trained staff.

Intensive care patients comprise a heterogeneous group of patients presenting with a wide range of medical conditions and injuries. Patients in ICUs mainly fall into the following categories: patients with acute organ dysfunction, patients that have undergone major procedures including surgery, and patients receiving end-of-life care[20]. In consequence, the main activities involved in the daily practice of critical care providers include: 1) to resuscitate and provide care for patients with potentially reversible organ dysfunction and death 2) to prevent and treat complications, and 3) engaging in decisions regarding the extent of life-supporting therapy for patients whose likelihood of survival is poor[20].

1.2.1. Predictors of mortality

Mortality in intensive care patients depends on a variety of factors with variable contributions. Age, comorbidity, and severity of the acute illness are well-known predictors of mortality in ICU patients [36-38]. The severity of illness is measured by the use of predictive scoring systems. The four major ICU risk stratification systems are the Acute Physiologic and Chronic Health Evaluation (APACHE)[39], the Simplified Acute Physiologic Score (SAPS) [40], the Mortality Prediction Model (MPMO)[41], and the Sequential Organ Failure Assessment (SOFA)[42,43]. Common for all predictive instruments is that they provide severity scores for each patient based on clinical health information and/or physiological and laboratory data, typically within the first days of ICU admission. Due to limited value in predicting mortality in

individual patients[44], predictive scoring systems are mainly used for standardizing research and comparing the quality of patient care across ICUs.

In addition to factors associated with the acute illness, pre-admissions characteristics unrelated to the acute event, such as age and comorbidity, significantly impact ICU admission and outcomes[38]. Although age and comorbidity often co-vary as the severity of comorbid conditions increase with age[4,45], both are independent predictors of mortality in ICU-patients[36,37]. Despite no international consensus on how to measure comorbidity, the Charlson comorbidity index (CCI) is the most widely used index of comorbidity when predicting mortality[46,47].

Regarding the impact of age on mortality in ICU patients, studies of elderly ICU patients indicate poor survival of these patients, but with substantial variations in short and long-term mortality[48-50]. Studies of life expectancy after intensive care treatment indicate that patients in the youngest age group benefit the most from ICU treatment in terms of life years gained from ICU-admission[51]. Nonetheless, triage of ICU patients based on age alone is insufficient as well as ethically challenging. Improved prediction tools, also involving parameters such as pre-existing comorbidity and daily life activity, is needed to help identify elderly ICU patients where ICU treatment is likely to be futile[22,48,50].

1.2.2. Gender-related differences

Several studies have shown an overrepresentation of males in intensive care[52-54] and that male ICU patients are more likely to receive invasive treatment[55]. Although gender-related differences may be multifactorial and reflect differences in disease patterns between male and female ICU patients, a gender-biased decision-making process cannot be ruled out. Thus, possible gender-related differences should be addressed in descriptive studies of ICU populations to gain more knowledge regarding the disparities in clinical characteristics between male and female ICU patients and possible differences in predisposing factors.

1.2.3. End of life care

A less commonly reported parameter than comorbidity and severity of illness is the decision to forgo life-sustaining therapy either by withholding or withdrawing treatment in patients receiving intensive care [56,57]. With large intercountry variations, decisions to forgo life-

sustaining therapy are used in ICUs to reduce the prolongation of suffering in patients who are not likely to survive hospital admission[58]. Withholding or withdrawal of life-sustaining therapy is of importance when evaluating differences in mortality between ICU populations, and should therefore be included when describing an ICU population.

1.3. Substance abuse

1.3.1. Psychoactive substances

Psychoactive substances comprise a group of chemical substances that influence a persons` nervous system causing alterations in perception, consciousness, cognition, or behavior[59]. They include a wide range of substances with different characteristics, pharmacological effects, and dangers, ranging from legal substances such as alcohol and prescription drugs to illegal substances such as recreational drugs. The pharmacological effects of psychoactive substances may be divided into three main categories based on the effect on the user: 1) stimulants 2) depressants, and 3) hallucinogens[60]. Some substances may have combined effects, i.e. alcohol that is both a stimulant and a depressant.

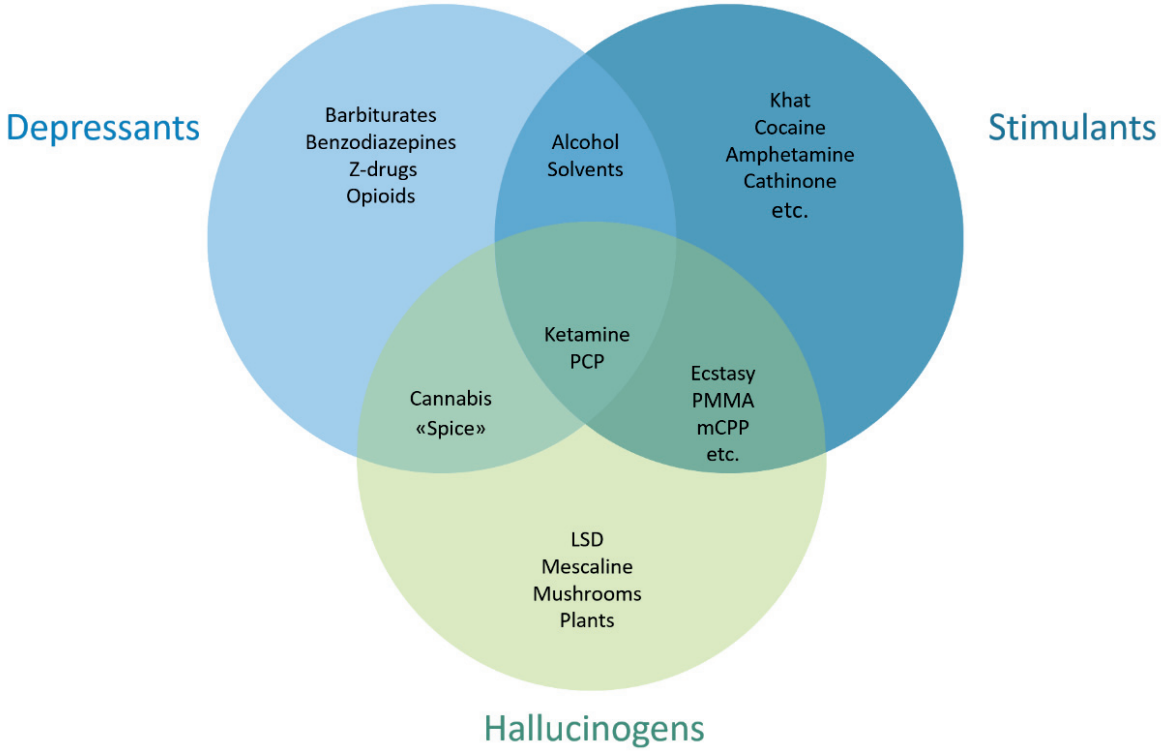

Figure 2. Effects of psychoactive substances. Source: The Norwegian institute of Public health [60]

The harmful effects caused by alcohol or any drug of potential abuse is largely determined by the following factors[61]:

1. The physical harm to the user caused by the drug itself.
2. Consequences of risk behavior associated with substance use
3. The tendency of the drug to induce dependence
4. The effect of alcohol and drug use on families, community, and society, including health care costs

1.3.2. Physical harm due to alcohol and drug use

The likeliness of a drug to cause physical harm is mainly related to the substance's acute toxicity and its likelihood to cause health problems in the long term[61]. Thus, when evaluating the physical health consequences of alcohol and drug use, it is useful to distinguish between a) *acute* physical harm due to the pharmacological effects of the substance and b) *chronic* physical harm due to repeated use.

Complications associated with acute alcohol or drug use, such as intoxications, are common causes of ICU admission. The majority of such complications are caused by the pharmacological effects of substance abuse on vital physiological functions such as respiratory function, the cardiovascular system, or level of consciousness, necessitating supportive care[62,63]. Since the toxic effects may affect multiple organs, critical care providers must have detailed knowledge regarding common side effects of drugs of abuse.

Repeated, excessive use of alcohol and drugs is associated with a wide range of adverse health effects [64,65 66]. Among chronic alcohol-related complications, alcoholic liver disease, in particular, is associated with significantly increased hospital mortality in intensive care patients[67] . Severe renal disease is among the potential consequences of chronic long-term use of recreational drugs[66], particularly among intravenous drug users. In addition to causing severe organ complications, long-term excessive use of alcohol and drugs may also increase the patients' susceptibility to other types of critical illness, such as sepsis and respiratory infections [25,33,64,68-70]. In patients with drug abuse , the route of administration is also of importance, since intravenous drug administration may cause secondary harms including transmission of blood born viruses, such as hepatitis and HIV[61].

1.3.3. Risk behavior associated with substance use

Alcohol and drug use is associated with increased risk of injuries and trauma, accidental drownings, and burns[71,72 73,74]. Trauma is a common cause of admission to intensive care, but the prevalence of alcohol and drug-related injuries in Norwegian ICU patients is little studied. However, considering the high prevalence of alcohol and illicit drug use in Norwegian emergency departments[75], the proportion is likely to be high.

1.3.4. Dependence

A common feature of substances of abuse is that they encourage repeated use[61]. Dependence refers to a cluster of physiological, behavioral, and cognitive symptoms where the user experiences a strong desire to take the substance, and use of the substance takes on a higher priority than other tasks. Physiological dependence, or addiction, also entails tolerance development, i.e., a need for increasing doses to obtain the same effect. An awareness of potential tolerance development is particularly important when caring for intensive patients since patients with substance dependence frequently need higher doses of analgesia and sedation than other patients [31 27]. Furthermore, physiological dependence may cause withdrawal symptoms due to the discontinuation or dose reduction of the substance of abuse, commonly complicating the care for critically ill patients[27,76].

1.3.5. Societal effects of substance abuse

Alcohol and drug abuse cause extensive health-related and social problems as well as high health care costs. Since intensive care treatment represents the most resource-demanding medical care, increased knowledge regarding how substance abuse affects the Norwegian ICU populations is of importance when evaluating the societal effects of alcohol and drug abuse.

Norway is among the countries which have committed to the WHOs global strategy to reduce the harmful use of alcohol[12,77]. Studies indicate that hospital admissions represent an opportune moment for intervention in patients with alcohol and drug-related conditions [78,79]. Increased understanding of the mechanisms by which acute and chronic substance abuse affect the ICU population may contribute to better and more targeted therapeutical

and preventive measures, potentially reducing the overall harmful effects of alcohol and drugs.

2. Aims and objectives

The overarching aim of this thesis was to provide knowledge that could improve the quality of treatment and the decision-making process in intensive care and substance abuse-related therapy to reduce morbidity and mortality. By collecting detailed descriptive data on a mixed ICU population in Oslo, we aimed to gain more knowledge regarding predisposing factors, cause of admissions, treatment, and outcomes overall and within subgroups of the ICU population. Furthermore, by investigating the scope of alcohol and drug-related conditions, we aimed to gain more insight into the mechanisms by which substance abuse of alcohol and drugs influence ICU populations.

More specifically, the study had the following objectives:

- To study the overall characteristics of the ICU population by describing the preadmission and clinical characteristics of the ICU patients and comparing the characteristics and mortality within subgroups (paper I).
- To study patients with substance abuse-related ICU-admissions (abbreviated SARA), overall and within subgroups. This included describing whether the cause of ICU admission was associated with *acute* or *chronic* substance abuse as well as eventual injury mechanisms in patients with substance abuse-related trauma (paper II).
- To compare SARA and non-SARA patients on selected variables such as age, comorbidity, diagnostic categories, and mortality (paper II).
- To study the prevalence and clinical impact of *chronic* substance abuse of alcohol or drugs (referred to as substance use disorders (SUD)) *regardless* of the cause of ICU-admission, and compare SUD with non-SUD patients on clinical parameters and mortality (paper III).

3. Material and Methods

3.1. Design and setting

The study had a prospective observational cohort design and included intensive care patients admitted to the intensive care units (ICUs) at the Oslo University Hospital Ullevaal and the Diakonhjemmet Hospital from February 3rd, 2014 to February 2nd, 2015. A one-year frame was chosen in order to include seasonal variations.

The Oslo University hospital Ullevaal is a tertiary referral hospital with comprehensive medical services, including trauma, neurosurgery, and percutaneous cardiac intervention for Eastern Norway (3.0 million inhabitants). In addition, it serves as a local hospital for one-third of Oslo's population (647,676 inhabitants; 2015). The Diakonhjemmet Hospital serves as a local hospital for 115,000 inhabitants in Oslo. Five intensive care units participated in the study; the medical, cardiac, surgical, and neurosurgical ICUs at the Oslo University Hospital, Ullevaal, and the mixed medical/surgical intensive care unit at the Diakonhjemmet hospital. Since the post-operative units at the study hospitals did not participate in the study, no patients with elective thoracic or cardiac surgery were included. In order to avoid individuals being represented multiple times, only the first admission of each patient during the study period was registered (*Figure 3 below*).

3.2. Inclusion criteria

The following inclusion criteria were set to select the more resource-demanding ICU patients; age ≥ 18 years and 1) Intubation regardless of the length of stay and/or 2) ICU length of stay ≥ 24 hours, and dysfunction of ≥ two organ systems. When defining organ dysfunction, we included organ systems used when addressing acute organ failure in sepsis patients[80]. This includes organ dysfunction of the respiratory, cardiovascular, metabolic, CNS, hematological, liver, and renal system (Appendix).

3.3. Participants

Of the 995 ICU admissions filling the inclusion criteria, 91 patients were excluded due to missing consent or language problems. The median age for the patients not included was 54 years (range 18-89), and 63% were males. Of the remaining 904 admissions, 43 (4%) were

readmissions of previously included patients and therefore excluded from the analysis, leaving 861 patients for inclusion.

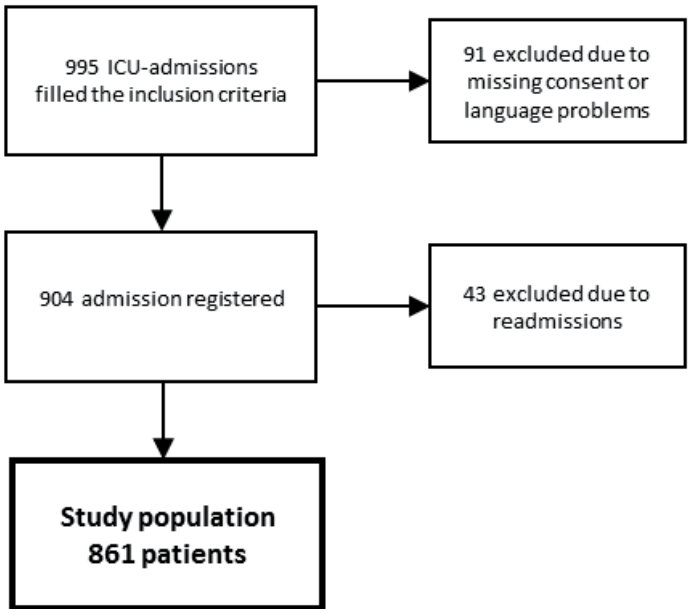

Figure 3. Flow chart of the inclusion process

3.4. Ethics

Ethics approval was granted by the Norwegian Regional Ethics Committee (REK), case number 2012/12601. During the first months of the inclusion period, it became clear that some groups of patients were particularly challenging to include due to external conditions or the severe nature of the disease. After separate application, exemptions for consent were made for patients 1) unable to give their consent themselves without next of kin that could be asked instead 2) admitted with acute poisoning and 3) who died during ICU-treatment. Of the 861 patients included, 670 (78%) were included by consent; 309 by the patient and 361 by next of kin.

3.5. Overall methodological approach

The overall methodological approach for the present study was to study pre-admission and clinical characteristics of the ICU population with particular emphasis on the impact of substance abuse. Predefined descriptive data were collected consecutively using a standardized registration form based on information from the medical records, laboratory results, and a questionnaire regarding prior alcohol and drug use.

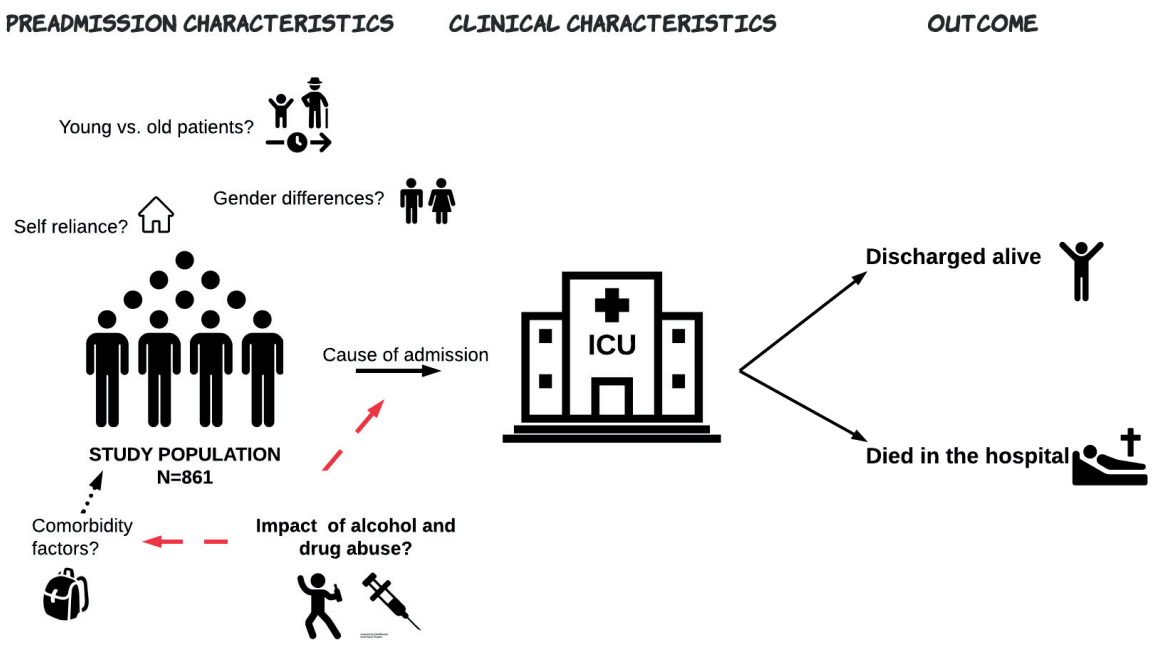

Figure 4. Characteristics and outcome

3.5.1. Baseline characteristics

The following variables were used for all three papers when describing the study population; age; sex; Charlson comorbidity index (C.I.I) [46]; main diagnostic category based on the APACHE system; SAPS II[40] and SOFA scores (sequential organ dysfunction assessment)[42,43] at admission; length of stay; mechanical ventilator support; duration of mechanical ventilation; ICU-mortality and total hospital mortality (ICU-mortality included). Type of admission was registered as defined by the SAPS II system: 1) Medical admission: No surgery within 1 week prior to ICU admission. 2) Surgical admission: a) Scheduled surgical patients - elective surgery within 7 days of ICU admission and b) Non-scheduled surgical patients: acute surgery (scheduled less than 24 h in advance) within 1 week prior to ICU admission.

3.5.2. Evaluation of substance abuse

Terms and definitions

Since "drugs" may refer to various psychoactive substances, the term was limited to the drugs listed in the drug screening test DUDIT[81]. This includes a variety of recreational

drugs/illicit substances as well as some prescriptive drugs such as opioids and benzodiazepines.

Two acknowledged classification systems are used to address alcohol and drug use; the ICD-10 criteria developed by WHO [82] and the US DSM-V diagnostic system (Diagnostic and Statistical Manual of Mental Disorders)[83] developed by the American Psychiatric Association. In this thesis, we will use the term "substance abuse", used by the DSM-criteria, when referring to acute or chronic patterns of alcohol or drug use that is causing damage to a person's health (i.e., necessitating hospital treatment)[84], largely corresponding to the ICD-10 term "harmful use" [82].

Long-term excessive use of alcohol or drugs may be associated both with and without symptoms of dependence. While the ICD-10 criteria distinguish between harmful use and dependence, the DSM-V criterias[83] use substance use disorder (SUD) as an umbrella term for substance abuse and dependence with subgroups mild, moderate, and severe depending on the number of criteria met. For this study we used the term "substance use disorders" when referring to patients with severe alcohol or drug misuse.

Two separate classification criteria used when addressing substance abuse

When evaluating the impact of substance abuse on the ICU population, we wanted to study a wide range of substance abuse-related conditions and include harmful effects of both *acute* and *chronic* substance abuse of alcohol and drugs. Due to the heterogeneity of patients with substance abuse-related conditions, and in order to gain more insight into the mechanism by which acute and chronic substance abuse affected the ICU- population, we chose to separately address:

1. Substance abuse as cause of ICU-admission, abbreviated SARA (paper II)
2. Chronic substance abuse – referred to as substance use disorders (SUD) – *regardless* of cause of ICU-admission (paper III)

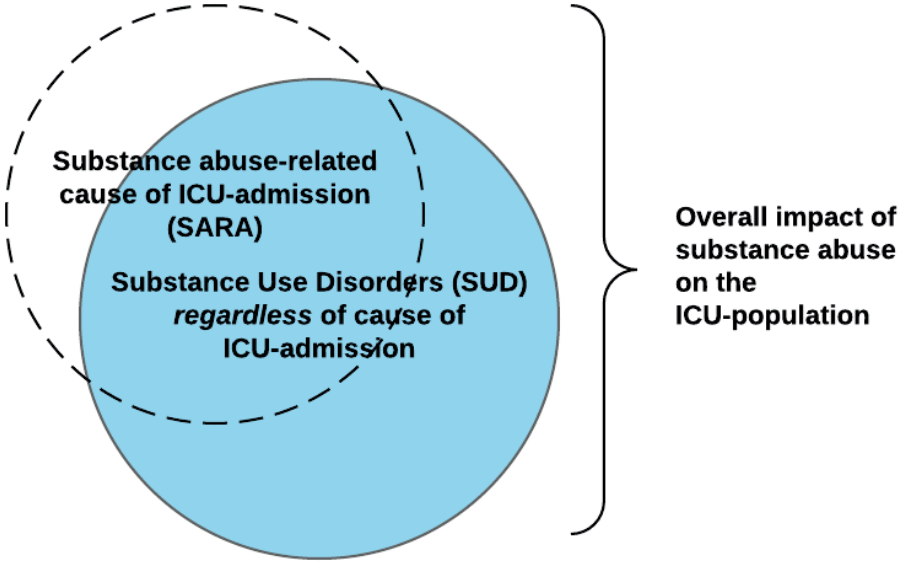

Figure 5. The relationship between SARA and SUD

The registrations and the evaluation of whether a patient had SARA and/or SUD, was made by a small group of study personnel consisting of physicians and nurses on the wards trained in the classification methodology. Regular consensus meetings were held in order to reduce interrater variability.

3.5.3. Questionnaire

Rationale behind the choice of screening tools

The AUDIT test, developed by the WHO, is among the most commonly used screening tools for alcohol and has also been validated when answered by proxy in some populations[85]. Correspondingly, the Drug Use Disorder test DUDIT [81] is a ten-question screening tool developed by the Karolinska Institute in Sweden for problematic drug use.

When developing the questionnaire (Appendix) for the present study, brevity was considered important for the feasibility of the inclusion process. The full AUDIT was considered too time consuming in the ICU-setting. Instead we therefore chose to use the short version of the AUDIT test, the AUDIT C[86], recommended for emergency settings. Correspondingly, since the full DUDIT test was considered too extensive, we chose to include the first question of the DUDIT test addressing the frequency of recreational drug use and prescription drug use. In addition, we added specifications regarding the last time of intake

and the specific drug(s) used on that occasion, and the most frequently used drug(s) during the last week and the last year (Appendix).

Questions regarding alcohol and drug use are often avoided in clinical practice, possibly due to fear of offending the patients or their next of kin[87]. Consequently, we added questions regarding smoking habits at the beginning of the questionnaire to ease the transition to the questions regarding alcohol and drug use. Furthermore, we referred to the questionnaire as a questionnaire addressing "lifestyle factors," a methodical approach we experienced as helpful in the inclusion process.

Questionnaire completion

The completion of the questionnaire was not mandatory for participation in the study. However, of the 670 patients included by consent, 620 (93%) completed the questionnaire regarding prior alcohol and drug use (flow chart). Of these, the patient provided the information in 271 (44%) of the cases and next of kin in 349 (56%) of the cases. For the remaining 241 patients included without a questionnaire, substance abuse evaluation was based on information from medical records and laboratory results alone. Of these 241, 90 patients were classified with SARA and/or SUD by using the following criteria: SARA-patients were classified based on toxicology results and S-ethanol. Patients were classified with drug use disorder if they had a history of intravenous drug abuse, collateral information indicating excessive drug use, or previous hospitalizations due to drug use. Correspondingly, patients were classified with alcohol use disorders if they had chronic medical complications attributable to alcohol misuse, previous alcohol-related hospitalizations or referral to follow-up, or if collateral information strongly indicated long-term excessive alcohol use.

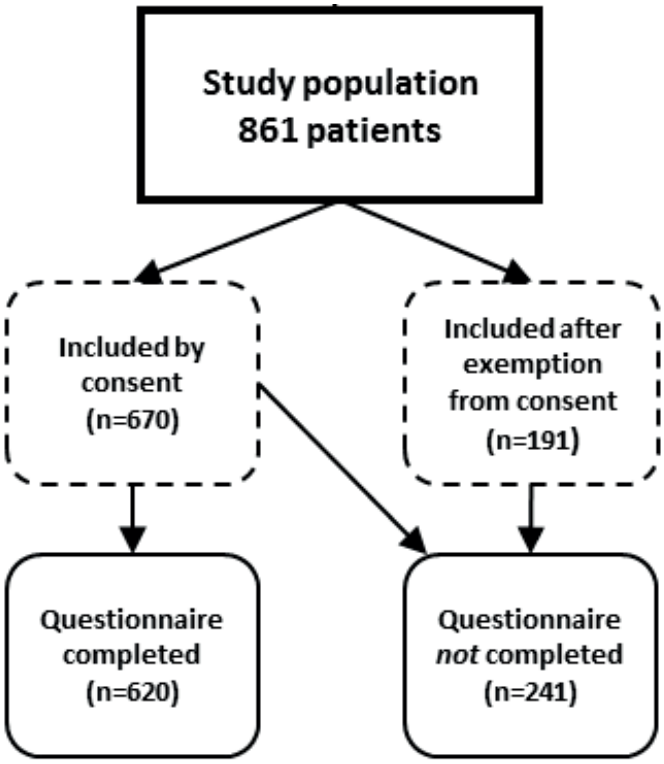

Figure 6. Inclusion and questionnaire completion

3.6. Methodological aspects concerning paper I

3.6.1. Descriptive variables presented in paper I

In addition to the baseline characteristics, the following variables were presented in paper I:

- **Additional preadmission characteristics :**
  Living situation; living at home with or without home care (self-reliant), nursing home etc., pre-existing chronic disease; including chronic pulmonary disease, cardiac disease, diabetes, polypharmacy; number of prescribed medications before admission (none, 1-4, 5-7, 8 or more)
- **Treatment details and complications:**
  Supportive treatment such as non-invasive ventilator support, vasopressor treatment, renal replacement therapy. Sepsis either as cause of admission or complication and primary source of the infection (i.e. respiratory disease, abdominal disease etc.). For patients who died in the ICU, decisions regarding limitations of life-sustaining treatment were registered including a) Withholding treatment i.e. the decision not to

start or increase a life- sustaining intervention or b) Withdrawing treatment i.e. the decision to stop a life-sustaining intervention.

- **Discharge location:**
  Among the surviving patients, post-discharge location was registered (home, nursing home etc.)

3.6.2. Subgroup analysis for paper I

The patients were subdivided in the following subgroups for the descriptive analysis:

1. **Male vs. female patients**
   Preadmission and clinical characteristics were compared in order to study potential gender-related differences between male and female ICU-patients.
2. **Medical vs. surgical patients within age groups**
   The material was stratified into medical and surgical admissions as defined by the SAPS II system as described above. Furthermore, the patients were subdivided in age groups 18-59 and 60 above since the WHO define patients older than 60 years as elderly.

3.7. Methodological aspects concerning paper II

3.7.1. Classification of substance abuse-related ICU admissions

Substance abuse related-admissions, abbreviated SARA, were defined as ICU admissions associated with the use of alcohol or with drugs. Patients with ICU admissions associated with use of other medications, such as cardiovascular medication or anti-depressives, were *not* considered substance abuse-related, and neither were patients with a history of substance abuse but non-SARA causes of admission. The criteria used when defining SARA-admissions were based on the criteria used in a Scottish study of alcohol-related ICU-admissions[88] with the addition of drug-related conditions.

Patients classified with SARA were categorized into three subgroups based on whether the cause of admission was:

A. Directly related to acute alcohol or drug abuse

Acute intoxication as well as direct complications of acute alcohol or drug abuse, such as overdose-related cardiac arrest, rhabdomyolysis, and injection-related injury or disease**.**

B. **Indirectly influenced by acute alcohol or drug abuse**

Injuries and illness in intoxicated patients. The injury mechanisms studied included road traffic accidents, falls, burns, violence/ assault-related trauma, strangulation, and drowning.

C. **A medical complication causally related to chronic alcohol or drug Abuse**

Based on the ICD-10 criteria, these included the following: alcohol withdrawal syndrome; alcoholic cirrhosis with hepatic failure and/or upper gastrointestinal tract bleeding secondary to portal hypertension; alcoholic pancreatitis; seizures, heroin nephropathy.

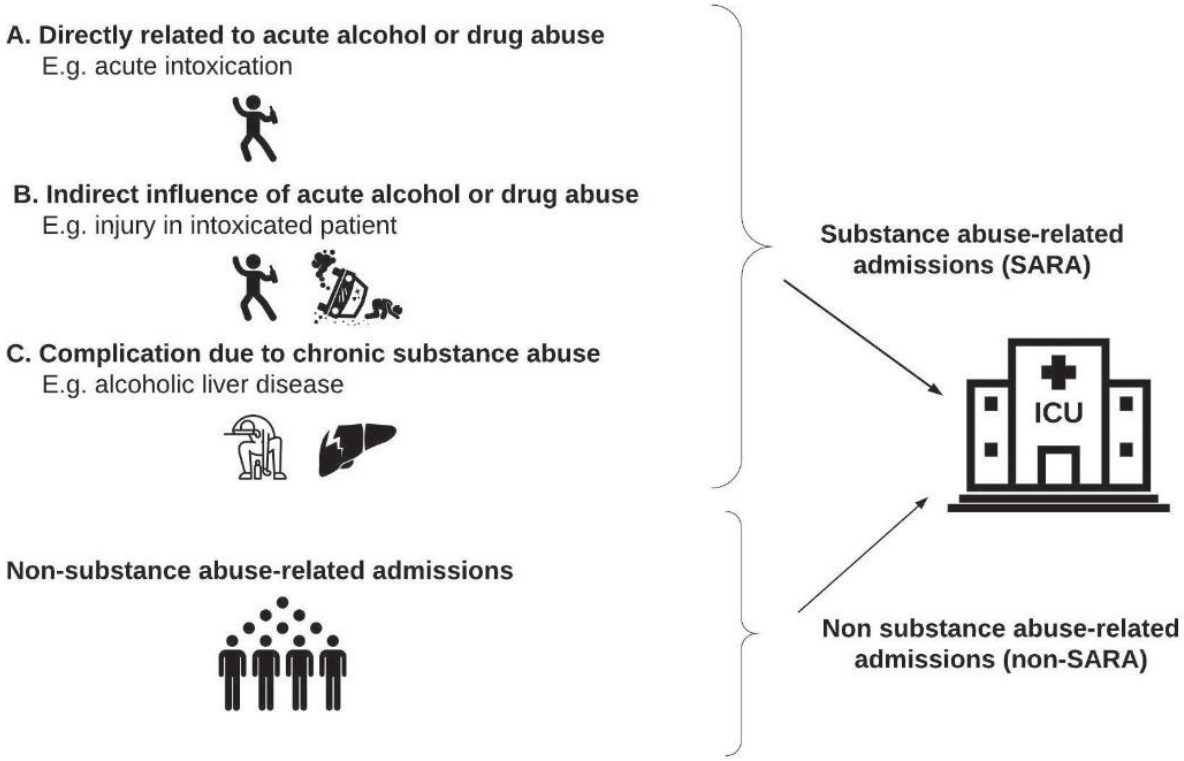

Figure 7. Subgroup classification of substance abuse-related admissions

3.7.2. Evaluation of SARA

Tests for toxicology and S-ethanol were analyzed as soon as possible after admission to the ICU. Due to insufficient information toxicology results, 9 patients from the original data set

were excluded for the descriptive analysis in this paper, leaving 852 patients. For patients classified with SARA, the admission was classified as associated with acute alcohol or drug exposure (A or B above) if toxicology results were positive and not explained by therapeutic medication administration or home medications. For patients with substance abuse-related trauma, the concentrations of alcohol at the time of injury were calculated using a mean elimination rate of 0.015% per hour[89] to evaluate the degree of influence of alcohol at the time of injury. In addition, patients were classified with SARA when collateral information strongly suggested that the patient was intoxicated at the time of injury.

3.7.3. Other variables registered and subgroup analysis

For patients classified with SARA, the main type of substance abuse (alcohol/illicit drugs /prescription drugs) was registered. Injury mechanisms (i.e., road traffic accidents, fall-related injuries, and violence-related) were registered in patients with substance abuse-related trauma. For the descriptive analysis, we compared SARA and non-SARA patients overall and within subgroups (A, B, C). Furthermore, to study the age and gender distribution of SARA-patients, the material was subdivided into age groups 18-39, 40-59, 60-79 and 80 and above.

3.8. Methodical aspects concerning paper III

3.8.1. Classification of substance use disorders

Patients were classified with substance use disorders, abbreviated SUD, when fulfilling ≥1 of the following criteria:

1. **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 [90,91]. 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).
2. **Documented medical condition causally related to chronic substance abuse of alcohol or drugs based on the ICD-criteria.**

This included: hepatic encephalopathy, GI hemorrhage due to varices or alcoholic gastritis, alcoholic hepatitis, alcoholic liver failure, alcohol related seizures, alcohol withdrawal, heroin nephropathy

3.8.2. Evaluation of SUD

Although the majority of patients classified with alcohol use disorders had AUDIT-C scores ≥ 8 points, patients where collateral information (from medical records and/or next of kin) strongly indicated current substance abuse were also classified as SUD despite discrepancy with the information given in the questionnaire. In addition, patients with manifest complications of chronic substance abuse were classified as SUD regardless of current alcohol or drug consumption (criteria 2. above). Overall, 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.

3.8.3. Other registrations and subgroup analysis

Based on the 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. Preadmission and clinical characteristics were compared for patients with and without SUD, overall and within subgroups. In order to address the overall impact of substance abuse on the ICU population (patients with SARA and/or SUD), Information regarding substance abuse-related admissions (presented in paper II) was added in the descriptive analysis. Here, the 9 patients excluded from the descriptive analysis in paper II were classified as non-SARA patients. When evaluating the impact of SUD on hospital mortality, separate analyses were made for medical and surgical patients and patients with sepsis.

3.9. Statistical analysis

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. For paper I and II, the Chi-square test was used when comparing proportions, and an independent samples t-test was used when comparing means. P values < 0.05 were considered statistically significant. For paper III, statistical tests were replaced by precision of estimates (95% confidence intervals) in order to meet the STROBE criteria as requested by the reviewers.

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. This included adjusting for age, but not for comorbidity or diagnostic categories, since these were considered possible consequences of the alcohol or drug exposure.

4. Summary of the results

4.1. Overview

The three papers included in this thesis describe different characteristics of the study population (figure 1). Paper I describes the preadmission and clinical characteristics of the study population, overall and in subgroups. Paper II addresses substance abuse as predisposing factor for ICU-admission. Paper III addresses the clinical impact of chronic substance abuse in the ICU-population *regardless* of cause of admission. The main results are briefly described, more details are provided in the papers.

Baseline characteristics	
Number of patients*	861
Age, median years (range)	63 (18-95)
Males n (%)	567 (66%)
Type of admission n (%)	
_Medical	537 (62%)
_Surgical	324 (38%)
Charlson comorbidity index (mean ± SD)	2.3 ± 2.2
SAPS II score (mean ± SD)	46.0 ± 18
SOFA score at admission (mean ± SD)	7.4 ± 3.5
Main diagnostic categories n (% of total)	
Trauma	191 (22%)
Cardiovascular disease	180 (21%)
Sepsis	116 (13%)
Respiratory	88 (10%)
Gastrointestinal	81 (10%)
Neurologic/CNS	73 (8%)
Poisoning	65 (8%)
Cancer	23 (3%)
Other	44 (5%)
Treatment details and mortality	
Length of stay, median days (IQR)	4.5 (1.9-9.8)
Mechanical ventilation n (%)	632 (73%)
Length of mechanical ventilation, median days	3 (1-8.4)
Death in the ICU n (%)	205 (24%)
Death in the hospital n (%)	279 (32%)
**Due to missing it toxicology results, 9 patients were excluded from the analysis in paper II, leaving 852 patients*	

Table 1. Overall descriptive characteristics of the study population

4.2. Main results paper I

Of the 861 patients included, 672 (78%) had pre-existing chronic disease before admission, with cardiovascular and pulmonary disease being most prevalent. Nonetheless, almost 80% of the patients were self-reliant without home care services before admission. Male patients constituted two-thirds of the study population and were in majority in all diagnostic categories and all age groups except for patients aged 90 and above. When compared to female patients, males were significantly younger (median years 61 vs. 64), and more likely to receive mechanical ventilation and vasopressor therapy. There was no difference in mortality between the genders.

Compared to medical patients, surgical patients were significantly younger (median years 60 vs. 64), more likely to be self-reliant before admission, and to receive mechanical ventilation. In the age group 18-59, medical patients had a much higher prevalence of pre-existing chronic disease than surgical patients (Charlson comorbidity index 0.7 vs. 2.0), while there was no such difference in patients 60 years and older.

Trauma was the most common diagnostic category in surgical patients across the age groups. In medical patients, poisoning (56/217,26%) was the most common diagnostic category in patients aged 18-59, while cardiovascular disease (124/320, 39%) and sepsis (63/320, 20%) were most common among patients 60 years or older. Overall, medical patients had higher hospital mortality than surgical patients, but within the age groups, this difference was only significant in patients aged 60 years and above. For both medical and surgical patients, ICU and hospital mortality increased steadily with age. However, medical patients in the older age group had a higher tendency of dying in the ward.

Among patients who died in the ICU, decisions regarding limitations of life-sustaining treatments were made in nearly 90% of the cases. Total hospital mortality was 279/861 (32%). Of the surviving patients, almost 80% of the surviving patients were discharged home or to rehabilitation.

4.3. Main results paper II

In this paper, 9 patients were excluded from the descriptive analysis due to missing toxicology results, leaving 852 patients. Of these 852, 168 (20%) of the patients had substance abuse-related cause of admission (SARA), of which 102 (12%) were mainly alcohol-related and 66 (8%) drug-related.

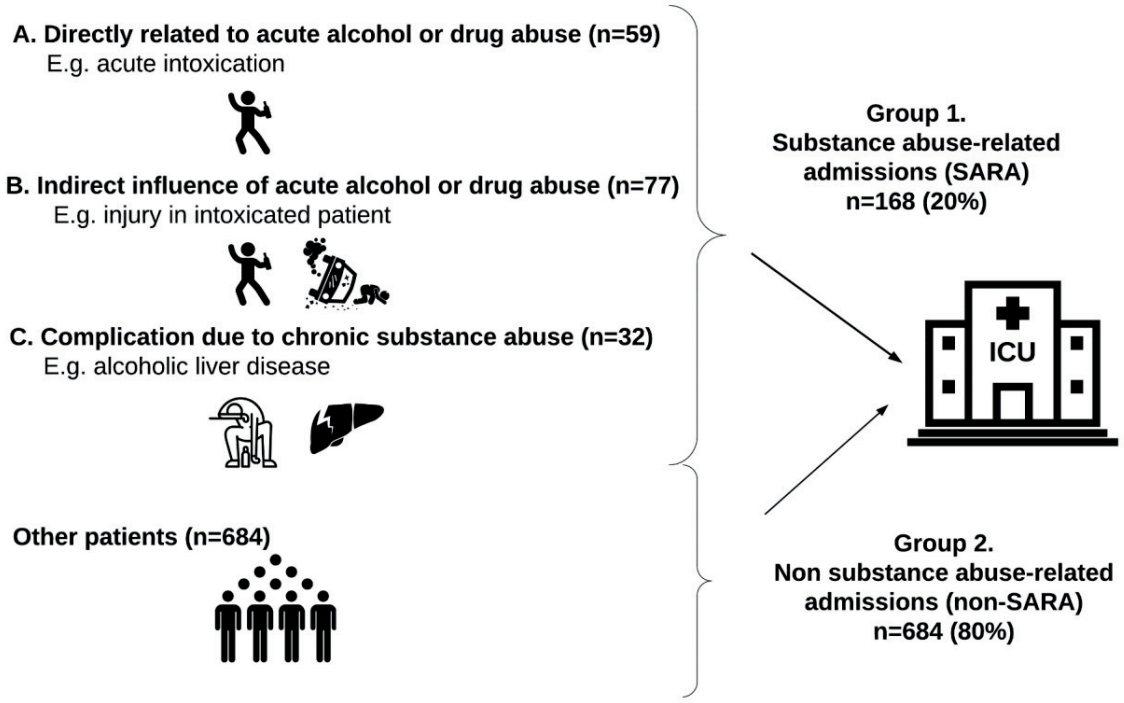

Figure 8. Patients with substance abuse-related admissions, overall and in subgroups

Of the 168 SARA-admissions, 136 (81%) were associated with acute substance abuse; 59 in group A (direct acute cause, i.e., intoxication) and 77 in group B (indirect acute cause, i.e., substance abuse-related trauma). Complications due to chronic substance abuse (group C) were the cause of admission in 32 of the patients.

Compared to non-SARA patients, SARA-patients were significantly younger (median age 48 vs. 66 years) and more likely to be males. Surgical patients had a higher proportion of SARA than medical patients (75/315 (24%) vs. 93/537 (17%)), of which nearly all (72/75, 96%) were indirectly influenced by acute substance abuse (group B). Overall, more than one-third of the trauma patients were determined to be under the influence at the time of injury, mainly by alcohol. Injury mechanisms varied between age groups. While violence-related injuries and

road traffic accidents primarily involved younger trauma patients, fall-related injuries were more evenly distributed across the age groups. In patients aged 60-79, 16/47(34%) of the patients with fall-related injuries, and 14/33 (42%) of the patients with head injuries and intracranial bleeding, were influenced by alcohol at the time of injury.

In medical patients, poisoning was the diagnostic category with the highest proportion of SARA-patients (52/65, 80%), of which the majority were due to illicit drug use. Although SARA-admissions directly associated with *acute* substance abuse (group A) was most common in medical patients, nearly one-third of the SARA-admissions (29/93, 31%) were caused by complications of *chronic* substance abuse (group C), mainly due to alcohol.

Overall hospital mortality was similar for SARA and non-SARA-patients but differed significantly between the subgroups. SARA-patients group B (indirect cause, see *Figure 8*) had significantly lower mortality compared to non-SARA-patients, even when adjusted for age (OR 0.5, $p<0.05$).

4.4. Main results paper III

Overall, 222/861 (26%) patients were classified with substance use disorders (SUD): 137 (16%) with alcohol use disorders (AUD) and 85 (10%) with drug use disorders (DUD). Of the 222 SUD-patients, 130 (59%) had substance abuse-related cause of ICU admission (SARA), while 92/222 (41%) had *a non*-substance abuse-related cause of admission (*non*-SARA).

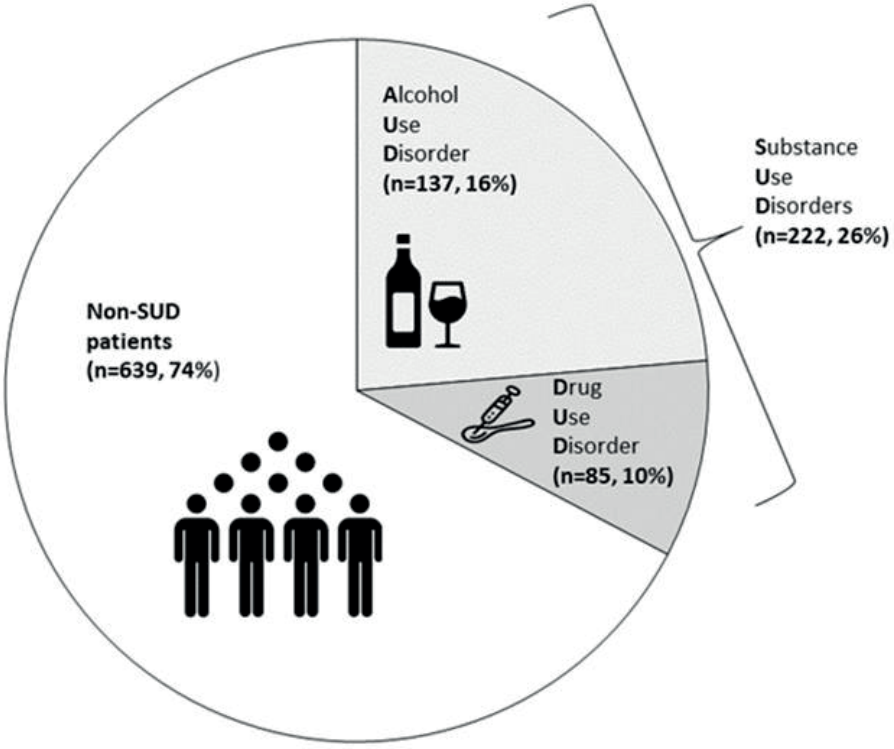

Figure 9. Patients with substance use disorders, overall and in subgroups

Preadmission and clinical characteristics differed markedly between AUD and DUD-patients. When compared to non-SUD patients, DUD-patients were significantly younger (median age 42 vs. 65 years), had lower Charlson comorbidity index (1.3 vs. 2.4), and lower SAPS II scores (41 vs. 46). AUD-patients had higher SOFA scores (8.0 vs. 7.3), while age and comorbidity index were similar to non-SUD patients. Although DUD was most prevalent among patients with poisoning and AUD was most prevalent among patients with gastrointestinal disease and trauma, SUD patients were present within all diagnostic categories.

Overall hospital mortality was similar for SUD and non-SUD patients, but subgroup analysis showed diverging trends for AUD and DUD-patients, reflecting the heterogeneity of SUD-patients. DUD-patients had significantly lower mortality than non-SUD patients (OR 0.4 (95%CI 0.2-0.8), but this difference disappeared when adjusting for age. AUD-patients had

age-adjusted mortality similar to that of non-SUD patients, but AUD was associated with higher age-adjusted mortality in medical patients and patients with sepsis (OR 1.7 (95%CI 1.0-2.8) and OR 2.6 (95%CI 1.1-6.2), respectively).

4.5. Combined and additional results

4.5.1. Overall impact of substance abuse on the ICU-population

When combining the results from paper II and III, we found that 260/861 (30%) of the patients were classified with either substance abuse-related cause of ICU-admission (SARA) and/or underlying substance use disorder (SUD). The 9 patients excluded from the SARA-analysis in paper II were registered as non-SARA patients. Compared to patients without substance abuse (non-SUD/non-SARA patients), patients with substance abuse (SARA and/or SUD) were significantly younger (median age 54 years vs. 66 years), more likely be males (203/260, 78% (95%CI 73-83%) vs. 364/601, 61% (95%CI 57-65%), and to be admitted due to poisoning, trauma and gastrointestinal disease. Although hospital mortality was lower in patients with substance abuse than in patients without, this difference was not statistically significant (68/260, 26% (95%CI 21-32%) vs. 211/601, 35% (95%CI 31-39%).

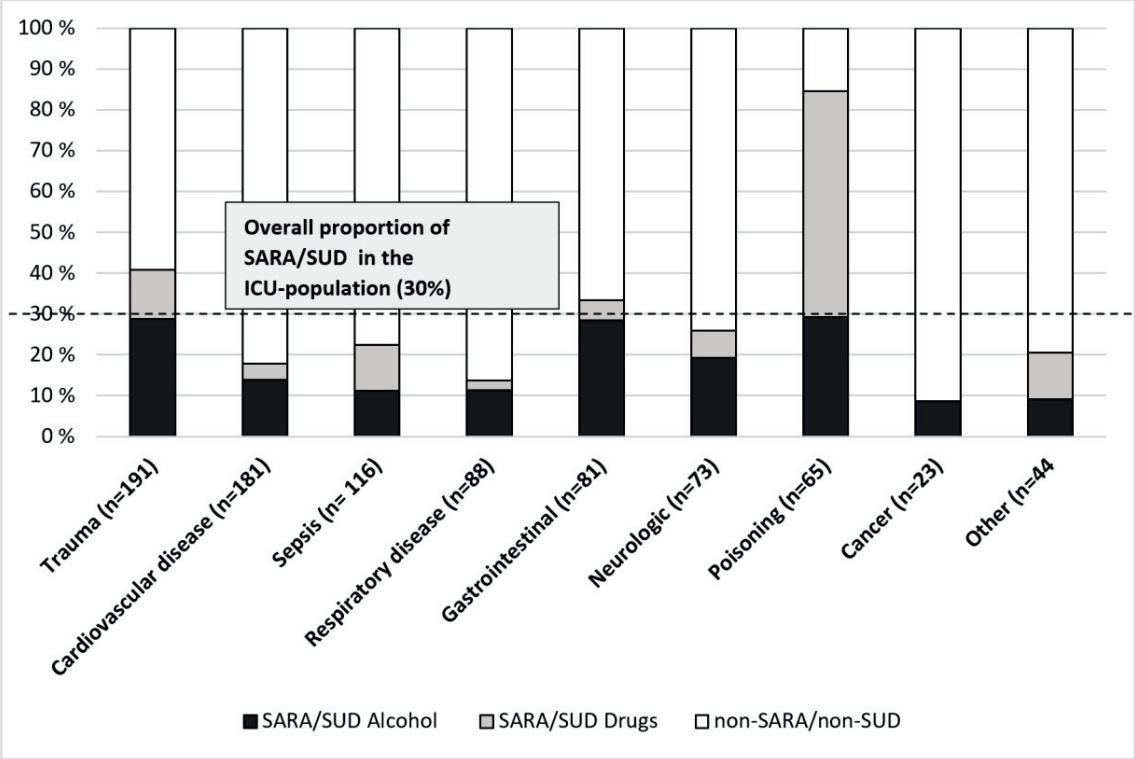

Figure 10. Proportion of patients with SARA and/or SUD within diagnostic categories

Of the 260 patients classified with SARA and/or SUD, 38 (15%) of the patient had SARA, but did not fill the criteria for SUD (described in paper II). Further, 130 (50%) had combined SARA and SUD (described in both paper II and III), while 92 (35%) had underlying SUD but *non*-substance abuse-related cause of ICU-admission (only described in paper III).

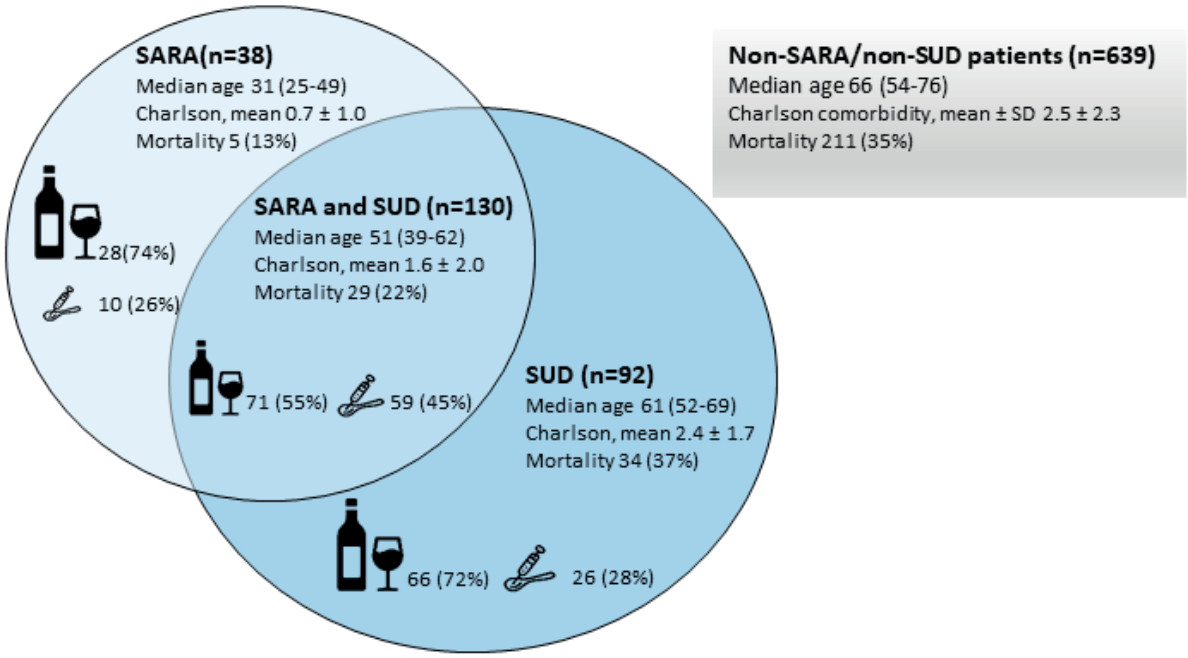

Figure 11. Comparison of patients with SARA and SUD

As shown in figure 11, patients *only* classified with SARA, were younger and had lower Charlson comorbidity index when compared to patients *without* substance abuse. Here, all the SARA-admissions were associated with acute substance abuse, such as poisoning or substance abuse-related trauma. Of the 222 SUD-patients, 130 (59%) had substance abuse-related cause of admission, while 92 (41%) had cause of admission *other* than substance abuse. Patients with drug use disorders (DUD) were more likely to have SARA when compared to patients with alcohol use disorders (AUD). Of the 85 DUD-patients, 59 (69%) had SARA, of which 56 were influenced by acute substance abuse. In comparison, 71 (52%) of the 137 AUD-patients had SARA, of which 42 were influenced by acute substance abuse and 29 were due to complications of chronic substance abuse.

4.5.2. Substance abuse, age and gender

Overall, 203/567, 35% (95%CI 32-40%) of male patients and 57/294, 19%, (95%CI 15-25%) of the female patients had either SARA and/or SUD, but the proportion of SARA/SUD-patients differed markedly between the age groups. While male patients had a twice as high proportion of SARA/SUD-patients as females in the age groups 18-39 and 40-59 (Table 2. below), there was no difference between the genders in the age group 60-79 years. Patients 80 years and older were not included in the table due to the low number of patients classified with SARA/SUD (n=2).

In patients aged 18-59 years, males with SARA/SUD had much higher hospital mortality than females with SARA/SUD. In this age group, 29 (52%) of the 56 male patients who died had had SARA/SUD. Of these, illicit drugs were the main substance of abuse in 16 of the patients, of which 14 patients had intravenous drug abuse. In comparison, 3 of 22(14%) deaths among female patients aged 18-59 had SARA/SUD. There was no significant difference in hospital mortality between male and female SARA/SUD patients in the age group 60-79.

	18 -39 years		**40-59 years**		**60-79 years**	
	Male n= 100	Female n=39	Male n=167	Female n=71	Male n=241	Female n=136
SARA and/or SUD, total	56 (56%)	11 (28%)	84 (50%)	17 (24%)	63 (26%)	27 (20%)
Main substance of abuse						
_Alcohol	21 (21%)	4 (10%)	43 (26%)	9 (13%)	62 (26 %)	24 (18%)
_Drugs (Illicit substances or prescription drugs)	35 (35%)	7 (18%)	41 (24%)	8 (11%)	1 (0.4%)	3 (2%)
Hospital mortality						
Overall	17 (17%)	8 (21%)	39 (23%)	14 (20%)	89 (37%)	53 (39%)
_SARA/SUD patients	11 (11%)	1 (3%)	18 (11%)	2 (3%)	24 (10%)	11 (8%)
_non-SARA/non-SUD patients	6 (6%)	7 (18%)	21 (12%)	12 (17%)	65 (27%)	42 (31%)

Table 2. Distribution of patients with SARA and/or SUD across age groups and gender

5. Discussion

5.1. Main findings

The present study describes preadmission and clinical characteristics of a mixed medical and surgical ICU population in Oslo included during a one-year period from 2014 to 2015. The inclusion criteria were set to select the more resource-demanding and severely ill ICU patients. Consequently, the mean SAPS score of 46 was considerably higher than the average score of 38 reported by the Norwegian intensive care registry in 2014[92]. Almost three-quarters of the patients received mechanical ventilation. The high severity of illness and level of treatment was reflected in a hospital mortality rate of 32%, almost twice as high as the average 17% reported for the overall Norwegian ICU population[92]. Trauma and cardiovascular disease were the most common diagnostic categories, reflecting the regional function of the Oslo University hospital Ullevaal. Two-thirds of the ICU population were males, a significantly higher proportion than the 53% males proportion among patients admitted to the Oslo University Hospital Ullevaal during the inclusion period. This overrepresentation of males is in line with prior international studies[53,93].

One-fifth of the ICU admissions were directly or indirectly associated with alcohol or drug abuse (SARA), of which the majority were associated with acute substance abuse. Furthermore, one-quarter of the ICU patients had underlying substance use disorder (SUD) of alcohol or drugs, reflecting the burden of chronic substance abuse on the ICU population. Overall, 30% of the patients had either substance abuse-related cause of ICU admission and/or underlying SUD of alcohol or drugs. These findings demonstrate 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.

5.2. Descriptive characteristics

5.2.1. Preadmission characteristics

The median age was 63 years, in line with the median age for patients admitted to regional hospitals in Norway[92]. Overall, 56 % of the patients were 60 years and older and 12% were 80 years and above. The mean Charlson comorbidity index was 2.3, reflecting the high level

of pre-existing chronic disease in the study population. As expected, comorbidity increased significantly with age, and nearly half of patients aged 60 and above had Charlson scores 3 or more. Cardiac and pulmonary disease were the most common chronic disease categories, reflecting the burden of non-communicable disease in the Norwegian population[94]. Although almost 80% of the patients had pre-existing chronic disease, the vast majority were self-reliant before admission indicating a relatively high level of function.

5.2.2. Main diagnoses and severity of illness

Trauma was the most common diagnostic category in surgical patients across the age groups. In medical patients aged 18-59, poisoning was the most common cause of admission, while cardiovascular disease and sepsis were most common among patients 60 years or older. Male patients were in majority within all diagnostic categories. Trauma and cardiovascular disease had the highest proportion of males, constituting three-quarters of the patients within these diagnostic categories.

The severity of illness was measured using the SAPS II and the SOFA scoring systems registered during the first 24 hours after ICU admission. SAPS II scores were similar across the diagnostic categories, except for cardiovascular disease, where the SAPS II scores were markedly higher. The high proportion of patients admitted after cardiac arrest may likely explain this finding. The mean initial SOFA score was 7.3 but varied significantly between the diagnostic categories reflecting differences in the severity of organ failure. Compared to patients within other diagnostic categories, patients with poisonings had comparatively lower SOFA scores, while patients with sepsis and cardiovascular disease had higher. We consider that the following factors may have contributed to the lower SOFA score in patients with poisoning. Firstly, the toxic effects of the substance of abuse commonly cause transient respiratory or CNS depression, involving fewer organ systems than in patients with other causes of critical illness. Secondly, younger age and lower prevalence of pre-existing chronic disease may also be important by making these patients less prone to developing other organ-related complications. The high SOFA scores in ICU patients with cardiovascular disease and sepsis are likely explained by the severe nature of these medical conditions, commonly affecting multiple organ systems.

Comparison between the genders showed similar SAPS II scores, but males had slightly higher initial SOFA scores than females. Surgical patients had lower SAPS II scores than medical patients, while SOFA scores were similar.

5.2.3. Treatment details

Surgical patients were significantly more likely to receive mechanical ventilation than medical patients, while non-invasive ventilation and renal replacement therapy were more commonly used in medical patients. Different guidelines for the use of mechanical ventilation in medical and surgical patients may explain this finding. In surgical patients, low GCS scores and complicated surgery are common indications for respiratory treatment, involving the vast majority of patients admitted to surgical ICUs. In medical patients, non-invasive treatment is preferred whenever possible, with severe respiratory dysfunction being the primary indication for mechanical ventilation.

Surprisingly, surgical patients had almost twice as long median length of stay in the ICU as medical patients, despite lower median age and less chronic disease. This difference may reflect the vast resources needed to treat severely ill trauma patients, including the need for repeated surgical procedures. Other possible explanations are the comparatively higher proportion of surgical patients receiving mechanical ventilation, the high number of neurosurgical patients, and the exclusion of postoperative patients.

Males were more likely than females to receive mechanical ventilation and vasopressor therapy. We consider the high proportion of males among patients with trauma and cardiovascular disease the main reason for this finding since these were the diagnostic categories with the highest proportion of patients receiving mechanical ventilation and vasopressor therapy. There were no significant differences in the level of treatment between the genders within each diagnostic category.

5.3. Impact of substance abuse

5.3.1. Substance use disorders

Overall, 19% of the males and 11% of the females were classified with alcohol use disorders. This is more than twice the estimated prevalence of AUD in the general Norwegian population, which is 8% for males and 3% for females[84]. The 10% prevalence of DUD in the

present study is many times higher than the estimated prevalence of 0.9% in Oslo[84]. This overrepresentation of patients with alcohol and drug use disorders is in line with previous studies[29,90], indicating that patients with excessive alcohol and drug use accumulate among patients receiving intensive care treatment.

5.3.2. Substance abuse as predisposing factor for ICU admission

Overall, 20% of the ICU population had a substance abuse-related cause of ICU admission (SARA). SARA-patients were divided into subgroups to gain more insight into the mechanisms by which acute and chronic substance abuse influenced the cause of ICU admission. The vast majority of SARA admissions were associated with acute substance abuse, indicating that substance abuse as a predisposing factor for ICU admission primarily reflects the harmful effects of acute alcohol and drug exposure.

SARA-admissions *directly* associated with acute substance use involved 7% of the study population and were mainly acute intoxications due to illicit substance abuse. These findings are in line with previous studies, confirming that acute intoxication is a common cause of admission in ICU-patients[95]. SARA-admissions *indirectly* influenced by acute substance abuse involved 9% of the study population. Of these, the majority were due to substance abuse-related trauma, with alcohol being the most common substance of abuse. More than one-third of the trauma patients were under the influence of substances of abuse at the time of injury, in line with previous studies of injured patients [28,75,96]. SARA-admissions associated with chronic substance abuse were the least common cause of SARA-admissions involving 4% of the study population. Alcohol was the most common substance of abuse and alcoholic liver disease being the most common cause of ICU admission.

5.3.3. Combined impact of SARA and SUD

Overall, 30% of the patients had either substance abuse-related cause of ICU admission and/or underlying substance use disorder. Although most prevalent in patients admitted with trauma, poisoning, and gastrointestinal disease, patients with substance abuse were present in all diagnostic categories. When combing the criteria for SARA and SUD, we found that 4% of the study population had SARA but did not fill the criteria for SUD, 15% had both SARA and SUD while 11% had SUD, but non-substance abuse related cause of admission. Patients only classified with SARA had ICU admissions associated with occasional alcohol and

drug use. These patients were comparatively younger, and had a lower prevalence of pre-existing chronic disease when compared to patients with SUD.

Among patients with SUD, DUD patients were more likely to have substance abuse-related admissions than AUD patients. Overall, 69% of DUD patients had SARA, of which nearly all were associated with acute substance abuse. This finding indicates that patients with excessive drug use predominately present with acute intoxication or substance abuse-related trauma when admitted to ICUs. In comparison, half of AUD patients had SARA. However, among AUD patients with SARA, the mechanisms by which acute and chronic substance abuse differed significantly between medical and surgical patients. While nearly all surgical AUD patients with substance abuse-related admissions were admitted due to alcohol-related trauma, complications of chronic substance abuse were the most common cause of subgroup of SARA among medical AUD patients. These findings demonstrate how harmful effects of excessive alcohol use may manifest differently in medical and surgical ICUs.

5.3.4. Substance abuse across age groups and gender

In patients younger than 60 years, more than half of the males had SARA and/or SUD, demonstrating the severe impact of substance abuse on young male patients. In this age group, male patients had more than twice as high a proportion of SARA/SUD-patients as female patients. The high number of males with illicit drug use and substance abuse-related trauma, mainly due to road traffic accidents and violence-related injuries, are likely explanatory factors. Furthermore, medicinal drugs such as antidepressants were not included in the definition of substance abuse in the present study. This may also be of importance since poisoning due to medicinal drugs are more common in female patients[3]. When excluding patients with substance abuse-related conditions, the proportion of males in patients aged 18-59 was reduced from 71% to 62%. Thus, the male dominance among patients with substance abuse-related conditions may partially explain the overall overrepresentation of males in this age group.

Although less prevalent than in the younger age groups, one-fifth of patients age 60 and above had SARA and or SUD. Of these, nearly all were in the age group 60-79. Alcohol was by far the most common substance of abuse in this age group, with alcohol-related falls

standing out as an important subgroup of alcohol-related admissions. Overall, one-third of the fall-related injuries in patients aged 60-79 were influenced by alcohol at the time of injury, reflecting some of the burden of alcohol misuse in elderly patients. The increased alcohol consumption in the elderly population combined with a reduced tolerance for the effects of alcohol may partially explain this finding[15]. Furthermore, older age is one of the key risk factors for falls potentially causing severe injuries[97]. Due to its impairment of the nervous system, including reduced motoric control, additional alcohol exposure may further increase the risk of serious injury in need of intensive care.

Surprisingly, in the age group 60 and above, there was no significant difference in the proportion of substance abuse-related conditions between the genders despite higher overall alcohol consumption in males than in females[98]. Differences in the absorption and metabolization of alcohol between the genders may explain this finding since females achieve higher alcohol-related concentrations than males after drinking equivalent amounts of alcohol.

5.3.5. Comparison with previous studies

Comparison with previous studies is challenging due to variations in case-mix, heterogeneity of definitions used, and differences in alcohol and drug use patterns between populations. The 30% prevalence of substance abuse-related conditions is higher than the 19% in a US ICU-study[29] and lower than the 39% described by de Wit et al. in a US study of mechanically ventilated medical patients[31]. Since only a few studies have addressed the impact of both alcohol and drugs within the same ICU population, distinguishing between patients with alcohol abuse and drug abuse may be of interest when comparing studies. The 19% proportion of patients with alcohol related-conditions in the present study is lower than in studies of alcohol-related conditions in Finnish[99] and Scottish ICUs[88]. Since both these countries have a much higher alcohol consumption than Norway[100], we consider differences in drinking patterns the main explanation. The 11% prevalence of drug-related conditions in the present study is higher than most other studies of drug-related ICU-admission[26,101]. However, in these studies, only admissions directly associated with acute drug use were registered, while we also registered patients with admissions indirectly influenced by acute

substance abuse and patients with underlying drug use disorders and non-substance abuse-related cause of admission.

5.4. Mortality

5.4.1. Hospital mortality across diagnostic categories, age groups and gender

Trauma and poisoning were the diagnostic categories with the lowest hospital mortality. The comparatively younger age, lower prevalence of pre-existing chronic disease, and lower severity of illness in patients with trauma and poisoning may explain this finding. Correspondingly, the high mortality in patients with cardiovascular disease is most likely explained by the comparatively higher severity of illness and prevalence of comorbid conditions. Comparison between the genders showed no difference in overall hospital mortality between male and female patients.

For both medical and surgical patients, ICU mortality and hospital mortality increased significantly with age. Nonetheless, presentation of mortality with increased age showed different trends for medical and surgical patients. In surgical patients, the mortality rate remained relatively low until the age of 70 and then increased steeply. For medical patients, both ICU mortality and hospital mortality increased linearly until the age of 70, but then these mortality curves diverged. This reflects a shift among elderly medical intensive care patients towards dying at the ward instead of in the ICU, in line with earlier findings[102].

5.4.2. Limitations of life-sustaining therapy

Decisions to forgo life-sustaining therapy, either by withholding or withdrawing treatment, are used in intensive care units to reduce the prolongation of suffering in patients who are not likely to survive the hospital admission. In the present study, decisions regarding limitations of life-sustaining treatment were made in 89% of the patients who died in the ICU surpassing the 81% reported in a study of end-of life-decisions in a Norwegian ICU-population [103]. Our findings are in line with international studies indicating an increased tendency of withholding and withdrawal of life sustaining treatment in the critically ill, particularly in Nordic ICUs[58]. Of the hospital survivors almost 80% were discharged home or to rehabilitation, indicating a low prevalence of futile treatment.

5.4.3. Substance abuse and hospital mortality

Evaluation of the impact of substance abuse on mortality is complicated due to the large variations in age, cause of admission, and patterns of abuse among patients with substance-abuse-related conditions. Overall, our results indicate that acute and chronic substance abuse had diverging impact on hospital mortality.

Possible explanations for the lower mortality in patients with acute alcohol or drug exposure are younger age, and the high proportion of patients admitted due to trauma or poisoning, the diagnostic categories with the lowest hospital mortality. Furthermore, a reversible impairment of vital physiological functions due to the toxic effect of alcohol or drugs is likely associated with better outcome than organ dysfunction due to severe disease or injury.

Among patients with SUD, hospital mortality varied markedly between patients with drug use disorders (DUD) and alcohol use disorders (AUD). When compared to patients without substance abuse, DUD-patients had lower hospital mortality, most likely explained by the high proportion of SARA-admissions due to acute substance abuse. However, this difference disappeared when adjusting for age. AUD was associated with increased age-adjusted mortality in patients with sepsis and in medical patients. The high mortality among AUD patients with sepsis is in line with previous findings[33]. Impaired immune function associated with chronic alcohol consumption is likely an important contributory factor[64,104]. 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 increased mortality in AUD-patients[105].

Despite no difference in overall mortality in male and female patients, males with substance abuse-related conditions had markedly higher mortality than females with substance abuse. This indicates that males had more severe poisonings than female patients, in line with previous findings [1]. Furthermore, it may also reflect significant differences in risk-behavior between the genders since males have both a higher risk of being involved in road traffic accidents and violence and an overall higher alcohol and drug consumption.

6. Clinical implications

To our knowledge, this is the first study describing the combined impact of acute and chronic abuse of both alcohol and drugs on a Norwegian ICU population. The findings, especially the high proportion of patients with substance abuse-related conditions, may inform the health authorities and decision-makers and demonstrate the need for enhanced prevention efforts.

Studies indicate that hospital admissions represent an opportune moment for intervention[78,79]. The present study demonstrates the diversity among patients with substance abuse-related conditions, and it is likely that effective preventive efforts may vary considerably between subgroups. For some patients with occasional substance abuse, hospital admission may represent a teachable moment by turning the ICU admission into a catalyst for change[78]. In contrast, patients with long-term chronic substance abuse represent a particularly challenging group demanding a broad and multifaceted approach, including psychiatric treatment.

More than 40% of the SUD-patients had a non-substance abuse-related cause of ICU admission. This demonstrates the importance of screening ICU patients for substance abuse regardless of diagnostic categories. The high response rate of the questionnaire used in the present study suggests that the implementation of routine screening for alcohol and drug abuse is feasible. Furthermore, since early identification of patients with substance abuse may have important therapeutic and prognostic implications[68], a more systematical identification of patients with substance abuse-related conditions may improve outcomes for these critically ill patients.

More than one-third of the trauma patients were influenced by alcohol or drugs at the time of injury. Since trauma patients are not routinely screened for substance abuse in Norwegian ICUs, a large proportion of patients with substance abuse-related trauma may be overlooked in clinical practice. Brief interventions have been shown particularly effective in trauma patients with unhealthy alcohol use[106]. Given the high prevalence of substance abuse among trauma patients in the present study, we suggest the implementation of a similar approach in Norwegian ICUs.

Although routine screening and increased awareness among the clinical staff may help identify patients with alcohol or drug abuse, there are several obstacles in handling substance abuse in the ICU setting. Self-discharge is common, and lack of time and knowledge on how to provide appropriate treatments are reported by health care providers[107]. Further research on how to address substance abuse among ICU patients is needed.

7. Methodological considerations

7.1. Study design and inclusion criteria

The study has a prospective observational design. Patients were included consecutively during a one-year period in order to include seasonal variations. We chose to include ICU patients from various types of ICUs (i.e., the medical ICU and neurosurgical ICU) since this allowed us to study the impact of substance abuse on patients within a wide range of diagnostic categories.

Inclusion criteria were set to select severely ill patients receiving high-level care and included patients aged 18 and above receiving mechanical ventilation and/or with a length of stay ≥ 24 hours combined with organ dysfunction of at least two organ systems. The reason for the choice of inclusion criteria was to select the more resource-demanding ICU patients since harmful effects of alcohol and drug abuse on this segment of the ICU population may have significant consequences for the ICU capacity. Consequently, we wanted to avoid confounding from "lighter" ICU patients with intoxication and substance abuse-related trauma with a need for observation rather than intensive care treatment.

When compared to the criteria used by NIR[108], our inclusion criteria have higher requirements to the level of treatment and organ dysfunction. Use of the criteria used by NIR in the present study would have led to a higher number of patients filling the criteria and a wider variation within the population in terms of treatment level and severity of illness. Thus, we consider the choice of inclusion criteria helpful in selecting patients with high severity of illness in line with the study's intention.

7.2. Methodological approach when addressing substance abuse

7.2.1. Two separate criteria when addressing substance abuse

In the present study, we used two separate classification criteria (SARA and SUD) when addressing the impact of alcohol and drug abuse on the ICU population. The main reason for this approach was that it allowed us to gain more insight into the extent and mechanisms by which acute and chronic substance abuse may influence the ICU population.

Although partially overlapping, it is essential to emphasize that we consider the two criteria equally important since they shed light on different aspects of the harmful effects of alcohol and drugs on the ICU population. When preparing for this study, it was also important that our approach when evaluating substance abuse would be transferable to clinical practice. Evaluation of SARA mainly reflects the direct and indirect harm due to acute substance abuse. Since the assessment of SARA is mainly based on toxicology and laboratory tests, an evaluation of SARA could be implemented as a routine procedure at ICU admission if desired. Furthermore, relating substance abuse to the cause of admission may also be of therapeutic value since it may provide an opening for motivational interviews regarding lifestyle changes that feel relevant both for the clinical staff and the patients.

The criteria for SUD were used to identify patients with excessive alcohol and drug use, regardless of the cause of admission, to reflect the burden of chronic substance abuse on the population. Patients seldom seek health care for alcohol or drug-related problems outside of the hospital. Thus, hospital admission represents a potential window of opportunity for addressing these issues. The main reason for addressing chronic substance abuse *regardless of the cause of admission* was to help increase clinical awareness regarding patients with underlying chronic substance abuse, but *a non*-substance abuse-related cause of admissions; a group of patients particularly easy to overlook in clinical practice.

By describing patients with SARA and SUD separately, we obtained a better understanding of the diversity of patients with substance abuse-related conditions than what would have been obtained if all patients with acute and chronic substance abuse were categorized as one group. Furthermore, when combined, the use of two criteria allowed us to separate SARA-patients with long-term excessive use from patients with accidental binge drinking or occasional drug use (SUD vs. non-SUD). This is clinically relevant since patients with excessive long-term use likely need a different follow-up than patients with occasional alcohol or drug use.

7.2.2. Background for the definition of SARA and SUD

The definition of SARA was based on the criteria used in a Scottish study of alcohol-related ICU admissions[88], with the addition of drug-related conditions. However, while the Scottish study classified patients with alcohol-related admissions as one group, we added subgroup

analysis based on whether the cause was directly or indirectly associated with acute or chronic patterns of abuse.

According to WHO, weekly drinking limits should not exceed 21 alcohol units per week for men and 14 alcohol units per week for women[64]. Nonetheless, health risks in response to alcohol consumption are highly individual, and universally applicable thresholds for high-risk drinking are therefore hard to define. Thus, we found the criteria for alcohol use disorders particularly challenging to define. For the AUDIT-C test (scores 0-12), a cut-off score of 4 points is commonly used in screening for alcohol misuse[109], but several recent studies have defined risk zones to select patients with different degrees of alcohol misuse[90,110-112] . For the present study, we wanted to select ICU patients with a high degree of alcohol misuse. We, therefore, chose a cut-off score of ≥8 since this is associated high probability of severe alcohol use disorder and increased risk of ICU-admission[90].

In addition to patients with audit scores above the cut-off limit and/or current drug use, all patients with manifest medical complications due to chronic substance (i.e., alcoholic liver failure) were classified with SUD, *regardless* of current alcohol or drug use. The main reason for this choice was that these were severe health consequences of alcohol and drug use we considered essential to include when addressing the clinical impact of chronic substance abuse on the ICU population.

7.3. Validity

For the questionnaire, we used the validated alcohol screening test AUDIT-C recommended for emergency settings[86]. The AUDIT-C is a short version of the AUDIT test, which also has been validated for proxy[85]. However, although there are several validated tools available for assessing excessive alcohol and drug use in clinical practice[86,113,114], there is limited information regarding the optimal assessment of such screening tools in critical care. Thus, more studies addressing the validity of alcohol- and drug-related screening tests in the ICU setting are needed.

A limitation in using the AUDIT-C test is that we used the same cut-off scores for all patients, despite lower tolerance for alcohol use in females and elderly patients. This may have led to an underestimation of severe alcohol misuse in these subgroups of the ICU population, and perhaps an overestimation of severe alcohol misuse in young, male patients with a higher

tolerance for alcohol use. Furthermore, an under-reporting of alcohol consumption is common[115] and may have occurred in some patients, representing a potential information bias.

Another weakness regarding the use of AUDIT C to estimate AUD is that it is based solely on alcohol consumption. Although an AUDIT-C score ≥ 8 is associated with high likeliness for AUD is only a probability measure. Therefore, this approach will have lower validity than the use of more comprehensive screening tools, which also address other consequences of excessive alcohol abuse, such as dependency symptoms.

Regarding the SARA classification used in the present study, there were no validated tools available that could measure whether the cause of ICU admission was related to substance abuse. Instead, our approach when addressing substance abuse as a predisposing factor for ICU admission was to define a descriptive classification system based on criteria used in a prior study of ICU patients [88]. These criteria were based on the ICD-10 criteria and included harmful effects of both acute and chronic patterns of abuse – factors we consider increasing the validity of the SARA criteria. Nonetheless, the association between the influence of substance abuse and the cause of admission inevitably had to include some extent of individual judgment. This, in turn, may contribute to reducing the validity of the SARA criteria.

7.4. Reliability

The evaluation of substance abuse was based on several sources, including medical records, toxicology and laboratory results, and the questionnaire regarding prior alcohol and drug use. Data were collected using a standardized registration form with pre-defined definitions of SARA and SUD. Thus, the reliability appears to be relatively high since the methodological approach helped clarify which patients should be classified with SARA and SUD.

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. In these cases, the information from the medical records had to be emphasized to a greater extent. Since information from medical records can often be incomplete, the evaluation of SUD may have been less reliable in some of these cases. In patients classified with SARA, not all positive urine toxicological tests were

confirmed with blood analysis, as this would have required more laboratory resources. Furthermore, in some cases, such as GHB intoxications, confirmation by laboratory results was not possible – cases in which the assessment of SARA had to be based entirely on clinical signs and anamnestic information. In this context, however, it is essential to emphasize that no patients were classified with SARA unless supplementary information strongly indicated that the cause of admission was directly or indirectly influenced by alcohol or drugs.

Reliability is often measured by repeating measurements (test-retest). If this principle were to be transferred to the present study, it would mean that every patient would have been classified independently by two or more study personnel. This was not done due to limited resources and therefore represents a potential weakness in the study. However, in order to contribute to more uniform registrations, the evaluation of whether a patient had SARA and/or SUD was made by a small group of study personnel trained in the classification methodology. Regular consensus meetings were held to reduce interrater variability. Although possible subjective bias in the decision-making process cannot be ruled out, we consider this methodological approach important in improving the overall reliability of our results.

7.5. Representativeness

We consider the choice of inclusion criteria helpful in selecting patients with high severity of illness, in line with the study's intention. Still, since these criteria differ from the criteria used by the Norwegian intensive care registry criteria, they may reduce the generalizability of our results to the overall Norwegian intensive care population. Furthermore, the inclusion criteria may also represent a limitation when addressing the scope of alcohol and drug-related conditions since cases of intoxications, particularly due to substances with short elimination half-lives, may have been missed.

The proportion of alcohol and drug-related admissions in an ICU population will depend on various factors such as age distribution, diagnostic categories, and patterns of abuse. Thus, the overall proportion of 30% of patients with substance abuse abuse-related conditions found in the present study cannot be directly applied to other ICU populations. Furthermore, the higher prevalence of substance abuse in larger cities, such as Oslo, compared to more

rural areas[84], and the high proportion of trauma patients in our study population, represent possible selection bias affecting the generalizability of our results. We believe this especially applies to the proportion of intravenous addicts, which was as high as 7% in our material and probably not representative of rural areas.

Nonetheless, the extensive use of subgroup analyses in the present study likely contributed to increasing the representativeness of our results within the subgroups of the ICU population. For example, we believe that the prevalence of substance abuse in trauma patients should be representative of other tertiary trauma centers in Norway and probably also in Scandinavia.

7.6. Statistics

For papers I and II, we used statistical tests when comparing the characteristics of subgroups. P-values < 0.05 were considered statistically significant. For paper III and the combined results, we instead used precision of estimates (Confidence interval, C.I.). From a statistical perspective, it would have been more appropriate to use precision of estimates for all papers since this is in line with the STROBE criteria for observational studies[116]. Nonetheless, we consider the descriptive parts regarding the scope of alcohol and drug-related conditions as the most important aspect of this study. From this point of view, the overall results were similar regardless of the statistical method.

When evaluating mortality, hospital mortality was used as the outcome measure. Since hospital mortality may be sensitive to referral and discharge patterns, 30-day mortality was added to the analysis presented in paper III. Mortality analysis using 30-day mortality showed similar results as when using hospital mortality. Logistic regression analysis was used to adjust for confounding variables when comparing mortality between subgroups. When evaluating the impact of substance abuse on hospital mortality, we adjusted for age but not for comorbidity and diagnostic category since these variables were considered possible consequences of alcohol or drug exposure.

7.7. Suggestions for future studies

Despite several limitations, we consider the use of a questionnaire provided important supplementary information regarding the patient's alcohol and drug use. We, therefore, suggest a similar approach in future studies of substance abuse in ICU patients. Due to the

risk for withdrawal symptoms, substance dependence is particularly important to identify in ICU patients. Although the AUDIT-C has been shown useful in identifying patients with a high probability of dependence[86], we suggest that the full AUDIT test, or other brief screening tools such as the Fast Alcohol Screening Tool (FAST)[117], should be considered in future studies since these may be more sensitive in identifying patients with dependence. Correspondingly, for patients with drug use, a short form of the DUDIT test using the four first questions appears to be a good choice[81,118].

Considering the heterogeneity of patients with substance abuse-related conditions, stratified mortality analysis within diagnostic categories would have been of interest. Such analyses were not possible in the present study due to the limited sample size but should be a topic for future studies concerning substance abuse in intensive care patients. Furthermore, while hospital mortality was used as an outcome variable in the present study, more studies of the long-term survival of ICU patients are needed to increase knowledge regarding these patients' long-term outcomes.

8. Ethical considerations

8.1. Inclusion of patients

The present study was consent-based and approved by the Norwegian Regional Ethics Committee. Nonetheless, several ethical aspects had to be taken into consideration when studying intensive care patients. Obtaining consent for study participation from ICU patients is challenging due to the nature of the critical illness and the frequent need for sedatives and supportive therapy. Consequently, communication, including the request for consent, must often go through next of kin. In the present study, we obtained more than half of the consents from next of kin. The disease course in critically ill patients is often short and abrupt, leaving relatives of intensive care patients in a demanding situation. This is essential to take into consideration when asking next of kin for consent. However, with a gentle and understanding approach, we experienced a high willingness to cooperate.

Despite an overall high participation rate, severely ill patients who died in the ICU proved challenging to include. In some cases, we refrained from asking next of kin for consent for respectful reasons, as this could be perceived as burdensome. Furthermore, some patients with intoxications were demanding to include due to reduced awareness, a short length of stay, and because their relatives neither were commonly present nor would be suitable to ask. Since omitting these patients would significantly impair the quality of the study, we chose to apply for exemption from consent for patients who died in the ICU and patients admitted with acute intoxication, which was granted. In addition, exemption from consent was granted for patients who could not consent themselves and did not have relatives who could be asked instead.

8.2. Information on alcohol and drug use

Interviewing patients and next of kin regarding alcohol and drug use can be challenging since such information may be perceived as private and potentially stigmatizing. Thus, to increase collaboration and participation in the study, it was essential to present the questionnaire in a neutral and non-judgmental manner. Furthermore, we experienced that informing patients or next of kin that knowledge regarding the patients' prior alcohol and drug use could help

optimize the quality of ICU treatment given, helped increase collaboration and participation in the study.

For patients with established severe substance abuse, the encounter with healthcare professionals may be characterized by mutual mistrust and fear of discrimination. Before conducting the study, we expected that these patients would be difficult to include. However, except for some patients with acute intoxications, which were hard to include for practical reasons, we experienced a high degree of collaboration from these patients, as long as they were treated with respect and empathy.

Overall, when including patients, we found it helpful that relatively few study personal performed these interviews since we then obtained experience in how to present the study information and questionnaires most efficiently. Based on this experience, we suggest that routine screening – if implemented in ICUs – should be performed by medical personnel trained in such procedures, preferably a dedicated nurse.

9. Conclusion

- In this mixed Norwegian ICU population, 30% of the patients had either substance abuse-related cause of ICU admission and/or underlying substance use disorder of alcohol or drugs. Of these, 19% were mainly alcohol-related and 11% drug-related. Thus, substance abuse was 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.

- One in five ICU admissions, and half of the admissions in the age group 18-39, were directly or indirectly associated with alcohol or drug abuse. Alcohol was the main substance of abuse among patients with substance abuse-related trauma, while illicit drug use was most common among patients with acute intoxications and in males younger than 40 years. More than one-third of the trauma patients were influenced by alcohol or drugs at the time of injury, reflecting the severe impact of substance abuse as a risk-increasing factor. Routine screening for alcohol and drugs should be considered implemented in trauma patients.

- Overall, 26% of the patients had underlying substance use disorders (SUD) of alcohol or drugs – much higher than the prevalence in the Norwegian population. More than 40% of SUD-patients had a non-substance abuse-related cause of ICU admission. This demonstrates the importance of screening ICU patients for substance abuse regardless of diagnostic categories. The high response rate of the questionnaire used in the present study indicates that the implementation of routine screening for alcohol and drug abuse is feasible.

- Total hospital mortality was 32%. For both medical and surgical patients, ICU mortality and hospital mortality increased significantly with age. Trauma and poisoning had the lowest hospital mortality, while cardiovascular disease had the highest mortality. Although overall hospital mortality was similar for patients with substance abuse compared to patients without, acute and chronic substance abuse had a diverging

impact on hospital mortality. While substance abuse-related trauma was associated with lower age-adjusted mortality, alcohol use disorders were associated with higher mortality in medical patients and patients with sepsis.

- Limitations of life-sustaining treatment were made in 89% of the patients who died in the ICU. Of the surviving patients almost 80% were discharged home or rehabilitation. This indicates a low prevalence of futile treatment.

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Appendix

Inclusion criteria

Age ≥ 18 years and ≥ 1 of the following 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 below.

Organ system	Definition of dysfunction	Source
Respiration	PaO_2/FiO_2 < 33 kPa	Sepsis criteria[1]
Cardiovascular*	Need for vasopressor to obtain MAP ≥ 70 mmHg	Sepsis criteria[1] / SOFA score[2]
Metabolic	pH ≤ 7.3 or BE ≥ 5, and lactate > 3mmol/L	Sepsis criteria[1]
CNS*	GCS ≤ 12	Sepsis criteria[1] / SOFA score[2]
Hematological*	Platelets ≤ 100x 10^9 /L	Sepsis criteria[1] / SOFA score[2]
Liver***	Bilirubin ≥ 34 µmol/L or INR ≥ 1.7	Sepsis criteria[1] / Child-Pugh
Renal**	Urine output < 0.5 ml/kg/hr × 6 hour / increased creatinine × 1.5 mg/L (≥26.4 µmol/L)	Sepsis criteria[1] / AKIN score[3]

*Value corresponding to SOFA score of ≥ 2
**Based on AKIN criteria level ≥ 1
***Values corresponding to Child-Pugh score ≥ 1

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Løpenummer | | | | |

Livsstil

– spørreskjema til alle intensivpasienter

Kjære pasient.
Vi ønsker å få mer kunnskap om intensivpasienters bruk av røyk, snus, alkohol og eventuelle rusmidler. Vi håper derfor at du kan bruke noen minutter til å svare på spørsmålene nedenfor. Svarene vil bli behandlet konfidensielt og vil kun brukes i forbindelse med studien. Takk for hjelpen!

1. Røyker du?	☐ Nei ☐ Nei, men jeg har røkt tidligere		☐ Av og til		☐Ja
2. Snuser du?	☐ Nei ☐ Nei, men jeg har brukt snus tidligere		☐ Av og til		☐Ja
3. Hvor ofte drikker du alkohol? *(Hvis svar «aldri» - gå til spørsmål 6.)*	☐ Aldri	☐ 1 gang i måneden eller sjeldnere	☐ 2-4 ganger i måneden	☐ 2-3 ganger i uken	☐ 4 ganger i uken eller mer
4. Hvor mange alkoholenheter drikker du vanligvis ved ett tilfelle?	☐ 1-2	☐ 3-4	☐ 5-6	☐7-9	☐10 eller flere
5. Hvor ofte - det siste året- har du drukket mer enn 5 alkohol-enheter? (*mer enn 4 enheter hvis du er kvinne?*)	☐ Aldri	☐ Sjelden	☐ Noen ganger i måneden	☐Noen ganger i uken	☐Nesten daglig
6. Bruker du andre rusmidler enn alkohol? I så fall, hvor ofte? (*sett ring rundt evt. stoff i liste på baksiden)*	☐ Aldri	☐ 1 gang i måneden eller sjeldnere	☐ 2-4 ganger i måneden	☐ 2-3 ganger i uken	☐4 ganger i uken eller mer
7. Bruker du beroligende eller sterke smertestillende medisiner (såkalte A og B preparater) oftere enn legen har anbefalt?	☐ Aldri	☐ 1 gang i måneden eller sjeldnere	☐ 2-4 ganger i måneden	☐ 2-3 ganger i uken	☐4 ganger i uken eller mer

En alkoholenhet = 1 liten flaske pils, 1 glass vin eller 1 drink

Løpenummer | | | | |

LISTE OVER STOFF (ikke alkohol)- sett kryss hvis aktuelt

☐**Cannabis** *Eks.:*	☐**Amfeta-miner** *Eks.:*	☐**Kokain** *Eks.:*	☐**Opiater** *Eks.:*	☐**Hallucino-gener** *Eks.:*	☐**GHB**	☐**Anabole steroider**	☐**Løsnings-midler** *Eks.:*	☐ **Andre inkl.** *Eks.:*
Marihuana Hasj Cannabis-olje	Amfeta-min Metam-fetamin Ritalin Dexamin	Crack Kokablad Kokain	Heroin Røyke-heroin Metadon Subutex	Ecstasy (MDMA) LSD Meskalin PCP(engle-støv) Fleinsopp Ketalar	GHB		Tynner Bensin Gass Løsemidler, lim Trikloretylen	Syntetiske cannabinoider ”Bath salts” Lystgass Amylnitritt

Annet_____

Ved ett eller flere kryss:
Hvilket stoff har du brukt mest det siste året?_____
Når tok du stoffet sist?_____
Hvilket stoff har du eventuelt brukt siste uken_____

TABLETTER – LEGEMIDLER

Tabletter regnes som stoff når du tar:

- Legemidler mer eller oftere enn legen har forskrevet
- Tabletter for å ha det moro, føle deg bra, bli «høy», eller prøve ut effekten
- Tabletter du har fått av en slektning eller venn
- Tabletter som du har kjøpt «svart» eller stjålet

Sett et kryss ved de tablettene du eventuelt har brukt som beskrevet over:

Beroligende legemidler/sovetabletter ☐			**Smertestillende legemidler ☐**		
Alopam Alprazolam Apodorm Barbital Dormicum Fenemal Flunipam Heminevrin	Imovane Mogadon Rivotril Rohypnol Sobril Somadril Stesolid	Stilnoct Valium Vival Xanor Xanor depot Zolpidem Zopiklon **Andre:** Disipal Akineton	Actiq Aporex Anervan Buprenorfin Cosylan Dolcontin Durogesic Etylmorfin Fentanyl Fortralin Hydrokon	Ketalar Ketamin Ketogan Ketorax Kodein Metadon Modiodal Morfin Morfin-skopolamin	Nobligan Oxycontin Oxynorm Paralgin Petidin Pinex Subutex Temgesic Tradolan Tramadol Tramagetic Annet Andre

Takk for at du besvarte våre spørsmål!

Papers

I

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ORIGINAL ARTICLE

Acute illness, Comorbidity and Mortality in a Norwegian Intensive Care Population

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Abstract

Background: The need for intensive care beds is high and expected to increase. Descriptive studies of the intensive care population may reveal differences in predisposing factors and outcome within subgroups and help identify areas in need of increased prevention efforts.

Objective: To describe preadmission and clinical characteristics of an intensive care population in Oslo, and to compare the characteristics and outcomes of selected subgroups of this ICU-population.

Method: Prospective observational cohort study of intensive care patients aged ≥ 18, admitted to two hospitals in Oslo during a one-year period. Acute illness characteristics, co-morbidity, limitations of life-sustaining treatment and hospital mortality were studied for the overall population and stratified for a) Gender and b) Medical and surgical patients within the age groups 18-59 years and 60 and above.

Results: We included 861 patients, 567 (66%) males; median age 63 years (range 18-95); 537 (62%) medical admissions and 324 (38%) surgical admissions. 632 (73%) received mechanical ventilation. Trauma (n = 191, 21%) and cardiovascular disease (n = 180, 20%) were the most common causes of admission. In patients aged 18-59, poisoning caused 56/217 (26%) of the medical admissions and medical patients had a higher prevalence of pre-existing chronic disease (157/217, 72% vs. 69/160, 43%) and Charlson comorbidity index (mean 2.0 vs. 0.7, $p < 0.001$) than surgical patients. In patients aged 60 and above, comorbidity was similar, but medical patients had a higher hospital mortality (143/320, 45% vs. 58/164, 34%, $p < 0.05$). 205 (24%) died in the ICU, and limitations of life-sustaining treatment were made in 183 (89%) cases 279(32%) died during the hospital stay. Of the 582 surviving patients 455 (78%) were discharged to home or rehabilitation, 88 (15%) to nursing homes and 39 (7%) to other institutions.

Conclusion: In patients younger than 60 years, trauma and poisoning were the most common causes of admission. Within this age group, medical patients had much higher prevalence of preexisting chronic disease than surgical patients, suggesting differences in predisposing factors. The majority of the surviving patients were discharged to home or to rehabilitation, indicating a low prevalence of futile intensive care.

Introduction

Intensive care units (ICU) provide advanced health care for seriously injured and ill patients, demanding vast economic resources. The population is aging and the need for intensive care beds is expected to increase considerably over the next decades [1]. This will have serious implications for planning and financing of the health care system. Descriptive studies of intensive care patients are needed to ensure that the health services can meet future needs [2].

Evaluation of ICU services are challenging due to variations in ICU-beds availability and case-mix in different intensive care populations. The selection of pa-

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tients may also vary between local and regional hospitals and these differences are important to address when studying ICU patients. Patients with medical and surgical admissions are often treated in specialized ICUs and may have different needs. Thus, separate description of medical and surgical ICU patients may be useful in the planning of future intensive care treatment.

Age, co-morbidity and severity of illness are important predictors of mortality in intensive care patients [3]. Since co-morbidity increases significantly with age [4], stratification in age groups is important when describing ICU populations. Comparison of the characteristics of medical and surgical patients - within age groups - may reveal differences in predisposing factors, comorbidity factors and outcome [5] that may help identify areas in need of increased prevention efforts.

On this background our study had the following aims:

1. To describe the age and gender distribution, co-morbidity factors, diagnostic categories, limitations of life-sustaining treatment and hospital mortality of a mixed ICU population in Oslo.

2. To compare a) Male and female patients and b) Medical and surgical patients within age groups on selected parameters.

Material and Methods

Study design and population

The study had a prospective observational cohort design and included intensive care patients admitted to the intensive care units (ICUs) at the Oslo University hospital Ullevaal and the Diakonhjemmet Hospital in the period February 3rd 2014 to February 2nd 2015. The Oslo University hospital Ullevaal is a tertiary referral hospital with comprehensive medical services including trauma, neurosurgery and percutaneous cardiac intervention for Eastern Norway (3.0 million inhabitants). In addition, it serves as a local hospital for one third of Oslo's population (647,676 inhabitants; 2015).

The Diakonhjemmet hospital serves as a local hospital for 115,000 inhabitants in Oslo. Five intensive care units participated in the study; the medical, cardiac, surgical and neurosurgical ICUs at the Oslo Universitiy hospital, Ullevaal and the mixed medical/surgical intensive care unit at the Diakonhjemmet hospital (Table 1). Since the post-operative units at the study hospitals did not participate in the study, no patients with elective thoracic or cardiac surgery were included. In order to avoid individuals being represented multiple times, only the first admission of each patient during the study period was registered.

Inclusion criterias were age ≥ 18 years and 1) Intubation regardless of length of stay and/or 2) ICU length of stay ≥ 24 hours, and dysfunction of ≥ two organ systems (see Appendix). Of the 995 ICU-admissions filling the inclusion criteria (Figure 1), 91 patients were excluded due to missing consent or language problems. Median age for these patients was 54 (range 18-89), and 63% were males. Of the remaining 904 admissions, 43 (4%) were readmissions of previously included patients and therefore excluded from the analysis.

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 without next of kin that could be asked instead 2) Admitted with acute poisoning and 3) Who died during ICU treatment.

Stratification

The material was stratified into medical and surgical admissions as defined by the SAPS II system: 1) Medical: No surgery within 1 week prior to ICU admission. 2) Surgical: a) Scheduled surgical patients - elective surgery within 7 days of ICU admission and b) Non-scheduled surgical patients: acute surgery (scheduled less than 24 h in advance) within 1 week prior to ICU admission. The World Health Organization define patients above 60 years as elderly. We therefore subdivided the patients in age groups 18-59 and 60 and above.

Registrations

Data were consecutively collected using a standardized registration form and included the following variables: Age; gender; preadmission living situation (living at home without home care (self-reliant), living at home with home care, nursing home etc.); Charlson comorbidity index (C.I.I) [6]; main diagnostic category based on the APACHE system;

Table 1: Description of the ICUs participating in the study.

Intensive care units	ICU beds	Number of admissions pr. year	Nurse: Patient ratio
Oslo University Hospital, Ullevaal			
1. Medical	6	450	1.3:1
2. Cardiac	3	150	1:1
3. Surgical, general	10	420	2:1
4. Neurosurgical	6	220	2:1
Diakonhjemmet Hospital			
5. Mixed general	4	300	1:1
Total	29	1540*	

*Numbers pr. 2018.

SAPS II score [7]; SOFA (sequential organ dysfunction assessment) [8] at admission; length of stay; mechanical ventilator support; duration of mechanical ventilation; non-invasive ventilator support; renal replacement therapy; post-discharge location (home, nursing home etc.); ICU-mortality and total hospital mortality (ICU-mortality included). For patients who died in the ICU, we registered decisions regarding limitations of life-sustaining treatment including a) Withholding treatment (the decision not to start or increase a life-

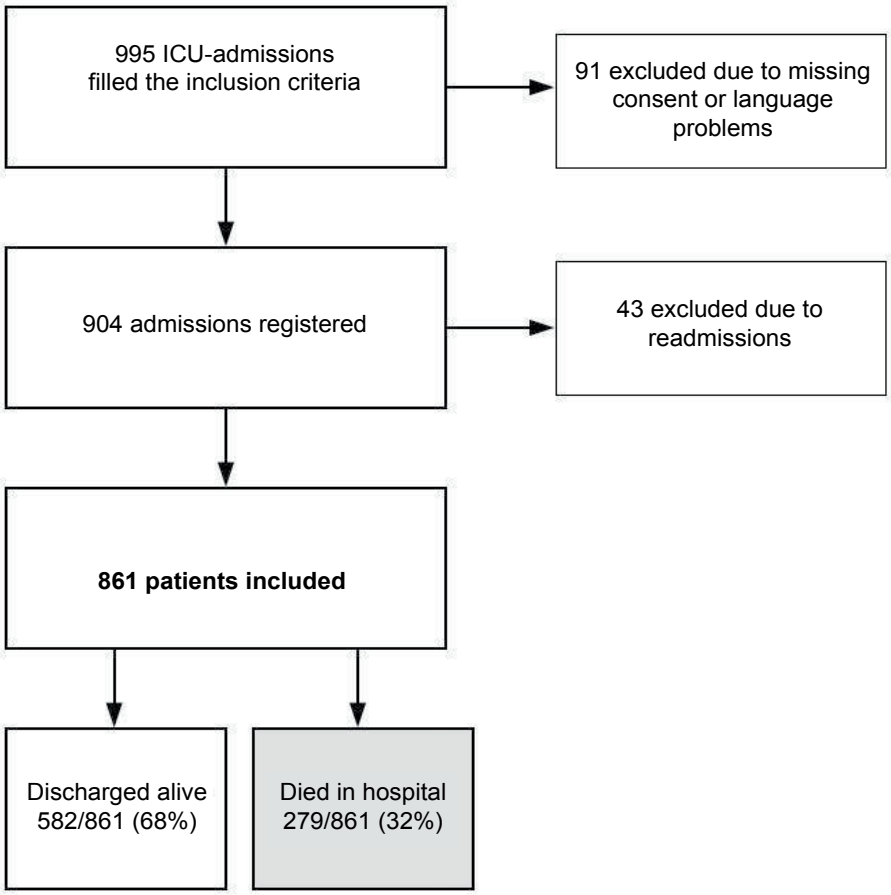

Figure 1: Flow-chart of the patients included in the study.

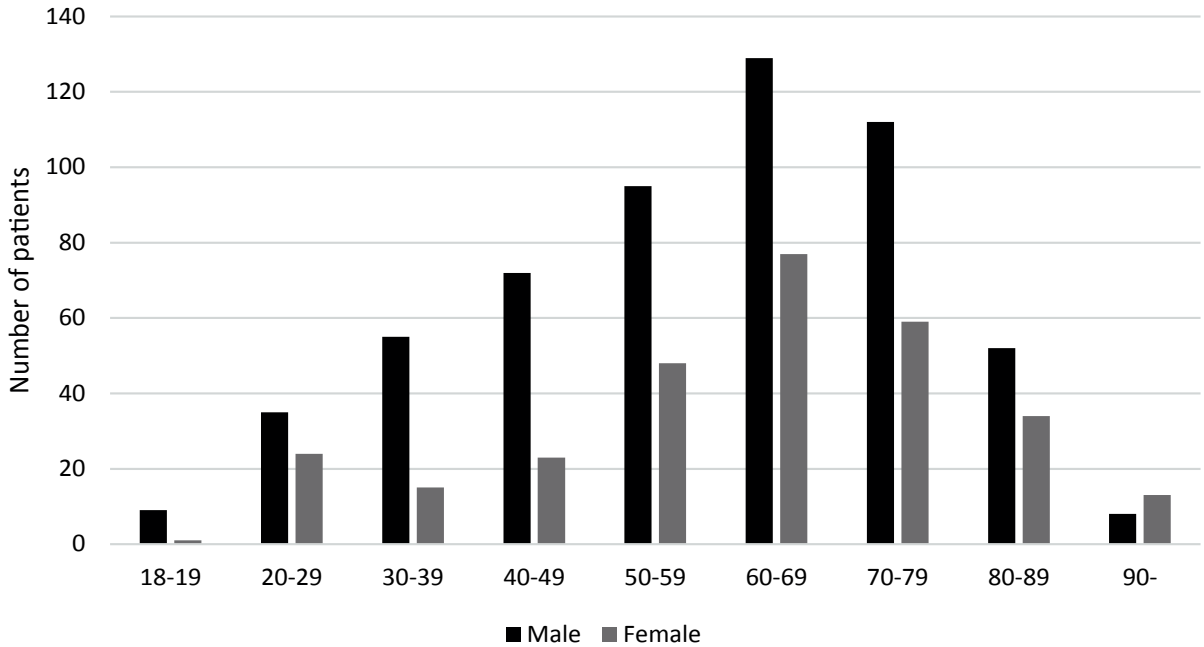

Figure 2: Distribution of male/female patients within age groups.

sustaining intervention) or b) Withdrawing treatment (the decision to stop a life-sustaining intervention) [9].

Statistics

Chi square test was used when comparing proportions and an independent samples t-test was used when comparing means. IBM SPSS® version 25.0 for Windows (Armonk, NY, USA) was used for the statistical analysis. P values < 0.05 were considered statistically significant.

Results

Study population

Of the 861 patients included (Figure 1), 567 (66%) were males, 537 (62%) were medical admissions and 324 (38%) were surgical admissions, of which 27 were scheduled and 297 non-scheduled. Median age was 63 years (range 18-95). Male patients were younger than female patients (median age 61 vs. 64, p = 0.03), and were in majority within all age groups except for patients aged 90 and above (Figure 2). Surgical patients were younger than medical patients (median age 60 vs. 64, p < 0.01).

Characteristics of the overall study population stratified for medical and surgical patients, are presented in Table 2, Table 3, Table 4 and Table 5.

Overall, mean Charlson comorbidity index (CCI) was 2.3, and 672 (78%) of the patients had pre-existing chronic disease at admission (Table 2). In the age group 18-59, medical patients had higher mean Charlson co-morbidity index (CCI) (2.0 vs. 0.7, p < 0.001) and prevalence of pre-existing chronic disease than surgical patients (157/217, 72% vs. 69/160, 43%, p < 0.001). Comorbidity was similar in the age group 60 and above and between the genders. Of the patients included,

Table 2: Pre-admission characteristics.

	All patients	18-59 years (n = 377)		60 years and above (n = 484)	
	N = 861	Medical n = 217	Surgical n = 160	Medical n = 320	Surgical n = 164
Males n (%)	567 (66%)	145 (67%)	121 (75%)	199 (62%)	102 (62%)
Charlson co-morbidity index, mean ± SD	2.3 ± 2.2	2.0 ± 2.2	0.7 ± 1.3*	3.0 ± 2.2	2.7 ± 2.1
Chronic disease n (%)					
Known chronic disease	672 (78%)	157 (72%)	69 (43%)*	298 (93%)	148 (90%)
No prior chronic disease	189 (22%)	60 (28%)	91 (57%)*	22 (7%)	16 (10%)
Common chronic disease categories[1]					
Cardiovascular disease n (%)	343 (40%)	45 (21%)	21 (13%)	195 (61%)	82 (50%)
Chronic pulmonary disease n (%)	167 (20%)	24 (11%)	9 (6%)	101 (32%)	33 (21%)
Diabetes n (%)	136 (16%)	29 (13%)	4 (3%)	70 (22%)	33 (20%)
Polyfarmacy, regular medication n (%)					
None	213 (25%)	70 (32%)	97 (61%)*	27 (9%)	19 (12%)
1-4	358 (42%)	93 (43%)	49 (31%)	113 (35%)	102 (62%)
5-7	145 (17%)	26 (12%)	8 (5%)	85 (27%)	26 (16%)
≥ 8	145 (17%)	28 (13%)	6 (4%)	94 (29%)	17 (10%)
Living situation n (%)					
Home without home care	679 (79%)	178 (82%)	143 (89%)*	221 (69%)	137 (84%)*
Home with home care	90 (10%)	13 (6%)	2 (1%)	63 (20%)	12 (7%)
Nursing home or institution	50 (6%)	6 (3%)	0 (0%)	30 (9%)	14 (9%)
Homeless	11 (1%)	6 (3%)	4 (2%)	1 (0.3%)	0
Other[2]	24 (3%)	11 (5%)	8 (6%)	4 (1%)	0
Unknown	8 (1%)	3 (1%)	3 (2%)	1 (0.3%)	1 (0.6%)

[1]Each patient may have more than one disease; [2]Incl. psychiatric and drug abuse institutions; *p < 0.05.

Table 3: Main diagnostic categories n (%).

	All patients N = 861	18-59 years (n = 377)		60 years and above (n = 484)	
Main diagnosic categories n (%)		Medical n = 217	Surgical n = 160	Medical n = 320	Surgical n = 164
Trauma	191 (22%)	0	119 (74%)	0	72 (44%)
Cardiovascular disease	180 (21%)	47 (22%)	3 (2%)	124 (39%)	6 (4%)
Sepsis	116 (13%)	41 (19%)	2 (1%)	63 (20%)	10 (6%)
Respiratory	88 (10%)	16 (7%)	3 (2%)	53 (17%)	16 (10%)
Gastrointestinal	81 (10%)	17 (8%)	12 (8%)	17 (5%)	35 (21%)
Neurologic/CNS	73 (8%)	22 (10%)	12 (8%)	27 (8%)	12 (7%)
Poisoning	65 (8%)	56 (26%)	0	9 (3%)	0
Cancer	23 (3%)	4 (2%)	4 (3%)	5 (2%)	10 (6%)
Other	44 (5%)	14 (7%)	5 (3%)	22 (7%)	3 (2%)

Table 4: Severity of illness and treatment.

	All patients (N = 861)	18-59 years (n = 377)		60 years and above (n = 484)	
		Medical n = 217	Surgical n = 160	Medical n = 320	Surgical n = 164
SAPS II, mean ± SD	46.0 ± 18	41.7 ± 19	39.0 ± 14	52.3 ± 19	46.8 ± 16*
SOFA admission, mean ± SD	7.4 ± 3.5	7.1 ± 4	6.8 ± 3	7.7 ± 4	7.4 ± 3
ICU-length of stay (LOS), median days (IQR)	4.5 (1.9-9.8)	3.5 (1.3-7.7)	6.2 (2.3-14.5)*	3.7 (1.8-7.3)	6.9 (3.0-14.5)*
Transferred to other hospital during ICU-stay, n (%)	214 (25%)	52 (24%)	43 (27%)	76 (24%)	43 (26%)
Intubated patients, n (%)	632 (73%)	152 (70%)	158 (99%)*	164 (51%)	158 (96%)*
Mechanical ventilator support time, days, median(IQR)	3 (1-8.4)	2.8 (0.5-7.0)	2.0 (0.5-10.0)	3.0 (1.1-7.0)	4.0 (1.0-10.6)
Non-invasive ventilator support n (%)	227 (26%)	46 (21%)	22 (14%)	129 (40%)	30 (18%)*
Renal replacement therapy n (%)	91 (11%)	38 (17%)	12 (8%)*	26 (8%)	15 (9%)
Vasopressor therapy n (%)	575 (67%)	117 (53%)	121 (75%)*	202 (63%)	135 (82%)*
Sepsis[1]					
Total n (%)	210 (24%)	61 (28%)	26 (16%)	84 (26%)	39 (24%)
Primary source:					
Respiratory n (%)	88 (10%)	28 (13%)	5 (3%)	45 (14%)	10 (6%)
Abdominal organs n (%)	45 (5%)	4 (2%)	11 (7%)	9 (3%)	21 (13%)
Soft tissue n (%)	25 (3%)	11 (5%)	5 (3%)	7 (2%)	2 (1%)
Urinary tract n (%)	19 (2%)	4 (2%)	0	14 (4%)	6 (1%)
Catheter-related infection n (%)	11 (1%)	4 (2%)	2 (1%)	4 (1%)	6 (1%)
CNS n (%)	11 (1%)	6 (2%)	3 (2%)	2 (1%)	0
Endocarditis n (%)	5 (0.5%)	3 (1%)	0	1 (1%)	1 (1%)
Other n (%)	2 (0.2%)	0	0	1 (0.5%)	1 (0.5%)
Origin unknown n (%)	9 (1%)	4 (2%)	0	3 (1%)	2 (1%)

[1]Sepsis as main diagnose (n = 116) or complication (n = 94). *p<0.05

679 (79%) were self-reliant without home care services before admission. The proportion of self-reliant patients was higher in surgical than medical patients (178/217, 82% vs. 143/160, 89%, p < 0.05 and 137/164, 84% vs. 221/320, 69%, p < 0.01 respectively) and in male compared to female patients (460/567, 81% vs. 219/294, 74% p < 0.03). Overall, mean SAPS II was 46, and mean SOFA score at admission 7.4.

Diagnostic categories

Trauma and cardiovascular disease were the most common diagnoses (Table 3). Average age differed markedly between the diagnostic categories (Figure 3). The categories trauma and poisoning were dominated by younger patients (median age 53 and 41. respectively). Poisoning caused 56/217 (26%) of the medical admissions in the age group 18-59 (Table 3), and 30/65 (46%) in the subgroup below 40 years. Trauma caused 119/160 (74%) of the surgical admissions in patients aged 18-59 (Table 3), and 56/75 (75%) of the subgroup below 40. In the age group 60 and above, the most common diagnoses in medical patients were cardiovascular disease (124/320, 39%) and sepsis (63/320, 20%). Trauma (72/164, 44%) and gastrointestinal disease (35/164, 21%) were the most common diagnoses in surgical patients.

Male patients were in majority within all diagnostic categories. Trauma and cardiovascular disease had the highest proportion of males (75% and 76%, respectively).

210/861 (24%) of the study sample had sepsis (Table 4), either as the main diagnosis (n = 116) or complication. Respiratory infection was the most common primary source of sepsis in medical patients of both age groups, as opposed to abdominal infection in surgical patients.

Treatment

Overall, 632 (73%) patients received mechanical ventilation (Table 4) The proportion of intubated patients were significantly higher in males than in females (438/567, 77% vs. 194/294, 66%, p < 0.01). Across the age groups, more surgical than medical patients received mechanical ventilation (158/160, 99% vs. 152/217, 70%, p < 0.001 and 158/164, 96% vs. 164/320, 51%, p < 0.001) as well as vasopressor therapy (121/160, 75% vs. 117/217, 53%, p < 0.001 and 135/164, 82% vs. 202/320, 63%, p < 0.001). Non-invasive ventilation was more frequently used in the treatment of medical patients, but the difference was only significant in the age group 60 and above (129/320, 40% vs. 30/164, 18%, p < 0.001). In the age group 18-59, the proportion of patients receiving renal replacement therapy (RRT) was more than twice as high in medical compared to surgical patients (38/219, 17% vs. 12/161, 8%, p < 0.01). There was no difference in the proportion receiving RRT among patients above 60.

In both age groups, median length of stay in the

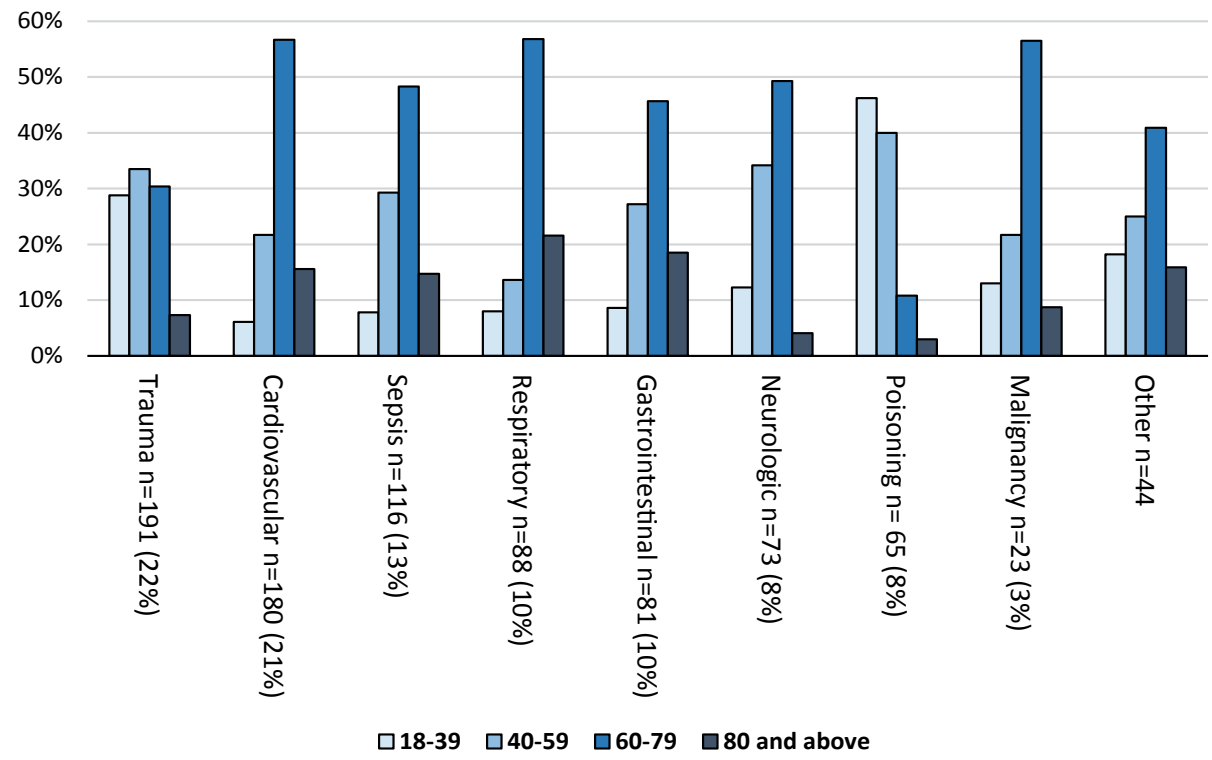

Figure 3: Age distribution within diagnostic categories.

Table 5: Outcome.

	All patients N = 861	18-59 years (n = 377)		60 years and above (n = 484)	
		Medical n = 217	Surgical n = 160	Medical n = 320	Surgical n = 164
ICU mortality n (%)	205 (24%)	38 (18%)	24 (15%)	94 (29%)	49 (30%)
Treatment restrictions, total n (%)	183 (21%)	27 (13%)	23 (14%)	85 (27%)	48 (29%)
_Withdrawal of treatment n (%)	141 (16%)	21 (10%)	22 (14%)	60 (19%)	38 (23%)
_Treatment withheld n (%)	42 (5%)	6 (3%)	1 (1%)	25 (8%)	10 (6%)
Hospital mortality n (%)	279 (32%)	50 (23%)	28 (17%)	143 (45%)	57 (35%)*
Discharge location for hospital survivors:					
_Home or rehabilitation n (%)	455 (53%)	146 (67%)	124 (77%)	111 (35%)	74 (45%)
_Nursing home n (%)	88 (10%)	10 (5%)	1 (1%)	55 (17%)	22 (13%)
_Other (including psychiatric institution) n (%)	39 (4%)	11 (5%)	7 (5%)	13 (4%)	11 (7%)

ICU was almost twice as long for patients with surgical compared to medical admissions (6.2 vs. 3.5, $p < 0.05$ and 6.9 vs. 3.7, $p < 0.01$ respectively). Separate analysis for intubated patients showed similar trends regarding length of stay (6.4 vs. 4.5 days, $p < 0.05$ and 6.2 vs. 4.5, $p = 0.04$), but no difference in median mechanical ventilator support time was seen between medical and surgical patients.

Outcome

Total hospital mortality was 279 (32%) and ICU mortality was 205 (24%) (Table 5). Decisions regarding limitations of life-sustaining treatments were made in 183/205 (89%) of the patients who died in the ICU. The proportion of patients with limitations of life-sustaining treatment was higher in surgical than medical patients in the age group 18-59 (23/24, 96% vs. 27/38, 71%, $p < 0.02$). There were no such difference in patients older than 60 years or between the genders. ICU-mortality were similar for medical and surgical patients across the age groups (Table 5) and for male and female patients (128/567, 23% vs. 77/294, 26%, $p = 0.23$).

Presentation of hospital mortality with increasing age (Figure 4a and Figure 4b) showed different trends for medical and surgical patients. For medical patients (Figure 4a), the mortality increased steadily with age, but for patients 70 years and above, the curves for ICU and hospital mortality diverged. Among patients below 50, the mortality curve peaks in the age group 30-39. In

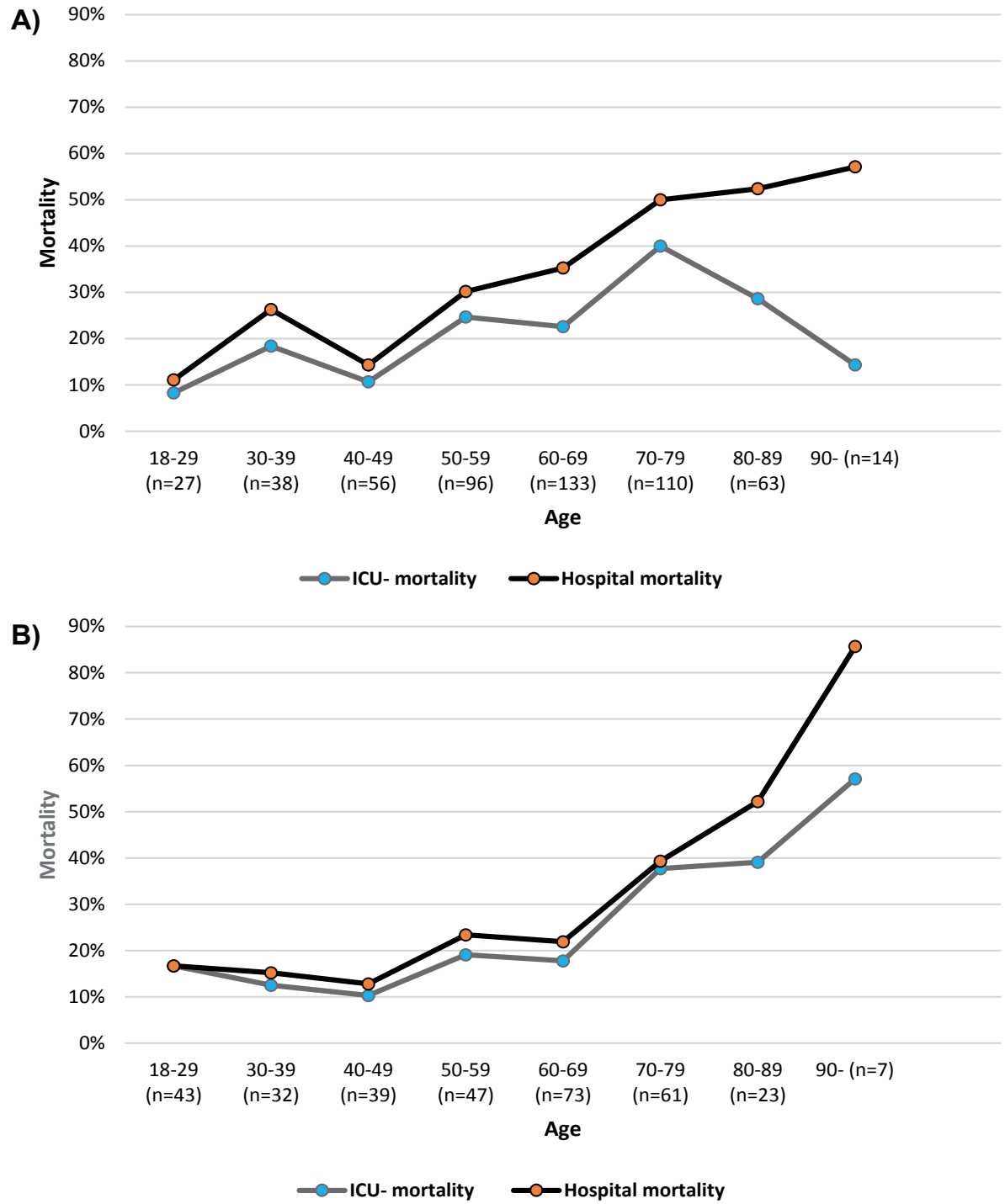

Figure 4: a) Hospital mortality with increasing age, medical patients (n = 537); b) Hospital mortality with increasing age, surgical patients (n = 324).

this age group 5/10 deaths were caused by overdose-related cardiac arrest. For surgical patients (Figure 4b), both the ICU- and hospital mortality were relatively stable until the age of 70, from where it increased rapidly.

Comparison of medical and surgical patients showed a higher hospital mortality in medical patients in the age group above 60 (143/320, 45% vs. 57/164, 35%, $p < 0.05$), but not in the youngest age group (Table 5). Separate analysis of intubated patients showed a significantly higher hospital mortality among medical patients in both age groups (43/152, 28% vs. 28/158, 18%, $p < 0.03$ and 84/164, 51% vs. 55/158, 35%, $p < 0.01$).

Within the diagnostic categories, patients with cardiovascular (100/180, 56%), gastrointestinal (28/81, 35%) and respiratory disease (29/88, 33%) had the highest hospital mortality rate. Patients with trauma (41/191, 22%) and poisoning (9/65, 14%) had the lowest hospital mortality (Table 6).

Table 6: ICU and hospital mortality within diagnostic categories.

Main diagnostic categories	ICU mortality n (% of diagnostic category)	Hospital mortality n (% of diagnostic category)
Trauma	34/191 (18%)	41/191 (22%)
Cardiovascular	74/180 (41%)	100/180 (56%)
Sepsis	20/116 (17%)	29/116 (25%)
Respiratory	18/88 (21%)	29/88 (33%)
Gastrointestinal	18/81 (22%)	28/81 (35%)
Neurologic/CNS	23/73 (32%)	24/73 (33%)
Poisoning	7/65 (11%)	9/65 (14%)
Cancer	7/23 (30)	12/23 (52%)
Other	4/44 (16%)	7/44 (16%)
Total	205 (24% of total)	279 (32% of total)

Of the 582 surviving patients, 455 (78%) were discharged home or to rehabilitation, 88 (15%) to nursing home, and 39 (7%) were discharged to other locations including psychiatric institutions (Table 5).

Discussion

The present study describes preadmission characteristics, main causes of admission, treatment details and outcome of a large, mixed intensive care population in Oslo. Mean SAPS score was 46, which is considerably higher than the average score of 38 reported by the Norwegian intensive care registry (NIR) in 2014 [10]. Almost three quarters of the patients received mechanical ventilation. Trauma and cardiovascular disease were the most common diagnostic categories, reflecting the regional function of the Oslo University hospital Ulleval as a tertiary referral hospital.

Age and gender distribution

Median age was 62, in line with median age for patients admitted to regional hospitals in Norway [10]. Two thirds of the patients were males, a significantly higher proportion than the 53% male proportion among patients admitted to the Oslo University Hospital Ullevaal during the period. The high number of patients with trauma and cardiovascular disease may partly explain this finding. Nonetheless, males were in majority within all diagnostic categories and age groups, with the exception of the oldest patients (90+). This overrepresentation of males receiving intensive care treatment is in line with prior international studies [11,12]. Possible explanations are older age among the females and different pattern of disease manifestations for similar diagnoses for male and female patients. Nonetheless, a gender-biased decision-making process cannot be ruled out and should be investigated further.

Medical patients constituted two thirds of the study population. More than 90% of the surgical patients had non-scheduled surgical admissions. Inclusion of patients from postoperative units would have increased the number of patients with scheduled surgical admission. However, for this study we intended to study ICU patients with a high severity of illness, and therefore decided not to include postoperative units.

Pre-admission characteristics

Although the majority of patients had prior chronic disease, almost 80% of the patients were self-reliant without home care before admission. Thus, the majority of the patients had a relatively high level of function before admission. Comparison of the preadmission characteristics of medical and surgical patients showed several differences. Firstly, the proportion of self-reliant patients was significantly higher in surgical than medical patients across the age groups. Secondly, in the age group 18-59, surgical patients had significantly lower Charlson comorbidity index than medical patients, reflecting a much lower prevalence of pre-existing chronic disease. These findings suggests differences in predisposing factors for ICU admissions between medical and surgical patients that should be further investigated.

Treatment

A surprising finding was that surgical patients had almost twice as long median length of stay (LOS) in the ICU as medical patients, despite lower median age and less chronic disease. There are several possible explanations. Firstly, this difference is likely to reflect the vast resources needed in the treatment of severely ill trauma patients, including the need of repeated surgical procedures.

Secondly, among the patients who died in the hospital, a greater proportion of the surgical patients died in the intensive care unit as opposed to in medical patients where a higher proportion died at the ward (Figure 4a and Figure 4b). Other possible explanations are the high number of neurosurgical patients and the exclusion of postoperative patients.

Mortality

The high severity of illness and level of care of the study population was reflected in a hospital mortality rate of 32%, almost twice as high as the average 17% mortality reported by NIR [10]. As expected, hospital mortality increased significantly by age, reflecting increased frailty, comorbidity and reduced ability of elderly patients to withstand acute disease. In patients older than 60, medical patients had a higher hospital

mortality. Interestingly, presentation of mortality within age groups showed different trends for medical and surgical patients. For surgical patients the mortality rate remained relatively low until the age of 70, and then increased steeply. We consider the high proportion of trauma patients and the lower burden of comorbidity in the younger age groups of surgical patients as main explanatory factors. For medical patients, the intensive care mortality and the hospital mortality increased linearly until the age of 70, but then diverged. This is in line with earlier findings [13] and reflects a shift towards dying at the ward instead of in the ICU among elderly intensive care patients.

For medical patients a peak in hospital mortality occurred for patients aged 30-39. Among the patients who died in this age group, half of the deaths were overdose-related cardiac arrests. Poisoning was the most common cause of admission in medical patients aged 18-59 and caused almost half of the admissions in patients younger than 40 years. These findings are in line with prior studies [14,15], and confirm that substance abuse causes a significant proportion of preventable ICU-admission in young patients.

The association between trauma and substance abuse is well known [16,17]. Since trauma was the dominating diagnostic category among patients with surgical admissions, alcohol and drug exposure may have had an indirect influence on ICU admission in a significant proportion of these patients.

Limitations of life-sustaining treatment is common in European ICUs, but with substantial intercountry variability [9]. In our study population, limitations of life-sustaining treatments (as defined in the methods) occurred in almost 90% of the patients who died in the intensive care. This proportion is very high and surpasses the findings by Skjaker, et al. [18] in a study of end-of life-decisions in a Norwegian ICU-population. In comparison, our study population had a higher median age and severity of illness (SAPS II 46 vs. 42) and a different distribution of diagnostic categories including a much higher proportion of trauma patients. Our findings confirm the increased tendency of withholding and withdrawal of life sustaining treatment in the critically ill described in international studies [19], particularly in Nordic ICUs [9]. Of the hospital survivors, almost 80% were discharged to home or rehabilitation, indicating a low prevalence of futile intensive care treatment.

Strengths and limitations

The patient cohort in the present study is large, and contains intensive care patients from many specialties. Data was collected prospectively and the registrations were made by a small number of study personnel. The present study conveys a comprehensive set of descriptive data particularly regarding pre-admission characteristics of the intensive care population. Comparison of medical and surgical patients within age groups is a strength because it allowed detection of subtle differences between the subgroups.

Evaluation of ICU services is challenging due to variations in ICU-beds availability and case mix between different intensive care populations. This is a limitation when trying to generalize the findings of this study to other populations or settings.

In order to simplify the analysis, patients with scheduled and non-scheduled admissions were described as one group. This merging represents a possible limitation since there may be l differences in the characteristics of these patients.

Conclusions

1. In the age group 18-59 years, medical patients had a considerably higher prevalence of pre-existing chronic disease score compared to surgical patients, suggesting differences in predisposing factors. Trauma and poisoning were the most common causes of admissions. Since these diagnostics categories represent possibly preventable ICU-admissions, more focus on preventive efforts is needed.

2. In the age group 60 and above, comorbidity was similar in medical and surgical patients. Nonetheless medical patients had higher hospital mortality. While the majority of surgical patients within this age group died in the ICU, medical patients had a tendency of dying at the ward.

3. Limitations of life-sustaining treatment were made in almost 90% of the patients who died in the ICU, and the vast majority of the surviving patients were discharged home or to rehabilitation. This indicates a low prevalence of futile treatment.

Acknowledgements

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Appendix

Inclusion criteria ≥ 18 years and

1. Intubation regardless of length of stay and/or

2. ICU length of stay ≥ 24 hours and/or dysfunction of ≥ two organ systems

Definition of organ dysfunction: Based on definitions for acute organ failure in sepsis [20]. *The value was set equivalent to a SOFA score [8] of ≥ 2 **For renal dysfunction the definition was based on AKIN criteria level ≥ 1. ***Liver dysfunction was defined based on the Child-Pugh score.

Organ system	Definition of dysfunction	Source
Respiration	PaO_2/FiO_2 < 33 kPa	Sepsis criteria
Cardiovascular	Need for vasopressor to obtain MAP ≥ 70 mmHg	Sepsis criteria
Metabolic	pH ≤ 7.3 or BE ≥ 5, and lactate > 3mmol/L	Sepsis criteria
CNS*	GCS ≤ 12	Sepsis criteria/SOFA score
Hematological*	Platelets < 100x 10^9 /L	Sepsis criteria/SOFA score
Liver***	Bilirubin ≥ 34 μmol/L or INR ≥ 1.7	Sepsis criteria/Child Pugh
Renal**	Urin output < 0.5 ml/kg/hr × 6 hour/increased creatinine × 1.5 mg/L (≥26.4 μmol/L)	Sepsis criteria/AKIN score

II

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ORIGINAL ARTICLE

Substance abuse-related admissions in a mixed Norwegian intensive care population

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Background: Alcohol and drug abuse are potentially modifiable risk factors for critical illness. The aims of this study were to describe patients with substance abuse-related admissions (abbreviated SARA) in a mixed intensive care (ICU) population in Oslo, and to compare these patients with patients with non-SARA.

Methods: Cross-sectional prospective study of a mixed medical and surgical ICU-population in Oslo, Norway. Data were collected consecutively using a questionnaire, medical records, and toxicology results. SARA included admissions due to acute or chronic complications of alcohol or drug abuse, as well as substance abuse-related injuries.

Results: Of the 852 patients included, 168 (20%) had SARA; 102 (12%) alcohol-related and 66 (8%) drug-related. Male patients aged 18-39 had the highest proportion of SARA (47/97, 49%). Among the trauma patients, 69/182 (38%) were influenced by alcohol and drugs at the time of injury. Patients with SARA were significantly younger (median age 48 vs 66), had lower Charlson comorbidity index (mean 1.4 vs 2.5) and shorter length of stay (median days 2.4 vs 4.9), than non-SARA patients. Hospital mortality was similar when adjusting for age (OR 0.8, $P = .27$, non-SARA as reference).

Conclusion: Overall, one in five ICU admissions was associated with substance abuse. For male patients aged 18-39 this ratio was nearly half. More than one third of the trauma patients were influenced by alcohol or drugs at time of injury.

1 | INTRODUCTION

Acute and chronic complications of substance abuse are common causes of admission to intensive care units (ICUs).[1-3] In addition, substance abuse is associated with increased risk of injury and trauma[4-6] often in need of critical care. In ICUs, substance abuse is associated with increased resource utilization, complication rate, and mortality.[7-10] The need for intensive care beds is expected to increase considerably during the coming decades.[11,12] Since substance abuse represents a potentially modifiable risk factor for critical illness, increased knowledge regarding these mechanisms is important for preventive medicine and public health.

Reported rates of alcohol and drug-related ICU-admissions are in the range of 12%-28%[2,3,13] and 4%-14%[1,14,15], respectively. However, due to differences in inclusion criteria, case-mix, and alcohol- and drug-use patterns between countries, the findings of one study may not be valid in other populations. Furthermore, only few studies have addressed the proportion of both alcohol and drug-related admissions within the same ICU-population.[16] Thus, more descriptive studies of ICU-patients with substance abuse-related admissions due to both alcohol and/or drug use in different intensive care populations are needed.

Per capita consumption of alcohol and drugs is an important determinant for substance abuse-related diseases and injuries in a population. According to the EMCDDA (European Monitoring Center for Drugs and Drug Addiction), Norway has one of the highest reported rates of overdose-related deaths in Europe.[17] Alcohol consumption in Norway, although relatively low compared to other European countries, has increased by 40% during the last 20 years.[18]

Based on cross-sectional data of a mixed medical and surgical ICU population in Oslo,[19] the aims of this study were to describe characteristics of patients with substance abuse-related admissions (abbreviated SARA), overall and within subgroups, and to compare patients with and without SARA on selected parameters.

Editorial Comment

Active substance abuse or intoxication is thought to be common among patients admitted to intensive care units. In this analysis from a large city ICU cohort, the authors describe the proportions and characteristics of ICU patients with admissions associated with alcohol or drug abuse. Major trauma and younger age were strongly associated with this kind of risk behavior.

2 | METHODS

2.1 | 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 in the period February 3rd 2014 through February 2nd 2015.[19] The Oslo University Hospital Ullevaal is a tertiary referral hospital with comprehensive medical services including trauma and neurosurgery for Eastern Norway (3 million inhabitants). In addition, it serves as a local hospital for one third of Oslo's population (647 676 inhabitants; 2015). The Diakonhjemmet Hospital serves as a local hospital in Oslo (for 115 000 inhabitants). The medical, cardiac, surgical, and neurosurgical ICUs at Ullevaal Hospital and the mixed medical/surgical ICU at the Diakonhjemmet Hospital participated in the study. In order to avoid individuals being represented multiple times, only the first admission of each patient during the study period was registered.

2.2 | Participants

We studied patients ≥18 years with the following inclusion criteria: (a) Intubation regardless of length of stay *and/or* (b) ICU length of stay ≥24 hours and dysfunction of ≥two organ systems as defined in *appendix*. Of the 995 ICU-admissions meeting the inclusion criteria, 43 (4%) were readmissions of previously included patients and 91 patients were excluded due to missing consent (median age 54, range 18-89, 63% males). Of the 861 patients included in the original dataset,[19] 9 (1%) patients were removed from further analysis due to insufficient information regarding alcohol and drug use, leaving 852 patients for inclusion.

2.3 | Data collection and classification

SARA were defined as ICU-admissions associated with use of alcohol or with drugs listed in the drug screening test DUDIT.[20] The criteria for SARA were based on a study of alcohol-related ICU-admissions in Scotland,[21] with the addition of drug-related conditions. Patients with ICU admissions solely associated with use of other medications, such as cardiovascular medication or anti-depressives were not considered substance abuse-related, and neither were patients with a history of substance abuse but non-SARA causes of admission. The relationship between substance abuse and cause of admission was determined by physicians and nurses on the wards trained with individual sessions in the classification methodology. Regular consensus meetings were held in order to reduce interrater variability. Patients classified with SARA were categorized into three subgroups (Figure 1) based on whether the cause of admission was:

A. Directly related to acute alcohol or drug abuse
   Acute intoxication as well as direct complications of acute alcohol or drug abuse, such as overdose-related cardiac arrest, rhabdomyolysis, and injection-related injury or disease.

B. Indirectly influenced by acute alcohol or drug abuse
   Injuries and illness in intoxicated patients. The injury mechanisms studied included road traffic accidents, falls, burns, violence/assault-related trauma, strangulation, and drowning.

C. A medical complication causally related to chronic alcohol or drug abuse
   Based on the ICD-10 criteria, these included the following: alcohol withdrawal syndrome; alcoholic cirrhosis with hepatic failure and/or upper gastrointestinal tract bleeding secondary to portal hypertension; alcoholic pancreatitis; seizures, heroin nephropathy.

Data were collected consecutively using a standardized registration form with information from a questionnaire regarding prior alcohol and drug use, as well as the patient's medical records and laboratory results, including toxicology results. Tests for toxicology and S-ethanol were analyzed as soon as possible after admission to the ICU. Admissions were classified as associated with acute alcohol or drug exposure (A or B above) if toxicology results were positive and not explained by therapeutic medication administration or home medications. In order to evaluate the degree of influence of alcohol at the time of injury, the concentrations of alcohol at the time of injury were calculated using a

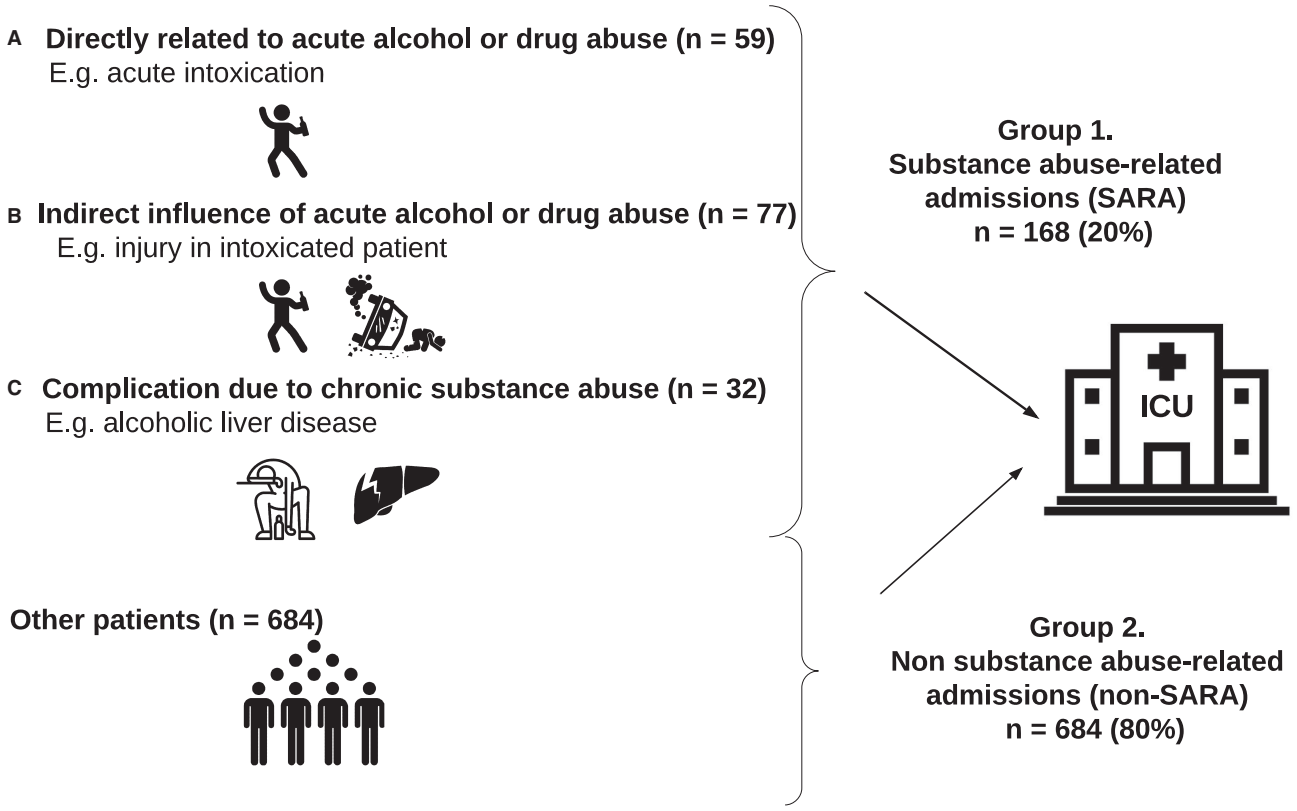

FIGURE 1 Subgroup classification of substance abuse-related admissions

mean elimination rate of 0.015% per hour.[22] In addition, patients were classified with SARA when collateral information strongly suggested that the patient was intoxicated at the time of injury.

Other variables registered included the following: age; sex; main type of substance abuse (alcohol/illicit drugs/prescription drugs); Charlson comorbidity index (CII)[23]; main diagnostic category based on the APACHE system; injury mechanism; SAPS II score[24]; SOFA (sequential organ dysfunction assessment)[25,26] at admission; length of stay; use and duration of mechanical ventilator support; ICU-mortality, and total hospital mortality (including ICU-mortality). Type of admission was based on the SAPS II system: (1) Medical: No surgery within 1 week prior to ICU admission. (2) Surgical: (a) scheduled surgical—elective surgery within 7 days of ICU admission and (b) non-scheduled surgical—acute surgery (scheduled less than 24 h in advance) within 7 days of ICU admission.

2.4 | Stratification

In the original dataset[19] the patients were stratified in age groups 18-59 and 60 and above, based on the WHO definition of elderly patients. However, in order to provide more nuanced data regarding the characteristics of patients with SARA, the patients were subdivided in the following age groups; 18-39, 40-59, 60-79, and 80 and above. In addition, the material was stratified for gender and medical vs surgical admissions.

2.5 | Sample size

The total number of patients was estimated 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 of less than 3.5 percent points for any given answer. This was considered to be sufficient for the purpose of the study.

2.6 | 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 (a) unable to give their consent themselves and not having next of kin who could be asked, (b) admitted with acute poisoning, and (c) who died during ICU treatment. Of the 852 patients included, 665 (78%) were included by informed consent given by the patient (n = 306) or next of kin (n = 359).

3 | RESULTS

3.1 | Study population

Of the 852 patients included, 537 (63%) were medical and 315 (37%) were surgical patients, of whom 27 had scheduled and 288

TABLE 1 Substance abuse-related admissions within age groups, male vs female patients

	All patients	18-39		40-59		60-79		80 and above	
n (%)	N = 852	Male n = 97	Female n = 39	Male n = 164	Female n = 71	Male n = 238	Female n = 136	Male n = 60	Female n = 47
Substance abuse-related admissions									
Overall n (%)	168 (20%)	47 (49%)*	10 (26%)	57 (35%)*	11 (16%)	27 (11%)	15 (11%)	0	1 (2%)
Subgroups n (%)									
Acute alcohol or drug abuse									
A. Direct influence n (%)	59 (7%)	21 (22%)	5 (13%)	20 (12%)	6 (9%)	1 (0.5%)	5 (4%)	0	1
B. Indirect influence n (%)	77 (9%)	25 (26%)	5 (13%)	25 (15%)	3 (4%)	14 (6%)	5 (4%)	0	0
Chronic substance abuse									
C. Complication of chronic abuse n (%)	32 (4%)	1 (1%)	0	12 (7%)	2 (3%)	12 (5%)	5 (4%)	0	0
Main agent									
Alcohol n (%)	102 (12%)	17 (18%)	5 (13%)	36 (22%)	5 (7%)	27 (11%)	11 (8%)	0	1
Illicit drugs n (%)	57 (6%)	30 (31%)	3 (8%)	21 (13%)	3 (4%)	0	0	0	0
Prescription drugs n (%)	9 (1%)	0	2 (5%)	0	3 (4%)	0	4 (3%)	0	0

*Significant differences between the genders within the age groups, $P < .05$.

had non-scheduled admissions. Median age was 63 years (range 18-95), and 559 (66%) were males. Mean SOFA score on admission was 7.4, 623 (73%) patients received mechanical ventilation and 274 (32%) died in the hospital. Overall, 168 (20%) patients had substance abuse-related admissions (SARA); 102 (12%) were mainly alcohol-related and 66 (8%) drug-related (Table 1). Of the 168 patients with SARA, 59 (35%) patients were in group A (direct acute cause), 77 (46%) in group B (indirect acute cause), and 32 (19%) in group C (chronic cause) (Figure 1).

3.2 | Age and gender distribution

In the age groups 18-39 and 40-59, males had twice as high proportion of SARA as females, as opposed to no difference between the genders in patients 60 years and older (Table 1). Male patients aged 18-39 had the highest prevalence of SARA (Table 1). In this group, drug-related admissions were most common, whereas alcohol-related admissions dominated in males older than 40 years and in females of all age groups (Table 1).

3.3 | Diagnostic categories

SARA were more common in surgical patients than in medical patients (75/315 (24%) vs 93/537 (17%), $P < .05$). Among the diagnostic categories, poisoning had the highest proportions of SARA (52/65, 80%). Here, drug abuse was more common than alcohol abuse (Figure 2). Seven of the patients admitted due to poisoning had overdose-related cardiac arrests, all males with non-shockable initial cardiac rhythm and fatal outcome (Table 2).

Of the 182 trauma patients, 69 (38%) were determined to be under the influence at time of injury, mainly because of alcohol (53/69, 77%) (Figure 2). Violence-related injuries had the highest proportion of substance abuse (15/23, 65%), followed by fall-related injuries (39/103, 38%) and road traffic accidents (14/62, 23%). Injury mechanisms varied between age groups. While violence-related injuries and road traffic accidents involved mostly younger trauma patients, fall-related injuries were more evenly distributed across the age groups. In the age group 60-79, 16 (34%) of the 47 patients with fall-related injuries were influenced by alcohol at the time of injury. Of the 33 patients in this age group with head injuries and intracranial bleeding, 14 (42%) were influenced by alcohol at the time of injury.

3.4 | Comparison of patients with and without substance abuse-related admissions

Overall, patients with SARA were younger, had a higher proportion of males, and lower Charlson comorbidity index (Table 3) compared to non-SARA patients. However, within the subgroups A, B, and C, these differences were only significant for patients with admissions influenced by acute substance abuse (group A and B) (Table 3).

Median length of stay was shorter among SARA patients in group A when compared with patients with non-SARA. There were no such differences for patients in group B and C (Table 3). Among

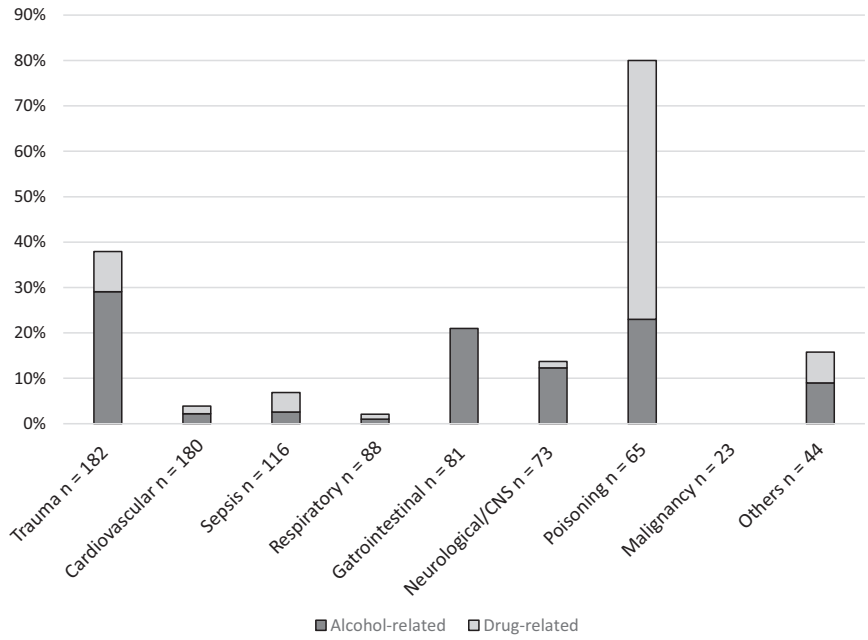

FIGURE 2 Proportion of substance abuse-related admissions within diagnostic categories

TABLE 2 Patients with overdose-related cardiac arrests, all males with fatal outcome

Age	Main toxic agent	Route of intake
48	Alcohol, 420 mg/dL[a]	Per oral
47	Alcohol, 460 mg/dL[a]	Per oral
39	Heroin	Intravenous
36	Heroin	Intravenous
32	Heroin	Intravenous
31	Opioids	Per oral
31	Opioids	Per oral

[a]Conversion factor from mg/dL to mmol/L is 0.22.

intubated patients, median time of mechanical ventilation was shorter in SARA patients group A and B compared to patients with non-SARA (Table 3).

Hospital mortality was lower in patients with SARA overall when compared with patients with non-SARA, but this difference disappeared when adjusting for age (Table 4). However, SARA patients in group B had significantly lower mortality compared to patients with non-SARA even when adjusted for age (Table 4).

4 | DISCUSSION

In this study, one in five of all patients and nearly half of the male ICU-patients aged 18-39 had admissions associated with alcohol or drug abuse. Severity of illness was high and almost three quarters of the overall study population received mechanical ventilation. These findings confirm that substance abuse is an important predisposing factor for ICU-admissions.

4.1 | Comparison with previous studies

Comparison with previous studies is challenging due to variations in case-mix, the heterogeneity of definitions used, and differences in alcohol and drug use patterns between populations. This study differs from previous studies of substance abuse in the ICU in particularly two aspects. Firstly, while most prior studies included all patients admitted to the ICU, the inclusion criteria of this study were set to select only the more resource demanding ICU-patients. One consequence of this choice was that patients with acute intoxications who did not receive mechanical ventilation or had two-organ dysfunction and length of stay less than 24 hours, were not included. The exclusion of these patients may have contributed to lowering the rate of drug-related admissions. Secondly, the definition used for substance abuse-related admissions (SARA) only included patients whose cause of admission was associated with alcohol or drug abuse. This is in contrast to other studies where patients with chronic substance abuse *not* related to cause of admission were also included.[2,21]

In line with previous studies, SARA were particularly frequent among young males.[2,16] However, gender differences differed markedly between age groups. SARA were twice as frequent in males as in females among those younger than 60 years, whereas there was no significant gender difference in those older than 60 years. The male dominance in the youngest age groups may be due to differences in drug use patterns between young male and female patients and a particularly high proportion of drug-related admissions among males aged 18-39.

4.2 | Trauma and substance abuse

Trauma was the most common diagnostic category in our study, and more than one third of the trauma patients were determined to be

TABLE 3 Comparison of patients with and without substance abuse-related admissions, overall, and within subgroups

	1. Substance abuse-related admissions (SARA)				2. Non substance abuse-related admissions (non-SARA)
	Overall	Subgroups			
		Acute alcohol and drug abuse		Chronic substance abuse	
		A Direct influence	B Indirect influence	C Complication of chronic abuse	
	n = 168	n = 59	n = 77	n = 32	n = 684
Pre-admission characteristics					
Age, median years (IQR)	48 (26-61)**	42 (33-51)**	46 (30-60)**	63 (54-71)	66 (54-75)
Males n (%)	131 (78%)**	42 (71%)	64 (83%)**	25 (78%)	428 (63%)
Charlson comorbidity score, mean ± SD	1.4 ± 1.9**	1.2 ± 1.8**	0.8 ± 1.1**	3.2 ± 2.5	2.5 ± 2.3
Main agent					
Alcohol	102 (61%)	14 (24%)	57 (74%)	31 (97%)	—
Illicit drugs	57 (34%)	37 (63%)	19 (25%)	1 (3%)	—
Prescription drugs	9 (5%)	8 (14%)	1 (1%)	0	—
ICU admission					
Medical admission	93 (55%)*	59 (100%)	5 (7%)	29 (91%)	444 (65%)
Surgical admission	75 (45%)*	0	72 (94%)	3 (9%)	240 (35%)
SAPS II score, mean ± SD	44 ± 18*	47 ± 20	42 ± 15*	43 ± 22	47 ± 18
Sofa score admission, mean ± SD	7.0 ± 3.3	7.0 ± 4.0	7.1 ± 3.0	6.8 ± 3.2	7.5 ± 3.4
Mechanical ventilation (MV) n (%)	138 (82%)*	46 (78%)	76 (99%)**	16 (50%)*	485 (71%)
Time of MV, median (days), IQR	1 (0.5-6)*	0.5 (0.5-2.5)**	1 (0.5-6)*	5 (0.5-9.5)	4 (1.4-9.5)
Length of stay, median (days), IQR	2.4 (1-7.4)*	1.3 (0.6-5.4)**	3.2 (1.3-7.7)	5.0 (1.7-10.6)	4.9 (2.2-19.8)
Mortality					
ICU mortality n (%)	21 (13%)**	7 (12%)*	6 (8%)**	8 (25%)	179 (26%)
Hospital mortality n (%)	34 (20%)**	9 (15%)*	10 (13%)**	15 (47%)	240 (35%)

*$P < .05$.

**$P < .001$ and when compared with patients with non-substance abuse-related admissions.

under the influence of alcohol or drugs at the time of injury. These findings are in line with previous studies of alcohol and drug use in injured patients.[4,27,28] In patients aged 60-79, one-third of the fall-related injuries, and more than 40% of the patients with head injuries with intracranial bleeding were influenced by alcohol at the time of injury. This reflects some of the burden of alcohol misuse in the elderly and should be much stronger emphasized in the prophylactic efforts made by governmental organizations and public health bodies.

4.3 | Subgroup analysis

Despite the heterogeneity of patients with SARA, these patients are commonly categorized as one group when compared with non-SARA patients. The subgroup analysis used in this study revealed marked differences in pre-admission and clinical characteristics, particularly between patients with acute and chronic patterns of substance abuse.

In this study, more than 80% of SARA were directly (group A) or indirectly (group B) associated with acute substance abuse. SARA patients group A and B were significantly younger, had lower prevalence of pre-existing chronic disease, and shorter time of mechanical ventilation when compared with patients with non-SARA. Drug abuse dominated in group A, whereas alcohol abuse was most common in group B.

When compared with non-SARA patients, hospital mortality was lower for SARA patients groups A and B. However, when adjusting for age, this difference remained significant only for SARA group B. The admissions in SARA group A were mostly due to acute intoxications, a diagnostic category usually associated with a relatively low mortality.[1,15,29] The lack of difference in mortality between SARA patients group A and non-SARA patients in this study was surprising. The high mortality among patients with overdose-related cardiac arrests in group A (Table 2) may explain this finding. SARA patients group B, on the other hand, were mostly trauma patients, the diagnostic category with the lowest hospital mortality.[19] Among the trauma patients there were no

TABLE 4 Comparison of hospital mortality for patients with and without substance abuse-related admission (SARA)

	Crude hospital mortality (Odds ratio)	*P*-value	Age-adjusted hospital mortality (Odds ratio)	*P*-value
Non-substance abuse-related admissions (n = 684) (reference category)	1	—	1	—
Substance abuse-related admissions				
Overall (n = 168)	0.5	<.001	0.8	.27
Subgroups				
A. Directly related to acute alcohol or drug abuse (n = 59)	0.3	<.01	0.6	.26
B. Indirect influence of acute alcohol or drug abuse (n = 77)	0.3	<.001	0.5	<.05
C. Complication of chronic substance abuse (n = 32)	1.6	.18	1.8	.11

difference in hospital mortality for SARA and non-SARA patients when adjusting for age. Thus, we consider the low mortality of the trauma patients the main reason for the low mortality of SARA patients group B.

In contrast to groups A and B, patients with medical conditions due to chronic substance abuse (group C) did not show major differences in pre-admission and clinical characteristics when compared with non-SARA patients. This is in contrast to most previous studies of ICU patients with chronic substance abuse, where especially patients with alcohol use disorders had comparatively long ICU stay and higher mortality.[7,10] However, when evaluating these findings it is important to clarify that patients whose chronic substance abuse was unrelated to cause of admission were *not* classified as SARA in this study.

4.4 | Clinical implications

To our knowledge, this is the first study describing substance abuse-related admissions (SARA) in a Norwegian ICU-population. Considering the high proportion of SARA found in our study—especially among young males—we believe our findings should be of value for the health authorities by demonstrating a need for enhanced prevention efforts.

Studies indicate that hospital admissions represent an opportune moment for intervention.[30,31] Routine screening of high-risk populations, such as trauma patients, as well as increased awareness among the clinical staff may, help identify patients that could benefit from follow-up. There are, however, several obstacles in the handling of substance abuse in the ICU-setting. Self-discharge is common and lack of time and knowledge on how to provide appropriate treatments are reported by health care providers.[32] Further research on how to address substance abuse among ICU patients is needed.

This study demonstrates the diversity among patients with SARA. It is likely that the preventive efforts needed for the different subgroups varies considerably. Patients with long-term chronic substance abuse represent a particularly challenging group, demanding a broad and multifaceted approach including psychiatric treatment. In contrast, patients with ICU-admissions due to occasional substance abuse may respond to a different approach. Brief interventions have been shown particularly effective in trauma patients with unhealthy alcohol use.[33] Considering that more than one third of the trauma patients in this study were under the influence at the time of injury, we suggest implementation of a similar approach.

4.5 | Strengths and limitations

The present patient cohort is large and contains intensive care patients from many specialties receiving high level care. Data were collected consecutively and included use of a questionnaire, in addition to information from medical records and laboratory results. We used a wide definition of SARA, and included both alcohol- and drug-related admissions, as well as both acute and chronic patterns of substance abuse. Subgroup analysis was a strength, since it demonstrated the heterogeneity among patients with SARA and revealed differences in the impact of substance abuse on subsegments of the ICU population.

A weakness in this study is possible subjective bias in the decision-making process on whether an admission was classified as substance abuse-related or not. However, this registration was made by a small number of study personnel with regular consensus meetings held to reduce inter-rater variability. In addition, not all positive urine toxicological tests were confirmed with blood analysis, as this would have required more laboratory resources.

Due to the inclusion criteria, patients with drug intoxications with ICU stay shorter than 24 hours who did not receive mechanical ventilation, were not included in this study. This represent a weakness since cases of intoxications, particularly due to the new psychoactive substances with short elimination half-lives, may have been missed. Furthermore, although hospital readmissions are common among patients with substance abuse, only the patient's first admission was registered in this study. As such, the number of patients with SARA type A may have been underestimated.

5 | CONCLUSION

- One in five ICU admissions, and nearly half of the admissions of male patients aged 18-39, were associated with alcohol or drug abuse.
- Alcohol was the main substance of abuse among patients with substance abuse-related trauma, while illicit drug use was most common among patients with acute intoxications and in males younger than 40 years.
- More than one third of the trauma patients were influenced by alcohol or drugs at the time of injury, reflecting the severe impact of substance abuse as a predisposing factor in trauma patients. Routine screening for alcohol and drugs should be considered in these patients.
- The burden with head injuries and intracranial bleedings as a result of alcohol use in the elderly is significant, and should be addressed properly in prophylactic work.

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CONFLICT OF INTEREST

Professor Dag Jacobsen and Dr Fridtjof Heyerdahl are shareholders of "Orphan Diagnostics" developing diagnostic strips for the use in methanol & ethylene glycol poisonings. Dr Fridtjof Heyerdahl is shareholder of Epiguard (transportation systems for patients with contagious diseases). We have no other conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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III

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CLINICAL INVESTIGATION

acta Anaesthesiologica Scandinavica

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

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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.

Abbreviations: 95% CI, 95% confidence interval; AUD, alcohol use disorder; DUD, drug use disorder; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; OR, odds ratio; SARA, substance abuse-related cause of ICU-admission; SUD, substance use disorder.

This work was carried out at the Oslo University Hospital, Ullevaal and the Diakonhjemmet Hospital, Oslo, Norway.

1 | 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.

Editorial Comment

In this prospective observational study, researchers from Oslo found that as many as 26% of patients admitted to their ICUs reported having a substance use disorder. Among medical admissions, there was some association between reported alcohol abuse and increased hospital mortality.

2 | METHODS

2.1 | 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 3 February 2014 and 2 February 2015.[16] We included patients ≥18 years with at least one of the following inclusion criteria: (i) Intubation regardless of length of stay *and/or* (ii) ICU length of stay ≥24 hours *and* dysfunction of ≥two organ systems as defined in Appendix S1. 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).

2.2 | 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 S2). Preadmission and clinical variables were registered as described in Appendix S3. Outcome measures were ICU-mortality and total hospital mortality.

2.3 | Substance use disorder

The term 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 (i) alcohol use disorders (AUD) and (ii) 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.

2.4 | 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

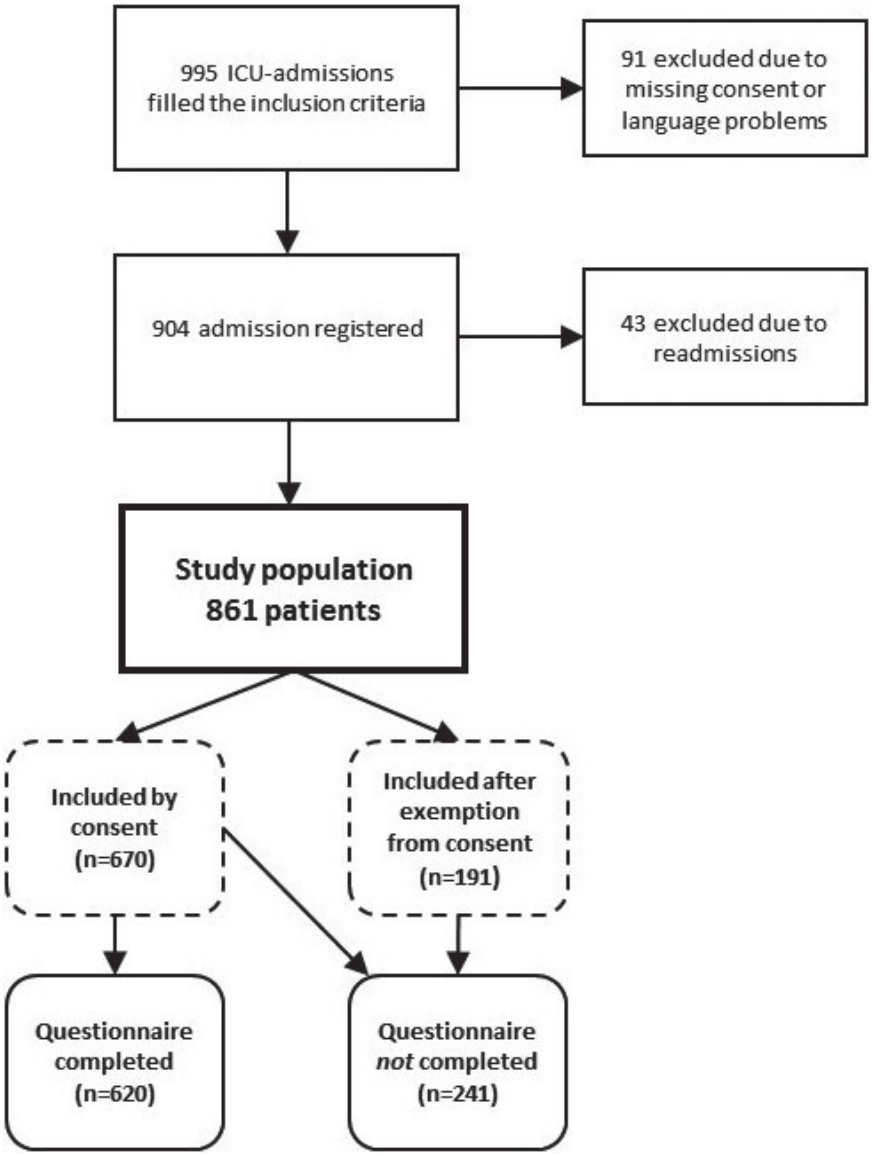

FIGURE 1 Flowchart of the inclusion process

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. Sixteen patients were classified with AUD despite an AUDIT C score <8. Of these, seven patients had secondary complications of chronic substance abuse, while for nine 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.

2.5 | 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 (i) unable to give their consent themselves and without next of kin who could be asked, (ii) admitted with acute poisoning and (iii) who died during ICU treatment.

2.6 | 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 (eg mortality), the length of the confidence interval will be longer.

2.7 | 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.

3 | RESULTS

3.1 | Prevalence of SUD

Of the 861 patients included, 222 (26%) were classified with 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.

3.2 | 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 a 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.

3.3 | 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% CI 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%).

3.4 | 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

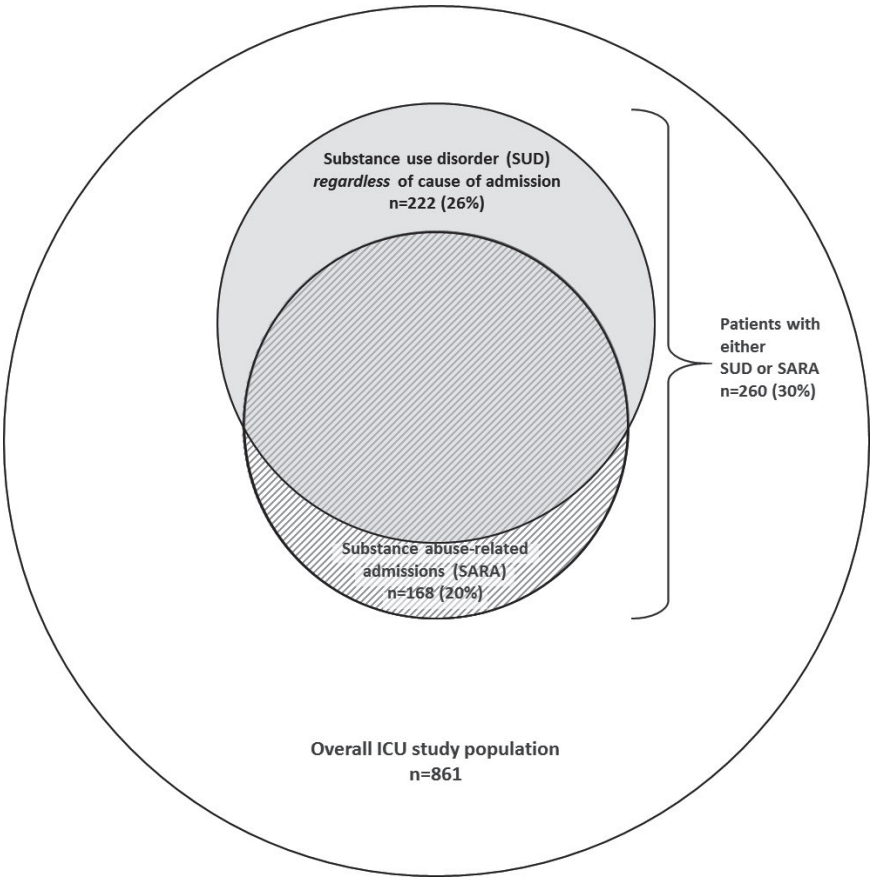

FIGURE 2 Patients with chronic substance abuse (SUD) and patients with substance abuse-related admissions (SARA) in the ICU-population

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).

4 | DISCUSSION

In this study, one in four ICU-patients, and almost half of males aged 30-59, had an underlying 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.

4.1 | Prevalence of SUD

In this 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]

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

	SUD patients (n = 222)			
		Subgroups		
	SUD, total (n = 222)	AUD (n = 137)	DUD (n = 85)	Non-SUD patients (n = 639)
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 h)	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) n (%)	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% CI)				
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% CI)				
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)

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.

4.2 | 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.

4.3 | 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]

4.4 | Methodological considerations

In this 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.

4.5 | 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 SUD 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.

4.6 | 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.

5 | 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 SUD.
- More than 40% of SUD-patients had *non*-substance abuse-related cause of ICU-admission demonstrating the importance of screening for substance abuse *regardless* of cause of admission.

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CONFLICTS OF INTEREST

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.

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.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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