FACULTY OF MEDICINE AND HEALTH SCIENCES

EPIDEMIOLOGY AND CLINICAL OUTCOMES OF PATIENTS WITH ALCOHOL USE IN THE ICU: A SYSTEMATIC REVIEW AND META-ANALYSIS

Robin Van Cappellen
Student number: 01600205

Supervisor: Professor Dr. Eric Hoste

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine

Academic year: 2020 – 2021

GHENT UNIVERSITY

Voorwoord

Bij de realisatie van deze masterproef horen bedankingen.

Allereerst was deze thesis niet mogelijk geweest zonder de onophoudelijke ondersteuning van Professor Dr. Hoste. Zijn constructieve feedback, medisch-wetenschappelijk inzicht en relevante aanvullingen waren van een onnoemelijke meerwaarde. Daarbovenop was hij de voorbije 2 jaar steeds toegankelijk voor vragen omtrent dit onderwerp en bereid om met uitgebreid advies deze vragen te beantwoorden.

Tot slot wil ik alle gezinsleden, vrienden en kennissen bedanken waarmee ik lief en leed heb kunnen delen omtrent dit werkstuk.

TABLE OF CONTENTS

Abbreviations	
ALI	Acute Lung Injury
AP	Alcoholic pancreatitis
APACHE II SCORE	Acute physiology + age points + Chronic health points
ARDS	Acute respiratory distress syndrome
ARLD	Alcohol-related liver disease
ASA	American Society of anesthesiology Physical Status Score
AUD	Alcohol Use Disorder (as defined by the DSM-V)
AUDIT	Alcohol use disorder identification test
AWD	Alcohol withdrawal delirium
AWS	Alcohol withdrawal syndrome
BAC	Blood alcohol concentration
CAGE	Concern/Cut + Apparent/Annoyed + Grave/guilty + Evidence/Eye opener
CAM-ICU	Confusion assessment screen for the ICU
ICU	Intensive Care Unit
ISS	Injury severity score
LOS	Length of stay
MD	Mean difference
MICU	Medical Intensive Care Unit
OR	Odds Ratio
RR	Risk Ratio
SICU	Surgical Intensive Care Unit
SMAST	Short Michigan alcohol screening test
TBI	Traumatic Brain Injury
TICU	Traumatic Intensive Care Unit

Nederlandstalige samenvatting

Alcoholgebruik stoornissen komen in de wereld vaak voor en treft 5% van de mensen wereldwijd (1, 2). Deze masterproef wou kijken hoe zich dat vertaalt naar de dienst intensieve zorg. Dit werd gedaan door een systematische review en meta-analyse. Alcohol gebruik werd berekend in 28.4% van de patiënten op de dienst intensieve zorg en deze hadden meer mechanische ventilatie, meer mortaliteit en een langer verblijf in het ziekenhuis. Een limiterende factor was het gebruik van veel definities van alcoholgebruik. Concluderend gebruikt 28.4% van de patiënten op de dienst intensieve zorg alcohol en zij doen het klinisch slechter vergeleken met non-alcohol gebruikers.

1 Abstract

Background and aims: Alcohol use is widely spread in the Western world. Around 5% of the word population suffers from an alcohol use disorder and is associated with higher morbidity and mortality (1, 2). In the ICU harmful alcohol use is estimated around 10%-33% and these alcoholics are known to have worse outcomes (3-6). This systematic review tries to find a clear answer about prevalence and clinical outcomes in the ICU.

Methods: a systematic review and meta-analysis. Search has been done in Medline, Embase and Web Of Science from January 1960 until March 2020. Only cohort studies, and matched-case reports were used. Meta-analyses used Mantel-Haenszel method and random-effects. I^2 was assessed to evaluate heterogeneity. Risk of bias was evaluated using the *Cochrane's Tool to Assess Risk of Bias in Cohort Studies.*

Results: a median prevalence of 26.5% (IQR 20%) and a proportional prevalence of 28.4% (95% CI [0.267, 0.346], p< 0.0001) was found for alcohol use in the ICU. The alcohol use group had a mean age difference of -6.9y ([-10.46,-3.39], p<0.001), a RR male prevalence of 1.23 ([1.11;1.36], p<0.001), RR pneumonia of 1.21 ([0.88;1.67], p=0.24), a RR mechanical ventilation of 1.53 ([1.24;1.87], p<0.0001), mechanical ventilation days mean difference of 5.72d ([-1.21;12.65], p=0.11), a RR ARDS of 1.10 ([0.99;1.23], p=0.07), an ICU LOS mean difference of -0.35d ([-13.91,13.22], p=0.96), a hospital LOS mean difference of 1.49d ([0.14;2.85], p=0.03), 30d-mortality RR of 1.70 (1.49;1.94], p<0.001), a RR ICU mortality of 1.47 ([1.07;2.00], p=0.02), and a hospital mortality RR 1.13 ([0.97;1.30], p=0.11).

Conclusion: alcohol use is prevalent in 28.4% of the patients in the ICU and they are likely to perform worse in clinical outcomes compared to their non-drinking counterparts.

2 Background

2.1 ALCOHOL USE IN THE POPULATION

Alcohol use disorder (AUD) is often quoted as one of the most common mental disorders globally (2, 7). AUD's is defined by the DSM-V as: a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by specific symptoms, occurring within a 12-month period and has to have at least 2 out of 11 criteria (8). Estimations are that 8.6% of men and 1.7% of women were living with AUD all over the world in 2016 (2). In the United States 7.8% of men and 4.2% of women were diagnosed with AUD (9). The prevalence of drinking is higher among men than women (10). In Europe the prevalence of alcohol dependence is estimated around 8.7% in the primary care setting (11). AUD's are more prevalent in middle income and high income countries (2). In these developed countries the alcohol use is more widespread accepted, more accessible and sometimes even promoted (1, 2).

Alongside the use of AUD for one type of Alcohol-Related Disorders, the DSM-V has four more definitions for problematic alcohol intake or the consequences thereof. A first one is ‘alcohol intoxication’ and is characterized by behavioral or psychological changes that occur after drinking alcohol. A second one is ‘alcohol withdrawal’. This occurs after a period of cessation or reduction in alcohol use. The third one is ‘other alcohol-induced disorders’ and this spans a wide array of disorders of organs which are affected by alcohol. Lastly there is ‘unspecified alcohol-related Disorder’ and refers to all the manifestations of alcohol use that cannot be categorized under the previous classifications (8).

Beside the DSM-V, the ICD-11 has its own parallel system for diagnosing its 8 different types of alcohol use. The first definition is ‘episode of harmful use of alcohol’ and should be interpreted as a single episode of alcohol use that could lead to damage of the patient or his or her surroundings. The second definition is ‘harmful pattern of use of alcohol’. This is categorized as the use of alcohol that can cause damage to a patient or the people surrounding the patient. The third category is ‘alcohol dependence’ and is defined as a disorder of regulation through continued intake of alcohol. The fourth category is ‘alcohol Intoxication’ and is defined by the condition of the patient after taking alcohol and consists of primarily neurological symptoms. The fifth category is ‘alcohol withdrawal’ and is described as a cluster of symptoms that happen after de cessation of alcohol. The seventh definition associated with alcohol use is ‘alcohol-induced delirium’ and is defined as a change in mental awareness after or during the intake of alcohol. The eighth definition is ‘alcohol-induced psychotic disorder’ and consists of mostly psychotic-like changes in the perception of the patient

that occur during or after the intake of alcohol. The last category is 'other alcohol-induced disorders' and consists out of dementia or amnesia caused by the intake of alcohol (12).

2.2 Burden of disease

AUD's are associated with a higher mortality and a vast burden of disease due to medical consequences (2). Connor et al. suggests that up to 60 types of illnesses can be attributed to alcohol (1). The WHO Global status report on alcohol and health from 2018 estimates there are 3 million deaths related to alcohol: this provokes 5.3% of all deaths worldwide (13).

Furthermore the same report of WHO suggests that 5.1% of the global burden of disease and injury is correlated to alcohol intake (13). Another study suggests that 4% of the global burden of disease is alcohol related (2). In addition, people who suffer from alcoholism, also suffer in addition often from at least one additional psychological illness (1). In summary, alcohol use causes health impairment.

2.3 Screening and detection

Screening and detection of people with problematic alcohol use is not as easy as it sounds. There are tools available for alcohol screening but only 5.9% of people who are possibly at risk for problematic drinking are screened (2). Another study performed in 2011 puts forward a higher number: 1 out of 6 adults who acknowledged binge drinking were asked by their physician about their drinking habits (9). The tools for screening exist firstly out of the AUDIT-T or AUDIT-C questionnaires (*Appendix A*). The latter test consists out of the first three questions of the AUDIT-T test. After being interviewed, the patient receives a score out of 40 for the AUDIT-T and a score out of 12 for AUDIT-C. The higher the score, the higher the risk the patient has of being an at-risk drinker. The sensitivity and specificity is nearly equal for both tests: being around 70%-90% (4). The best sensitivity and specificity of these test is attained when the cut-off value is chosen at greater or equal to four, or if it is chosen at greater or equal to five (9). A second type of questionnaire is the SMAST questionnaire (Short Michigan alcohol Screenings test). The full questionnaire is linked in *Appendix A*.

A third way to screen your patient is by asking the patient about his drinking habits (9). In the primary health care only 30.3% to 39.9% of patients with an AUD were recognized as having an AUD (2). An earlier review claims that only 50% of people with AUD could be diagnosed if their physician solely relies on his clinical skills (1). But that can only be done if the patient is honest about his drinking pattern or if he understand he has an alcohol problem (4). Hence there are a lot of people who could be helped, but are not.

2.4 TREATMENT

Consequently AUD's are extremely undertreated in the primary care. A study suggests that globally only 21.9% of patients known with AUD were treated for their alcohol problems (2). A study performed by the Substance Abuse and Mental Health Services Administration (SAMHSA) concludes that only 8.3% of the 15.8 million adults who needed alcohol treatment got their treatment (9). In Europe only one out of four people with alcohol dependence received medical help by their GP for their alcohol dependence (11). An European study performed in 2015 claims that people who undergo treatment suffer more from old age, liver disease, anxiety disorders, and severe mental distress (11). On top of this, the label alcoholic still has a stigma attached (2).

There are different treatments for AUD's in the outpatient primary care, but there is no overall best method.

Presently the best treatment for AUD's exist out of cognitive behavioral therapy and primarily twelve step groups. Patients who undergo these therapies are more abstinent after one year than their control group taken from the general population (9, 14).

The medical treatment approved by the FDA and the EMA for AUD's exist at present out of acamprosate, disulfiram and oral naltrexone (15). The effect of Disulfiram has only been showed proven effective in open label studies. In randomized controlled trials (RCT's) Disulfiram had no statistical significant better outcomes than placebo. Acamprosate has been shown in meta-analyses to reduce the risk of restarting to drink in abstinent patients, but it did not help people who were actively binge drinking. Naltrexone's results were statistical significant in RCT's, but the clinical results were marginally better (10).

2.5 PHYSIOLOGY OF ETHANOL

2.5.1 Metabolization of ethanol

Alcohol is absorbed through passive diffusion for roughly 20% through the stomach wall and for 80% in the small intestine. This absorption is influenced by a number of factors. Alcohol is affected by hepatic first-pass metabolism. This effect is greater if the amount of ingested alcohol is smaller. Ethanol distribution follows two-compartment kinetics. The distribution is also mostly affected by the total body weight (16).

The biggest portion of metabolization of alcohol takes place in the hepatocytes and is done by the enzyme acetyl dehydrogenase (ADH) and the CYP2E1 apolipoproteine. 1% of alcohol is

conjugated with glucuronic acid and is excreted by the urine. 2 to 5% is excreted unchanged through the lungs, urine and sweat (16).

The first step in the primary metabolization of alcohol is reversible and is done by ADH with NAD+ (nicotinamide adenine dinucleotide) as its coenzyme (16). ADH is also located in the gastric mucosa. In men, more ADH is found in the gastric wall in comparison to women. This could be a reason why women are more vulnerable to alcohol (17). This step is done in the cytosol of the hepatocyte and gives acetaldehyde as product. The next step is nonreversible and exist to form acetate by oxidizing acetaldehyde through an ADH located in the mitochondria with NAD+ as coenzyme. The change of NADP to NAD+ causes metabolic discomfort after ingesting alcohol. The final step exist out of oxidizing acetate in the Krebs cycle with carbon dioxide and water as final products (16).

Ethanol is eliminated using zero-order kinetics. This means the enzyme activity of the liver is saturable, even when you up the alcohol intake. The rate-limiting step is the reoxidation of NADH+ to NAD+. The CYP2E1 apolipoproteine is induced in heavy drinkers and enhances their elimination of ethanol out of the bloodstream. Ethanol metabolism is also enhanced by eating (16).

2.5.2 Pathophysiology of ethanol

The physiology of alcohol use has been widely researched. Ethanol has a wide array of effects on the human body. It affects the brain, lungs, heart, liver, kidneys, pancreas, muscles and the eyes (3). Alcohol upregulates the N-methyl-D-aspartate (NMDA) receptor and downregulates the gamma-Aminobutyric acid A (GABA-A) receptor. This causes an excitability of the nervous system. Withdrawal is the manifestation when these mechanisms are reverted. Alcohol stimulates the transmission of dopamine's, endogen opioids, and endogen cannabinoids (2, 3). Alcohol gives a rewarding effect which is caused by the release of dopamine in the mesolimbic system. The mesolimbic system affects the areas of the brain which are responsible for the regulation of cognitive control (9).

Alcohol use also causes a shift in the balance of electrolytes and can cause alcoholic ketoacidosis. The ketoacidosis is caused by keto-acids, lactic acids, and acetatic acids and is found in 25% of the alcoholic population. When these keto-acids come in contact with bicarbonate in the extracellular space, this reaction generates carbon dioxide and water. This decrease in bicarbonate causes an increase of the anion gap (18). Hypophosphatemia can occur in 50% of patients in the first days after their hospitalization (18).

2.5.3 Genetic research

There has also been genetic research done into the cause of AUD's. Most twin studies suggest 50% of AUD's were heritable (2). There exist polymorphism for the enzyme ADH which is responsible for the metabolism of ethanol. This enzyme is a pentamer and for each of these subunits there has been ethnic polymorphisms described (16).

2.6 DESCRIPTION OF THE CONDITION

A meta-analyses from the United Kingdom suggests that one out of five in-hospital patients are using alcohol harmfully and that one out of ten is alcohol-dependent (5). In the ICU, patients with alcohol problems are even more commonly seen, but different studies give different prevalence for people with alcohol use admitted to the ICU. These numbers range from 10% to 25% of patients admitted to the ICU with an alcohol-related problem; some data suggest even as high as 40% of ICU admissions are alcohol related. In contrast to this a study reported that only 25% of these patients get recognized in the ICU as having an alcohol-related problem (4). Compared to the primary care or general population this is a higher prevalence. There are several scales available for assessment of alcohol use or the onset of delirium (CAGE, AUDIT, AUDIT-C, FAST, SMAST or CAM-ICU: *Appendix A*), but often these are not used because of practical issues (3, 4).

2.6.1 Clinical outcomes of patients with alcohol use in the ICU

Patients who have been identified with a background of an alcohol-related problem, have in the ICU a higher mortality, more withdrawal syndromes, prolonged length of stay and this for both the ICU and in-hospital length of stay (3). As for clinical outcomes, these patients do worse in comparison to their counter group who do not use alcohol. Alcoholic patients have more risk at developing, sepsis, ARDS, need for ventilation, and pneumonia (4).

So all in all, these patients are worse off when it comes to burden of disease, medical treatment and clinical outcomes, nonetheless alcohol use is a very common problem in patients in a hospital setting and ICU setting (19).

2.6.2 Treatment of patients with alcohol use in the ICU

The first things to do when treating a patient with alcohol withdrawal is to see whether the patient has enough fluids and if electrolytes are in the physiologic range (19). Up next the physician has to regulate B12 deficiency. Vitamin B12 deficiency can cause Wernicke encephalopathy and anemia. Gastro-intestinal complications are common and dangerous and more specifically gastrointestinal hemorrhage or pancreatitis. Liver dysfunction and cardiomyopathy are diseases

which may not be lost out of sight in the overall treatment (19). Benzodiazepines have been the go-to drug for treating and preventing AWS, DT and seizures since 1969 (19). Phenobarbital can be used if the patient suffers from benzodiazepines resistant AWS. Propofol can be given if patients do not respond to high dose benzodiazepines. Dexmedetomidine is approved to be given as an sedative in the ICU. For the use of Baclofen, Ketamine, Carbamazepine and Valproic Acid, or Enteral Ethanol is not enough evidence gathered that could justify their use in the ICU. Antipsychotics are given as an adjuvant therapy for they diminish the symptoms of hallucinating (19).

2.7 How the intervention might work

Ethanol has a wide array of effects on the human body. It affects different organs and systems: brain, lungs, heart, liver, kidneys, pancreas, muscles and the eyes (3). Therefore the hypothesis would expect that alcoholic patients suffer more harm.

The hypothesis is that the alcohol population will have worse clinical outcomes. This study also puts forward that it will affect more men than women and alcohol use would be more prevalent among older patients. The prevalence will estimated around 20-30%. ARDS, pneumonia and sepsis could be more prevalent among alcoholic patients. Ventilation days are hypothesized to be higher and mechanical ventilation to be more prevalent among alcoholics. If the mechanical ventilation days are hypothesized to be longer, the length of stay in the ICU and hospital will be also be prolonged. The alcoholic trauma population could consist of a younger male compared to the older alcoholic male population that is hypothesized to be more prevalent among the medical ICU.

2.8 Why it is important to do this review

In the past there have been attempts done to get a grip on the epidemiology of patients with alcohol use on the intensive care unit, but this has not been done in a complete and thoroughly systematic review or meta-analysis. This systematic review and meta-analysis tries to fill this void.

2.9 Objectives

The main objective of this systematic review is to assess the epidemiology of patients with alcohol abuse admitted to the ICU. This will be done by looking at the age of these patients, gender differences, and geographic comparison. In this way ICU-personnel gains data on alcohol use. This could give doctors and nurses more insight into which patients use alcohol and what to expect from

them when it comes to clinical outcomes. This study will incorporate both patients admitted with chronic and acute alcohol intoxication and will try to give an epidemiologic insight into the full aspect of alcohol use in the intensive care. This study will make a distinction between patients with alcohol use admitted to the medical ICU, the cardiac ICU, the burn unit, the trauma ICU, the surgical ICU and a mixed ICU setting. The aim of this study is to make specific meta-analyses for each of these subgroups of patients.

The secondary outcomes exists out of mortality (30-day and one year) and the length of stay of these patients, both in ICU and in the hospital. Whether these patients need assisted ventilation and for how long. To see whether these patients have an alternate pattern of developing delirium in comparison to patients admitted to the ICU without alcohol use. Whether these patients develop more ARDS. And as a last objective this study looks into whether these patients develop more infections (sepsis and pneumonia) and which type of pathogens infect them ccompared to patients without ethanol abuse.

2.9.1 Prevalence

The prevalence of alcohol abuse in the ICU will be evaluated and this for the burn unit, the cardiac care unit, the medical ICU, chirurgic ICU, trauma ICU and a mixed ICU setting. The next step is to map it out for geographic locations. This study will make use of the countries and a color code will make a distinction between the different prevalence's based on lower than 15%, 15-30% or higher than 30%.

2.9.2 Difference in alcohol use for sex and age

Earlier research shows that alcohol use is more prevalent among men, but there is no clear data if this is also true for the ICU (2). Meta-analysis will be performed if data is available.

2.9.3 Alcoholic pancreatitis

There has been a link found between alcohol and acute pancreatitis in a meta-analysis when the intake is more than 4 drinks a week (20). There is already evidence for a link between alcohol and chronic and acute pancreatitis. Pancreatitis is still a dangerous illness for it has a high mortality rate. (21). This study reports on the prevalence of alcoholic pancreatitis in an alcoholic ICU population. Meta-analysis will be performed if data is available.

2.9.4 Liver cirrhosis

Around 20% of chronic alcoholics develop liver cirrhosis (22). A meta-analysis done in 2010 found that the mortality was higher than morbidity for patients with alcohol use and liver cirrhosis. The

relative risk of mortality was 14.7 for women and 7 for men (23). This shows that liver cirrhosis could cause relative high mortality among alcoholics. This systematic review wants to map out the prevalence of liver cirrhosis. Meta-analysis will be performed if data is available.

2.9.5 Alcohol withdrawal delirium

Alcohol withdrawal syndrome is a combination of symptoms that occur one to three days after the cessation of chronic alcohol intake and can present itself as a hypoactive or an hyperactive state (24). The most common symptoms are seizures, hallucinations, sweating, tachycardia, hypertension and delirium tremens. Delirium tremens has a mortality that ranges between one to five percent (24). This study examines the prevalence.

2.9.6 Sepsis

In experimental study's there are arguments found to believe that alcohol causes a suppression of the immune systems which could lead to a higher mortality in people with alcohol abuse (25). The ICU mortality for patients with sepsis is 25%. In contrast to patients without sepsis, the mortality is 16% as shown in the ICON study (26). The clinical relevant scale to objectify sepsis is the SOFA-score. This systematic review reports on the prevalence of sepsis.

2.9.7 Pneumonia

Pneumonia is still a major cause for death and morbidity. Furthermore it is often a reason for patients to be admitted to the ICU. In alcoholics pneumonia could be more prevalent on account of impaired upper airway reflexes (27). Other explanations could be that the immune system of the host is altered or that the patient is colonized by more virulent pathogens (4). The prevalence of pneumonia in patients with alcohol use in the ICU will be assessed. Meta-analysis will be performed if data is available.

2.9.8 ARDS

Acute respiratory distress syndrome (ARDS) is commonly occurring complication in ICU patients. It makes up to 10% of all ICU admissions and is diagnosed in more than 20% of patients requiring mechanical ventilation. On top of this has ARDS a high mortality rate: between 35 to 40% (28). A meta-analysis done by Simou et al. shows that there is a correlation between alcohol intake and the risk of developing ARDS. The study found a 1.89 OR increase of ARDS in people who have a high alcohol intake (29). One articles claim that patients who were known with a history of alcohol use were twice as likely to developed ARDS in comparison to people who did not have alcohol use in their history (3). This systematic review tries to map out the prevalence of ARDS and alcohol use in the ICU. Meta-analysis will be performed if data is available.

2.9.9 Mechanical Ventilation

Mechanical ventilation is common in the ICU. The purpose of this study is to see whether people with alcohol use are more often and prolonged mechanical ventilated. Meta-analysis will be performed if data is available.

2.9.10 ICU length of stay and Hospital length of stay

The length of stay in the ICU and in the hospital are correlated with the gravity of the illness and the resource utilization. This review investigates the ICU LOS and hospital LOS of patients with alcohol use. Meta-analysis will be performed if data is available.

2.9.11 Mortality

Patients admitted to the ICU have a high mortality. This review wants to investigate whether the patients with alcohol abuse have a higher mortality in comparison to the ICU population which does not suffer from alcohol abuse through meta-analysis. This review will differentiate the 30-day mortality, one year mortality, ICU mortality and hospital mortality. Meta-analysis will be performed if data is available.

3 Methods

The research question has been formulated using the PICO-technique. The population is the adult (>15y) alcoholic ICU population. The intervention could not be defined as an intervention for this review is an review of studies. The control group is defined as the adult non-alcoholic ICU patients. For outcomes are mortality, infections, LOS, mechanical ventilation and epidemiology chosen. A full description of the outcomes is given in the objectives section above.

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

This systematic review incorporated all cohort and case-control study designs. Retrospective as well as prospective cohort study designs were accepted. The option for inclusion of case-controls studies stems from the knowledge that case-controlled studies in epidemiologic research delivers the same results, with the only downside being they have less power (30). No narrative reviews or systematic reviews have been incorporated. The article had to be a full article and had to be fully accessible to be included, this means that no (reference) abstracts will be included. The cohort studies were supposed to have an intervention group that has been exposed to alcohol, be it

acutely or chronic. Studies that incorporated a control arm were seen as necessary for the use in the meta-analysis. Articles in English, Dutch, German and French were accepted.

3.1.2 Types of participants

The study population existed out of people admitted to the intensive care with and without ethanol use. Both male and female adult patients are included in the systematic review. Children till the age of fifteen are excluded, for the scope of the study is aimed at the adult population. The counterargument for not putting the bar at the legal drinking-age of 18 or 21 is that 15 years is often the cut-off value for transferring these patients from pediatric care to adult care (the physiology of a 15 year old often resembles more the physiology of an adult instead the physiology of a child). Most studies included a population which was 18 years or older, except for most trauma studies.

3.1.3 Types of Interventions

The intervention was aimed at people with ethanol use admitted to the intensive care unit. No distinction was made between a chronic alcohol abuse or a onetime intoxication due to binge-drinking e.g. both types of patients and the spectrum of alcohol presentation in between were accepted. This review did not incorporate studies that made no distinction between alcohol and illicit drugs or other addictive substances. This review accepted studies where the definition of alcohol is defined by the BAC, AUDIT, CAGE, SMAST, DSM-IV or DSM-5 definitions, ICD-10 or ICD-11 definitions, liver cirrhosis, alcoholic pancreatitis, AWS or AWD, or studies where the physician has performed the anamnesis in search of alcohol use.

3.2 Search methods for identification of studies

PubMed, Embase and Web of Science have been used to search databases. For each database was its own search strategy constructed. The first search was performed on November 7, 2019 and the last search was performed on March 15, 2020. There was no time limit used. This means all articles between January first of 1960 and the fifteenth of March 2020 were available for acceptance.

3.3 Electronic searches

3.3.1 PubMed

For searching MEDLINE there has been made use of Mesh-Terms. On top of this there was also searched in [TIAB]. The full MEDLINE search is referred in *Appendix B*.

3.3.2 Embase

Emtree-terms were used for searching Embase. There has been made use of ti,ab, exp and mj. The full Embase search is referred to in *Appendix B*.

3.3.3 Web of Science

The search in Web of science was done through TS. The full Web of Science search is given in *Appendix B*.

3.3.4 Searching other resources

The reference list of reviews or articles about the subject were scanned for eligible articles which could not be located through the search (3, 4, 31).

3.4 DATA COLLECTION AND ANALYSIS

3.4.1 Selection of studies

5,637 articles were located by using the search strategy.

The selection process and search in Medline, Embase and Web of Science has been done by one researcher. A first selection of the articles has been done based on relevance to the topic and eligibility criteria by scanning the title and abstract. The articles were inspected closer by scanning for relevance to ICU and alcohol use.

This delivered 427 articles in total. The next step was to remove the duplicates by using built-in software in Endnote™. Some duplicates who were not recognized by Endnote™ as being duplicates, were removed by hand. A total of 127 duplicates have been removed.

The studies which were accepted after scanning the title and abstract (n=300) were downloaded into Endnote™. There was a map made “all articles” in Endnote™. In the next step these articles were categorized in groups in Endnote: BICU (Burn ICU), MICU (Medical ICU), SICU (Surgical ICU), CICU (Cardiac Intensive Care unit), TICU (Traumatic intensive Care Unit), Mixed ICU, and “exclusion articles”. The group “exclusion articles” were further divided into groups: “only abstract”, “no access to article”, “comment article”, “non-ICU population”, “no relevant data”, “no alcoholic population”, “other drugs”, “proceedings paper”, “review”, “pediatric population”, and “non-inclusion language”. The groups BICU, MICU, CCU, TICU and epidemiology were added in Endnote to a group set named “definitive articles”. These articles were submitted into a Excel™ file. These articles were marked in the Excel™ file and were discussed in consultation with Prof. Dr. E. Hoste to see whether these articles could be included.

3.4.2 Data extraction and management

All data extraction has been performed by one researcher. The data extraction has been done by copying the data into an Excel™ sheet. The title, first author, year of publication, method of analyzing alcohol status, study design, how many patients the study included (and how many elements the arms of the study contained), location of study, what the subject of the study was, and quantitative data was entered.

For the alcohol and control arms of the study the different outcomes were extracted: the age (mean, SD), the sex distribution (n or %), APACHE II or APACHE III (mean, SD), SAPS (mean, SD), hospital LOS (mean, SD), ICU LOS (mean, SD), ICU mortality (n or %), Hospital mortality (n or %), 1-year mortality (n or %), 30d-mortality (n or %), 90d-mortality (n or %), mechanical ventilation (n or %), mechanical ventilation days (mean, SD), pneumonia (n or %), sepsis (n or %), ARDS (n or %), acute pancreatitis (n, % or qualitative data), ARLD (n , % or qualitative data), delirium (n or %), AWS (n or %). For the burn unit was the TBSA (%), full thickness (%) and inhalation injury (n or %) extracted.

Sometimes for the LOS the data was given in hours. If this was the case, the hours were recalculated to days for the meta-analysis (e.g. LOS= 46h was entered as LOS= 1.92 days). The same was done for the prevalence. If only the absolute numbers were given (n), there was sometimes a need to recalculate to percentages (%) or vice versa. If the data was not given in the right unit, the available data were incorporated in a Excel™ document. For example: if only the range or IQR was given instead of the SD, this range or IQR was noted down. For the Surgical ICU was additionally the ASA and ISS extracted and for the Burn Unit the TBSA% if it was available in the article.

3.4.3 Assessment of risk of bias in included studies

The risk of bias has been evaluated by using Cochrane's *Tool to Assess Risk of Bias in Cohort Studies.* The full list of question has been given in *Appendix D*. These questions were answered by using a code: "++" (very low risk of bias) and "- -" (very high risk of bias).

3.4.4 Measures of treatment effect

This review made use of risk ratio (RR) and mean difference (MD) in its meta-analysis to analyze the clinical outcomes. Meta-analysis will be accompanied by an 95% CI.

If the intervention arms of the studies existed out of more than 2 arms (e.g a control arm, an at-risk arm, and an alcohol dependency arm), the meta-analysis always compared the control and the most heavy alcohol users.

3.4.5 Dealing with missing data

If studies could not be located, the principal author was contacted through email. 1 author was successfully contacted out of 14 studies (32). 10 authors' email address could not be located (33-43). 3 out of 4 authors whose e-mail could be retrieved (32, 44, 45), could not be contacted for their email address was invalid or not any longer in use. If the first email was not responded to, a second reminder email was sent 14 days later. The first email was sent on April 14, 2020. A reminder email was sent on April 28, 2020. This did deliver one extra article eligible for assessment (32).

3.4.6 Assessment of heterogeneity

Heterogeneity of the meta-analysis's were evaluated by using the I^2. Forest plots were used to visualize the heterogeneity between articles. The heterogeneity will be classified as:

% heterogeneity	Qualitative explanation
0% - 25%	Heterogeneity is probably unimportant
25% - 50%	Low heterogeneity
50% - 75%	Mild heterogeneity
75% - 100%	High heterogeneity

Table 1 Heterogeneity index.

3.4.7 Assessment of reporting biases

ClinicalTrials.gov was assessed to retrieve any non-reported studies and their unreported data.

3.4.8 Data synthesis

Meta-analysis were used for combining data across studies. They used the Mantel-Haenszel method and random effects. If the heterogeneity was lower than 25%, the meta-analysis used fixed effects, above that a random effects analysis was reported. The built-in feature in RevMan 5 was used to perform the meta-analyses. Excel was used to build bar charts and boxplots. The software of OpenMeta-Analyst was used to calculate the meta-analysis of proportions, for this function was not integrated in RevMan. The same methodology will was used as in RevMan.

The world map for displaying world prevalence has been copyright free retrieved from *your-vector-maps.com*.

Excel has been used to calculate the bar charts and boxplots.

3.4.9 Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed using the Burn Unit, MICU, SICU, TICU and a mixed ICU setting. Heterogeneity will be evaluated through the I^2.

4 Results

A total of 100 articles were included in this review after applying inclusion and exclusion criteria (fig. 1).

A total of 188 articles were extracted out of MEDLINE. Embase delivered 93 articles and Web Of Science delivered 140 articles. On top of this another 7 articles were added through snowballing.

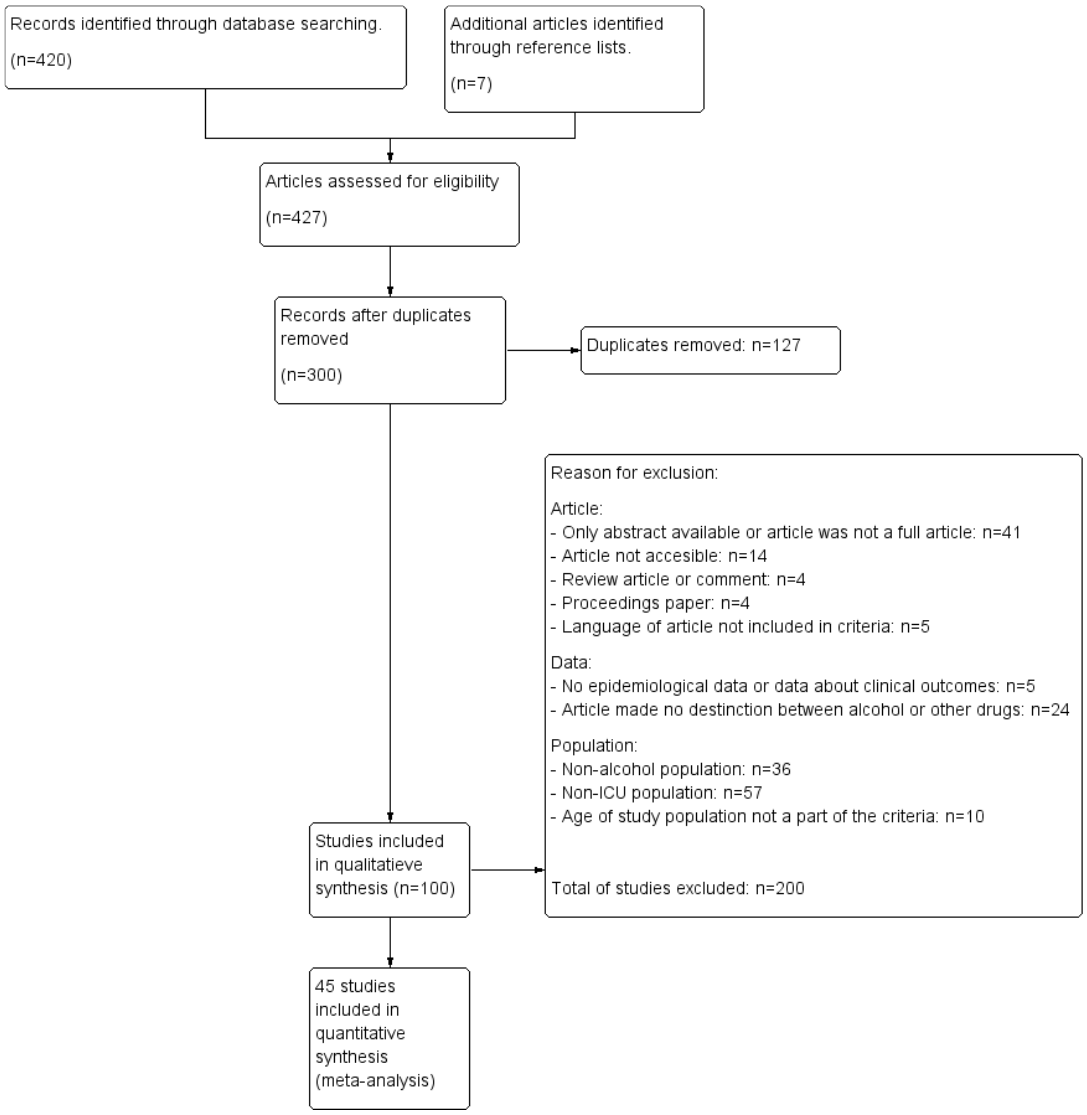
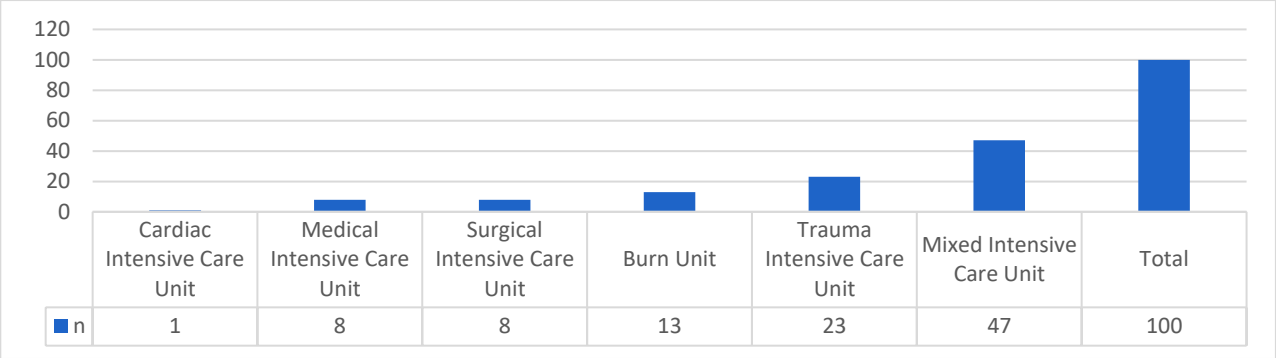


Figure 1. PRISMA Flowchart of articles.

4.1 STUDIES INCLUDED

For the full list of included studies with their characteristics this study refers to *Appendix C*.



	Cardiac Intensive Care Unit	Medical Intensive Care Unit	Surgical Intensive Care Unit	Burn Unit	Trauma Intensive Care Unit	Mixed Intensive Care Unit	Total
n	1	8	8	13	23	47	100

Table 2. Included articles per ICU setting.

4.2 RISK OF BIAS IN INCLUDED STUDIES

For the full list of risk of bias we refer to *Appendix E*.

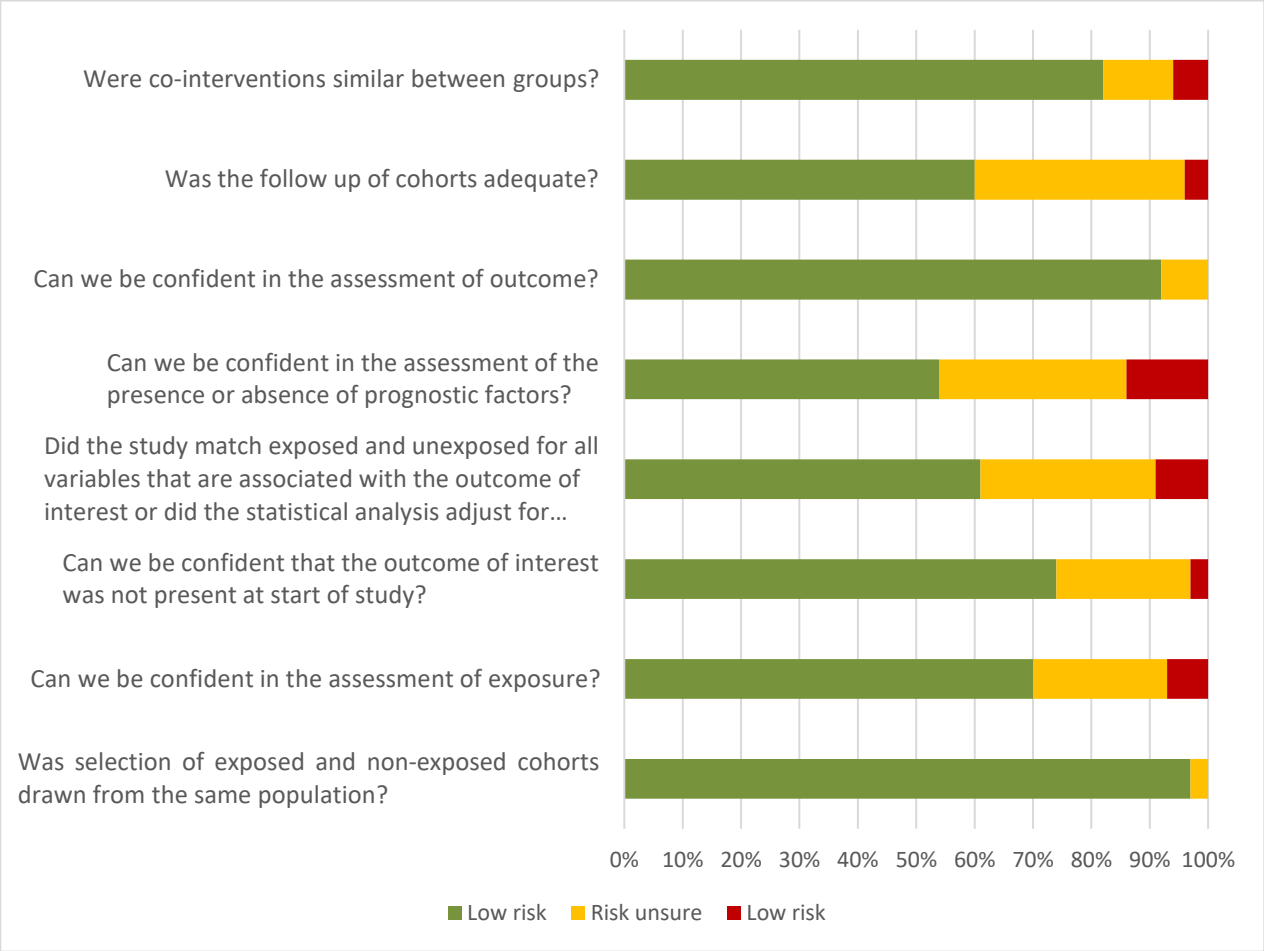
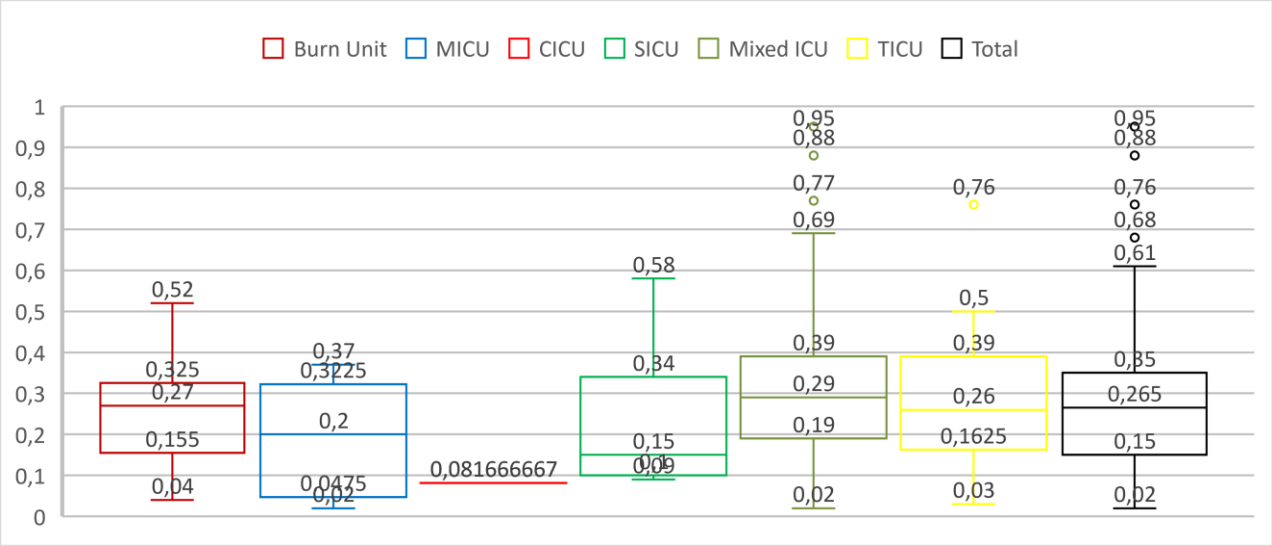


Table 3. Risk of bias table (n=100) using Cochrane's Tool to Assess Risk of Bias in Cohort Studies.

4.3 SYSTEMATIC REVIEW

4.3.1 Overall prevalence

The full list of descriptive statistics is given in *Appendix G*.



Boxplot 1. Boxplot of prevalence per ICU type and total. Median, 1st quartile, 3rd quartile, minimum, and maximum are displayed in percentage.

4.3.2 Burn Unit

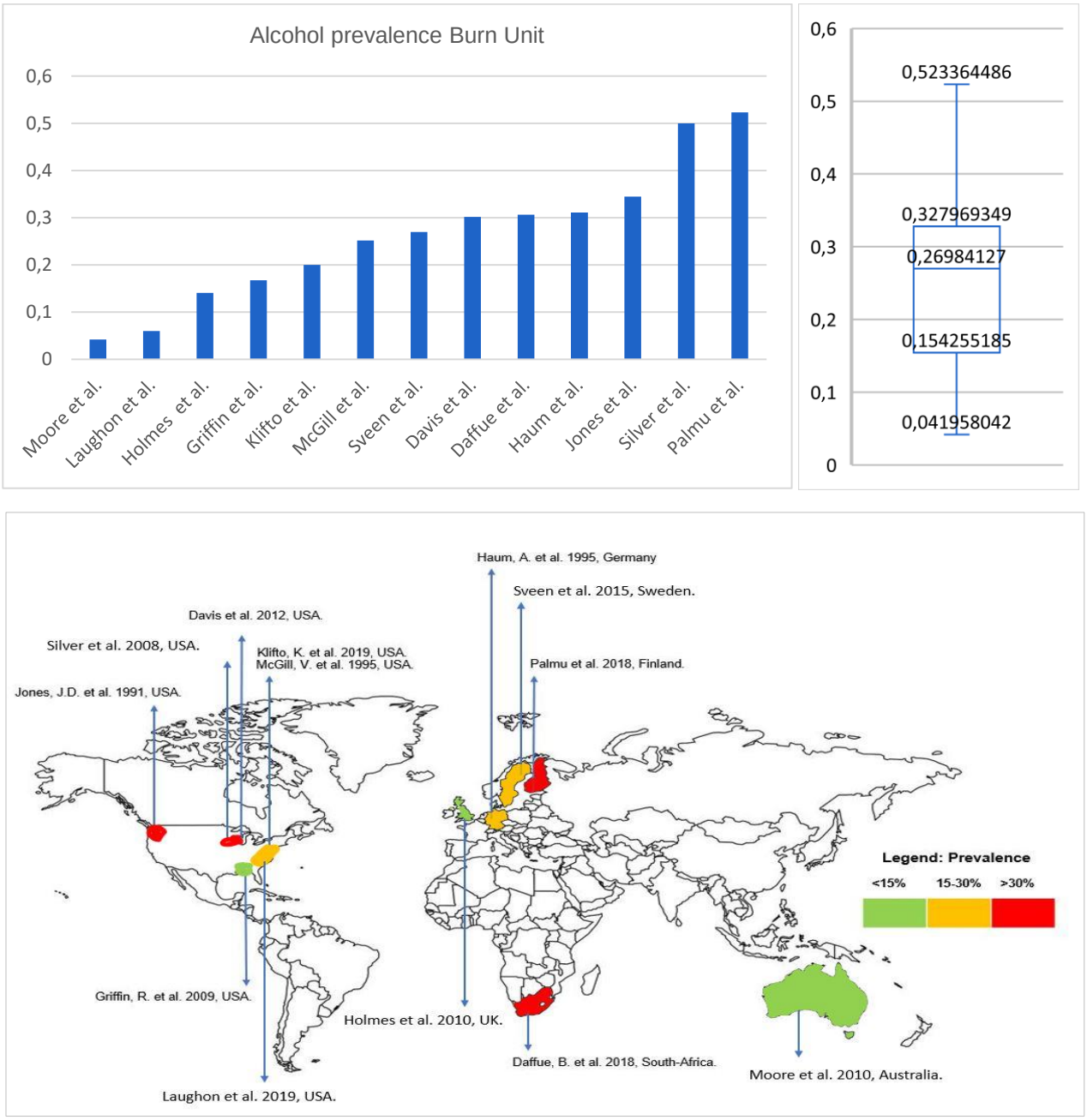
Study	Year	Country	Study design	N	M/F	Alcohol definition
Jones, et al.	1991	USA	Retrospective	87	-	BAC≥100mg/dl
Haum et al.	1995	Germany	Retrospective/Prospective	225	79/21	BAC>10 mg/dl
McGill et al.	1995	USA	Retrospective	290	81/19	Toxicological screen
Silver et al.	2008	USA	Matched-case control	48	88/22	BAC>30 mg/100 ml
Griffin al.	2009	USA	Retrospective	614	75/25	BAC: 0, <100mg, >100mg)
Holmes et al.	2010	UK	Retrospective	1293	-	Anamnesis
Moore et al.	2010	Australia	Retrospective	12	-	BAC >0 mg/dl
Davis et al.	2012	USA	Prospective	53	62/38	BAC: 0, <80mg, >80mg
Sveen et al.	2015	Sweden	Prospective	63	92/8	AUDIT-T
Daffue et al.	2018	South-Africa	Prospective	49	-	Anamnesis
Palmu et al.	2018	Finland	Prospective	107	70/30	SCID, AUDIT

Klifto et al.	2019	USA	Retrospective	115	-	BAC>30mg/dl
Laughon et al.	2019	USA	Retrospective	7202	-	BAC>0 mg/dl

Table 4. Overall study characteristics. Male to female ratio is in %.

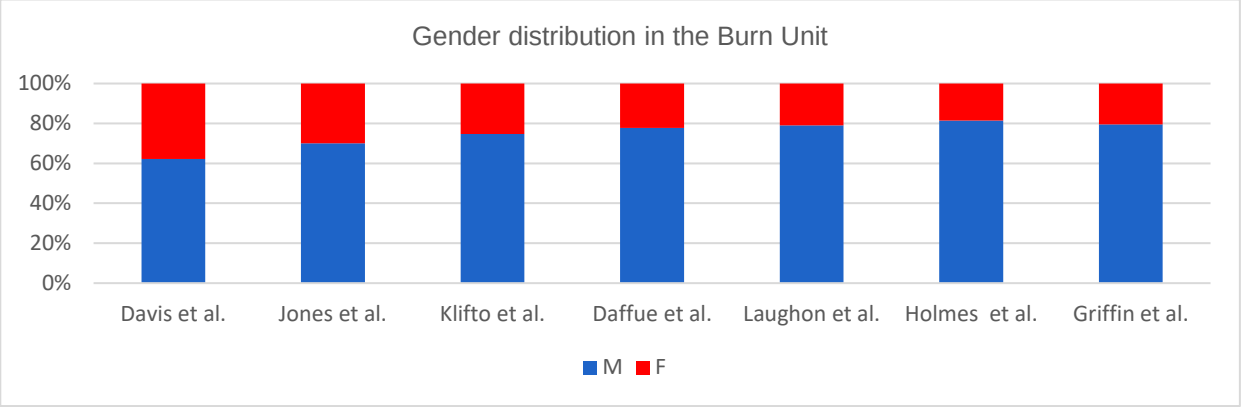
4.3.2.1 Prevalence

The alcohol prevalence starts at 4.2% and rises up to 52.4%. Median is 0.270 with an IQR of 0.174 (Bar chart, boxplot and world map 1).

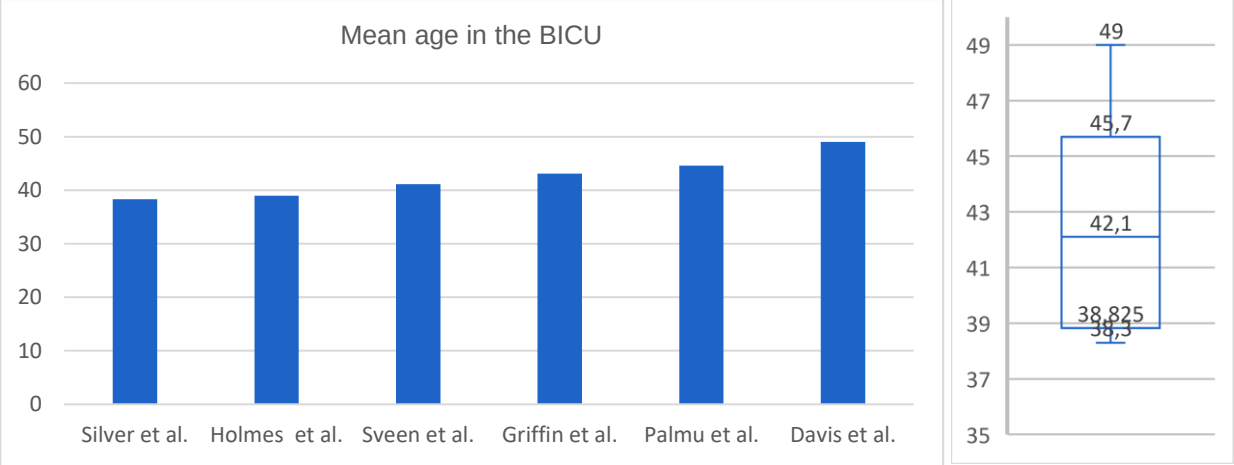


Bar chart, boxplot and world map 1. Alcohol prevalence in the Burn Unit (46-58).

4.3.2.2 Gender and age



Bar chart 1. Gender distribution of the alcoholic group (47, 49, 50, 53, 54, 56, 59).



Bar chart and boxplot 1. Mean age in years of the alcohol groups in the BICU. On the right is the boxplot displayed (48, 49, 52, 53, 57, 58).

4.3.2.3 Pneumonia

A high blood alcohol has a higher risk pneumonia (RR for pneumonia: 2.06, 95% CI 1.04–4.09), but a low to moderate BAC has a protective effect for line-infections (moderate BAC: RR 0.53, 95% CI 0.07–4.11. High BAC: RR 0.85, 95% CI 0.19–3.82) (49). Alcoholics had a significantly longer need for intravenous antibiotics (22 ± 23 vs 11 ± 16, p=0.05) (56). People with alcohol use are more prone to candidemia (OR: 14.22 (CI 95% 2.5-8.1, p=0.03) (46). Davis et al. did not found any differences in pneumonia rates between binge-drinkers and non-drinkers (53).

4.3.2.4 Mechanical ventilation

The Matched-control cohort of Silver et al. reported a significant higher amount of ventilator days for BAC positive patients (4.23 days vs 14.85 days, p<0.05) (57). Similar outcomes are found in

moderate and high BAC positive group (6.2 days and 4.8 days vs. 2.1 days) (49). The study performed by Klifto et al. found an OR for intubation 1.6 (95 CI 0.6-4.2) for patients with alcohol use (50).

4.3.2.5 ICU LOS and Hospital LOS

A longer ICU LOS and hospital LOS was found for both acutely intoxicated patients and chronic alcoholics (55-57). In contrast to this, Davis et al. did not found any differences In LOS between binge-drinkers and non-drinkers in both the ICU and the hospital (53).

4.3.2.6 Mortality

A higher mortality is prevalent among acutely intoxicated alcoholic (46% vs 13%) (56). There was a significantly higher mortality of chronic alcoholics compared to non-alcoholics (55). A matched-control cohort found a higher mortality among BAC positive patients (n=8 vs n=4) (50).

4.3.3 Cardiac Intensive Care Unit

The study done by Azarasa et al. found in Iran that 49/600 (8.1%) patients were using alcohol. Alcohol abuse was found in 47/49 patients and dependence was found in 4/49 patients. They did not found any differences for clinical outcomes between their alcoholic group or the control group (60).

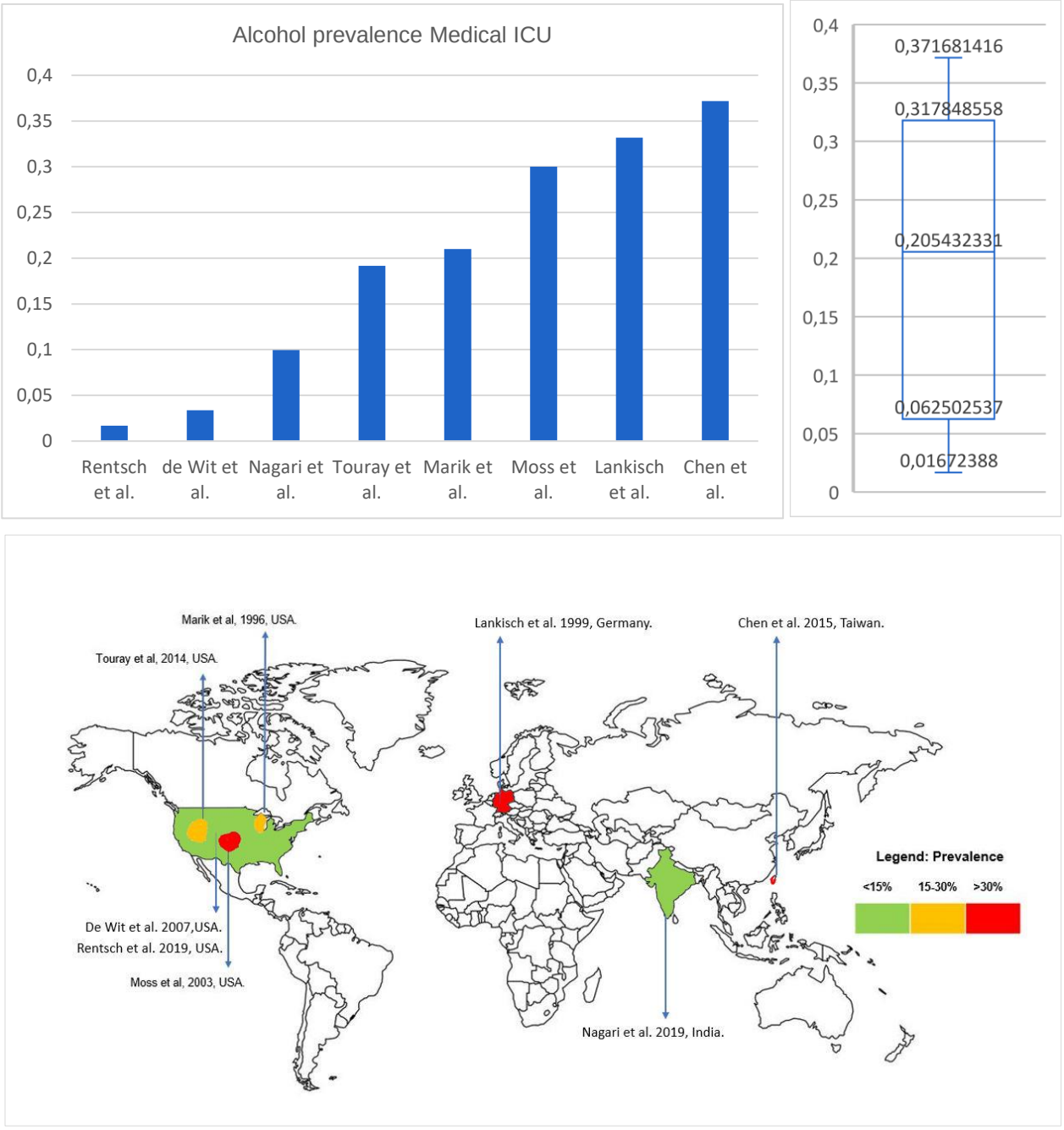
4.3.4 Medical ICU

Study	Year	Country	Study design	n	M/F	Alcohol definition
Marik et al.	1996	USA	Prospective	200	-	Anamnesis
Lankisch et al.	1999	Germany	Prospective	208	-	Alcoholic pancreatitis
Moss et al.	2003	USA	Prospective	220	59/42	SMAST
de Wit et al.	2007	USA	Retrospective	785 602	55/45	ICD-9
Touray et al.	2014	USA	Retrospective	266	59/41	Anamnesis
Chen et al.	2015	Taiwan	Retrospective	226	-	Cirrhosis
Nagari et al.	2019	India	Prospective	1582	-	RASS and CAM-ICU
Rentsch et al.	2019	USA	Retrospective	155 550	-	ARD

Table 5. Overall study characteristics. Male to female ratio is in %.

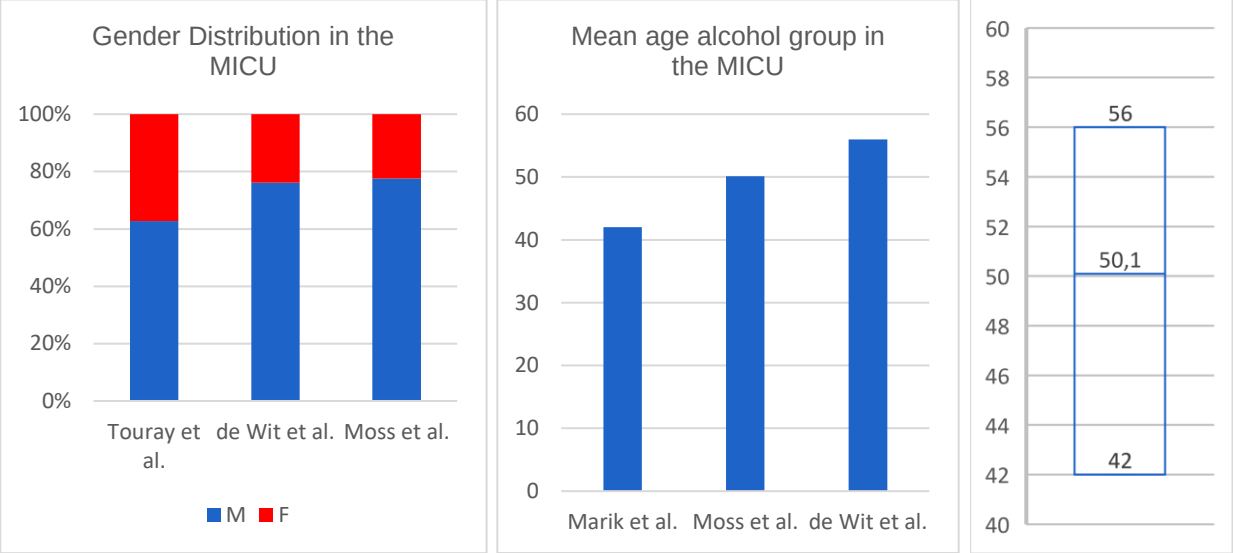
4.3.4.1 Prevalence

The alcohol prevalence starts at 1.7% and rises up to 37.2%. The Median is 0.205 with an IQR of 0.255 (Bar chart, boxplot and world map 2).



Bar chart, boxplot and world map 2. Alcohol prevalence in the MICU (61-68).

4.3.4.2 Gender and age



Bar chart and boxplot 2. Gender distribution of the alcoholic group in the MICU (65, 69, 70). On the right is the mean age in years of the alcohol groups in the MICU with its boxplot displayed (61, 62, 69).

4.3.4.3 Liver Cirrhosis

Liver failure and alcoholic hepatitis were respectively found in 12% and in 5% of ethanol related MICU admissions. Both disease were more common in men (M/F: 10/1 for liver failure and 1.5/1 for alcoholic hepatitis) (61). A study performed in Taiwan found that 49.7% of their alcohol cirrhotic patients were younger dan 65 years (68).

4.3.4.4 Delirium

Nagari et al. found that alcohol use gave an OR of 6.54 (95% CI 3.76-11.4, p=0.0001) for developing delirium. Delirium was found in 79% of patients known with alcohol consumption, this in contrast to 6% who developed delirium of the patients who did not use alcohol (64).

4.3.4.5 Sepsis

Using the SMAST questionnaire, Moss et al. found that 30% of patients suffering from septic shock had an history of chronic alcohol abuse. When looking at the SOFA score, patients with chronic alcohol abuse had higher values of coagulation (62).

4.3.4.6 Pneumonia

People with a history of alcohol use were more likely to develop pneumonia ($p<0.001$) (62). Another study came to the conclusion that patients with AUD were found to have a lower chance of having pneumonia (63). In the study performed by Touray et al. alcohol use gave an OR of 8.64 (95% CI 1.54-48.51, p=0.014) to be diagnosed with legionella pneumophilia (65).

4.3.4.7 Mechanical ventilation

AUD gave an OR of 1.8 for mechanical ventilation need, but AUD did not prolong the duration of ventilation (63). Similar results were found in the population of Moss et al. that more patients suffering from chronic alcohol abuse needed mechanical ventilation (85% vs 63%, p=0.001) (62). The study by Marik et al. found a higher percentage of mechanical ventilation among the control group (61)

4.3.4.8 ARDS

ARDS was found to be more prevalent among chronic alcoholic patients (70% vs 31%, p<0.001, relative risk: 2.28; 95% CI 1,51–3,42). Chronic alcohol abuse was found to give an OR of 3.70 for ARDS. People who self-reported having a chronic alcohol abuse were more likely to develop ARDS (62).

4.3.4.9 ICU LOS and Hospital LOS

The ICU LOS was found to be longer for the ethanol related admissions compared to the non-ethanol related group (11±5 vs 7±1, p<0.05) (61).

4.3.4.10 Mortality

One study found a non-statistically higher mortality among the alcoholic group compared to the non-alcoholic group (21% vs 9%) (61).

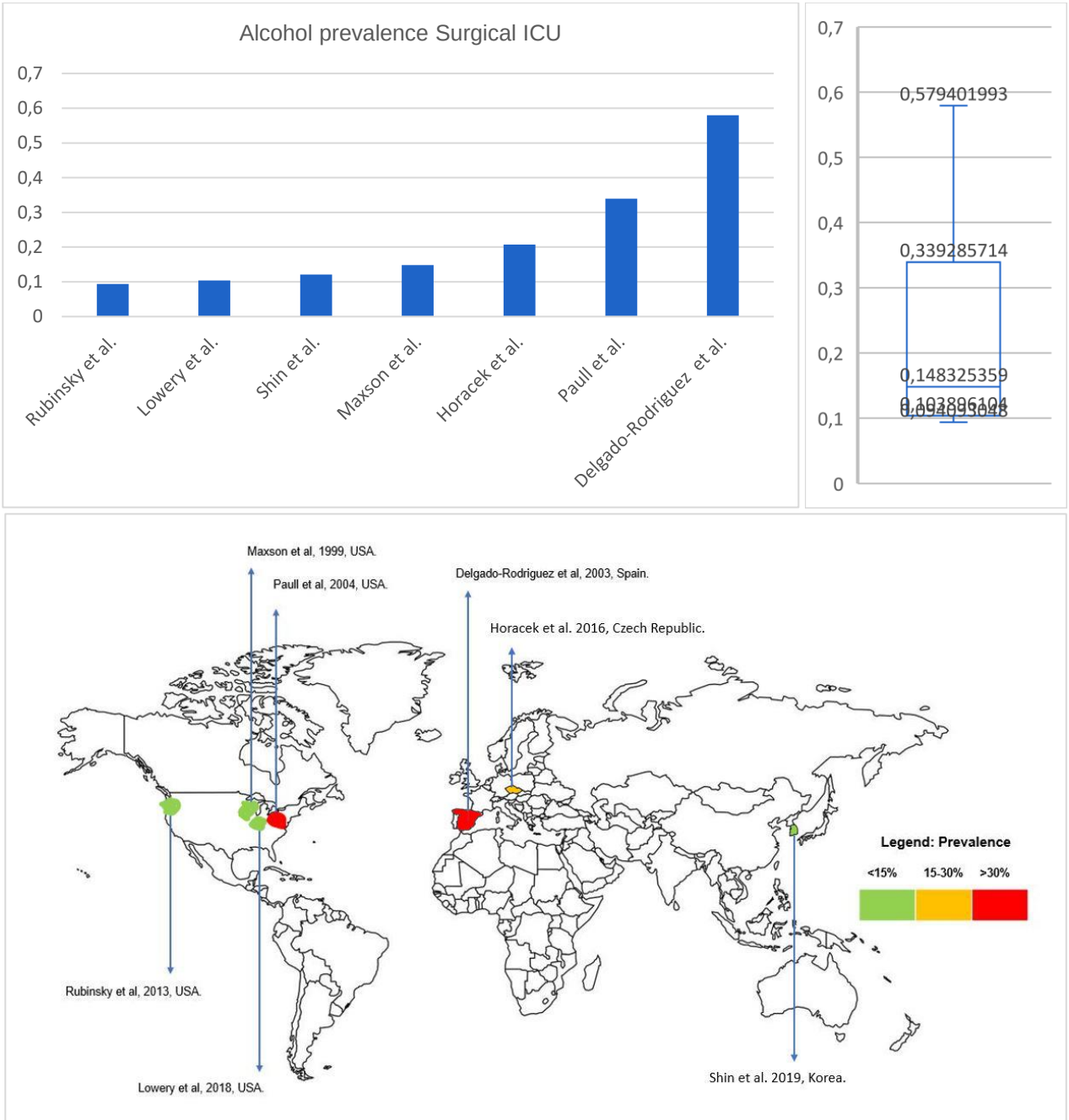
4.3.5 Surgical ICU

Study	year	Country	Study design	n	M/F	Alcohol definition
Maxson et al.	1999	USA	Prospective	321	76/24	CAGE>2
Delgado-Rodriguez et al.	2003	Spain	Prospective	1505	44/56	Anamnesis
Paull et al.	2004	USA	Prospective	56	-	DSM-IV
Rhodes et al	2001	Austria	Prospective	88 504	-	Not defined
Rubinsky et al.	2013	USA	Retrospective	1913	-	ADUTI-C
Horacek et al.	2016	Czech Republic	Prospective	140	-	RASS, anamnesis
Lowery et al.	2018	USA	Prospective	86	76/24	AUDIT and BAC
Shin et al.	2019	Korea	Retrospective	99	-	CAM

Table 6. Overall study characteristics. Male to female ratio is in %.

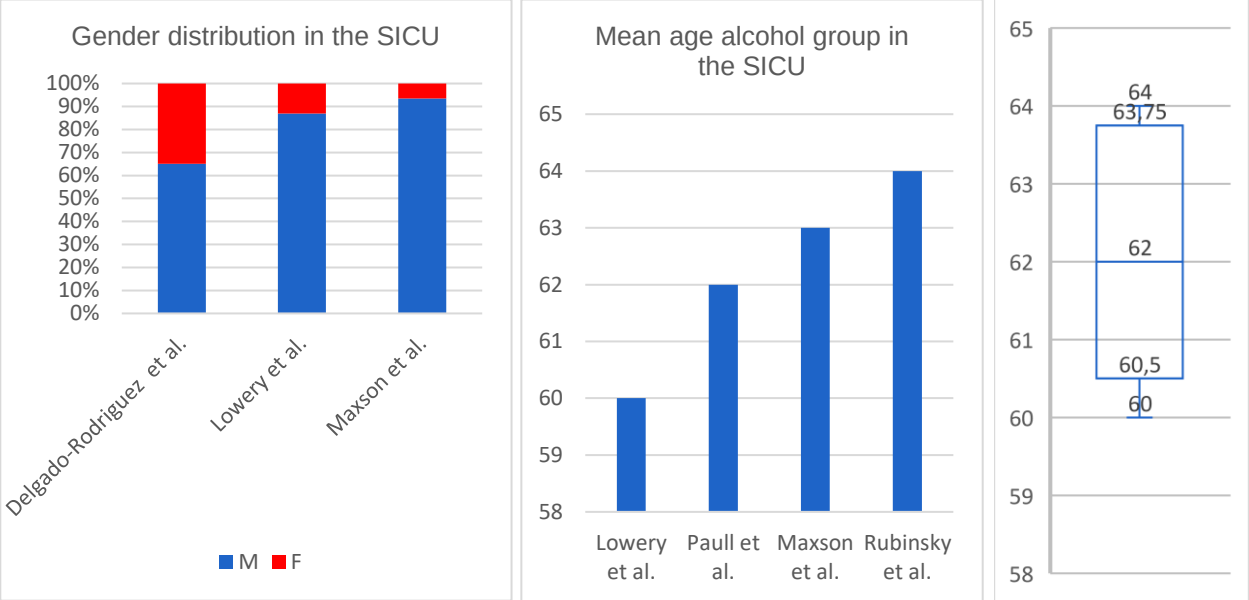
4.3.5.1 Prevalence

The alcohol prevalence starts at 9.4% and rises up to 58.0%. Median (0.149) and IQR (0,235) are given (Bar chart, boxplot and world map 3).



Bar chart, boxplot and world map 3. Alcohol prevalence in the SICU (71-76).

4.3.5.2 Gender and age



Bar chart and boxplot 3. Gender distribution of the alcoholic group in the SICU (71, 72, 74). On the right is the mean age in years of the alcohol groups with its boxplot displayed (71, 73, 74, 77).

4.3.5.3 Delirium

In one article AWS was found to be more prevalent among the alcohol abuse group (12.9% vs 1.7%, p=0.006) (71). An history of alcohol use gave a longer duration of delirium (respectively: 73.63±45.20 hours vs 59.54±30.61 hours, p<0.05) (76). Delirium was higher among elderly that used alcohol (30% vs 9%, p=0.005) (75).

4.3.5.4 Alcoholic pancreatitis

Lankisch et al. found that patients suffering from pancreatitis with an alcoholic etiology had more necrotizing pancreatitis. These patients also needed more frequent mechanical ventilation (19% compared to 6% of the patients that had biliary pancreatitis). The ICU LOS and mortality was found to be slightly higher compared to other etiologies. (67).

4.3.5.5 Sepsis

In the matched-cohort study by Paull et al. sepsis was found to be more prevalent among the alcoholic group (2 vs 0, p=0.11) (73).

4.3.5.6 Pneumonia

Pneumonia was found to be more prevalent in the alcohol abuse group (29.0% vs 10.7%, p=0.008) (71). These results were confirmed in a matched cohort study: there was a higher prevalence of pneumonia in alcoholic patients (31.6% vs 8.1%, p=0.05) (73).

4.3.5.7 Mechanical ventilation

The matched-cohort study performed by Paull et al. showed that the alcohol group needed a higher number of ventilation days (11.7 ± 7.4 vs 0.7 ± 0.4d, p=0.04) (73). Similar results were found for lung transplant patients with recent use of alcohol, they needed 3 times longer mechanical ventilation (p=0.037) (74).

4.3.5.8 ICU LOS and Hospital LOS

In two studies a lower LOS hospital was found for the alcohol group (71, 73). In contrast to this, Rubinsky et al. found that patients who reported higher AUDIT-C scores, had an increased hospital and ICU LOS (77). Patients who had recent use of alcohol had a 1.5 times longer hospital LOS (p=0.028). The ICU LOS was also higher (p=0.008) (74). Maxson et al. did not found any statistical significant difference in hospital and ICU LOS between their alcohol abuse and control group (71).

4.3.5.9 Mortality

Paul et al. found a higher postoperative mortality for their alcoholic patients (2% vs 0%), but the 3-year mortality was found to be slightly higher for the nonalcoholic group (alcoholic group: 58% ±16%, nonalcoholic group: 61% ±10%, p=0.20) (73).

4.3.6 Mixed ICU setting

Study	Year	Country	Study design	n	M/F	Alcohol definition
Burnham et al.	2004	USA	Prospective	20	63/37	SMAST>2
Muhlberg et al.	2005	Germany	Retrospective	5883	-	BAC
Uusaro et al.	2005	Finland	Prospective	893	65/35	Anamnesis
O'Brien et al.	2006	USA	Retrospective	11 651	66/34	ICD-9
Ouimet et al.	2007	Canada	Prospective	820	-	ICD-SC, RASS
Blanco et al.	2008	Spain	Prospective	2 619	-	Chronic use
Faria et al.	2008	France	Prospective	7	-	Alcohol hepatitis
Gacouin et al.	2008	France	Prospective	358	33/67	Anamnesis, SMAST
Van Rompaey et al.	2009	Belgium	Prospective	523	-	Delirium
de Wit et al.	2010	USA	Retrospective	40	-	SMAST>2
Lam et al.	2010	Hong Kong	Retrospective	265	-	Anamnesis
McKenny et al.	2010	Ireland	Prospective	275	88/12	AWS, AP, Cirrhosis

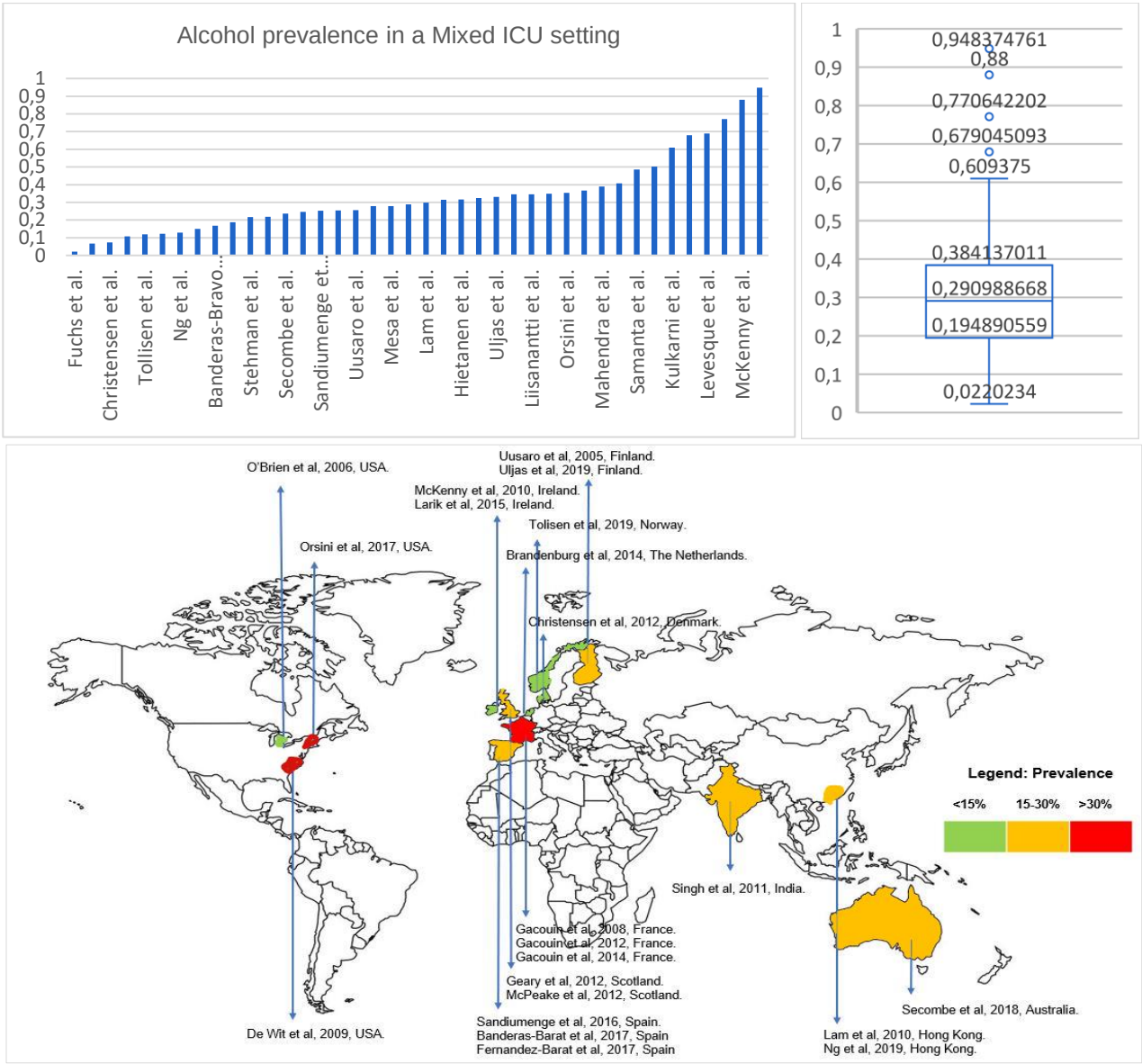
Monte et al.	2010	Spain	Retrospective	16 848	-	AWS
Singh et al.	2011	India	Retrospective	138	-	Alcohol use
Christensen et al.	2012	Denmark	Prospective	16 848	59/41	Disulfiram use
Fuchs et al.	2012	Multicenter	Retrospective	19 510	-	Not defined
Gacouin et al.	2012	France	Prospective	281	62/38	SMAST
Geary et al.	2012	Scotland	Prospective	838	56/44	ICD-10
Levesque et al.	2012	France	Prospective	377	-	Cirrhosis
Brandenburg et al.	2014	Netherlands	Retrospective	7 331	-	APACHE II
Gacouin et al.	2014	France	Prospective	662	66/34	NIAAA + SMAST
Levesque et al.	2014	France	Prospective	592	-	Cirrhosis
Larkin et al.	2015	Ireland	Retrospective	346	60/40	Anamnesis
McPeake et al.	2015	Scotland	Prospective	580	59/41	ICD-10, FAST
Stehman et al.	2015	USA	Prospective	11 850	67/33	BAC+
Walkey et al.	2015	USA	Retrospective	3 666	-	Not defined
Sandiumenge et al.	2016	Spain	Prospective	509	68/32	Anamnesis
Banderas-Bravo et al.	2017	Spain	Prospective	119	-	Not defined
Fernandes et al.	2017	Portugal	Retrospective	170	-	Alc. Hep.
Fernandez-Barat et al.	2017	Spain	Prospective	222	-	Anamnesis
Hietanen et al.	2017	Finland	Retrospective	899	-	Anamnesis
Kanova et al.	2017	Czech Republic	Prospective	332	-	CAM-ICU
Liisanantti et al.	2017	Finland	Retrospective	403k	-	Alcohol use
Mesa et al.	2017	Latin-America	Prospective	230	-	RASS, CAM-ICUU
Orsini et al.	2017	USA	Prospective	65	-	Acute intoxication
Smith et al.	2017	Canada	Retrospective	130	-	Not defined
Cilloniz et al.	2018	Spain	Retrospective	6 403	-	Alcohol use
Kulkarni et al.	2018	India	Prospective	64	-	APASL
Mehandra et al.	2018	India	Prospective	100	-	Alcoholism
McPhail et al.	2018	UK	Retrospective	31 363	-	Cirrhosis
Secombe et al.	2018	Australia	Retrospective	2 670	74/26	Anamnesis
Lone et al.	2019	Scotland	Retrospective	6 053	58/42	ARLD

Ng et al.	2019	Hong Kong	Retrospective	270	-	BAC>0 mg/dl
Samanta et al.	2019	India	Prospective	759	-	AP
Stewart et al.	2019	Scotland	Retrospective	257	61/39	FAST, ICD-10
Tollisen et al.	2019	Norway	Prospective	852	66/34	Questionnaire
Uljas et al.	2019	Finland	Retrospective	2 532	-	AUDIT

Table 7. Overall study characteristics. Male to female ratio is in %.

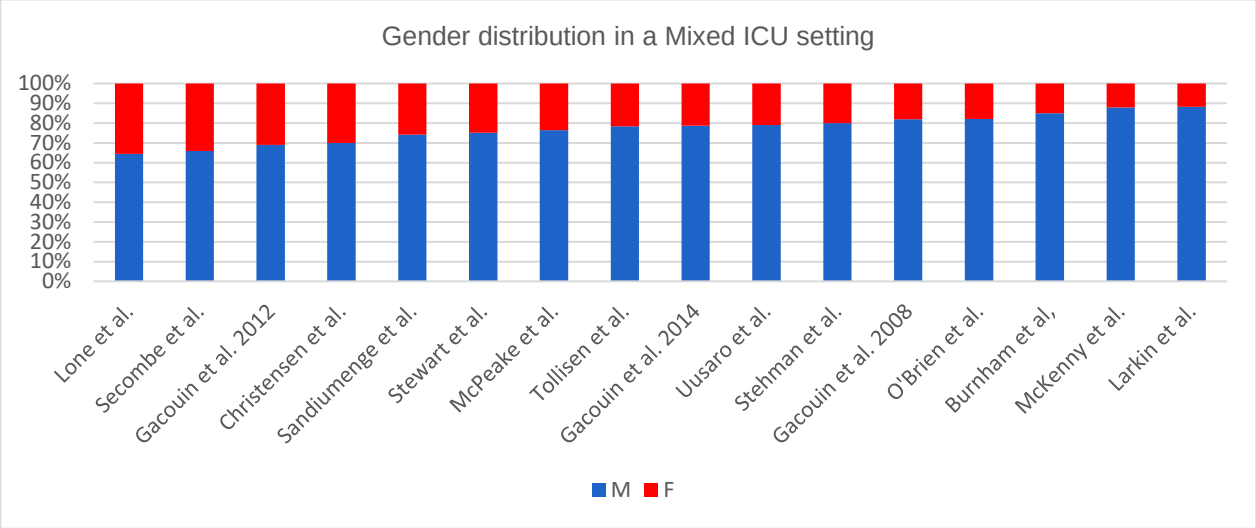
4.3.6.1 Prevalence

The alcohol prevalence starts at 2.2% and rises up to 94.8%. The median (29.4%) and IQR (19.5%) are given below (Bar chart, boxplot and world map 4).

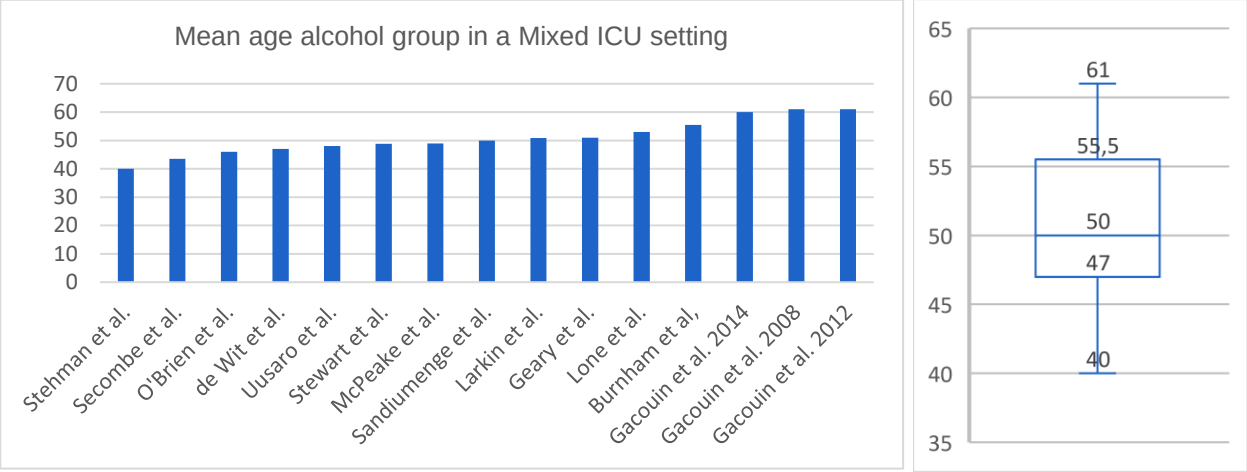


Bar chart, boxplot and world map 4. Alcohol prevalence in a mixed ICU setting (78-102).

4.3.6.2 Gender and age



Bar chart 2. Gender distribution of the alcohol group (78-80, 83, 85, 86, 88, 94, 103-110).



Bar chart and boxplot 4. Mean age in years of the alcohol groups in a mixed ICU with on the right the boxplot (78-81, 86, 88, 94, 103-107, 109-111).

4.3.6.3 Delirium

Ouimet et al. found in delirious surgical-medical ICU patients that alcoholism gave an OR 2.03 (CI 1.26–3.25) for developing delirium (112). A higher OR of 3.23 for developing delirium by drinking 3 units of alcohol a day was found in the study performed by Van Rompaey et al. (102). Stewart et al. found that their alcohol dependent group had a higher OR (OR: 3.28, p=0.007) compared to their at-risk group (OR: 1.33, p=0.495) (113). When looking at CAM+ and CAM- patients, Kanova et al. found a higher percentage of alcohol use among the CAM+ patients (39% vs 14%) (114).

4.3.6.4 Liver Cirrhosis

One study reported about 7 patients hospitalized with Pneumocystis pneumonia came to the conclusion that patients with alcoholic hepatitis have a diminished immune system and are prone to the same illnesses as an immune incompetent patient (100). In the study of Christensen et al. 51.7% of their alcoholics with complications suffered from alcohol cirrhosis (85). A study performed in France found that 68% of their cirrhotic patients were caused by an alcohol related etiology (115). A London based study found that the prevalence of cirrhosis rose from 1.6% in 1998 to 3.1% in 2012 and 35% of their ICU patients had ARLD (116).

Among patients with cirrhosis and a severe alcoholic hepatitis infection, the ICU mortality was 61% and the hospital mortality 74% (115). An Indian study looked at patients with acute on liver failure. 60.93% of cirrhosis was caused by alcohol use. Active alcoholism caused in the study 37% of the active insults and the mortality was high among these patients (66.6%) (117).

ALD patients versus a severe comorbidity group and a general ICU cohort needed more mechanical ventilation, had a higher ICU LOS (2.7 vs 2.2d, $p<0.001$), and had shorter Hospital LOS (12d vs 14d, $p<0.001$) (103).

4.3.6.5 Alcoholic pancreatitis

One study compared alcoholic pancreatitis (AP) with pancreatic caused by gallstones. This study by Samanta et al. found that alcoholic pancreatitis was more prevalent compared to gallstone pancreatitis (48.5% vs 32.4%). AP patients were more likely to have necrotizing pancreatitis ($p=0.05$) (118).

4.3.6.6 Sepsis

39% of the BAC+ patients in the study by Orsini et al. had an elevated SOFA-score (93).

The study performed by O'Brien et al. found an adjusted OR of 1.54 (95% CI, 1,25 – 1,91; $p<0.001$). Septic shock was also associated with alcohol dependence and gave an OR of 1.75 (95% CI, 1,25-2,45, $p< 0.001$). On top of this the same study reported that the non-septic and non-HIV infections were more prevalent among their alcohol dependent group (30.4% vs 16.4%, $p=0.001$) (79). McPeake et al. found an OR of 1.67 for developing sepsis for their AUD patients (89). The same results were non-statistically confirmed in the study by Stewart et al: sepsis was more prevalent among the alcohol dependence group compared to the low-risk group (48.8% vs 38.9%, $p<0.163$) (113).

The study performed by Gacouin et al. found that at-risk drinkers (more than 5 drinks a week) were more prone to bacterial infections or VAP's than abstinent drinkers (respectively: hazard ratio 1.92, p=0.009 and a hazard ratio of 1.76, p=0.04). The percentage of sepsis was naturally higher among their at-risk group: 18% vs 8%, p<0.001 (80). Similar results were found in the study performed by de Wit et al. and found that 32% of their septic patients suffered from AUD (81).

4.3.6.7 Pneumonia

Respiratory infections were twice as likely to be among the alcoholic group (78). Similar results were found by Gacouin et al. and 65% of their at-risk drinkers were diagnosed with pneumonia, compared to 49% of their abstinent group (80). A third study done by Mahendra et al. in India found that alcoholism in the last year was a major risk factor for developing pneumonia in adults (adjusted OR (95% CI): 7.88 (2.04-30.41), p=0.003) (101).

Not specifically pneumonia, but pleural-pulmonary infections made up 37% of the non-at-risk drinkers, compared to 32% of the at-risk drinkers (p=0.4) (86). When looking at *Pseudomonas Aeruginosa* (ICUAP), alcohol abuse caused for a decreased chance of developing ICUAP in these patients (OR 0.49, p=0.052) (90).

4.3.6.8 Mechanical ventilation

The need for mechanical ventilation was found to be non-statistically higher for AUD septic patients compared to AUD negative septic patients (62% vs 59%, p=0.89). In the same study, the duration of ventilation was non-statistically non-different for both groups (4d vs 4d, p=0.59) (81). When looking at toxicology screens, Orsini et al found that 34% of their alcoholic patients needed mechanical ventilation (93). The alcohol misuse group In the study of Secombe et al. needed more ventilation: 30% vs 20% (p<0.01) (94). Walkey et al. found that their mechanical ventilation cohort had more moderate to heavy alcohol users (11% vs 4% in the no mechanical ventilation group) (99).

When looking at their alcohol–related admission, Geary et al. found that these patients needed longer ventilation (2d vs1d, p>0.005) (111). Christensen et al. found in contrast to this that their alcohol group needed less mechanical ventilation compared to the abstinent group (85).

4.3.6.9 ARDS

After evaluating the bronchoalveolar lavages of 24 patients, Burnham et al. found that sE-selectins were elevated in chronic alcohol abuse patients (defined by SMAST). These soluble E-selectin are an important step in the pathogenesis of ARDS (110).

4.3.6.10 ICU LOS and Hospital LOS

The ICU LOS was found to be shorter for the patients in the alcoholic group in the study by Uusaro et al. (78). A shorter ICU LOS for their AUD group was also found in the study by de Wit et al. (3d vs 5d, p=0.33) (81). Opposite results were found in the study of Gacouin et al., their at-risk drinking group had a longer ICU LOS and a relatively even long hospital LOS (respectively: 8d (4–15) vs 10d (5–22), p<0.05. 26d (16–42) 26d (12–43), p<0.05) (80). The hospital LOS was found to be shorter for the AUD group among septic patients in the study by de Wit et al. (8d vs 9d, p=0.82) (81). The ICU LOS was found to be higher for the alcohol misuse group in the Australian study (2.1d vs 1.9d; p<0.05) (94). Stewart et al also found that their alcohol dependence group had a longer ICU LOS compared to their low-risk group (9.9d vs 7.0d, p<0.020) (113).

Muhlberg et al. found that the ICU LOS was not higher in elderly alcoholic patients compared to younger alcoholic patients (119).

4.3.6.11 Mortality

ICU mortality was found to be higher among at-risk drinkers (23% vs 13%, p<0.05) (80). De Wit et al. confirmed non-statistically the same results: an ICU mortality of 23% among their AUD septic patients, compared to 19% mortality in the AUD negative group (p=0.74) (81).

Alcohol dependence was found in one study to be associated with a decreased hospital mortality among those without sepsis (OR: 0.94; 95% CI 0,72 - 1,24) and with an increased mortality among septic patients (OR: 1.46; 95% CI 1,01 – 2,11) (79). In a Spanish multicenter study was a strong association found (OR 2.92) between hospital mortality in septic patients and alcoholism (95%, CI 1.01-8.93, p=0.04) (120).

A higher 30-day mortality was found among the alcohol positive group (24.4% vs 19%) (83). In the study by Christensen et al. was the 30-day mortality was higher for the alcoholics (19.7% vs 33.6%) (85). When looking at 90d-mortality in patients with ALI, the severe alcohol-misuse group was more likely (36% vs 26) (121).

McPeake et al. found an higher chance for ICU mortality and hospital Mortality when looking at the 6-month mortality (2.28 OR for ICU mortality (p=0.012) and a 2.43 OR for hospital mortality (p=0.004) (89).

One year mortality was found to be lower for non-at risk drinkers (91, 104). The 3-year mortality was highest for the alcoholics with complications and higher AUDIT scores is associated with an increased 3-year mortality (OR: 1.06, p=0.07) (85, 97).

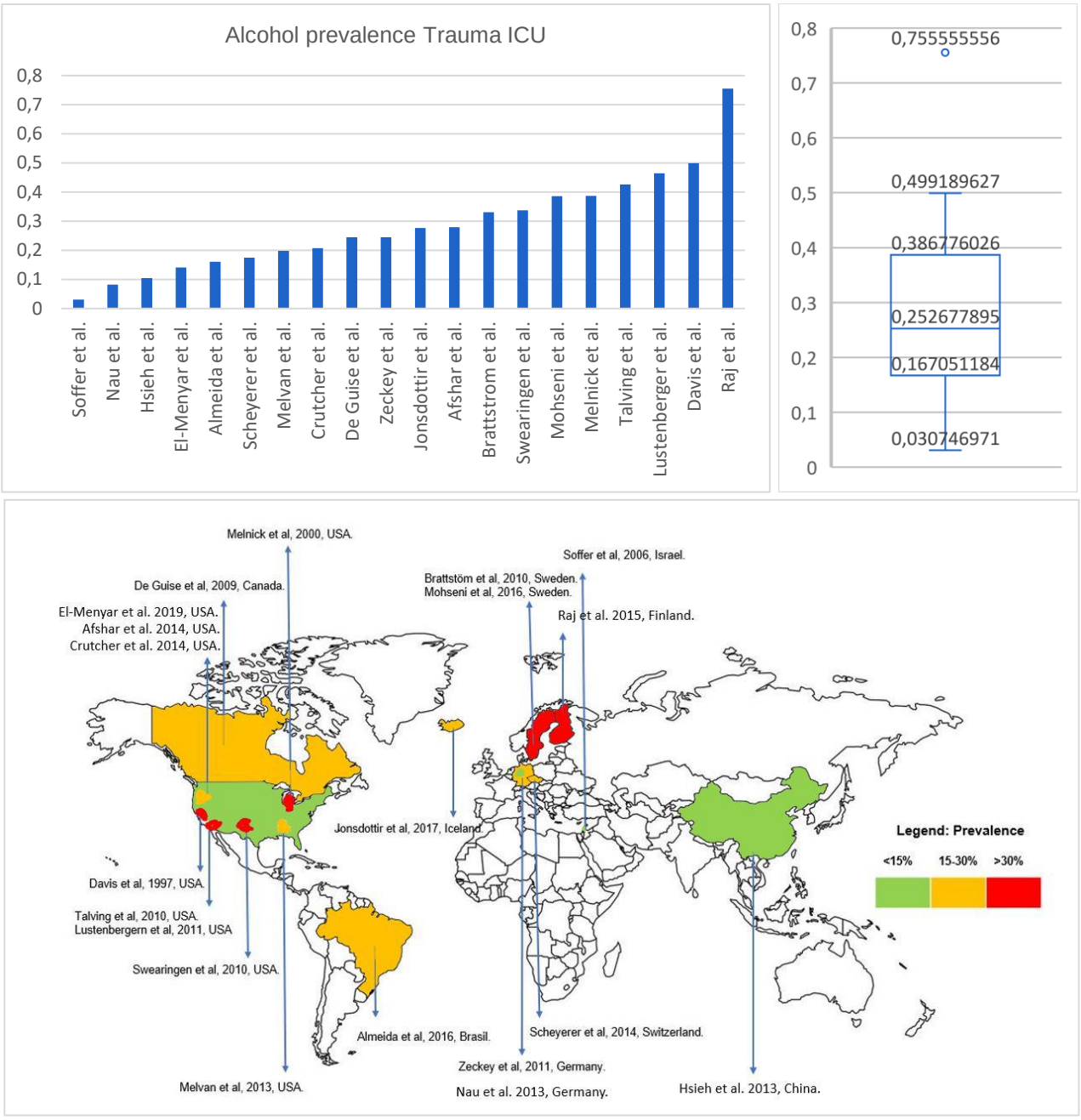
4.3.7 Trauma ICU

Study	Year	Country	Study Design	N	M/F	Alcohol definition
Davis et al.	1997	USA	Retrospective	1 234	-	BAC≥0,08mg/dl
Melnick et al.	2000	USA	Retrospective	496	65/35	DSM-III
Soffer et al.	2006	Israel	Retrospective	5529	74/26	BAC≥50 mg/dl
De Guise et al.	2009	Canada	Retrospective	60	-	Anamnesis
Brattstrom et al.	2010	Sweden	Prospective	154	-	Not defined
Swearingen et al.	2010	USA	Retrospective	8735	72/28	BAC≥10 mg/dl
Talving et al.	2010	USA	Prospective	815	85/15	BAC>80mg/dl
Hadjizacharia et al.	2011	USA	Matched-control	772	-	BAC>0 mg/dl
Lustenberger et al.	2011	USA	Retrospective	439	84/16	BAC>0mg/dl
Zeckey et al.	2011	Germany	Retrospective	437	-	BAC≥0,1%
Hsieh et al.	2013	China	Prospective	5738	73/27	BAC>0 mg/dl
Melvan et al.	2013	USA	Retrospective	111	92/8	BAC>0 mg/dl
Nau et al.	2013	Germany	Retrospective	9 821	-	Cirrhosis
Afshar et al.	2014	USA	Retrospective	26 305	-	BAC>0 mg/dl
Crutcher et al.	2014	USA	Retrospective	10 611	-	BAC>0 mg/dl
Jawa et al.	2014	USA-Canada	Retrospective	19 369	-	AWS
Scheyerer et al.	2014	Switzerland	Retrospective	383	76/24	BAC>0,5‰
Gustafson et al.	2015	USA	Retrospective	2 482	-	BAC>0 mg/dl
Raj et al.	2015	Helsinki	Retrospective	405	-	BAC>0 mg/dl
Almeida et al.	2016	Brazil	Prospective	87	-	Anamnesis
Mohseni et al.	2016	Sweden	Retrospective	352	77/23	BAC>0.072 mg/dl
Jonsdottir et al.	2016	Iceland	Retrospective	583	-	BAC>0 mg/dl
El-Menyar et al.	2019	USA-Qatar	Retrospective	681	97/3	BAC>0 mg/dl

Table 8. Overall study characteristics. Male to female ratio is in %.

4.3.7.1 Prevalence

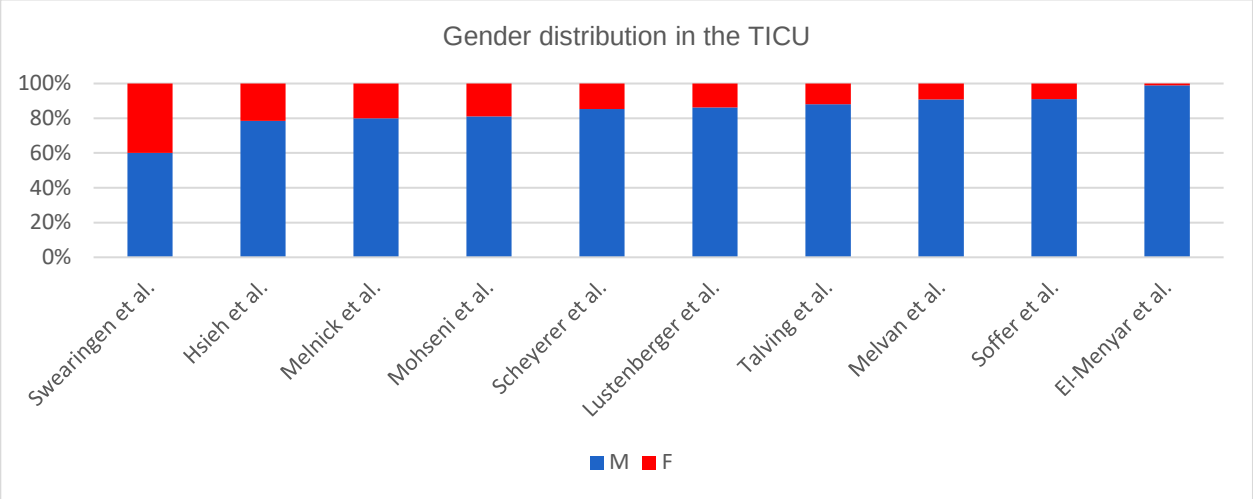
The alcohol prevalence starts at 3.1% and rises up to 75.6%. Median is 0.253 with an IQR of 0.220 (Bar chart, boxplot and world map 5).



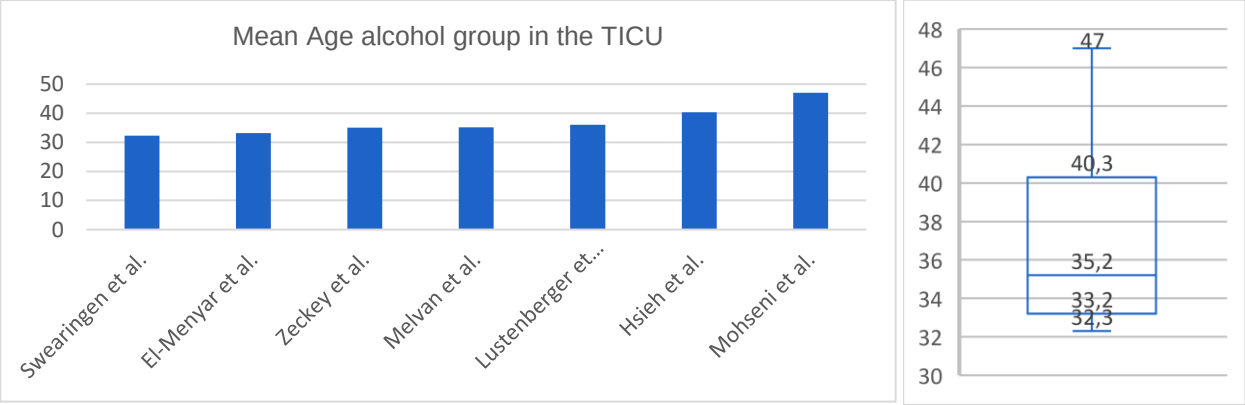
Bar chart, boxplot and world map 5. Alcohol prevalence TICU (122-141).

Afshar et al. found that in 26 305 trauma admissions, 1.9% of their BAC negative group (n=18 945) had chronic alcohol abuse and 23.9% of their BAC positive group (n=7 360) had chronic alcohol abuse (p<0.001) (134).

4.3.7.2 Gender and age



Bar chart 3. Gender distribution of the alcoholic group (123, 124, 127-129, 131, 132, 136, 139, 141).



Bar chart and boxplot 5. Mean age in years of the alcohol groups in the TICU. On the right is the boxplot displayed (127, 129-132, 139, 141).

4.3.7.3 Delirium

Alcohol withdrawal was found in 0.82% of 19 369 trauma admission spanning 10 years (142).

4.3.7.4 Liver Cirrhosis

Liver cirrhosis was found in 0.7% of the cases among the German Trauma Registry of the German Society for Trauma Surgery (133). When doing a matched-pair analysis, Nau et al. found that sepsis was more prevalent among their cirrhotic patients compared to their healthy trauma patients (6% vs 12%, p=0.20) (133).

4.3.7.5 Sepsis

The prevalence of sepsis was in two studies found to be lower among the alcohol group (129, 143). Zeckey et al. found an OR of 0.84 for sepsis (130). After doing a multivariate log regression analysis, Melvan et al. found an OR of 4.1 for ethanol use and developing infection. After performing

a Univariate logistic regression analysis Brattström et al. discovered that positive blood alcohol was a predictor of MOF (126).

4.3.7.6 Pneumonia

Two articles found a higher percentage of pneumonia among their BAC positive group in the Trauma ICU and two articles found less pneumonia in their BAC positive group compared to their control group (125, 128, 135, 143).

4.3.7.7 ARDS

Three articles reported on ARDS and 2 found a lower percentage of ARDS for their alcoholic group (12% vs 22% and 2.5 vs 3.4%) (128, 129). Afshar et al. found more ARDS among BAC-positive patients: 5.9% vs 5.3% (134).

4.3.7.8 Mechanical ventilation

Afshar et al. found a higher rate of mechanical ventilation among their BAC-positive group (28.0% vs 18.1%, $p<0.001$) (134). The group with a positive blood alcohol had had more ventilator days compared to their control group (135, 136).

4.3.7.9 ICU LOS and Hospital LOS

Five articles reported that their alcohol group had a shorter ICU LOS compared to their control group (122, 123, 127, 130, 139). Five articles reported a longer stay in the ICU for their BAC positive group (128, 129, 131, 133, 135). Five articles found a shorter hospital LOS for the BAC positive group (122, 127, 129, 130, 133). Five other articles discovered a longer hospital LOS for their alcohol group (123, 128, 131, 135, 139).

4.3.7.10 Mortality

A higher hospital mortality among the BAC+ group was reported by seven articles (127, 130, 131, 135, 136, 139, 143). A lower mortality among the alcohol group was reported by six articles (123, 128, 129, 137, 138, 141). A 6-month mortality was reported by Raj et al. and was found to be higher among the BAC=0 compared to BAC<2,3‰ or BAC≥2,3‰ (34% vs 18% vs 26%) (137). Gustafson et al. found that patients with a positive BAC+ and an elevated lactate and base deficit had a lower mortality and a shorter hospital LOS (144). A Swedish study calculated an OR of 1.9 for the mortality when using alcohol (CI 95% 0.77-4.8, p=0.15) and a 1-year mortality of 1.1 (CI 95% 0.55-2.3, p=0.7) (139).

4.4 META-ANALYSES

For the full list of meta-analyses this study refers to *Appendix F*. The table below shows a brief synopsis of the meta-analyses and subgroup-analysis.

Outcome	Studies	n	I^2	95% CI	P
Alcohol prevalence	**88**	**1 042 958**	**99.86%**	**0.284 [0.267, 0.346]**	P<0.0001
Burn Unit	13		97.15%	0.248 [0.190, 0.306]	P<0.0001
CCU	1		/	0.082 [0.060, 0.104]	P<0.0001
MICU	8		99.47%	0.105 [0.091, 0.120]	P<0.0001
SICU	7		99.48%	0.227 [0.030, 0.424]	P<0.0001
Mixed ICU	22		99.86%	0.334 [0.280, 0.388]	P<0.0001
TICU	20		99.8%	0.287 [0.227, 0.346]	P<0.0001
Age (MD)	**18**	**811 904**	**100%**	**-6.93 [-10.46, -3.39]**	P=0.0001
Burn Unit	2		0%	-1.26 [-6.12, 3.60]	P=0.61
CCU	1		/	/	P<0.0001
MICU	2		86%	-9.51 [-15.14, -3.89]	P<0.0001
SICU	3		81%	-3.82 [-5.44, -2.20]	P<0.0001
Mixed ICU	4		95%	-8.50 [-14.42, -2.57]	P=0.005
TICU	6		96%	-0.52 [-2.44, 1.40]	P=0.59
Male prevalence (RR)	**40**	**864 209**	**99%**	**1.23 [1.11, 1.36]**	**P<0.0001**
Burn Unit	7		62%	0.94 [0.84, 1.06]	P=0.31
MICU	3		99%	1.89 [0.85, 4.17]	P=0.12
SICU	3		71%	1.53 [1.27, 1.84]	P<0.0001
Mixed ICU	16		44%	1.29 [1.25, 1.32]	P<0.0001
TICU	11		99%	1.11 [0.93, 1.33]	P<0.0001
Delirium (OR)	**3**	**2000**	**98%**	**7.14 [0.58, 87.16]**	**P=0.12**
MICU	1		/	/	P<0.001
Mixed ICU	2		0%	2.37 [1.41, 3.97]	P=0.001

Sepsis (RR)	**12**	**809 951**	**93%**	**1.24 [0.90, 1.72]**	**P=0.19**
Burn Unit	2		0%	1.32 [0.67, 2.59]	P=0.42
MICU	1		/	0.71 [0.69, 0.74]	P<0.0001
SICU	1		/	9.50 [0.48, 188.48]	P=0.14
Mixed ICU	7		92%	1.21 [0.75, 1.95]	P<0.0001
TICU	1		/	2.02 [1.63, 2.51]	P<0.0001
Pneumonia	**12**	**800 096**	**96%**	**1.21 [0.88, 1.67]**	**P=0.24**
Burn Unit	1		-	0.74 [0.40, 1.36]	P=0.33
MICU	2		97%	1.10 [0.47, 2.59]	P=0.82
SICU	2		0%	2.92 [1.65, 5.19]	P=0.0002
Mixed ICU	3		89%	1.41 [0.84, 2.39]	P=0.20
TICU	4		75%	0.88 [0.49, 1.60]	P=0.68
ARDS	**5**	**28 441**	**0%**	**1.10 [0.99, 1.23]**	**P=0.07**
MICU	1		/	4.67 [0.43, 50.58]	P=0.21
Mixed ICU	1		/	0.90 [0.47, 1.73]	P=0.76
TICU	3		0%	1.11 [0.99, 1.23]	P=0.07
Mechanical ventilation					
Prevalence	**9**	**82 490**	**98%**	**1.53 [1.24, 1.87]**	**P<0.0001**
Burn Unit	1		/	1.50 [0.95, 2.38]	P=0.09
MICU	3		91%	1.30 [0.96, 1.75]	P=0.99
Mixed ICU	4		99%	1.66 [0.75, 3.65]	P=0.21
TICU	1		/	1.58 [1.51, 1.66]	P<0.0001
Days *	**3**	**10 748**	**93%**	**5.72 [-1.21, 12.65]**	**P=0.11**
Burn Unit	1		/	4.00 [-4.00, 12.00]	P=0.33
SICU	1		/	11.00 [7.67, 14.33]	P<0.0001
TICU	1		/	2.00 [1.37, 2.63]	P<0.0001
LOS					
ICU *	**14**	**38 175**	**100%**	**-0.35 [-13.91, 13.22]**	**P=0.96**

Burn Unit	2		27%	15.00 [7.04, 22.97]	P=0.0002
MICU	1		/	4.00 [2.48, 5.52]	P<0.0001
SICU	1		/	-0.31 [-1.11, 0.49]	P=0.45
Mixed ICU	1		/	-2.90 [-6.17, 0.37]	P=0.08
TICU	9		100%	-4.01 [-20.87, 12.84]	P=0.64
Hospital *	**13**	**38 421**	**98%**	**1.49 [0.14, 2.85]**	**P=0.03**
Burn Unit	2		59%	-5.11 [-16.74, 6.52]	P=0.39
SICU	2		98%	7.46 [-8.12, 23.04]	P=0.35
TICU	9		99%	0.91 [-0.54, 2.36]	P=0.22
Mortality					
30d	3	16 394	25%	1.70 [1.49, 1.94]	P<0.0001
1-year	3	1 861	92%	0.92 [0.50, 1.70]	P=0.79
ICU	9	9 498	87%	1.46 [1.07, 2.00]	P=0.02
Hospital Mortality	25	39 890	67%	1.13 [0.97, 1.30]	P=0.11

Table 9. Summary of the results of the meta-analyses.

5 Discussion

5.1 SUMMARY OF MAIN RESULTS

The results of this review and meta-analysis can give clinicians a global insight in the epidemiology and clinical outcomes of alcoholic patients in the ICU.

5.1.1 Primary outcomes

ICU Type	Median	IQR	Meta-analysis of proportions	
Burn Unit	27.0%	17%	24.8% [0.190, 0.306]	P<0.0001
CCU	-	-	8.2% [0.060, 0.104]	P<0.0001
MICU	20.0%	27.5%	10.5% [0.091, 0.120]	P<0.0001
SICU	15.0%	22.7%	22.7% [0.030, 0.424]	P<0.0001
Mixed ICU	29.0%	33.4%	33.4% [0.280, 0.388]	P<0.0001
TICU	27.0%	20.0%	28.7% [0.227, 0.346]	P<0.0001
Total	26.5%	20.0%	28.4% [0.267, 0.346]	P<0.0001

Table 10. Summary of median (IQR) and meta-analysis of proportions for the prevalence of alcohol use.

The alcohol prevalence was highest in a mixed ICU setting, followed by the TICU and the Burn Unit. This could be an indication that alcohol is more widely spread in non-specific ICU, but it is probably because the mixed ICU setting delivered more articles and consequently less selection bias. The high alcohol prevalence in the TICU could be explained by traffic accidents by intoxication of drivers and motorcyclists (145, 146). The high prevalence of alcohol in the Burn Unit could indicate that alcohol is often involved in burn accidents (e.g. barbecuing, smoking, campfires) (147).

5.1.2 Secondary outcomes

Alcohol users are younger compared to non-users (-6.93y, p=0.0001). Delirium is more prevalent among the drinking ICU population and seems more tenacious when people are more and longer drinking. In a mixed ICU setting alcohol using patients have an OR of 2.37 (p=0.001) for developing delirium. Not enough data was available to perform meta-analysis for the prevalence of cirrhosis or acute pancreatitis. More atypical pathogens seem to infect alcohol using patients (*Legionella Pneumophilia*, *Pneumocystis Pneumonia*, candidemia, but seemingly not for *Pseudomonas Aeruginosa*). For developing pneumonia, the SICU did deliver a statistical significant RR of 2.92 (p=0.0002). Alcohol leads to longer mechanical ventilation (RR 1.53, p<0.0001), longer hospital

LOS (1.49 days, p=0.03), and a higher 30d-mortality (RR 1.70, p<0.0001) and ICU mortality (RR 1.46, p=0.02).

5.2 Comparison with earlier research

The idea by Roberts et al. that one in five patients use alcohol harmfully could be confirmed by this systematic review (5). Some other review report a wide variance in prevalence from 10% up to 40% (3). The prevalence found in this review can narrow this range down to more or less a prevalence of 30% of alcohol use in the ICU. The trend that men drink more and are younger is confirmed by the meta-analysis in this study (albeit having a high heterogeneity) (1, 7). The theory that alcoholic or acutely intoxicated people are more susceptible to sepsis and ARDS found in other reviews or meta-analyses could not be statistically replicated in this meta-analysis (4, 29, 31).

In this meta-analysis the RR for sepsis was found having high heterogeneity and p=0.24. Only for the subgroup of the SICU did deliver a statistical significant RR of 2.92 (p= 0.0002). Multiple explanations could be proposed for these non-congruent findings. One reason therefore could be centered around the fact that this review did not differentiate between chronic alcoholics and acutely intoxicated patients and caused an incomparable study population. Chronic alcoholics could be more prone to alterations in their innate immune system for it induces NF-κB-mediated transcription of proinflammatory cytokines and genes. Whereas acute intoxication has mostly an effect on production of interleukins (148-150).

When looking at ARDS, this study found a non-statistically higher prevalence of ARDS among alcoholic patients (p=0.07). Tough earlier research showed a clear statistically higher chance of developing ARDS in alcoholics (3, 29). The cause of this difference is probably centered around the fact that this study was not critical enough in its definition of alcohol. Because the pathophysiology of ARDS is also fairly logical in alcoholic patients: their upper airway reflexes are impaired and could lead to more aspiration pneumonia's. This could lead to more pneumonia's and sepsis which can cause ARDS (4, 62). Mechanical ventilation is also more prevalent among alcoholics and is another risk factor for ARDS because of unintended alveolar damage (151).

5.3 Strengths and limitations: in vino veritas?

This study is a good starting point for the subject, but not the final answer to the question of alcohol use in the ICU. There are strengths, but mostly there are a lot of potential problems and limitation linked to this study.

One strength found in this study is the generalizability and broadness of the statistical data. The results found for the different subgroups of alcohol could give useful clinical info. But the broadness of the results is also its Achilles' heel as explained below.

A lot of problems and limitations of this study is centered around the broad definition of alcohol use accepted in this systematic review. One such problem is that the search has been done to wide in definition of alcohol presentation to get to-the-point answers and clear statistical evidence. There are a lot of standardized scales for defining alcohol, but often anamnesis was used in the articles or alcohol use was defined using pathologies (e.g. liver cirrhosis, delirium DSM-5).

This could mean that the results could be rather poor when it comes down to the comparability and could be the cause for high heterogeneity. It could have been better to limit the search to only one type of alcohol patients (e.g. liver cirrhosis, binge drinkers, SMAST-positive patients) than to look to the wider picture. But the starting point of this study was to get a broad an unlimited view on alcohol use in the ICU. Another problem with defining alcohol use and performing meta-analysis with different definitions for alcohol use is that some studies take BAC=0mg/dl as the control group, while other studies used for example low risk-drinkers as their control group. This could introduce two groups who are incomparable.

Another aspect that has to be taken in consideration is the response bias of patients when asked about their drinking pattern. In a trauma unit they evaluated self-reported drinking of patients with their BAC. They found that 7 out of 181 patients with a BAC>10mg/dl self-reported to not have been drinking (152). Underreporting is a factor that this review has not taken into account.

The risk of bias is reported as having medium risk tot low risk, but this is probably an understatement. The articles included are probably prone to more risk of bias.

Only one article about the Cardiac Intensive Care was found. One reason for lack of data about the cardiac intensive care unit could be that patients who are admitted to the cardiac intensive care unit do not reside for extended periods of time in that unit. Therefore there is not enough time to collect useful data about the patients.

A second item that was not assessed widely enough was delirium. Multiple explanations exist why the review did not deliver a lot of data. One of the most plausible is that the search was not sensitive enough for delirium or delirium tremens. One of the reason therefore is that alcoholic delirium was not translated into broad enough search terms: AWS for example. A second one is that there is not

yet much known about delirium prevalence in the ICU, though this explanation is rather unlikely because alcohol is known to be a reason for the development of delirium.

When it comes to geographic data, not much information was found about the continent Latin-America or Africa. Two explanations could be given. The first is that the search excluded Spanish articles, hence a lot of articles from Latin-America could be omitted. Another reason could be that in these continents intensive care is not as easy accessible and limited research is done in those ICU's. A cross-sectional research in Latin-America countries in 2017 found that the ICU's were lacking in ICU-nurses and technological resources were not widely available enough with mostly 7-14 ICU beds per hospital (153). In Africa the situation when it comes to ICU beds per capita is low and ranges from 0.1 bed per 100.00 people in Uganda to 9 beds per 100.000 people in South-Africa (154, 155).

A different aspect that has to be regarded is the formatting of the data. Most studies used median and IQR instead of mean and SD for reporting: age, LOS and mechanical ventilation days. These data could not be used for meta-analysis which could cause a involuntarily reporting bias. This study also did not recalculate this type of data for it could introduce errors.

5.4 Recommendations

More research could be done to get more clear statistical data about the different definitions of alcohol use in the ICU.

6 Conclusion

After performing a systematic review and meta-analysis of 100 articles about epidemiology of alcohol use in the ICU, this study comes to the conclusion that alcohol use in the ICU is relatively prevalent (28.4%, $p<0.0001$). Clinicians should be attentive to alcohol use in younger, male patients who require mechanical ventilation (RR 1.53, $p<0.0001$). Alcohol use leads to longer hospital LOS (1.49 days, $p=0.03$). On top of this alcoholic patients have a significant higher 30d-mortality (RR 1.70, $p<0.0001$) and ICU mortality (RR 1.46, $p=0.02$). In a mixed ICU setting alcohol using patients have an OR of 2.37 ($p=0.001$) for developing delirium. In a SICU alcohol using patients are more at risk of developing sepsis (RR of 2.92, $p=0.0002$). When a patient is using alcohol, clinicians could expect to encounter more atypical pathogens. It could be that the data would vary when using stricter definitions of alcohol use. The articles are probably prone to high risk bias and more research is required to get more concise and more clear statistical evidence.

7 Reference list

1. Connor JP, Haber PS, Hall WD. Alcohol use disorders. Lancet. 2016;387(10022):988-98.
2. Carvalho AF, Heilig M, Perez A, Probst C, Rehm J. Alcohol use disorders. Lancet. 2019;394(10200):781-92.
3. Moss M, Burnham EL. Alcohol abuse in the critically ill patient. Lancet. 2006;368(9554):2231-42.
4. Mehta AJ. Alcoholism and critical illness: A review. World J Crit Care Med. 2016;5(1):27-35.
5. Roberts E, Morse R, Epstein S, Hotopf M, Leon D, Drummond C. The prevalence of wholly attributable alcohol conditions in the United Kingdom hospital system: a systematic review, meta-analysis and meta-regression. Addiction (Abingdon, England). 2019;114(10):1726-37.
6. Westerhausen D, Perkins AJ, Conley J, Khan BA, Farber M. Burden of Substance Abuse-Related Admissions to the Medical ICU. Chest. 2019.
7. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015;72(8):757-66.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC2013.
9. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. Jama. 2018;320(8):815-24.
10. Wilsnack RW, Wilsnack SC, Gmel G, Kantor LW. Gender Differences in Binge Drinking. Alcohol Res. 2018;39(1):57-76.
11. Rehm J, Allamani A, Elekes Z, Jakubczyk A, Manthey J, Probst C, et al. Alcohol dependence and treatment utilization in Europe - a representative cross-sectional study in primary care. BMC Fam Pract. 2015;16:90.
12. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th Revision). 2018.
13. Global status report on alcohol and health. Geneva: World Health Organization; 2018.
14. Weisner C, Matzger H, Kaskutas LA. How important is treatment? One-year outcomes of treated and untreated alcohol-dependent individuals. Addiction (Abingdon, England). 2003;98(7):901-11.
15. Testino G, Leone S, Borro P. Treatment of alcohol dependence: recent progress and reduction of consumption. Minerva Med. 2014;105(6):447-66.
16. Norberg A, Jones AW, Hahn RG, Gabrielsson JL. Role of variability in explaining ethanol pharmacokinetics: research and forensic applications. Clin Pharmacokinet. 2003;42(1):1-31.
17. Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med. 1990;322(2):95-9.
18. Palmer BF, Clegg DJ. Electrolyte Disturbances in Patients with Chronic Alcohol-Use Disorder. N Engl J Med. 2017;377(14):1368-77.
19. Dixit D, Endicott J, Burry L, Ramos L, Yeung SY, Devabhakthuni S, et al. Management of Acute Alcohol Withdrawal Syndrome in Critically Ill Patients. Pharmacotherapy. 2016;36(7):797-822.
20. Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. Jop. 2009;10(4):387-92.
21. Goldacre MJ, Roberts SE. Hospital admission for acute pancreatitis in an English population, 1963-98: database study of incidence and mortality. Bmj. 2004;328(7454):1466-9.
22. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. Hepatology (Baltimore, Md). 1997;25(1):108-11.
23. Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev. 2010;29(4):437-45.
24. Mainerova B, Prasko J, Latalova K, Axmann K, Cerna M, Horacek R, et al. Alcohol withdrawal delirium - diagnosis, course and treatment. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015;159(1):44-52.
25. Napolitano LM. Sepsis 2018: Definitions and Guideline Changes. Surg Infect (Larchmt). 2018;19(2):117-25.

26. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med. 2014;2(5):380-6.
27. Joshi PC, Guidot DM. The alcoholic lung: epidemiology, pathophysiology, and potential therapies. Am J Physiol Lung Cell Mol Physiol. 2007;292(4):L813-23.
28. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. Jama. 2016;315(8):788-800.
29. Simou E, Leonardi-Bee J, Britton J. The Effect of Alcohol Consumption on the Risk of ARDS A Systematic Review and Meta-Analysis. Chest. 2018;154(1):58-68.
30. Faresjo T, Faresjo A. To match or not to match in epidemiological studies--same outcome but less power. Int J Environ Res Public Health. 2010;7(1):325-32.
31. Moss M. Epidemiology of sepsis: race, sex, and chronic alcohol abuse. Clin Infect Dis. 2005;41 Suppl 7:S490-7.
32. Koskela A, Liisanantti JH, Koskenkari J, Ohtonen P, Mäntyvaara T, Ala-Kokko T. Alcohol and other substance abuse in trauma patients admitted to ICU in Northern Finland. Journal of Substance Use. 2018;23(1):14-9.
33. Strasen L. Acute alcohol withdrawal syndrome in the critical care unit. Crit Care Nurse. 1982;2(6):24-6, 30-1.
34. Vazquezbarquero JL, Gaite L, Diezmanrique JF, Alvarez C, Herrera S, Vazquezbarquero A. THE CONTRIBUTION OF ALCOHOL-INTOXICATION TO HEAD-INJURIES. Eur J Psychiat. 1991;5(4):216-23.
35. Bernstein L, Jacobsberg L, Ashman T, Musagni G, Goodwin CW, Perry S. Detection of alcoholism among burn patients. Hosp Community Psychiatry. 1992;43(3):255-6.
36. Furst S, Habscheid W. PATIENTS ADMITTED TO A MEDICAL INTENSIVE-CARE UNIT WITH ACUTE-POISONING. Dtsch Med Wochenschr. 1993;118(23):849-53.
37. Henderson A, Wright M, Pond SM. Experience with 732 acute overdose patients admitted to an intensive care unit over six years. Med J Aust. 1993;158(1):28-30.
38. Fuller MG. ALCOHOL-USE AND INJURY SEVERITY IN TRAUMA PATIENTS. Journal of Addictive Diseases. 1995;14(1):47-54.
39. Kaufmann P, Hofmann G, Smolle KH, Lueger A, Pieber T, Brunner G, et al. Intensive care management of acute pancreatitis: recognition of patients at high risk of developing severe or fatal complications. Wien Klin Wochenschr. 1996;108(1):9-15.
40. Moss M, Bucher B, Moore FA, Moore EE, Parsons PE. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. Jama. 1996;275(1):50-4.
41. Spies CD, Neuner B, Neumann T, Blum S, Muller C, Rommelspacher H, et al. Intercurrent complications in chronic alcoholic men admitted to the intensive care unit following trauma. Intensive Care Med. 1996;22(4):286-93.
42. Cuny J, Chagnon JL, Lambiotte F. Prognosis of severe community-acquired pneumonia in alcoholic patients hospitalised in intensive care. Presse Med. 2003;32(25):1162-4.
43. Cruz JPS, Punjabi C, Lippmann M. Outcomes of Mechanically Ventilated Liver Failure Patients Admitted to the Intensive Care Unit. Clinical Pulmonary Medicine. 2016;23(6):252-7.
44. Mostafa SM, Murthy BV. Alcohol-associated admissions to an adult intensive care unit: an audit. Eur J Anaesthesiol. 2002;19(3):193-6.
45. Zauner C, Schneeweiss B, Kranz A, Klos H, Gendo A, Ratheiser K, et al. Heavy chronic alcohol abuse has no additional adverse effect on the function of extrahepatic organs and ICU mortality in patients with liver cirrhosis. Wien Klin Wochenschr. 1999;111(19):810-4.
46. Moore EC, Padiglione AA, Wasiak J, Paul E, Cleland H. Candida in burns: risk factors and outcomes. J Burn Care Res. 2010;31(2):257-63.
47. Laughon SL, Gaynes BN, Chrisco LP, Jones SW, Williams FN, Cairns BA, et al. Burn recidivism: a 10-year retrospective study characterizing patients with repeated burn injuries at a large tertiary referral burn center in the United States. Burns Trauma. 2019;7:10.
48. Holmes WJM, Hold P, James I. Alcohol and burns - Impact on a regional burns centre. Burns. 2009;35:S10-S1.
49. Griffin R, Poe AM, Cross JM, Rue LW, 3rd, McGwin G, Jr. The association between blood alcohol level and infectious complications among burn patients. J Burn Care Res. 2009;30(3):395-9.

50. Klifto KM, Quiroga L, Hultman CS. Substance use and inhalation injury in adult burn patients: retrospective study of the impact on outcomes. Burns Trauma. 2019;7:15.
51. McGill V, Kowal-Vern A, Fisher SG, Kahn S, Gamelli RL. The impact of substance use on mortality and morbidity from thermal injury. J Trauma. 1995;38(6):931-4.
52. Sveen J, Oster C. Alcohol Consumption After Severe Burn: A Prospective Study. Psychosomatics. 2015;56(4):390-6.
53. Davis CS, Esposito TJ, Palladino-Davis AG, Rychlik K, Gamelli RL, Kovacs EJ. Implications of alcohol intoxication at the time of burn and smoke inhalation injury: An epidemiologic and clinical analysis. Journal of Burn Care and Research. 2012;33(2):S201.
54. Daffue B, Moolman D, Ferreira S, Roos L, Schoeman L, Smit SJ, et al. The causes of burn wounds among adult patients treated at Pelonomi Tertiary Hospital, Bloemfontein. S Afr J Surg. 2018;56(3):31-6.
55. Haum A, Perbix W, Hack HJ, Stark GB, Spilker G, Doehn M. Alcohol and drug abuse in burn injuries. Burns. 1995;21(3):194-9.
56. Jones JD, Barber B, Engrav L, Heimbach D. Alcohol use and burn injury. J Burn Care Rehabil. 1991;12(2):148-52.
57. Silver GM, Albright JM, Schermer CR, Halerz M, Conrad P, Ackerman PD, et al. Adverse clinical outcomes associated with elevated blood alcohol levels at the time of burn injury. J Burn Care Res. 2008;29(5):784-9.
58. Palmu R, Partonen T, Suominen K, Vuola J, Isometsa E. Alcohol use and smoking in burn patients at the Helsinki Burn Center. Burns. 2018;44(1):158-67.
59. Holmes WJ, Hold P, James MI. The increasing trend in alcohol-related burns: it's impact on a tertiary burn centre. Burns. 2010;36(6):938-43.
60. Azarasa M, Azarfarin R, Changizi A, Alizadehasl A. Substance use among Iranian cardiac surgery patients and its effects on short-term outcome. Anesth Analg. 2009;109(5):1553-9.
61. Marik P, Mohedin B. Alcohol-related admissions to an inner city hospital intensive care unit. Alcohol Alcohol. 1996;31(4):393-6.
62. Moss M, Parsons PE, Steinberg KP, Hudson LD, Guidot DM, Burnham EL, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Critical care medicine. 2003;31(3):869-77.
63. de Wit M, Wan SY, Gill S, Jenvey WI, Best AM, Tomlinson J, et al. Prevalence and impact of alcohol and other drug use disorders on sedation and mechanical ventilation: A retrospective study. BMC Anesthesiology. 2007;7.
64. Nagari N, Suresh Babu M. Assessment of risk factors and precipitating factors of delirium in patients admitted to intensive care unit of a tertiary care hospital. British Journal of Medical Practitioners. 2019;12(2).
65. Touray S, Newstein MC, Lui JK, Harris M, Knox K. Legionella pneumophila cases in a community hospital: A 12-month retrospective review. SAGE Open Med. 2014;2:2050312114554673.
66. Rentsch CT, Tate JP, Steel T, Butt AA, Gibert CL, Huang L, et al. Medical Intensive Care Unit Admission Among Patients With and Without HIV, Hepatitis C Virus, and Alcohol-Related Diagnoses in the United States: A National, Retrospective Cohort Study, 1997-2014. J Acquir Immune Defic Syndr. 2019;80(2):145-51.
67. Lankisch PG, Assmus C, Pflichthofer D, Struckmann K, Lehnick D. Which etiology causes the most severe acute pancreatitis? Int J Pancreatol. 1999;26(2):55-7.
68. Chen CY, Wu CJ, Pan CF, Chen HH, Chen YW. Influence of Age on Critically Ill Patients with Cirrhosis. International Journal of Gerontology. 2015;9(4):233-8.
69. de Wit M, Best AM, Gennings C, Burnham EL, Moss M. Alcohol use disorders increase the risk for mechanical ventilation in medical patients. Alcohol Clin Exp Res. 2007;31(7):1224-30.
70. Moss M, Parsons PE, Steinberg KP, Hudson LD, Guidot DM, Burnham EL, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Critical Care Medicine. 2003;31(3):869-77.
71. Maxson PM, Schultz KL, Berge KH, Lange CM, Schroeder DR, Rummans TA. Probable alcohol abuse or dependence: a risk factor for intensive-care readmission in patients undergoing elective vascular and thoracic surgical procedures. Mayo Perioperative Outcomes Group. Mayo Clin Proc. 1999;74(5):448-53.

72. Delgado-Rodríguez M, Gómez-Ortega A, Mariscal-Ortiz M, Palma-Pérez S, Sillero-Arenas M. Alcohol drinking as a predictor of intensive care and hospital mortality in general surgery: A prospective study. Addiction. 2003;98(5):611-6.
73. Paull DE, Updyke GM, Davis CA, Adebonojo SA. Complications and long-term survival for alcoholic patients with resectable lung cancer. Am J Surg. 2004;188(5):553-9.
74. Lowery EM, Yong M, Cohen A, Joyce C, Kovacs EJ. Recent alcohol use prolongs hospital length of stay following lung transplant. Clin Transplant. 2018;32(6):e13250.
75. Shin YH, Yoon JS, Jeon HJ, Kim YB, Kim YS, Park JY. Postoperative delirium in elderly patients with critical limb ischemia undergoing major leg amputation: a retrospective study. Korean J Anesthesiol. 2018;71(4):311-6.
76. Horacek R, Krnacova B, Prasko J, Latalova K. Delirium as a complication of the surgical intensive care. Neuropsychiatric Disease and Treatment. 2016;12:2425-34.
77. Rubinsky AD, Bishop MJ, Maynard C, Henderson WG, Hawn MT, Harris AH, et al. Postoperative risks associated with alcohol screening depend on documented drinking at the time of surgery. Drug Alcohol Depend. 2013;132(3):521-7.
78. Uusaro A, Parviainen I, Tenhunen JJ, Ruokonen E. The proportion of intensive care unit admissions related to alcohol use: a prospective cohort study. Acta anaesthesiologica Scandinavica. 2005;49(9):1236-40.
79. O'Brien JM, Lu B, Ali NA, Martin GS, Aberegg SK, Marsh CB, et al. Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients. Critical Care Medicine. 2006;35(2):345-50.
80. Gacouin A, Legay F, Camus C, Volatron AC, Barbarot N, Donnio PY, et al. At-risk drinkers are at higher risk to acquire a bacterial infection during an intensive care unit stay than abstinent or moderate drinkers. Critical Care Medicine. 2008;36(6):1735-41.
81. de Wit M, Wiaterek GK, Gray ND, Goulet KE, Best AM, Clore JN, et al. Relationship between alcohol use disorders, cortisol concentrations, and cytokine levels in patients with sepsis. Crit Care. 2010;14(6):R230.
82. Lam SM, Lau AC, Yan WW. Over 8 years experience on severe acute poisoning requiring intensive care in Hong Kong, China. Hum Exp Toxicol. 2010;29(9):757-65.
83. McKenny M, O'Beirne S, Fagan C, O'Connell M. Alcohol-related admissions to an intensive care unit in Dublin. Ir J Med Sci. 2010;179(3):405-8.
84. Singh O, Javeri Y, Juneja D, Gupta M, Singh G, Dang R. Profile and outcome of patients with acute toxicity admitted in intensive care unit: Experiences from a major corporate hospital in urban India. Indian J Anaesth. 2011;55(4):370-4.
85. Christensen S, Johansen MB, Pedersen L, Jensen R, Larsen KM, Larsson A, et al. Three-year mortality among alcoholic patients after intensive care: a population-based cohort study. Crit Care. 2012;16(1):R5.
86. Gacouin A, Roussel M, Gros A, Sauvadet E, Uhel F, Chimot L, et al. Chronic alcohol exposure, infection, extended circulating white blood cells differentiated by flow cytometry and neutrophil CD64 expression: A prospective, descriptive study of critically ill medical patients. Annals of Intensive Care. 2012;2(1):1-10.
87. Gacouin A, Tadie JM, Uhel F, Sauvadet E, Fillâtre P, Letheulle J, et al. At-risk drinking is independently associated with ICU and one-year mortality in critically ill nontrauma patients. Critical Care Medicine. 2014;42(4):860-7.
88. Larkin CM, Fagan C. Significant reduction in alcohol-related admissions to an intensive care unit in Dublin. Ir J Med Sci. 2015;184(3):697-700.
89. McPeake J, Shaw M, O'Neill A, Puxty A, Forrest E, Quasim T, et al. Alcohol related admissions to ICU: An 18 month prospective cohort study. Critical Care Medicine. 2014;42(12):A1459.
90. Fernandez-Barat L, Ferrer M, De Rosa F, Gabarrus A, Esperatti M, Terraneo S, et al. Intensive care unit-acquired pneumonia due to Pseudomonas aeruginosa with and without multidrug resistance. J Infect. 2017;74(2):142-52.
91. Hietanen S, Ala-Kokko T, Ohtonen P, Käkelä R, Niemelä S, Liisanantti JH. Treatment Profile and 1-Year Mortality Among Nontraumatic Intensive Care Unit Patients With Alcohol-Related Health Problems. Journal of Intensive Care Medicine. 2017.

92. Liisanantti JH, Kakela R, Raatiniemi LV, Ohtonen P, Hietanen S, Ala-Kokko TI. Has the income of the residential area impact on the use of intensive care? Acta anaesthesiologica Scandinavica. 2017;61(7):804-12.
93. Orsini J, Din N, Elahi E, Gomez A, Rajayer S, Malik R, et al. Clinical and epidemiological characteristics of patients with acute drug intoxication admitted to ICU. J Community Hosp Intern Med Perspect. 2017;7(4):202-7.
94. Secombe PJ, Stewart PC. The impact of alcohol-related admissions on resource use in critically ill patients from 2009 to 2015: an observational study. Anaesth Intensive Care. 2018;46(1):58-66.
95. Ng F. Ten-year profile of acute poisoning patients presenting to an Accident and Emergency Department requiring intensive care in a regional hospital of Hong Kong. Hong Kong Journal of Emergency Medicine. 2019;26(1):3-14.
96. Tollisen KH, Bjerva M, Heyerdahl F, Jacobsen D. Substance abuse as co-morbidity factor in mechanically ventilated intensive care patients. Intensive Care Medicine Experimental. 2017;5(2).
97. Uljas E, Jalkanen V, Kuitunen A, Hynninen M, Hästbacka J. Prevalence of risk—drinking in critically ill patients, screened with carbohydrate-deficient transferrin and AUDIT-C score: A retrospective study. Acta Anaesthesiologica Scandinavica. 2019.
98. Fuchs L, Chronaki CE, Park S, Novack V, Baumfeld Y, Scott D, et al. ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive Care Med. 2012;38(10):1654-61.
99. Walkey AJ, Pencina KM, Knox D, Kuttler KG, D'Agostino RB, Sr., Benjamin EJ, et al. Five-Year Risk of Mechanical Ventilation in Community-Dwelling Adults: The Framingham-Intermountain Anticipating Life Support Study. J Am Geriatr Soc. 2015;63(10):2082-8.
100. Faria LC, Ichai P, Saliba F, Benhamida S, Antoun F, Castaing D, et al. Pneumocystis pneumonia: an opportunistic infection occurring in patients with severe alcoholic hepatitis. Eur J Gastroenterol Hepatol. 2008;20(1):26-8.
101. Mahendra M, Jayaraj BS, Limaye S, Chaya SK, Dhar R, Mahesh PA. Factors influencing severity of community-acquired pneumonia. Lung India. 2018;35(4):284-9.
102. Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for delirium in intensive care patients: a prospective cohort study. Crit Care. 2009;13(3):R77.
103. Lone NI, Lee R, Walsh TS. Long-Term Mortality and Hospital Resource Use in ICU Patients With Alcohol-Related Liver Disease. Critical Care Medicine. 2019;47(1):23-32.
104. Gacouin A, Tadie JM, Uhel F, Sauvadet E, Fillatre P, Letheulle J, et al. At-Risk Drinking Is Independently Associated With ICU and One-Year Mortality in Critically Ill Nontrauma Patients. Critical Care Medicine. 2014;42(4):860-7.
105. Sandiumenge A, Torrado H, Muñoz T, Alonso M, Jiménez MJ, Alonso J, et al. Impact of harmful use of alcohol on the sedation of critical patients on mechanical ventilation: A multicentre prospective, observational study in 8 Spanish intensive care units. Medicina Intensiva. 2016;40(4):230-7.
106. Stewart D, Kinsella J, McPeake J, Quasim T, Puxty A. The influence of alcohol abuse on agitation, delirium and sedative requirements of patients admitted to a general intensive care unit. J Intensive Care Soc. 2019;20(3):208-15.
107. McPeake JM, Shaw M, O'Neill A, Forrest E, Puxty A, Quasim T, et al. Do alcohol use disorders impact on long term outcomes from intensive care? Crit Care. 2015;19:185.
108. Tollisen KH, Bjerva M, Hadley CL, Dahl GT, Hogvall LM, Sandvik L, et al. Substance abuse-related admissions in a mixed Norwegian intensive care population. Acta anaesthesiologica Scandinavica. 2019.
109. Stehman CR, Moromizato T, McKane CK, Mogensen KM, Gibbons FK, Christopher KB. Association between blood alcohol concentration and mortality in critical illness. J Crit Care. 2015;30(6):1382-9.
110. Burnham EL, Moss M, Harris F, Brown LA. Elevated plasma and lung endothelial selectin levels in patients with acute respiratory distress syndrome and a history of chronic alcohol abuse. Critical care medicine. 2004;32(3):675-9.
111. Geary T, O'Brien P, Ramsay S, Cook B. A national service evaluation of the impact of alcohol on admissions to Scottish intensive care units. Anaesthesia. 2012;67(10):1132-7.
112. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med. 2007;33(1):66-73.
113. Stewart RB, Forgnone M, May FE, Forbes J, Cluff LE. Epidemiology of acute drug intoxications: patient characteristics, drugs, and medical complications. Clin Toxicol. 1974;7(5):513-30.

114. Kanova M, Sklienka P, Roman K, Burda M, Janoutova J. Incidence and risk factors for delirium development in ICU patients - a prospective observational study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2017;161(2):187-96.
115. Levesque E, Hoti E, Azoulay D, Ichai P, Habouchi H, Castaing D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. J Hepatol. 2012;56(1):95-102.
116. McPhail MJW, Parrott F, Wendon JA, Harrison DA, Rowan KA, Bernal W. Incidence and Outcomes for Patients With Cirrhosis Admitted to the United Kingdom Critical Care Units. Critical care medicine. 2018;46(5):705-12.
117. Kulkarni S, Sharma M, Rao PN, Gupta R, Reddy DN. Acute on Chronic Liver Failure-In-Hospital Predictors of Mortality in ICU. J Clin Exp Hepatol. 2018;8(2):144-55.
118. Samanta J, Dhaka N, Gupta P, Singh AK, Yadav TD, Gupta V, et al. Comparative study of the outcome between alcohol and gallstone pancreatitis in a high-volume tertiary care center. JGH Open. 2019;3(4):338-43.
119. Muhlberg W, Becher K, Heppner HJ, Wicklein S, Sieber C. Acute poisoning in old and very old patients: a longitudinal retrospective study of 5883 patients in a toxicological intensive care unit. Z Gerontol Geriatr. 2005;38(3):182-9.
120. Blanco J, Muriel-Bombin A, Sagredo V, Taboada F, Gandia F, Tamayo L, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Crit Care. 2008;12(6):R158.
121. Clark BJ, Williams A, Feemster LMC, Bradley KA, MacHt M, Moss M, et al. Alcohol screening scores and 90-day outcomes in patients with acute lung injury. Critical Care Medicine. 2013;41(6):1518-25.
122. Davis JW, Kaups KL, Parks SN. Effect of alcohol on the utility of base deficit in trauma. J Trauma-Injury Infect Crit Care. 1997;43(3):507-10.
123. Melnick DM, Maio RF, Blow FC, Hill EM. Does acute alcohol ingestion and/or chronic alcohol use among motor vehicle crash victims lead to a more complicated hospital course? Annu Proc Assoc Adv Automot Med. 2000;44:429-43.
124. Soffer D, Zmora O, Klausner JB, Szold O, Givon A, Halpern P, et al. Alcohol use among trauma victims admitted to a level I trauma center in Israel. Isr Med Assoc J. 2006;8(2):98-102.
125. De Guise E, Leblanc J, Dagher J, Lamoureux J, Al Jishi A, Maleki M, et al. Early outcome in patients with traumatic brain injury, pre-injury alcohol abuse and intoxication at time of injury. Brain Injury. 2009;23(11):853-65.
126. Brattstrom O, Granath F, Rossi P, Oldner A. Early predictors of morbidity and mortality in trauma patients treated in the intensive care unit. Acta anaesthesiologica Scandinavica. 2010;54(8):1007-17.
127. Swearingen A, Ghaemmaghami V, Loftus T, Swearingen CJ, Salisbury H, Gerkin RD, et al. Extreme blood alcohol level is associated with increased resource use in trauma patients. Am Surg. 2010;76(1):20-4.
128. Talving P, Plurad D, Barmparas G, DuBose J, Inaba K, Lam L, et al. Isolated Severe Traumatic Brain Injuries: Association of Blood Alcohol Levels With the Severity of Injuries and Outcomes. J Trauma-Injury Infect Crit Care. 2010;68(2):357-62.
129. Lustenberger T, Inaba K, Barmparas G, Talving P, Plurad D, Lam L, et al. Ethanol intoxication is associated with a lower incidence of admission coagulopathy in severe traumatic brain injury patients. J Neurotrauma. 2011;28(9):1699-706.
130. Zeckey C, Dannecker S, Hildebrand F, Mommsen P, Scherer R, Probst C, et al. Alcohol and multiple trauma: is there an influence on the outcome? Alcohol. 2011;45(3):245-51.
131. Hsieh CH, Su LT, Wang YC, Fu CY, Lo HC, Lin CH. Does Alcohol Intoxication Protect Patients from Severe Injury and Reduce Hospital Mortality? The Association of Alcohol Consumption with the Severity of Injury and Survival in Trauma Patients. Am Surg. 2013;79(12):1289-94.
132. Melvan JN, Mooney J, Bagby GJ, Hunt JP, Batson R, Greiffenstein P. Drug and alcohol use complicate traumatic peripheral vascular injury. J Trauma Acute Care Surg. 2013;75(2):258-65.
133. Nau C, Wutzler S, Dorr H, Lehnert M, Lefering R, Laurer H, et al. Liver cirrhosis but not alcohol abuse is associated with impaired outcome in trauma patients - A retrospective, multicentre study. Injury-Int J Care Inj. 2013;44(5):661-6.
134. Afshar M, Smith GS, Terrin ML, Barrett M, Lissauer ME, Mansoor S, et al. Blood alcohol content, injury severity, and adult respiratory distress syndrome. J Trauma Acute Care Surg. 2014;76(6):1447-55.
135. Crutcher CL, 2nd, Ugiliweneza B, Hodes JE, Kong M, Boakye M. Alcohol intoxication and its effects on traumatic spinal cord injury outcomes. J Neurotrauma. 2014;31(9):798-802.

136. Scheyerer MJ, Dutschler J, Billeter A, Zimmermann SM, Sprengel K, Werner CML, et al. Effect of elevated serum alcohol level on the outcome of severely injured patients. Emerg Med J. 2014;31(10):813-7.
137. Raj R, Skrifvars MB, Kivisaari R, Hernesniemi J, Lappalainen J, Siironen J. Acute alcohol intoxication and long-term outcome in patients with traumatic brain injury. J Neurotrauma. 2015;32(2):95-100.
138. Almeida KJ, Rodrigues AB, Lemos LE, Oliveira MCF, Gandara BF, Lopes Rda R, et al. Hemotransfusion and mechanical ventilation time are associated with intra-hospital mortality in patients with traumatic brain injury admitted to intensive care unit. Arq Neuropsiquiatr. 2016;74(8):644-9.
139. Mohseni S, Bellander BM, Riddez L, Talving P, Thelin EP. Positive blood alcohol level in severe traumatic brain injury is associated with better long-term functional outcome. Brain injury. 2016;30(10):1256-60.
140. Jonsdottir GM, Lund SH, Snorradottir B, Karason S, Olafsson IH, Reynisson K, et al. A population-based study on epidemiology of intensive care unit treated traumatic brain injury in Iceland. Acta anaesthesiologica Scandinavica. 2017;61(4):408-17.
141. El-Menyar A, Consunji R, Asim M, Mekkodathil A, Latifi R, Smith G, et al. Traumatic brain injury in patients screened for blood alcohol concentration based on the mechanism of injury. Brain Injury. 2019;33(4):419-26.
142. Jawa RS, Stothert JC, Shostrom VK, Yetter DL, Templin HR, Cemaj SK, et al. Alcohol withdrawal syndrome in admitted trauma patients. Am J Surg. 2014;208(5):781-7.
143. Hadjizacharia P, O'Keeffe T, Plurad DS, Green DJ, Brown CV, Chan LS, et al. Alcohol exposure and outcomes in trauma patients. Eur J Trauma Emerg Surg. 2011;37(2):169-75.
144. Gustafson ML, Hollosi S, Chumbe JT, Samanta D, Modak A, Bethea A. The effect of ethanol on lactate and base deficit as predictors of morbidity and mortality in trauma. Am J Emerg Med. 2015;33(5):607-13.
145. Kalsi J, Selander T, Tervo T. Alcohol policy and fatal alcohol-related crashes in Finland 2000-2016. Traffic Inj Prev. 2018;19(5):476-9.
146. Christophersen AS, Gjerde H. Prevalence of alcohol and drugs among car and van drivers killed in road accidents in Norway: an overview from 2001 to 2010. Traffic Inj Prev. 2014;15(6):523-31.
147. Swenson JR, Dimsdale JE, Rockwell E, Carroll W, Hansbrough J. Drug and alcohol abuse in patients with acute burn injuries. Psychosomatics. 1991;32(3):287-93.
148. Szabo G, Saha B. Alcohol's Effect on Host Defense. Alcohol Res. 2015;37(2):159-70.
149. Crews FT, Sarkar DK, Qin L, Zou J, Boyadjieva N, Vetreno RP. Neuroimmune Function and the Consequences of Alcohol Exposure. Alcohol Res. 2015;37(2):331-41, 44-51.
150. Vetreno RP, Crews FT. Current hypotheses on the mechanisms of alcoholism. Handb Clin Neurol. 2014;125:477-97.
151. Diaz R, Heller D. Barotrauma And Mechanical Ventilation. StatPearls. Treasure Island (FL): StatPearls Publishing

152. Sommers MS, Dyehouse JM, Howe SR, Wekselman K, Fleming M. "Nurse, I only had a couple of beers": validity of self-reported drinking before serious vehicular injury. Am J Crit Care. 2002;11(2):106-14.
153. Estenssoro E, Alegría L, Murias G, Friedman G, Castro R, Nin Vaeza N, et al. Organizational Issues, Structure, and Processes of Care in 257 ICUs in Latin America: A Study From the Latin America Intensive Care Network. Critical care medicine. 2017;45(8):1325-36.
154. Kwizera A, Dünser M, Nakibuuka J. National intensive care unit bed capacity and ICU patient characteristics in a low income country. BMC Res Notes. 2012;5:475.
155. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet. 2010;376(9749):1339-46.

8 Appendices

8.1 APPENDIX A

Alcohol screening questionnaire (AUDIT)

One drink equals:  12 oz. beer  5 oz. wine  1.5 oz. liquor (one shot)

Scoring:	0 points per question	1 point per question	2 points per question	3 points per question	4 points per question
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times a month	2 - 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	0 - 2	3 or 4	5 or 6	7 - 9	10 or more
3. How often do you have four or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, in the last year
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, in the last year
Add the score for each column:	+	+	+	+	
Total Score (add column scores) =					

AUDIT-C

Please circle the answer that is correct for you.

1. How often do you have a drink containing alcohol?					**SCORE**
Never (0)	Monthly or less (1)	Two to four times a month (2)	Two to three times per week (3)	Four or more times a week (4)	_____
2. How many drinks containing alcohol do you have on a typical day when you are drinking?					
1 or 2 (0)	3 or 4 (1)	5 or 6 (2)	7 to 9 (3)	10 or more (4)	_____
3. How often do you have six or more drinks on one occasion?					
Never (0)	Less than Monthly (1)	Monthly (2)	Two to three times per week (3)	Four or more times a week (4)	_____
TOTAL SCORE Add the number for each question to get your total score.					_____

Maximum score is 12. A score of ≥ 4 identifies 86% of men who report drinking above recommended levels or meets criteria for alcohol use disorders. A score of > 2 identifies 84% of women who report hazardous drinking or alcohol use disorders.

SHORT MICHIGAN ALCOHOL SCREENING TEST (SMAST)

NAME: _____ Date:_____

The following questions concern information about your involvement with alcohol during the past 12 months. Carefully read each countyment and decide if your answer is "YES" or "NO". Then, check the appropriate box beside the question.

Please answer every question. If you have difficulty with a countyment, then choose the response that is mostly right.

These questions refer to the past 12 months only.	**YES**	**NO**
1. Do you feel that you are a normal drinker? (by normal we mean do you drink less than or as much as most other people.).....		
2. Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking?.....		
3. Do you ever feel guilty about your drinking?.....		
4. Do friends or relatives think you are a normal drinker?.....		
5. Are you able to stop drinking when you want to?.....		
6. Have you ever attended a meeting of Alcoholics Anonymous (AA)?.....		
7. Has your drinking ever created problems between you and your wife, husband, a parent or other near relative?.....		
8. Have you ever gotten into trouble at work because of your drinking?.....		
9. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?.....		
10. Have you ever gone to anyone for help about your drinking?.....		
11. Have you ever been in a hospital because of drinking?.....		
12. Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?.....		
13. Have you ever been arrested, even for a few hours, because of other drunken behaviors?.....		
*** SMAST Score**.....		

** See scoring instructions for correct scoring procedures.*

8.2 APPENDIX B

MEDLINE search:
("Epidemiology"[Mesh] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR “length of stay”[Mesh] OR “icu length of stay”[TIAB] OR “intensive care length of stay”[TIAB] OR “intensive care unit length of stay”[TIAB] OR “hospital length of stay”[TIAB] OR “hospitalization”[TIAB] OR “hospitalization”[TIAB] OR “hospital mortality”[Mesh] OR “intensive care mortality”[TIAB] OR “icu mortality”[TIAB] OR “intensive care unit? Mortality”[TIAB] OR “mortality 1 year”[TIAB] OR “one year mortality”[TIAB] OR “30-day mortality”[TIAB] OR “30 day mortality”[TIAB] OR “thirty day mortality”[TIAB] OR “90-day mortality”[TIAB] OR “90 day mortality”[TIAB] OR “ninety day mortality”[TIAB] OR “alcohol withdrawal delirium”[Mesh] OR “delirium tremens”[TIAB] OR “infections”[Mesh] OR “respiration, artificial”[Mesh] OR “mechanical ventilation”[TIAB] OR "Pneumonia"[Mesh] OR “sepsis”[Mesh] NOT “Neonatal Sepsis”[Mesh] OR “Pancreatitis, Alcoholic”[Mesh] OR “Liver Cirrhosis, Alcoholic”[Mesh] OR "Respiratory Distress Syndrome, Adult"[Mesh]) AND (“alcoholism”[Mesh] OR “alcohol”[TIAB] OR “ethanol abuse”[TIAB] OR “alcohol abuse”[TIAB] OR “alcohol use”[TIAB] OR “ethanol use”[TIAB] OR “alcoholic intoxication”[Mesh] OR “binge drinking”[Mesh] OR “alcohol Drinking in College”[Mesh] OR “alcohol intake”[TIAB] OR “chronic alcohol abuse”[TIAB] OR “chronic ethanol abuse”[TIAB] OR “chronic ethanol use”[TIAB] OR “chronic alcohol use”[TIAB] OR “acute alcohol use”[TIAB] OR “acute ethanol use”[TIAB]) AND (“intensive care units”[Mesh] NOT “intensive care units, neonatal”[Mesh] NOT “intensive care units, pediatric”[Mesh] OR "Critical Care"[Mesh] OR ‘”CCU”[TIAB] OR “Critical care unit”[TIAB] OR “intensive care unit”[TIAB] OR “intensive care”[TIAB] OR “icu”[TIAB] OR “medical intensive care”[TIAB] OR “cardiac intensive care”[TIAB] OR “coronary intensive care”[TIAB] OR “burn unit”[TIAB] OR “thermal injury”[TIAB])

Embase search:
('epidemiology'/exp/mj OR 'prevalence'/exp/mj OR 'incidence'/exp/mj OR ‘length of stay'/exp OR 'hospital mortality'/exp OR ‘intensive care mortality’:ti,ab OR ‘icu mortality’:ti,ab OR 'mortality rate'/exp OR 'standardized mortality ratio'/exp OR 'surgical mortality'/exp OR ’30 day mortality’:ti,ab OR ’30-day mortality’:ti,ab OR ’90 day mortality’:ti,ab OR ’90-day mortality’:ti,ab OR ‘one year mortality’:ti,ab OR ‘1 year mortality’:ti,ab OR 'length of stay'/exp OR ‘icu length of stay’:ti,ab OR ‘intensive care unit? length of stay’:ti,ab OR ‘hospital length of stay’:ti,ab OR 'alcoholic delirium'/exp OR ‘alcohol withdrawal delirium’:ti,ab OR 'artificial ventilation'/exp OR 'assisted ventilation'/exp OR 'infection'/exp OR ('sepsis'/exp NOT 'newborn sepsis'/exp) OR ('pneumonia'/exp NOT 'neonatal pneumonia'/exp) OR 'alcoholic pancreatitis'/exp OR 'alcohol liver cirrhosis'/exp OR 'adult respiratory distress syndrome'/exp) AND (('alcohol abuse'/exp NOT 'underage drinking'/exp) OR 'alcohol blood level'/exp OR 'alcohol intoxication'/exp OR 'drinking behavior'/exp OR 'alcohol consumption'/exp OR 'alcoholism'/exp OR ‘chronic alcohol abuse’:ti,ab OR ‘chronic alcohol use’:ti,ab OR ‘chronic ethanol use’:ti,ab OR ‘chronic ethanol abuse’:ti,ab OR ‘alcohol intake’:ti,ab OR ‘alcohol use’:ti,ab OR ‘ethanol use’:ti,ab) AND ('intensive care'/de OR 'burn unit'/exp OR 'medical intensive care unit'/exp OR 'surgical intensive care unit'/exp OR 'stroke unit'/exp OR 'coronary care unit'/exp OR 'critical illness'/exp OR ‘icu’:ti,ab OR ‘ccu’:ti,ab OR ‘critical care unit’:ti,ab)

Web of science search:
TS=(“epidemiology” OR “prevalence” OR “incidence” OR “length of stay" OR "icu length of stay" OR “intensive care length of stay” OR “intensive care unit length of stay" OR "hospital length of stay” OR “hospitalisation” OR “hospitalization” OR "hospital mortality” OR "mortality 1 year" OR “one year mortality" OR “30-day mortality” OR “30 day mortality” OR “thirty day mortality” OR “90-day mortality” OR “90 day mortality” OR “ninety day mortality” OR "artificial respiration” OR “assisted aspiration” OR “mechanical ventilation” OR “assisted ventilation” OR “delirium” OR "alcohol withdrawal delirium" OR “alcohol delirium” OR “delirium” OR “delirium tremens” OR “infection” OR "pneumonia" OR “ARDS” OR “acute respiratory distress syndrome” OR “sepsis” OR “alcoholic” NEAR “pancreatitis” OR “alcoholic” NEAR “cirrhosis”) AND TS=(“alcoholism" OR "alcohol" OR "ethanol abuse" OR “ethanol use” OR "alcohol abuse" OR “alcohol use” OR "alcoholic intoxication" OR "binge drinking" OR "alcohol intake" OR “alcohol drinking” OR “alcohol intake” OR “alcohol drinking” OR “ethanol drinking”) AND TS=(“intensive care units" OR “intensive care unit” OR "intensive care" OR “icu” OR “burn unit” OR “cardiac intensive care” OR “coronary intensive care” OR “medical intensive care” OR “trauma” OR “trauma intensive care” OR “critical care” OR “critical care unit” OR “CCU” OR “surgical intensive care”)

8.3 APPENDIX C

Author	Country	Study design	Sample size (n)	Outcome(s)
Burn unit				
Jones et al. 1991	USA	Retrospective	87	Mortality, LOS, Mechanical ventilation
Haum et al. 1995	Germany	Retrospective and Prospective	225	Mortality, LOS
McGill et al. 1995	USA	Retrospective	290	Mortality
Silver et al. 2008	USA	Matched-case control	48	LOS, mortality, mechanical ventilation
Griffin et al. 2009	USA	Retrospective	614	LOS, mortality, mechanical ventilation, pneumonia, sepsis
Holmes et al. 2010	UK	Retrospective	1293	LOS
Moore et al. 2010	Australia	Retrospective	12	Candidemia in burn patients
Davis et al. 2012	USA	Prospective	53	LOS, mortality, mechanical ventilation, pneumonia, sepsis
Sveen et al. 2015	Sweden	Prospective	63	LOS
Daffue et al. 2018	South-Africa	Prospective	49	Prevalence
Palmu et al. 2018	Finland	Prospective	107	prevalence
Klifto et al. 2019	USA	Retrospective	115	LOS, mortality
Laughon et al. 2019	USA	Retrospective	7202	Prevalence
Cardiac care unit				
Azarasa, M. 2008	Iran	Prospective	600	Prevalence
Medical ICU				
Marik et al. 1996	USA	Prospective	200	LOS, mortality, mechanical ventilation, epidemiology, AWS, alcoholic hepatitis
Lankisch et al. 1999	Germany	Prospective	208	Alcoholic pancreatitis
Moss et al. 2003	USA	Prospective	220	ARDS, Sepsis
de Wit et al. 2007	USA	Retrospective	785 602	Mechanical ventilation
Touray et al. 2014	USA	Retrospective	266	Pneumonia
Chen et al. 2015	Taiwan	Retrospective	226	Cirrhosis
Nagari et al. 2019	India	Prospective	1582	Delirium
Rentsch et al. 2019	USA	Retrospective	155 550	Infection (HIV)
Surgical ICU				

Maxson et al. 1999	USA	Prospective	321	LOS Hospital and ICU, pneumonia, AWS
Delgado-Rodriguez et al. 2003	Spain	Prospective	1505	Mortality, epidemiology
Paull et al. 2004	USA	Prospective	56	LOS hospital, mortality, infections
Rhodes et al. 2011	Austria	Prospective	88 504	Hospital Mortality
Rubinsky et al. 2013	USA	Retrospective	1913	LOS Hospital and ICU
Horacek et al. 2016	Czech Republic	Prospective	140	Delirium
Lowery et al. 2018	USA	Prospective	86	LOS ICU and hospital, mechanical ventilation, epidemiology
Shin et al. 2018	Korea	Retrospective	99	Delirium
Mixed ICU				
Burnham et al. 2004	USA	Prospective	20	ARDS
Muhlberg et al. 2005	Germany	Retrospective	5883	Toxicology screens in elderly patients
Uusaro et al. 2005	Finland	Prospective	893	Epidemiology
O'Brien et al. 2006	USA	Retrospective	11 651	Sepsis, hospital mortality
Ouimet et al. 2007	Canada	Prospective	820	Delirium
Blanco et al. 2008	Spain	Prospective	2 619	Sepsis
Faria et al. 2008	France	Prospective	7	Infections
Gacouin et al. 2008	France	Prospective	358	Epidemiology
Van Rompaey et al. 2009	Belgium	Prospective	523	Delirium
de Wit et al. 2010	USA	Retrospective	40	Epidemiology, Sepsis
Lam et al. 2010	Hong Kong	Retrospective	265	Epidemiology
McKenny et al. 2010	Ireland	Prospective	275	ICU LOS, 30d-mortality
Monte et al. 2010	Spain	Retrospective	16 848	Epidemiology, Mortality, Mechanical Ventilation
Singh et al. 2011	India	Retrospective	138	Epidemiology
Christensen et al. 2012	Denmark	Prospective	16 848	30d-mortality, 3-year mortality
Fuchs et al. 2012	Multicenter (Greece-USA-Israel)	Retrospective	19 510	Elderly demographic
Gacouin et al. 2012	France	Prospective	281	Epidemiology
Geary et al. 2012 2012	Scotland	Prospective	838	Epidemiology, Mechanical ventilation
Levesque et al. 2012	France	Prospective	377	Cirrhosis, alcoholic hepatitis

Brandenburg et al. 2014	Netherlands	Retrospective	7 331	Epidemiology
Gacouin et al. 2014	France	Prospective	662	1 year mortality
Levesque et al. 2014	France	Prospective	592	cirrhosis
Larkin et al. 2015	Ireland	Retrospective	346	Epidemiology
McPeake et al. 2015	Scotland	Prospective	580	Epidemiology
Stehman et al. 2015	USA	Prospective	11 850	Mortality
Walkey et al. 2015	USA	Retrospective	3 666	Mechanical ventilation
Sandiumenge et al. 2016	Spain	Prospective	509	Mechanical ventilation
Banderas-Bravo et al. 2017	Spain	Prospective	119	Epidemiology
Fernandes et al. 2017	Portugal	Retrospective	170	Alcoholic hepatitis
Fernandez-Barat et al. 2017	Spain	Prospective	222	Pneumonia
Hietanen et al. 2017	Finland	Retrospective	899	One year mortality
Kanova et al. 2017	Czech Republic	Prospective	332	Delirium
Liisanantti et al. 2017	Finland	Retrospective	403 000	Epidemiology
Mesa et al. 2017	Latin-America	Prospective	230	Delirium
Orsini et al. 2017	USA	Prospective	65	Epidemiology, mechanical ventilation, sepsis
Smith et al. 2017	Canada	Retrospective	130	Epidemiology
Cilloniz et al. 2018	Spain	Retrospective	6 403	20 year changes
Kulkarni et al. 2018	India	Prospective	64	Cirrhosis
Mehandra et al. 2018	India	Prospective	100	Pneumonia
McPhail et al. 2018	UK	Retrospective	31 363	Cirrhosis
Secombe et al. 2018	Australia	Retrospective	2 670	ICU LOS, mechanical ventilation, epidemiology
Lone et al. 2019	Scotland	Retrospective	6 053	ICU and hospital LOS
Ng et al. 2019	Hong Kong	Retrospective	270	Epidemiology
Samanta et al. 2019	India	Prospective	759	Alcoholic pancreatitis
Stewart et al. 2019	Scotland	Retrospective	257	Epidemiology, ICU LOS, sepsis, delirium
Tollisen et al. 2019	Norway	Prospective	852	Epidemiology
Uljas et al. 2019	Finland	Retrospective	2 532	3-year mortality
Trauma ICU				
Davis et al. 1997	USA	Retrospective	1 234	LOS
Melnick et al. 2000	USA	Retrospective	496	Epidemiology, LOS, Mortality

Soffer et al. 2006	Israel	Retrospective	5529	Epidemiology
De Guise et al. 2009	Canada	Retrospective	60	Pneumonia, Sepsis
Brattstrom et al. 2010	Sweden	Prospective	154	Prevalence, MOF
Swearingen et al. 2010	USA	Retrospective	8735	Epidemiology, LOS, Mortality
Talving et al. 2010	USA	Prospective	815	Epidemiology, LOS, Mortality, Pneumonia, Sepsis, ARDS
Hadjizacharia et al. 2011	USA	Matched-control	772	Mortality, Pneumonia, Sepsis
Lustenberger et al. 2011	USA	Retrospective	439	Epidemiology, LOS, Mortality, Sepsis, ARDS
Zeckey et al. 2011	Germany	Retrospective	437	Epidemiology, LOS, Mortality
Hsieh et al. 2013	China	Prospective	5738	Epidemiology, LOS, Mortality
Melvan et al. 2013	USA	Retrospective	111	Epidemiology
Nau et al. 2013	Germany	Retrospective	9 821	LOS
Afshar et al. 2014	USA	Retrospective	26 305	Sepsis, ARDS
Crutcher et al. 2014	USA	Retrospective	10 611	LOS, Mortality, Pneumonia
Jawa et al. 2014	USA-Canada	Retrospective	19 369	AWS
Scheyerer et al. 2014	Switzerland	Retrospective	383	Epidemiology, LOS, Mortality
Gustafson et al. 2015	USA	Retrospective	2 482	Lactate and base deficit
Raj et al. 2015	Helsinki	Retrospective	405	Mortality
Almeida et al. 2016	Brazil	Prospective	87	Mortality
Mohseni et al. 2016	Sweden	Retrospective	352	Epidemiology, LOS, Mortality
Jonsdottir et al. 2016	Iceland	Retrospective	583	Prevalence
El-Menyar et al. 2019	USA-Qatar	Retrospective	681	Epidemiology, LOS, Mortality

8.4 APPENDIX D

Tool to Assess Risk of Bias in Cohort Studies	
Was selection of exposed and non-exposed cohorts drawn from the same population?	1
Can we be confident in the assessment of exposure?	2
Can we be confident that the outcome of interest was not present at start of study?	3
Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	4
Can we be confident in the assessment of the presence or absence of prognostic factors?	5
Can we be confident in the assessment of outcome?	6
Was the follow up of cohorts adequate?	7

Were co-interventions similar between groups?	8

8.5 APPENDIX E

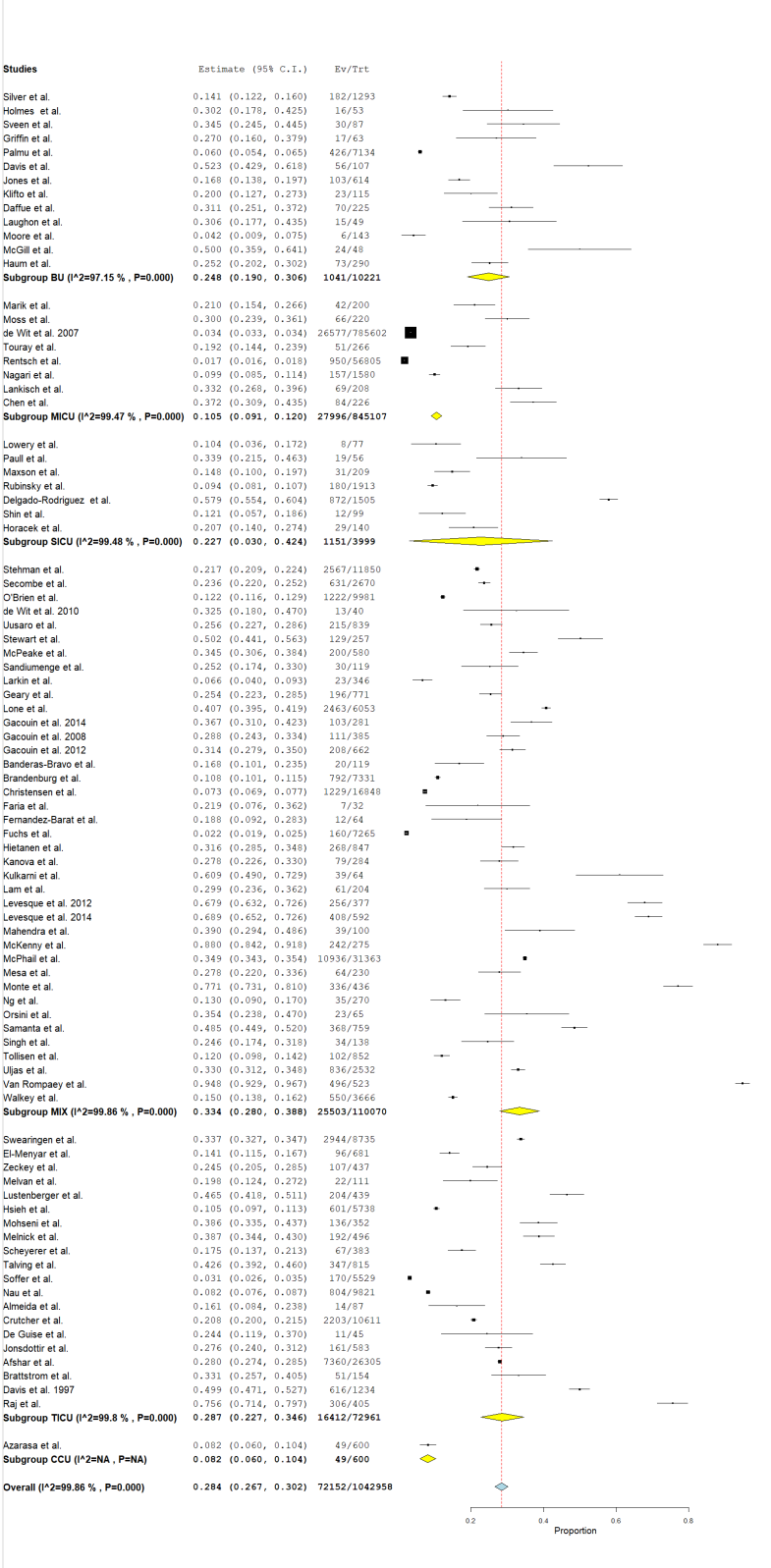
	Was selection of exposed and non-exposed cohorts drawn from the same population?	Can we be confident in the assessment of exposure?	Can we be confident that the outcome of interest was not present at start of study?	Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	Can we be confident in the assessment of the presence or absence of prognostic factors?	Can we be confident in the assessment of outcome?	Was the follow up of cohorts adequate?	Were co-interventions similar between groups?
Burn unit								
Jones et al. 1991	++	+	++	+	+	++	++	++
Haum et al. 1995	++	+	++	+	+	++	++	++
McGill et al. 1995	++	+	++	+	++	+	++	++
Silver et al. 2008	++	+	++	-	-	+	++	++
Griffin et al. 2009	++	+	++	++	++	++	++	++
Holmes et al. 2010	++	+	++	+	+	+	-	++
Moore et al. 2010	++	+	++	-	-	+	+	++
Davis et al. 2012	++	++	++	++	++	++	+	++
Sveen et al. 2015	++	++	++	++	++	++	++	++
Daffue et al. 2018	++	++	++	++	++	++	+	++
Palmu et al. 2018	++	++	++	+	+	+	++	++
Klifto et al. 2019	++	+	++	++	++	++	++	++
Laughon et al. 2019	++	+	++	+	++	++	++	++
Cardiac care unit								
Azarasa et al. 2009	++	++	++	+	+	++	+	++
Medical ICU								

Marik et al. 1996	++	++	++	-	-	+	+	++
Lankisch et al. 1999	++	+	++	-	-	+	+	++
de Wit et al. 2007	+	+	++	++	+	+	-	++
Moss et al. 2003	++	++	++	++	+	++	++	++
Touray et al. 2014	++	++	++	++	+	++	++	++
Chen et al. 2015	++	++	++	++	++	++	+	++
Nagari et al. 2019	++	++	++	++	++	+	++	++
Rentsch et al. 2019	++	++	++	++	++	++	+	++
Surgical ICU								
Maxson et al. 1999	++	++	++	-	++	+	-	++
Delgado-Rodriguez et al. 2003	++	++	++	+	++	+	+	++
Paull et al. 2004	++	++	++	+	++	++	+	++
Rhodes et al. 2011	++	++	++	-	+	+	+	++
Rubinsky et al. 2013	++	++	++	++	++	++	+	++
Horacek et al. 2016	++	++	++	+	++	+	-	++
Lowery et al. 2018	++	++	++	-	++	+	+	++
Shin et al. 2018	++	++	++	++	++	++	++	++
Mixed ICU setting								
Burnham et al. 2004	++	++	+	-	+	++	++	++
Muhlberg et al. 2005	++	++	+	+	+	++	++	++
Uusaro et al. 2005	++	++	++	++	++	+	++	++
O'Brien et al. 2006	++	++	++	++	++	++	++	++
Ouimet et al. 2007	++	++	++	++	++	++	++	++
Blanco et al. 2008	++	++	++	+	++	++	++	++
Faria et al. 2008	++	++	++	++	++	+	++	++
Gacouin et al. 2008	+	++	++	++	++	++	+	++
Van Rompaey et al. 2009	++	++	++	++	++	++	++	++
de Wit et al. 2010	+	+	++	++	++	++	++	++
Lam et al. 2010	++	++	++	++	++	++	++	++
McKenny et al. 2010	++	++	++	+	++	++	-	++
Monte et al. 2010	++	+	++	+	+	++	++	++
Singh et al. 2011	++	++	++	++	++	++	++	++
Christensen et al. 2012	++	-	++	++	++	++	++	++
Fuchs et al. 2012	-	+	++	+	++	++	+	++

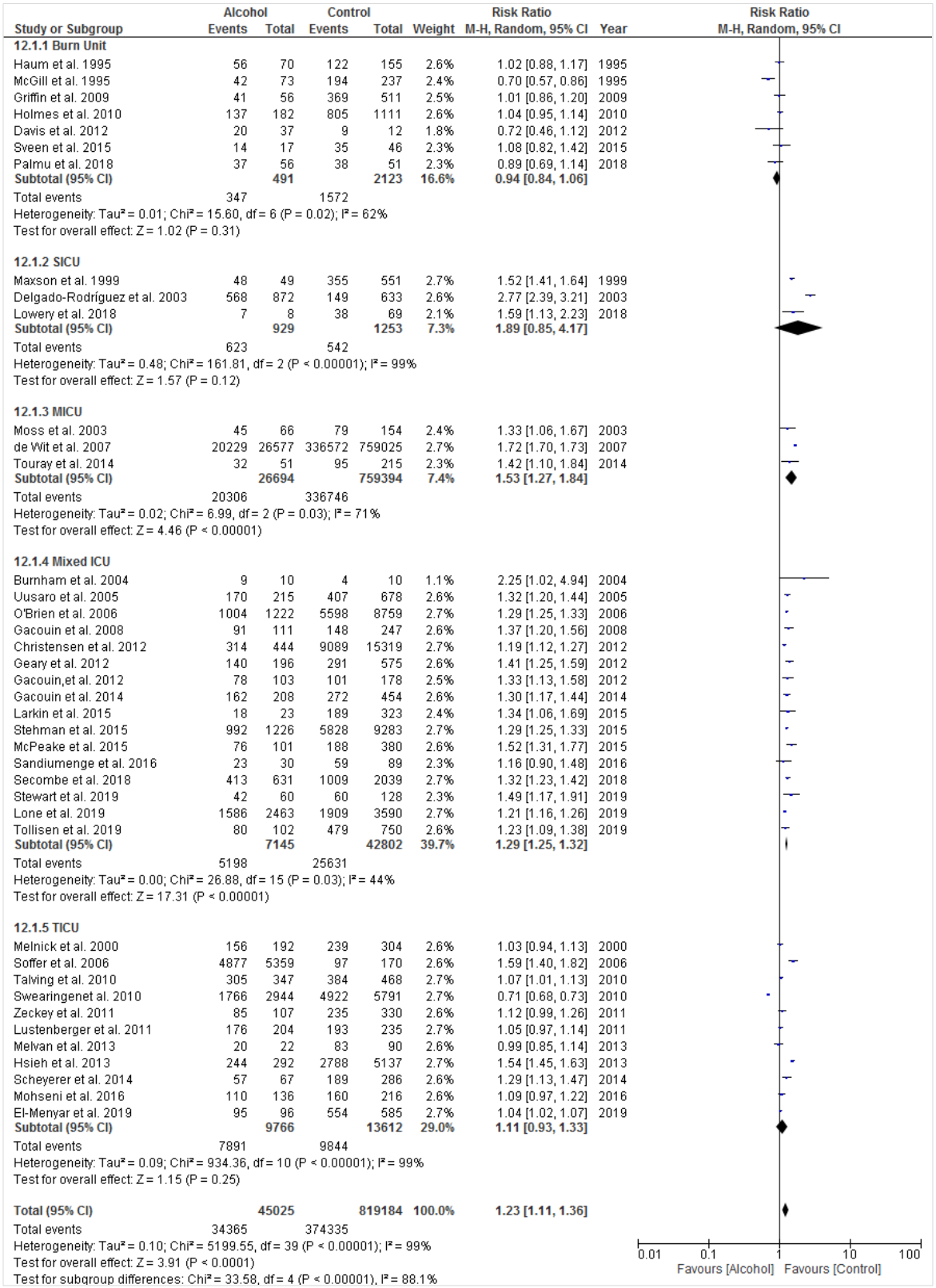
Gacouin et al. 2012	++	++	++	++	++	++	++	++
Geary et al. 2012	++	+	++	++	+	++	++	++
Levesque et al. 2012	++	+	++	++	++	++	++	++
Brandenburg et al. 2014	+	+	++	++	++	++	++	++
Gacouin et al. 2014	++	++	++	++	++	++	++	++
Levesque et al. 2014	++	+	++	++	++	++	++	++
Larkin et al. 2015	++	++	++	++	++	+	+	++
McPeake et al. 2015	++	+	++	++	++	++	++	++
Stehman et al. 2015	++	++	++	++	++	++	++	++
Walkey et al. 2015	-	++	++	++	++	++	++	++
Sandiumenge et al. 2016	+	++	++	++	++	++	++	++
Banderas-Bravo et al. 2017	+	++	++	++	++	++	++	++
Fernandes et al. 2017	--	++	++	++	++	++	++	++
Fernandez-Barat et al. 2017	++	+	+	++	++	++	++	++
Hietanen et al. 2017	++	+	++	++	++	+	+	++
Kanova et al. 2017	++	++	+	++	++	++	+	++
Liisanantti et al. 2017	-	++	+	+	+	++	++	++
Mesa et al. 2017	-	++	++	++	++	++	++	++
Orsini et al. 2017	++	++	++	++	++	+	++	++
Smith et al. 2017	+	++	++	+	+	++	++	++
Cilloniz et al. 2018	++	++	++	++	++	++	++	++
Kulkarni et al. 2018	++	++	++	++	++	++	++	++
Mahendra et al. 2018	++	+	++	-	+	++	++	++
McPhail et al. 2018	++	++	++	++	++	++	++	++
Secombe et al. 2018	++	++	++	++	++	++	++	++
Lone et al. 2019	+	++	++	++	++	++	++	++
Ng et al. 2019	++	-	+	+	+	++	++	++
Samanta et al. 2019	++	+	++	+	++	++	++	++
Stewart et al. 2019	++	++	++	+	+	++	++	++
Tollisen et al. 2019	+	++	++	+	+	++	++	++
Uljas et al. 2019	++	++	+	++	+	+	-	++
Trauma ICU								
Davis et al. 1997	++	+	++	-	-	-	++	++

Melnick et al. 2000	++	++	++	++	++	++	+	++
Soffer et al. 2006	++	-	+	-	+	++	+	++
De Guise et al. 2009	++	++	++	++	+	++	++	++
Brattström et al. 2010	++	++	++	++	++	++	+	++
Swearingen et al. 2010	+	-	++	++	-	++	++	++
Talving et al. 2010	++	++	++	++	+	+	++	++
Hadjizacharia et al. 2011	++	++	++	-	-	++	+	++
Lustenberger et al. 2011	++	++	++	+	++	++	++	++
Zeckey et al. 2011	++	+	++	-	++	++	++	++
Hsieh et al. 2013	++	+	++	+	+	++	++	++
Melvan et al. 2013	++	+	++	-	++	++	++	++
Nau et al. 2013	++	+	++	+	++	++	+	++
Afshar et al. 2014	++	+	++	+	-	++	++	++
Crutcher et al. 2014	-	+	++	+	-	-	++	++
Jawa et al. 2014	+	+	++	+	+	++	++	++
Scheyerer et al. 2014	++	++	++	++	++	+	++	+
Gustafson et al. 2015	+	+	++	+	++	++	++	++
Raj et al. 2015	++	+	++	+	+	++	++	++
Almeida et al. 2016	++	++	++	++	+	++	++	++
Mohseni et al. 2016	++	+	++	+	+	++	++	+
Jonsdottir et al. 2016	++	+	++	+	+	++	-	++
El-Menyar et al. 2019	++	+	++	+	+	+	++	+

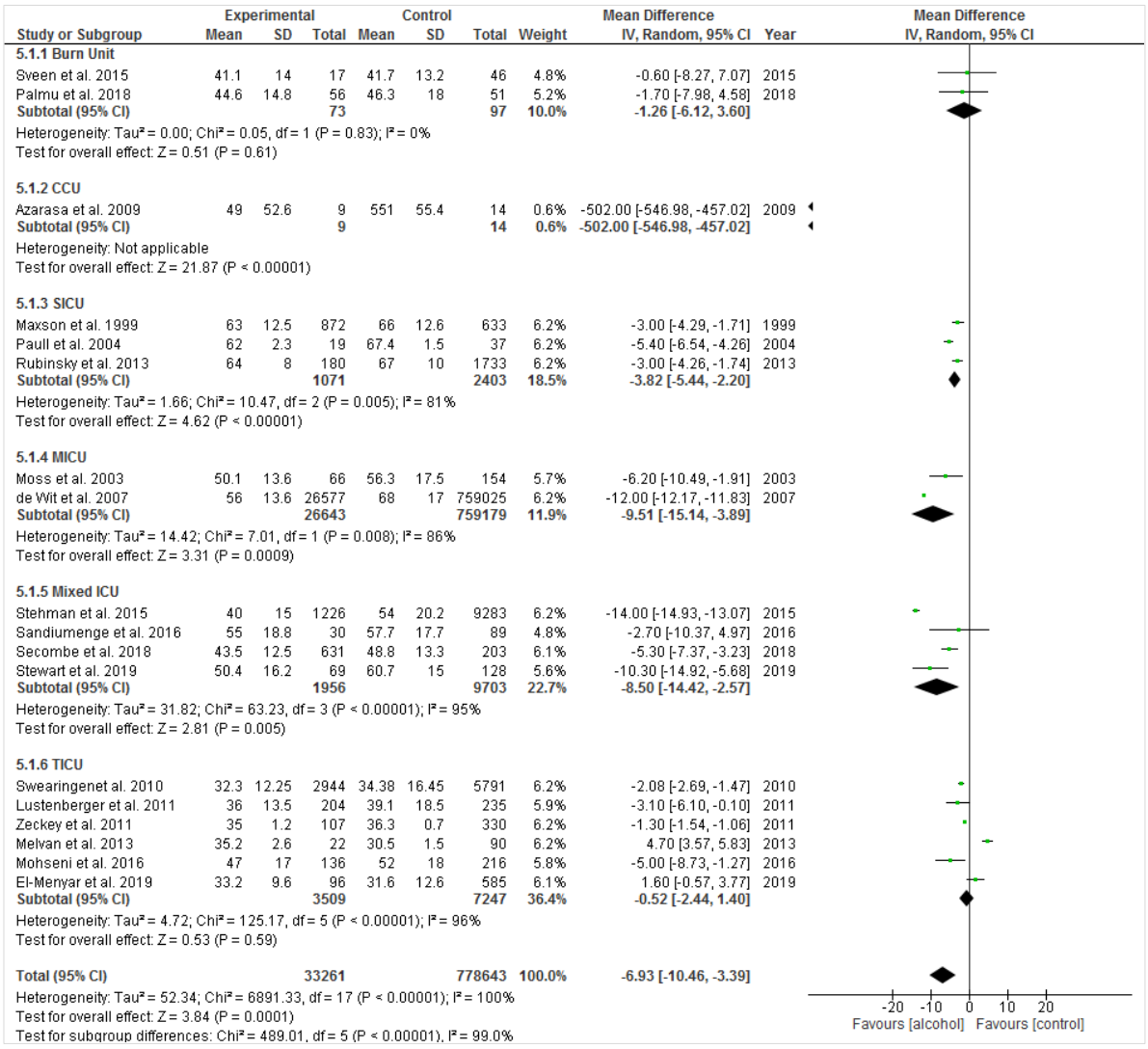
8.6 APPENDIX F



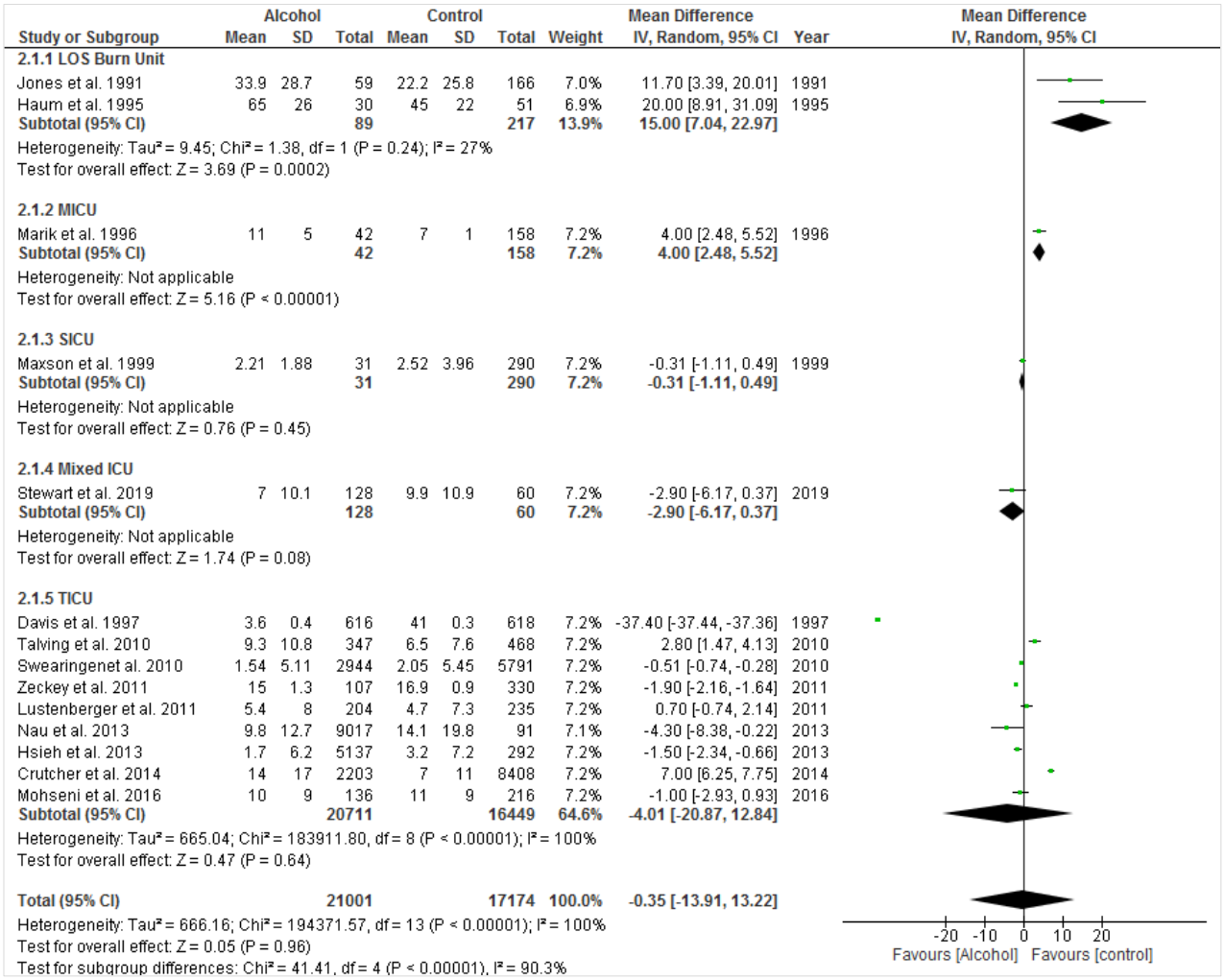
Forest plot 1. Alcohol prevalence.



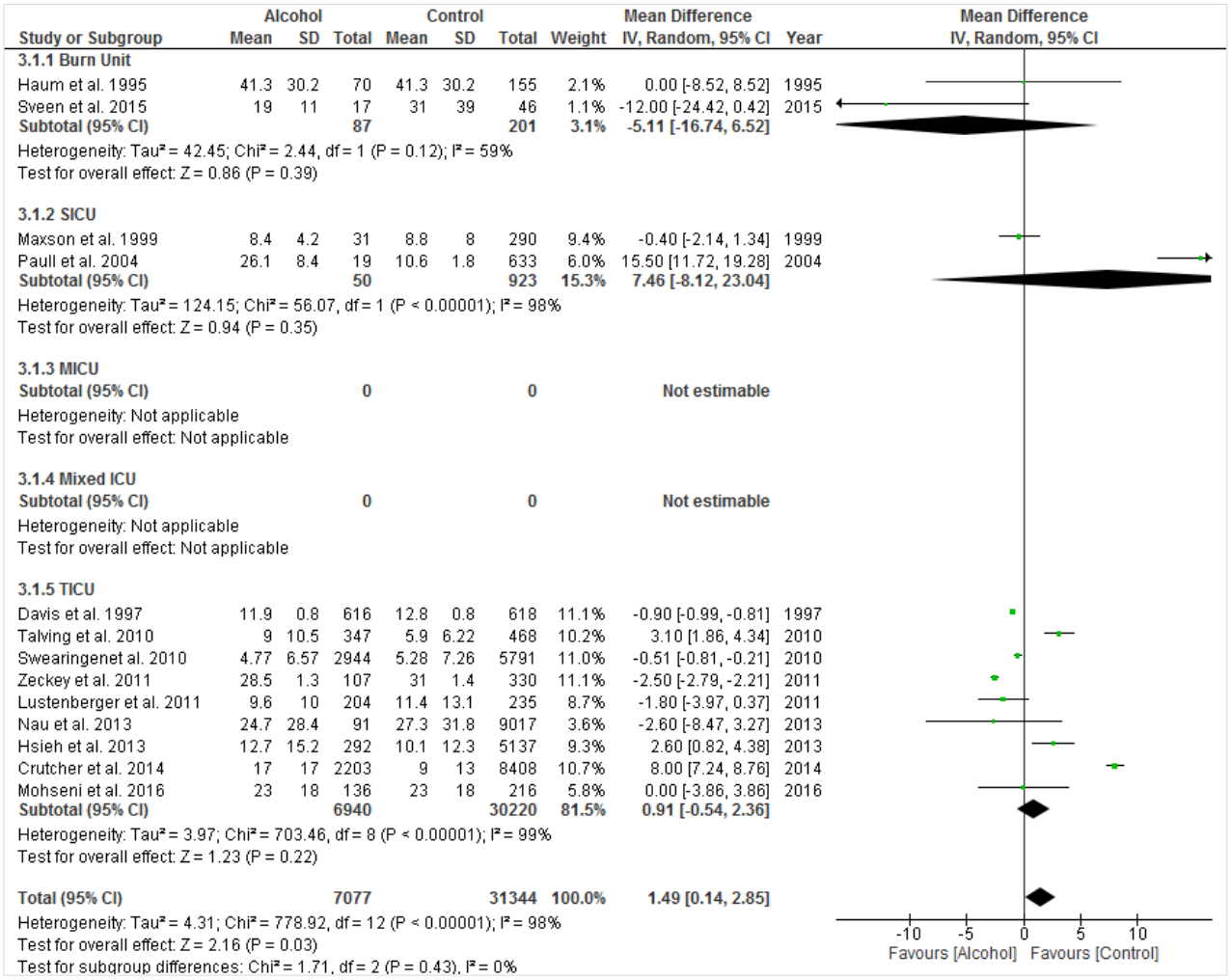
Forest plot 2. Male prevalence RR



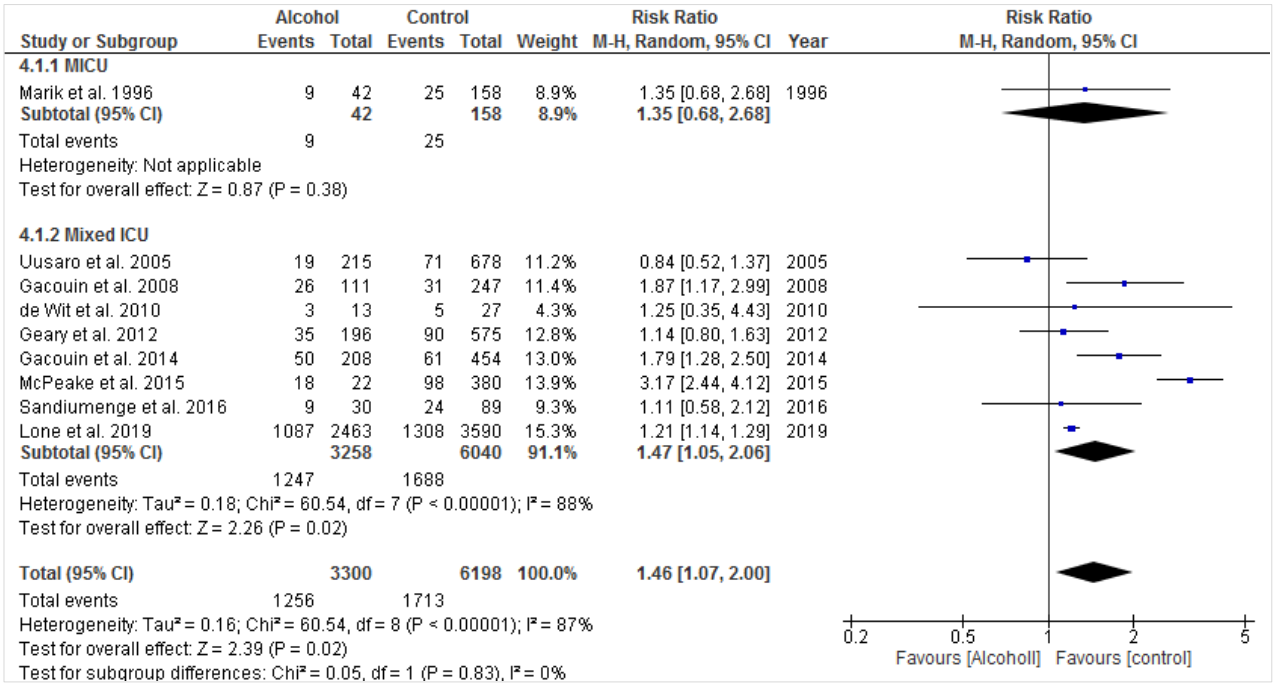
Forest plot 3. Mean age



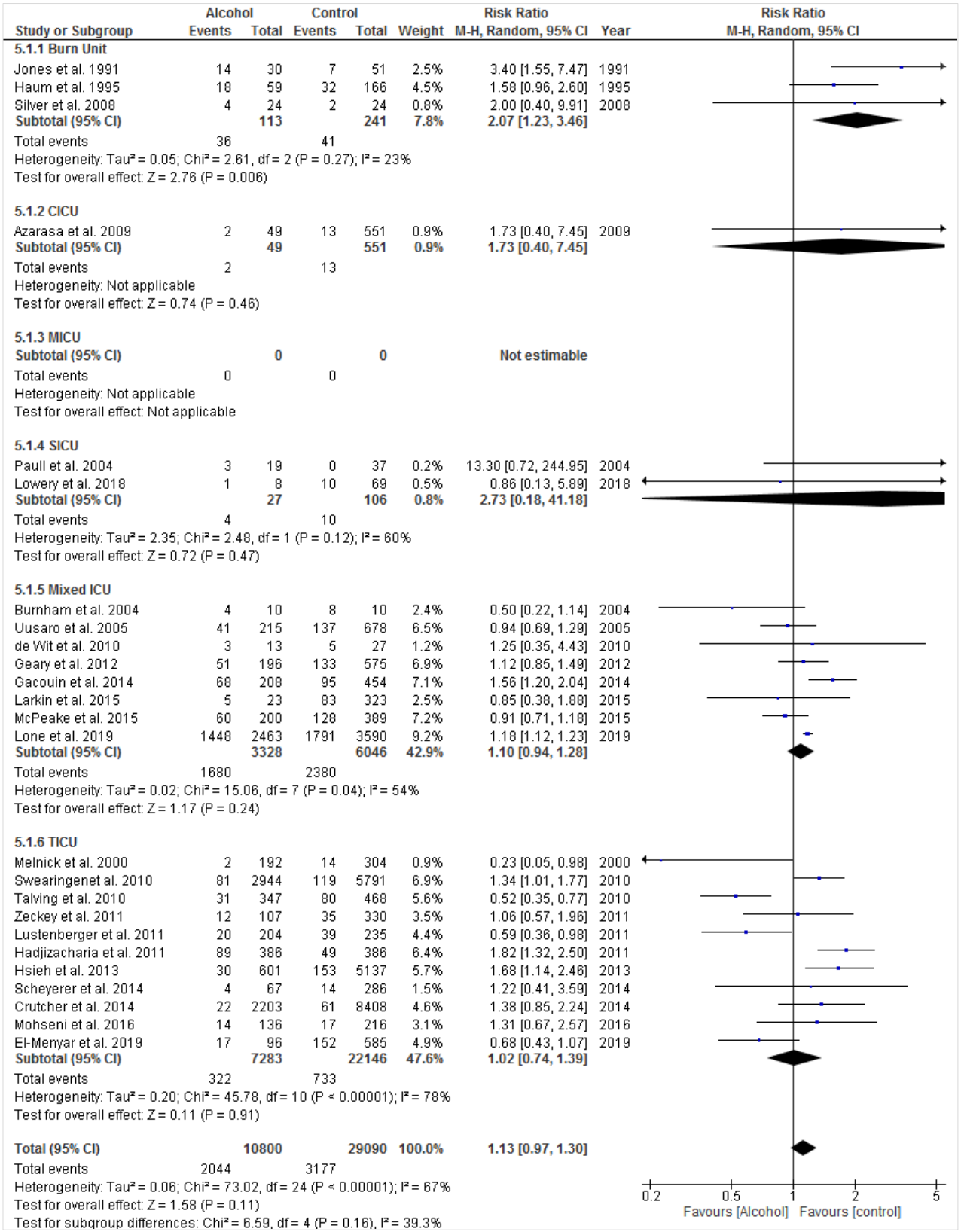
Forest plot 4. LOS ICU



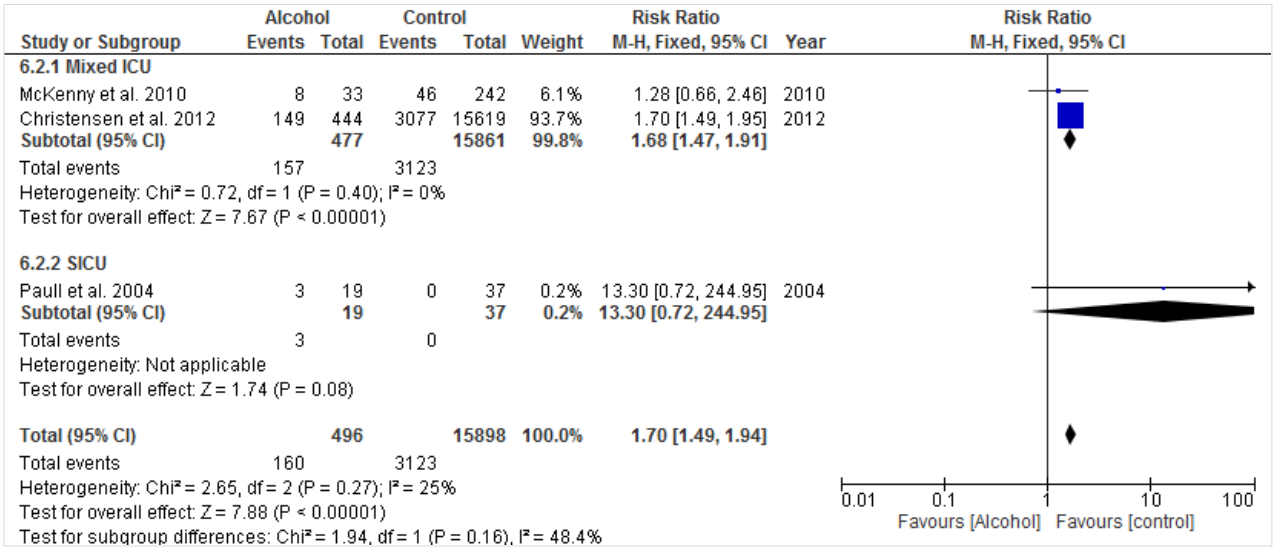
Forest plot 5. Hospital LOS



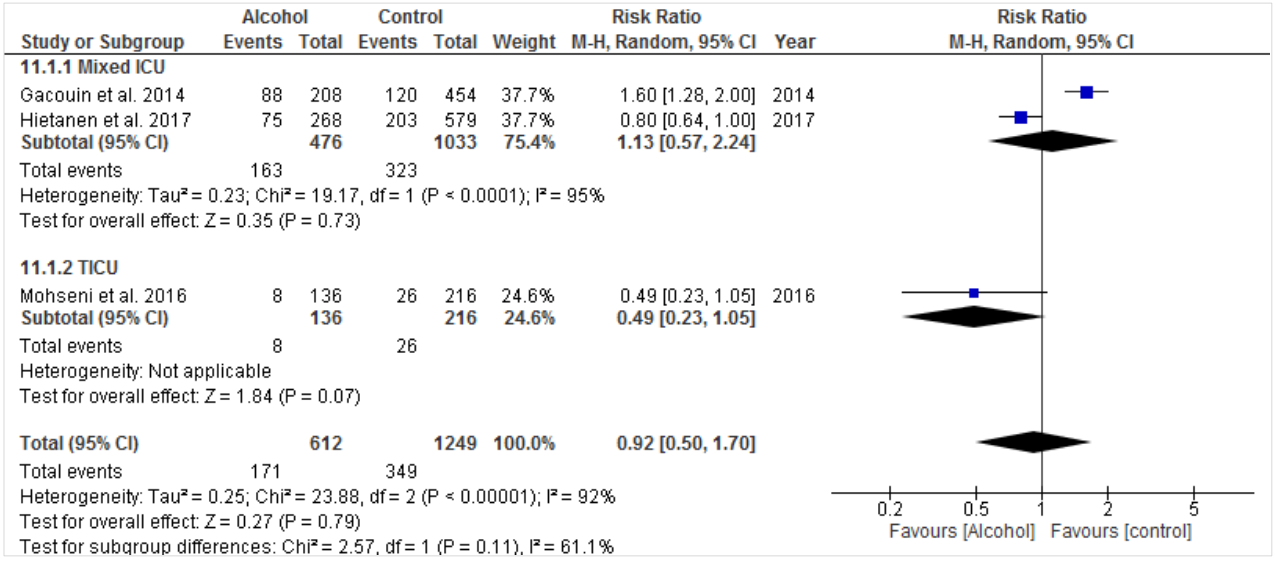
Forest plot 6. ICU Mortality



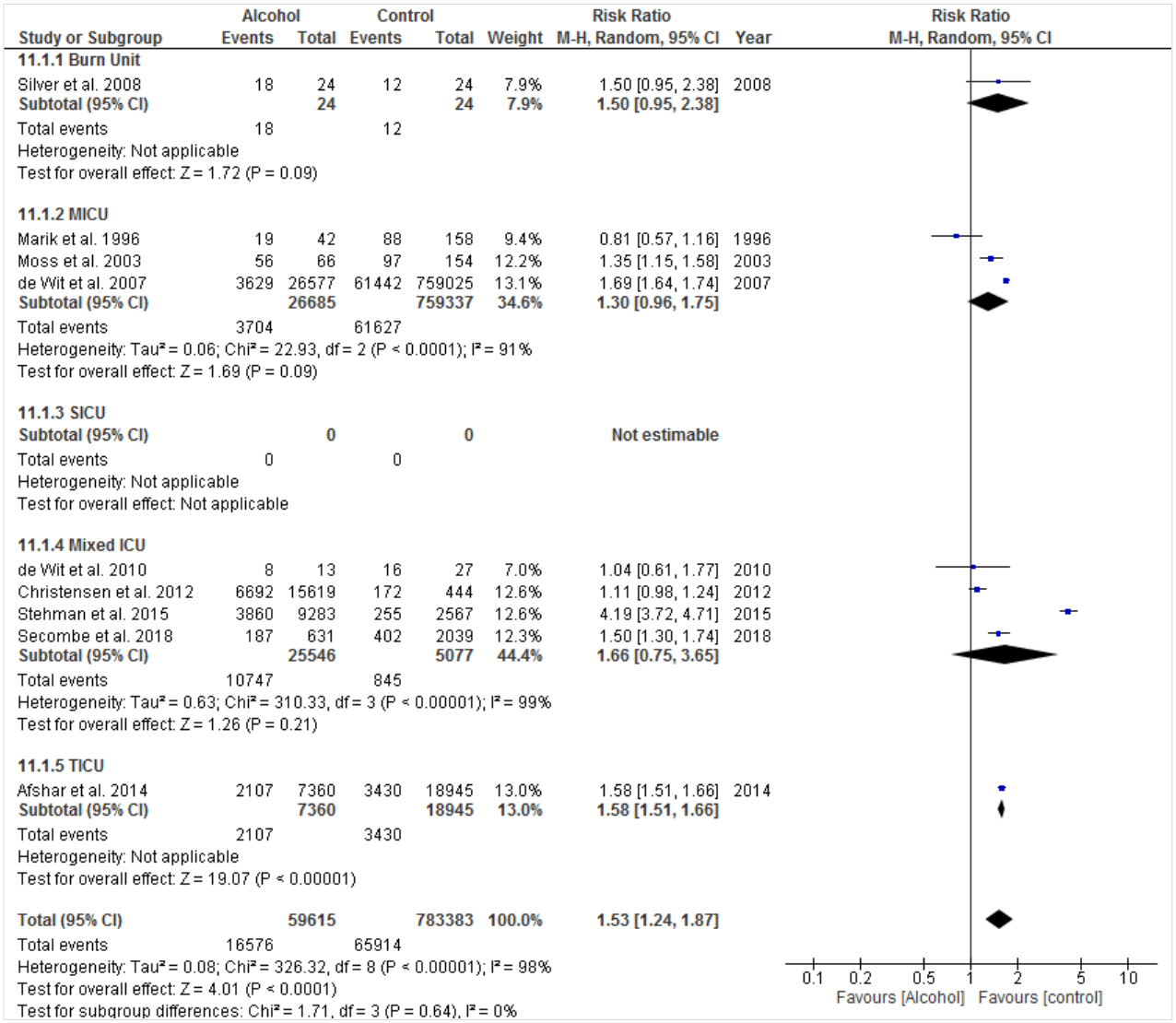
Forest plot 7. Hospital mortality



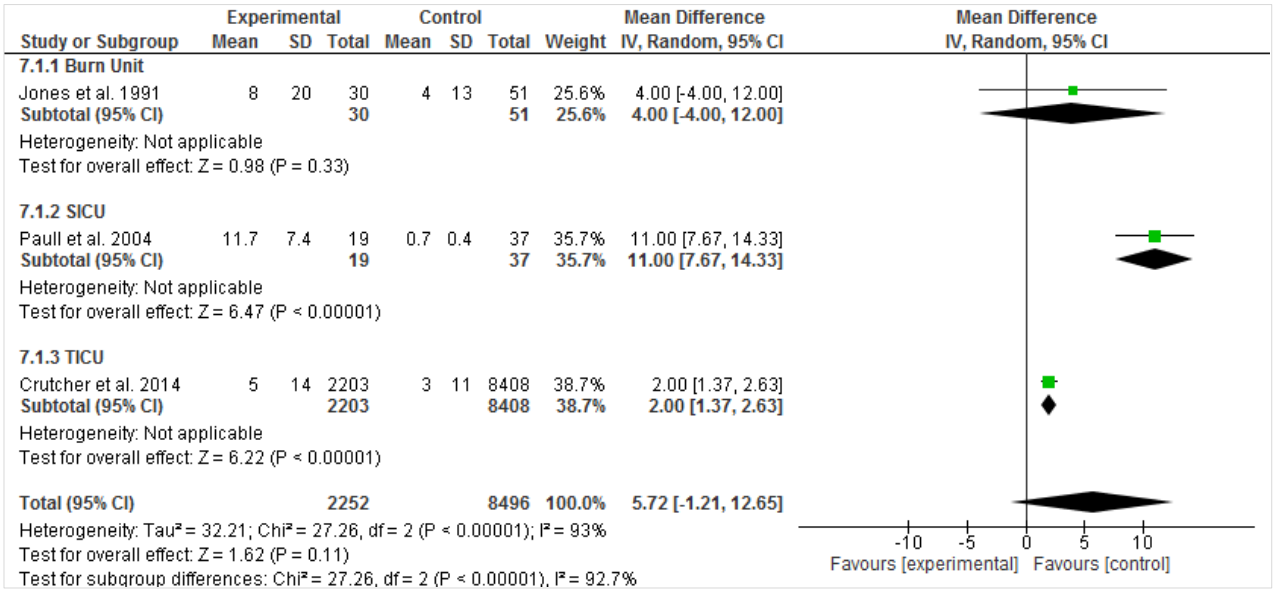
Forest plot 8. 30d-mortality



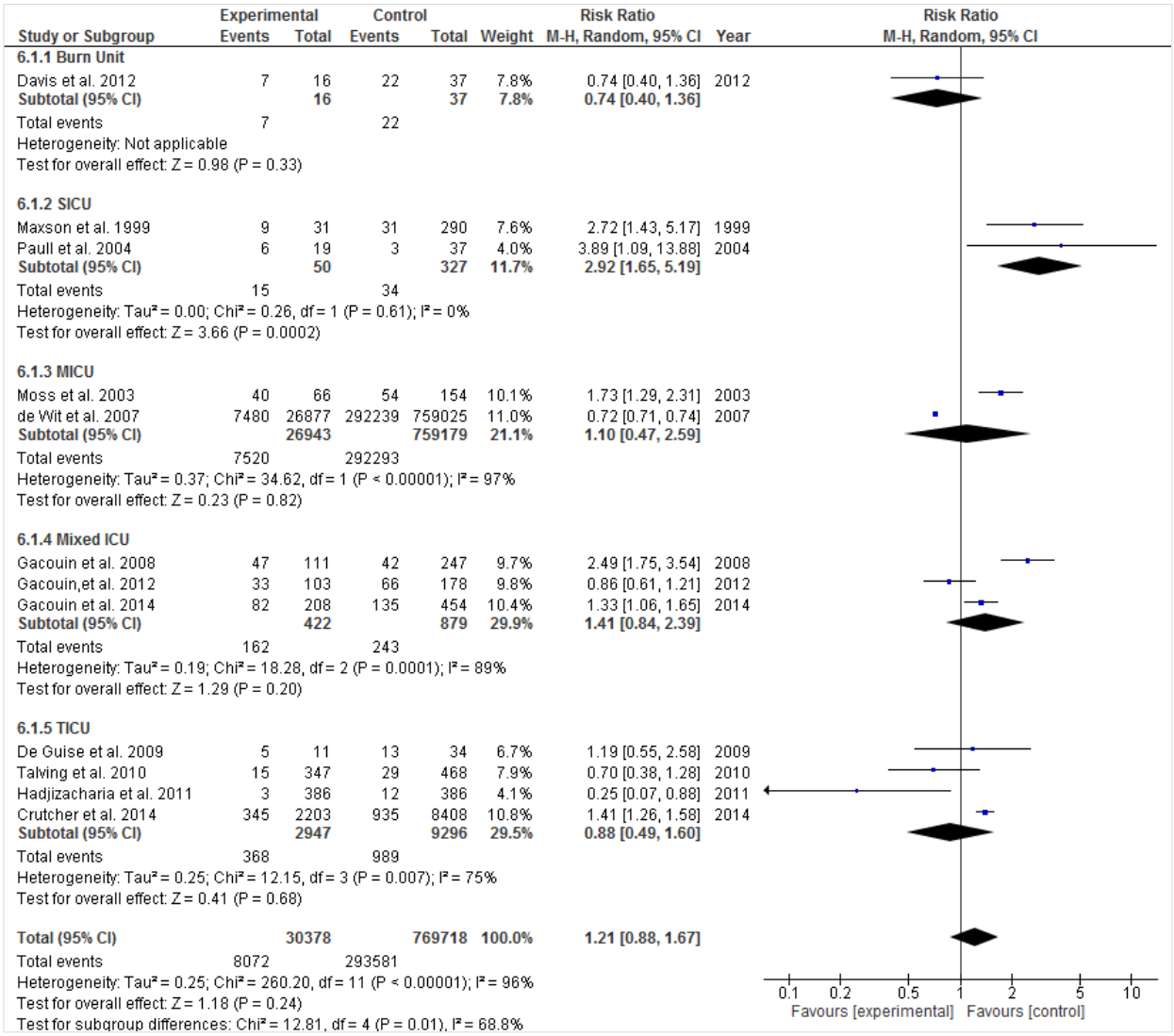
Forest plot 9. one-year mortality



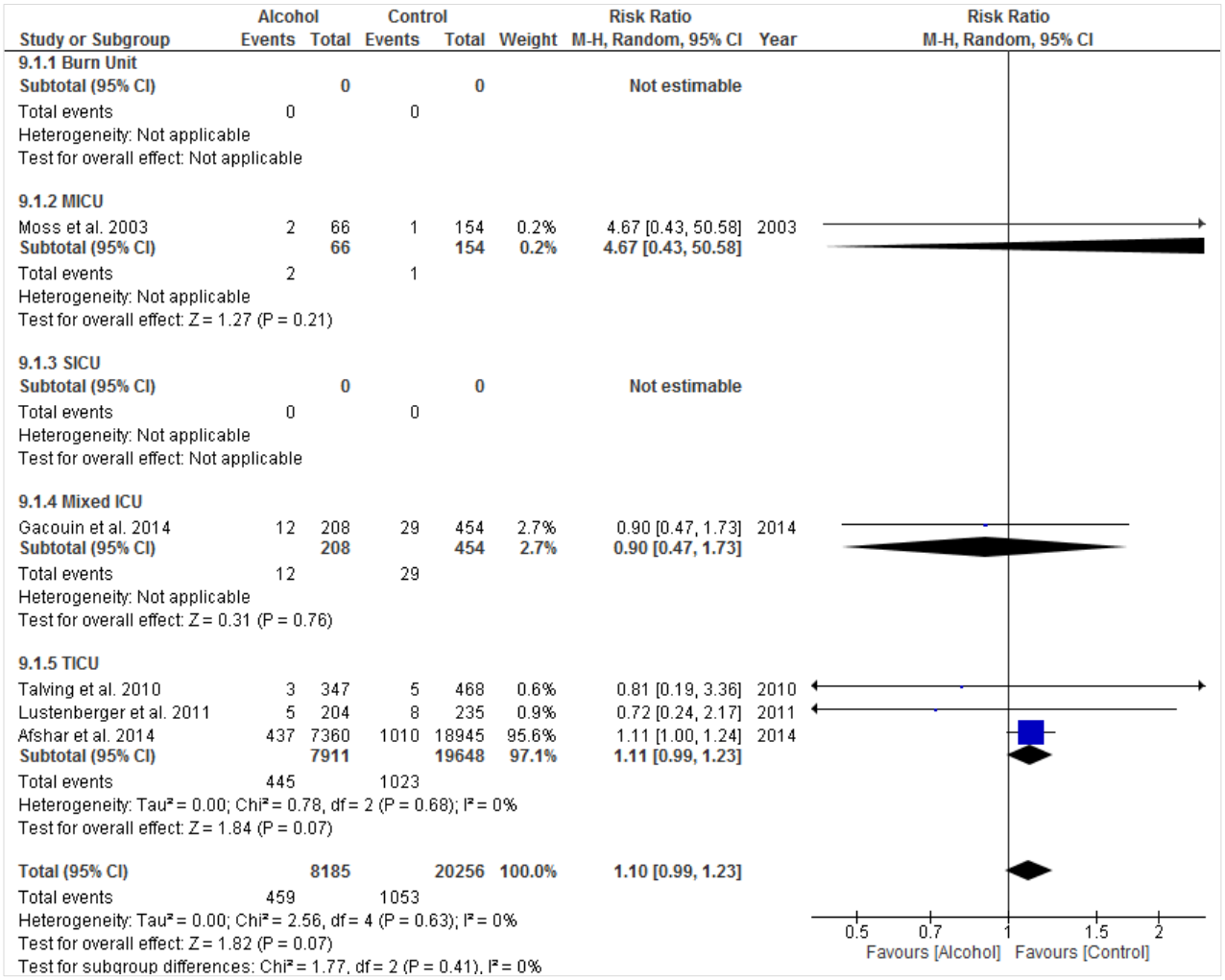
Forest plot 10. Mechanical ventilation prevalence



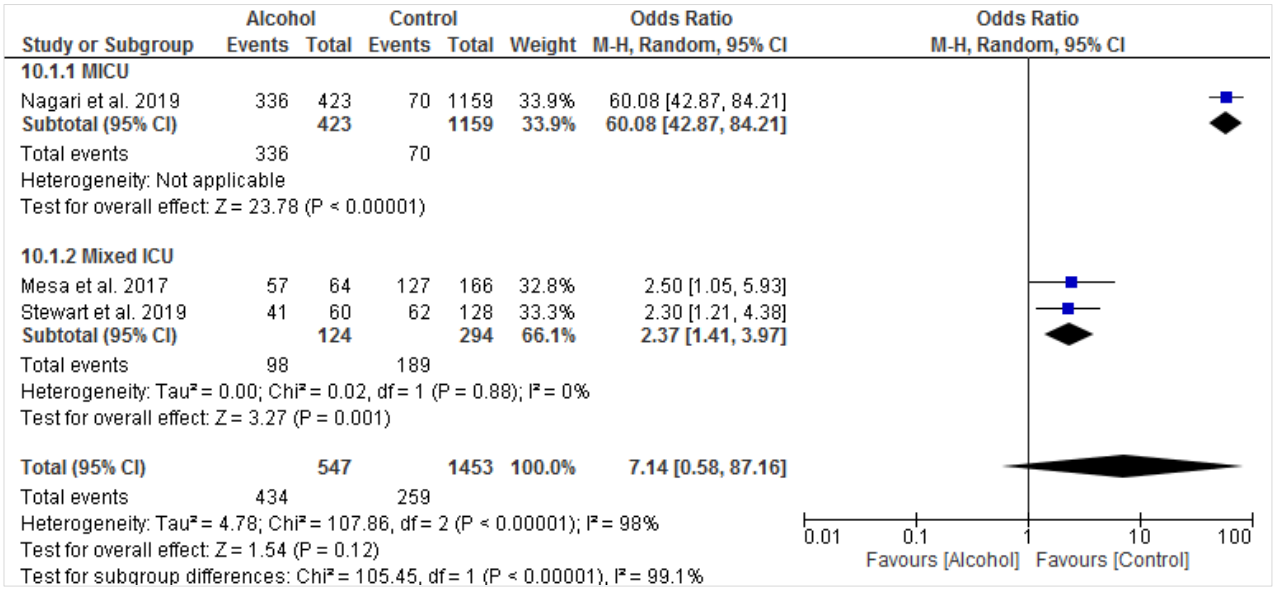
Forest plot 11. Mechanical ventilation days



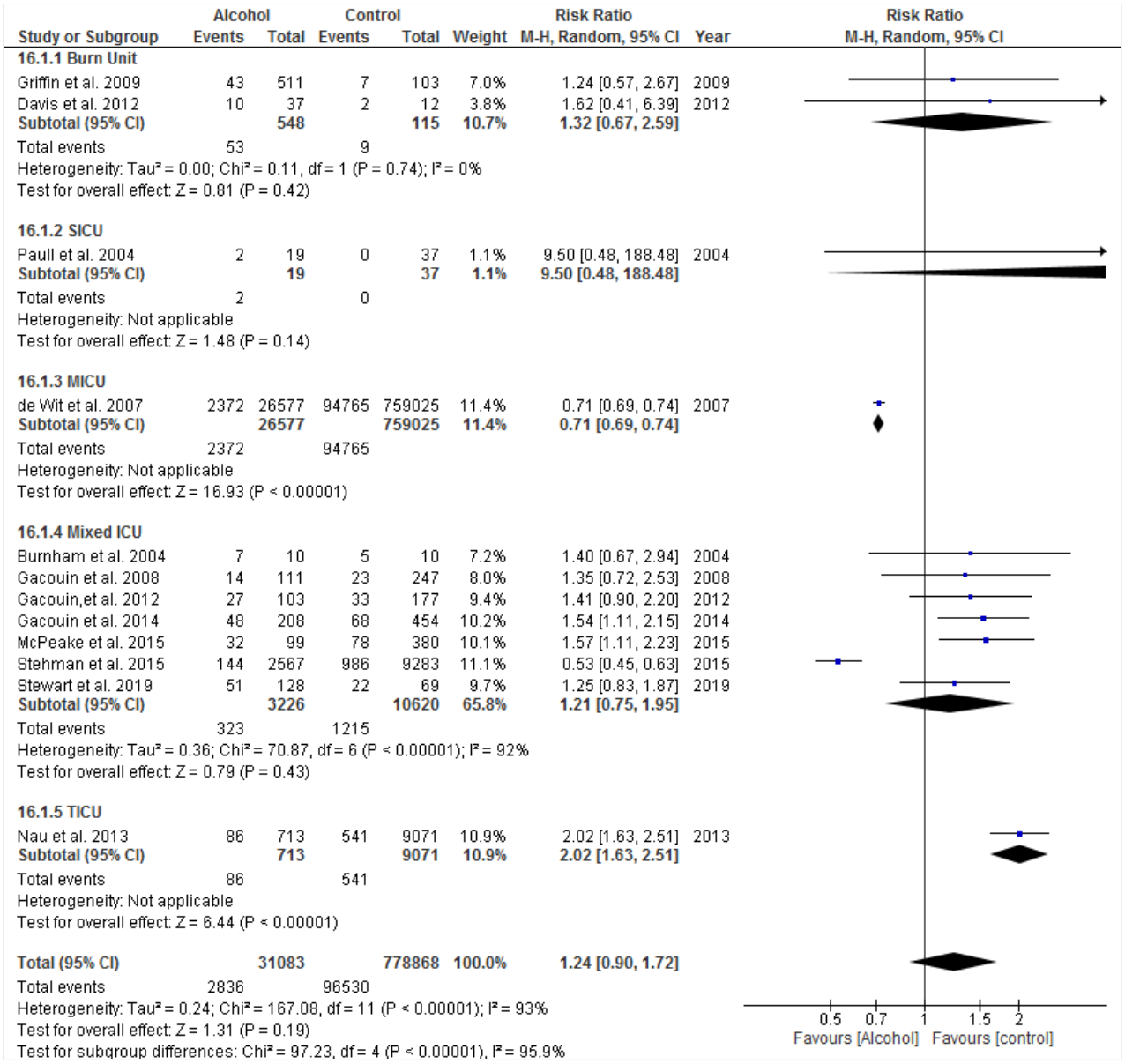
Forest plot 12. Pneumonia prevalence



Forest plot 13. ARDS prevalence



Forest plot 14. Delirium prevalence



Forest plot 15. Sepsis

8.7 APPENDIX G

Descriptive statistics of alcohol use prevalence					
	ICU Department			Statistic	Std. Error
Prevalence	Burn Unit	Mean		,2623	,04026
		95% Confidence Interval for Mean	Lower Bound	,1746	
			Upper Bound	,3500	
		5% Trimmed Mean		,2603	
		Median		,2700	
		Variance		,021	
		Std. Deviation		,14515	
		Minimum		,04	
		Maximum		,52	
		Range		,48	
		Interquartile Range		,17	
		Skewness		,295	,616
		Kurtosis		-,175	1,191
	MICU	Mean		,1938	,04762
		95% Confidence Interval for Mean	Lower Bound	,0811	
			Upper Bound	,3064	
		5% Trimmed Mean		,1936	
		Median		,2000	
		Variance		,018	
		Std. Deviation		,13469	
		Minimum		,02	
		Maximum		,37	
		Range		,35	
		Interquartile Range		,28	
		Skewness		-,098	,752
		Kurtosis		-1,624	1,481
	SICU	Mean		,2271	,06725
		95% Confidence Interval for Mean	Lower Bound	,0626	
			Upper Bound	,3917	
		5% Trimmed Mean		,2152	
		Median		,1500	
		Variance		,032	

		Std. Deviation		,17792	
		Minimum		,09	
		Maximum		,58	
		Range		,49	
		Interquartile Range		,24	
		Skewness		1,617	,794
		Kurtosis		2,259	1,587
	Mixed ICU	Mean		,3346	,03508
		95% Confidence Interval for Mean	Lower Bound	,2636	
			Upper Bound	,4056	
		5% Trimmed Mean		,3184	
		Median		,2900	
		Variance		,048	
		Std. Deviation		,21909	
		Minimum		,02	
		Maximum		,95	
		Range		,93	
		Interquartile Range		,20	
		Skewness		1,226	,378
		Kurtosis		1,244	,741
	TICU	Mean		,2865	,03834
		95% Confidence Interval for Mean	Lower Bound	,2062	
			Upper Bound	,3668	
		5% Trimmed Mean		,2744	
		Median		,2600	
		Variance		,029	
		Std. Deviation		,17147	
		Minimum		,03	
		Maximum		,76	
		Range		,73	
		Interquartile Range		,23	
		Skewness		1,001	,512
		Kurtosis		1,664	,992
	Total	Mean		,2888	,02040
			Lower Bound	,2482	

	95% Confidence Interval for Mean	Upper Bound	,3293	
	5% Trimmed Mean		,2735	
	Median		,2650	
	Variance		,037	
	Std. Deviation		,19134	
	Minimum		,02	
	Maximum		,95	
	Range		,93	
	Interquartile Range		,20	
	Skewness		1,242	,257
	Kurtosis		1,877	,508

a. Prevalence is constant when ICU Department = CICU. It has been omitted.