"ASSESMENT OF SERUM MAGNESIUM LEVELS IN ALCOHOL WITHDRAWAL AND ITS CORRELATION WITH SEVERITY OF ALCOHOL WITHDRAWAL STATE : A CROSS SECTIONAL DESCRIPTIVE HOSPITAL BASED STUDY"

Submitted by

Reg. No. BQ0121001

Dissertation

Submitted to

KLE Academy of Higher Education and Research, Belagavi, Karnataka.

*In partial fulfilment of the requirements for the degree o*f

M.D. (Doctor of Medicine)
in
Psychiatry

Department of Psychiatry

J. N. MEDICAL COLLEGE, KAHER

Belagavi– 590010, Karnataka, India.

December 2024/January 2025

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI

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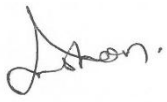
I, **BQ0121001.,** hereby declare that the thesis entitled "Assessment of Serum Magnesium Levels in Alcohol Withdrawal and its Correlation with Severity of Alcohol Withdrawal State: A Cross-Sectional Descriptive Hospital-Based Study," which was conducted at KLES Prabhakar Kore Hospital, JNMC Belagavi, is my original work. This research was carried out in the Department of Psychiatry under the guidance of Dr. Sameeran S. Chate, Head of the Department of Psychiatry, and was submitted to KAHER University, Belagavi, as part of the requirement for the degree.

The study was conducted over a period of one year, from 1st September 2022 to 31st August 2023. I confirm that this work has not been previously submitted to any other university or institution for any other degree, diploma, or title. All sources of information used in the preparation of this thesis have been duly acknowledged.



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ABSTRACT

Introduction: Alcohol withdrawal syndrome (AWS) is a common and potentially severe condition in patients with alcohol dependence. Magnesium deficiency is frequently observed in these patients and may influence the severity of withdrawal symptoms.

Objective: This study aimed to evaluate the correlation between serum magnesium levels and the severity of alcohol withdrawal symptoms in patients admitted for alcohol dependence syndrome at KLE Dr. Prabhakar Kore Hospital.

Methods: A prospective observational study was conducted involving 100 patients admitted with alcohol dependence syndrome. The severity of alcohol withdrawal symptoms was assessed using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. Serum magnesium levels were measured upon admission using colorimetric method and correlated with CIWA-Ar scores.

Results: The study found a significant inverse correlation between serum magnesium levels and the severity of alcohol withdrawal symptoms ($p < 0.01$). Patients with lower serum magnesium levels exhibited higher CIWA-Ar scores, indicating more severe withdrawal symptoms.

Conclusions: Magnesium deficiency is common among patients with alcohol dependence and is associated with increased severity of withdrawal symptoms. Monitoring and correcting serum magnesium levels should be considered in the management of alcohol withdrawal syndrome to potentially reduce symptom severity and improve patient outcomes. Routine screening for magnesium deficiency and appropriate supplementation is recommended as part of standard care for these patients.

Keywords: Alcohol withdrawal syndrome, serum magnesium, CIWA-Ar, hypomagnesemia, alcohol dependence.

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List of abbreviations

ACTH - Adrenocorticotropic hormone

AMPA - Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AWS – Alcohol withdrawal syndrome

AUD - Alcohol use disorder

CIWA-Ar - Clinical Institute Withdrawal Assessment for Alcohol, Revised

DSM: Diagnostic and statistical manual of mental disorders

DT: Dellirium tremens

ECF - Extracellular fluid

GABA - Gamma-aminobutyric acid

HDL - High-density lipoprotein

ICD 11: International classification of diseases 11th revision

Mg: magnesium

NAD - Nicotinamide adenine dinucleotide

NMDA - N-methyl-D-aspartate PTH - Parathyroid hormone

RBC - Red blood cell ROMK - Renal outer medullary potassium channel

TRPM - Transient receptor potential ion channels melastati.

WE: wernickes encephalopathy

WHO: World Health Organization

INTRODUCTION

Alcohol consumption significantly affects human health and contributes to numerous diseases. Recent findings link alcohol to over 200 health issues, including liver cirrhosis, cancer, cardiovascular diseases, and mental health disorders. The Global Burden of Disease Study, a comprehensive analysis of global health trends, identified alcohol as a leading risk factor for disability-adjusted life years (DALYs) worldwide[1].

Alcohol use disorder (AUD), a chronic condition characterized by uncontrollable alcohol consumption despite negative consequences, encompasses both physical and psychological dependencies. Physical dependence involves tolerance and withdrawal symptoms, while psychological dependence includes intense alcohol cravings.[2]

Alcohol withdrawal occurs when a person dependent on alcohol suddenly stops or reduces intake, resulting in symptoms from mild (anxiety, tremors, sweating, nausea, and insomnia) to severe (hallucinations, seizures, and delirium tremens). [2]

Magnesium deficiency is common in individuals undergoing alcohol withdrawal, often resulting from chronic alcohol consumption, poor diet, gastrointestinal damage, and increased urinary excretion of magnesium. This deficiency can exacerbate withdrawal symptoms such as muscle cramps, tremors, irritability, anxiety, confusion, and in severe cases, seizures and cardiac arrhythmias. [3]

Adequate magnesium levels are essential for nervous system function and muscle relaxation, and addressing this deficiency involves supplementation with oral or intravenous magnesium, depending on severity. Regular monitoring of magnesium levels is crucial during withdrawal to ensure timely intervention and reduce complications. Treating magnesium deficiency is part of a comprehensive approach to managing alcohol withdrawal, including medical supervision, hydration, nutrition, and medications, leading to improved health and recovery outcomes.[3]

Alcoholics may have magnesium loss in their urine, even when their blood magnesium levels are low. This is mostly caused by alcohol-induced diuresis, hormonal changes, electrolyte imbalance, renal tubular dysfunction, nutritional deficiencies, and increased catecholamines.[3]

Furthermore, hyponatraemia and hypokalaemia, particularly in cirrhotic patients experiencing a generalised volume overload state, are typical electrolyte abnormalities observed in these patients. [4]

Magnesium serves as a catalyst in various processes related to carbohydrate metabolism. The concentration of magnesium in extracellular fluid is 1.7–2.3 meq/L. Magnesium plays a significant role in modulating the immunological response, excitability of CVS, vasomotor tone, mitochondrial function, and Blood pressure[6]. The movement of magnesium within and outside cells is influenced by the mechanism of carbohydrates. Magnesium ions can enter cells through stimulation of beta adrenoreceptors, while ions can enter cells through insulin and vitamin B6.[7]

Hypomagnesemia is the word used to describe a reduction in total body magnesium levels. Reduced magnesium intake from diet, increased renal excretion, inadequate vitamin D, and decreased absorption of Magnesium ions from the GIT are the causes of deficiency of magnesium in alcoholics.[3]

An adult human needs five milligrams of magnesium per kilogram each day. The acute phase of alcohol withdrawal, characterized by increased plasma insulin concentration, hyperventilation with respiratory alkalosis, and high plasma concentration, may lead to hypokalemia and hypomagnesemia by promoting ion migrations into the cell.[9]

Acutely inebriated alcoholic individuals have also shown a decrease in Mg levels with an increase in serum alcohol concentration[10]. Although various investigations have documented magnesium deficiency in persons with chronic alcohol use, the connection between magnesium deficiency and the severity of alcohol withdrawal state has not been thoroughly examined. Consequently, this study aimed to shed light on the relationship between serum magnesium levels and severity of alcohol withdrawal. If so then magnesium supplementation in alcohol withdrawal can be used to hasten the recovery from delirium

The relationship between low magnesium levels and increased severity of alcohol withdrawal symptoms is a significant focus in clinical research, as evidenced by several key studies. Hillbom et al. investigated hypomagnesemia in patients experiencing delirium tremens, highlighting its prevalence and implications during severe alcohol withdrawal.

Gullestad et al. explored diagnostic methods for magnesium deficiency, emphasizing its clinical relevance in exacerbating withdrawal symptoms. Baraona et al. examined disturbances in magnesium metabolism among individuals with alcohol use disorders, underscoring its role in

influencing withdrawal severity. These studies collectively underscore the critical need for monitoring and managing magnesium levels to mitigate the intensity of alcohol withdrawal symptoms, thereby improving treatment outcomes for individuals with alcohol use disorders.

In India, studies on magnesium supplementation in the context of alcohol withdrawal are limited but growing in relevance due to the significant public health impact of alcohol use disorders in the country.

The rationale for studying magnesium supplementation lies in its critical role in neurophysiological functions and muscle relaxation, which are often compromised during alcohol withdrawal. Effective management of withdrawal symptoms, including tremors, muscle cramps, and anxiety, through magnesium supplementation could potentially improve treatment outcomes and reduce the risk of severe complications such as seizures and cardiac arrhythmias.[11]

While specific Indian studies on this topic may be limited, understanding the potential benefits of magnesium supplementation in alcohol withdrawal is crucial for developing tailored treatment strategies that address the unique health challenges faced by individuals with alcohol use disorders in India. Future research in this area could provide valuable insights into optimizing clinical care and enhancing recovery outcomes for affected individuals.

AIMS AND OBJECTIVES

1. To evaluate serum magnesium levels in participants experiencing alcohol withdrawal.

2. To determine the correlation between the level of serum mg and severity of alcohol withdrawal.

REVIEW OF LITERATURE

Since the beginning of recorded history, alcohol has been consumed for recreational purposes in most parts of the world. According to the latest global estimates from the WHO, approximately 5.1% of the global adult population is living with alcohol use disorders (AUD). Another study by the Global Burden of Disease Collaborative Network reported a 1.5% global AUD prevalence in 2019, highlighting variabilities between countries[10].

Alcohol is currently one of the most widely used psychoactive substances available on the market. It is known for inducing a state of relaxation and reduced inhibitions, which is often sought after in social settings.[11]

Research has indicated that refraining from alcohol intake is associated with a range of health advantages, such as enhanced sleep quality. Conversely, excessive alcohol consumption is linked to an elevated risk of specific types of cancer, cardiovascular disease, and stroke. [12]. The chronic intake of alcohol has also been linked to negative consequences, including cognitive impairment and an increased susceptibility to developing alcohol-related systemic illness [13].

Two principal diagnostic classification systems were employed to delineate AUD. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), developed by the American Psychiatric Association, characterizes AUD as a constellation of behavioural and physical symptoms encompassing withdrawal, tolerance, and craving [14].

The International Classification of Diseases 11th Revision (ICD-11), created by the World Health Organization, categorises AUD into two types: a harmful pattern of alcohol use and alcohol dependence. Alcohol dependence is defined by a strong internal urge to consume the substance, which leads to an inability to control its use, a lowered priority for other activities, and continued use despite negative consequences or harm.[15]

Alcohol use disorder may be defined by the emergence of tolerance resulting from brains homeostatic adaptations, alongside compulsive seeking and withdrawal symptoms upon cessation of alcohol.[16]

The symptoms of Alcohol Use Disorder (AUD) encompass a broad spectrum of behaviours, such as difficulty in controlling drinking and impulsivity (an inability to restrain excessive urges), diminished responses to natural rewards (reward deficiency), and maladaptive learning (increased significance of drug-related cues with chronic use). Additionally, AUD includes the development of opponent processes and poor decision-making [17]

Due to the reliance on alcohol for regular neural activity in individuals with Alcohol Use Disorder (AUD), cessation of alcohol consumption often leads to withdrawal [18]. Sudden cessation may result in acute withdrawal symptoms, including delirium, seizures, and cognitive dysfunction. Research has shown that these symptoms can be severe and may require medical intervention.[19]

However, the symptoms seen during alcohol withdrawal vary in severity depending on the amount and duration of ethanol consumption, as well as individual differences [20]. Withdrawal symptoms are often associated with hyperexcitability, such as insomnia, anxiety, palpitations, agitation, and even seizures, which are likely related to alterations in the functioning of the brain's inhibition system [21].

Because of its hydrophilic properties, alcohol effortlessly permeates all biological membranes and crosses the blood-brain barrier. Upon entry into the system, alcohol metabolism occurs in the liver as well as in the brain due to alcohol dehydrogenase (ADH), catalase, and P450 enzymes in both organs. These metabolic pathways result in the production of three main metabolites: acetaldehyde, salsolinol, and acetate. [22].

Upon reaching the brain, alcohol and its metabolites cause a range of disturbances, such as decreased glucose uptake, increased monocarboxylate uptake, and dopaminergic, GABAergic, and glutamatergic alterations [23].

EFFECT OF ALCOHOL ON BRAIN

The behavioural effects of alcohol, such as disinhibition and anxiolysis, primarily stem from its interaction with the GABA A receptors. Besides influencing GABA A receptor activity, alcohol can directly bind to and alter the function of various proteins, including

ionotropic glutamatergic (NMDA) receptors, alcohol dehydrogenase (ADH), and glycine receptors [24].

Additionally, alcohol has been observed to indirectly impact other neurotransmitters, such as dopamine, serotonin, opioid, and cholinergic systems. This occurs especially in brain areas involved in the mesolimbic reward pathway, including the amygdala, hippocampus, striatum, and ventral tegmental area (VTA), through interactions with GABAergic and glutamatergic neurons or their receptors [25.]

Chronic excessive alcohol consumption causes a chemical imbalance in the brain, prompting a homeostatic response to reestablish neurochemical equilibrium and maintain optimal function [26.] As the brain adapts to prolonged alcohol exposure, it creates a new balance where alcohol becomes crucial for normal neural function [27.] Individuals with Alcohol Use Disorder (AUD) develop increased tolerance to alcohol's effects, leading them to consume nearly toxic levels to achieve desired effects such as relaxation, anxiolysis, or disinhibition. Magnetic Resonance Spectroscopy (MRS) studies often reveal reduced cortical GABA levels in people with AUD, particularly during withdrawal [28].

Alcohol's primary action is thought to primarily influence glutamatergic and GABAergic signaling pathways, with the degree of alteration varying based on the individual's state (acute consumption, chronic consumption, or withdrawal). This process subsequently affects the activity of dopamine, endogenous opioids, and serotonin [29].

EFFECT ON GLUTAMATE AND GABA RECEPTORS:

Both preclinical and clinical research have demonstrated that alcohol inhibits the function of various glutamatergic receptors, including NMDA, AMPA, Kainate, and mGluR5 [29]. Additionally, alcohol interacts with and enhances the activity of GABAA and GABAB receptors. The combined effects on these glutamatergic and GABAergic receptors lead to an overall neuronal imbalance, which is believed to contribute to "blackout" episodes following acute heavy drinking and to excitotoxicity and the loss of synaptic plasticity [31].

EFFECT ON DOPAMINE AND SEROTONIN

Studies utilizing human transcranial magnetic stimulation (TMS), a non-invasive technique for neuromodulation that examines cortical inhibition mediated by GABA receptors, have confirmed that alcohol consumption increases GABAergic inhibitory neurotransmission while decreasing excitatory neurotransmission activated by NMDA receptors [32].As a downstream effect of alcohol consumption, there will be indirect increase of the release of dopamine and enhances acetylcholine activity from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), a key brain region associated with reward and motivation.[33]

Preclinical studies have also demonstrated that dopamine is released in the ventral striatum and NAc, contributing to the rewarding effects of drugs, and this effect can be amplified when nicotine is co-administered [34]. Additionally, the activation of central GABAergic neurotransmission, particularly through GABAB receptors, is linked to mesolimbic dopaminergic neurotransmission during rewarding processes, collectively contributing to the addictive properties of ethanol. [35]

The consumption of alcohol in the short-term leads to an increase in serotonin release, which is associated with the pleasurable aspects of drinking. Research has indicated that acute ethanol exposure boosts the activity of serotoninergic 5-HT3 receptors. With prolonged alcohol use, there can be changes in the expression and function of various other serotonin receptor subtypes, such as 5-HT2. However, it remains unclear whether these changes are a direct effect of alcohol or are the result of a complex series of events and adaptations.[36]

ALCOHOL USE DISORDER:

Alcohol Use Disorder (AUD) is diagnosed when an individual's drinking habits exceed established norms in terms of volume or frequency. One globally recognized tool for identifying AUD is the Alcohol Use Disorder Identification Tool (AUDIT), created by the World Health Organization (WHO) [42]. The classification of AUD has evolved and varies by country, but most healthcare and addiction specialists typically categorise AUD into two main types: binge drinking and heavy drinking [43].

Binge drinking involves consuming large quantities of alcohol in a short period (e.g. five or more drinks within less than two hours for men, and four or more drinks for women),

resulting in a blood alcohol concentration (BAC) exceeding 0.08 g/dL. This pattern of drinking leads to cognitive impairments, decreased inhibition, and reduced ability to voluntarily control alcohol intake. [44]

Heavy drinking is defined by weekly alcohol consumption that surpasses recommended limits, leading to a BAC of 0.1–0.2 g/dL, depending on the number of drinks. For men, consuming more than 15 standard alcoholic drinks per week is considered heavy drinking, whereas for women, the threshold is more than eight drinks per week. [45]

Heavy drinking contributes to neuronal atrophy and decreased white matter fibers [46], which are linked to a higher risk of dependence, anxiety, depression, cognitive deficits, impaired control over drinking behaviour, cardiovascular diseases, and other health issues. [47,48]

ALCOHOL WITHDRAWAL SYNDROME:

Alcohol withdrawal syndrome often occurs in individuals who regularly consume alcohol and then abruptly stop alcohol consumption. When alcohol consumption ceases suddenly, its inhibitory effects on the central nervous system (CNS) diminish, while the excitatory influence of glutamate on the CNS remains unopposed. This imbalance leads to overall CNS excitation, resulting in various clinical symptoms, such as autonomic hyperactivity (including increased heart rate, tremors, and sweating) and neuropsychiatric complications (like delirium and seizures).[49]

In addition to glutamate, dopamine is another neurotransmitter involved in alcohol withdrawal. Elevated dopamine levels in the CNS during alcohol use and withdrawal contribute to symptoms of autonomic hyperarousal. Repeated withdrawal episodes and the accompanying neuroexcitation can lower the seizure threshold, increasing the risk of withdrawal seizures and kindling.[50]

PATHOPHYSIOLOGY OF ALCOHOL WITHDRAWAL:

[55]Chronic alcohol consumption disrupts the equilibrium between the inhibitory neurotransmitter GABA and the excitatory neurotransmitter glutamate. GABA primarily mediates both pre-synaptic and post-synaptic inhibition, whereas glutamate is converted

into beta-aminobutyrate by glutamate decarboxylase. This enzyme, located in nerve endings, plays a crucial role in the formation of GABA in bodily fluids.

In the citric acid cycle, transamination occurs, a process catalyzed by the enzyme GABA, resulting in succinate production. Three distinct GABA receptors have been identified: GABA A, GABA B, and GABA C. GABA A and GABA B receptors are prevalent in the central nervous system, whereas GABA C receptors are found exclusively in the retina.

GABA-A, GABA-B, and GABA-C are types of ionotropic receptors that, when activated, permit chloride ions to enter neurons, altering their membrane potentials. Specifically, GABA-B receptors, which are G protein-coupled receptors, regulate the flow of potassium and calcium ions. GABA-A receptors are pentameric structures comprising six alpha, four beta, four gamma, one delta, and one theta subunit.[55]

Gamma-Aminobutyric Acid (GABA) A, GABA B, and GABA C receptors play distinct roles in neuronal inhibition. GABA A and GABA C receptors are ionotropic and, upon activation, permit chloride ions to enter neurons, resulting in rapid inhibitory postsynaptic potentials. In contrast, GABA B receptors are G protein-coupled and influence the flow of both potassium and calcium ions, leading to both pre- and post-synaptic inhibition. Specifically, the Gi component of GABA B receptors inhibits adenyl cyclase, which subsequently opens potassium channels, while the Go component inhibits or delays calcium influx.

Drugs such as benzodiazepines and barbiturates function as neuromodulators, enhancing chloride ion conductance through these receptors, thereby amplifying their inhibitory effects.[55]

Glutamate:

Approximately 75% of excitatory neurotransmission in the brain and spinal cord is mediated by glutamate. This neurotransmitter is synthesized via two primary pathways. In the first pathway, the enzyme GABA transaminase converts alpha ketoglutarate to glutamate. In the second pathway, glutamate released into the synaptic cleft is taken up by glial cells and converted to glutamine by the enzyme glutamine synthase. This glutamine then diffuses back into nerve terminals, where it is hydrolyzed by glutaminase to regenerate glutamate. The glutamate is then concentrated within synaptic vesicles by vesicular glutamate transporters.[56]

Glutamate acts on two types of receptors in the central nervous system (CNS): ionotropic and metabotropic receptors. Ionotropic glutamate receptors are further categorized into three subtypes: AMPA, kainate, and NMDA receptors. AMPA and NMDA receptors are present on all neurons in the CNS, while kainate receptors are found on presynaptic GABA-secreting nerve endings and glial cells. Notably, NMDA receptors, which are highly concentrated in the hippocampus, are implicated in memory and learning processes. The activation of AMPA and kainate receptors primarily involves the influx of sodium ions and the efflux of potassium ions, while NMDA receptor activation involves calcium influx in addition to sodium and potassium ion flow.[56]

Neuromodulator drugs, such as benzodiazepines and barbiturates, enhance the effects of GABA-A receptor activity, which increases chloride ion conductance and improves the signal-to-noise ratio in the brain.

[57]AMPA channels exhibit low calcium permeability, whereas NMDA channels have distinctive activation characteristics.

1. Glycine is required as a co-agonist for the activation of NMDA receptors, facilitating the receptor response to glutamate.
2. NMDA receptors are blocked by magnesium ions at the resting membrane potential. This blockage is relieved when the membrane is partially depolarized, an effect that occurs due to the activation of adjacent AMPA and kainate receptors.
3. The excitatory postsynaptic potentials (EPSPs) generated by the activation of AMPA and kainate receptors are typically larger and more rapid than those produced by NMDA receptors.

Acute alcohol intoxication enhances the activity of GABA receptors, particularly those containing delta subunits. Chronic alcohol consumption, however, results in the down-regulation of GABA receptors and an increased expression of NMDA receptors. When alcohol intake is suddenly stopped, this imbalance leads to glutamate-mediated central nervous system excitability. This excitability can cause neuropsychiatric complications such as delirium and seizures.[57]

Seizures during alcohol withdrawal are typically of the tonic-clonic type. The autonomic arousal and hallucinations that occur are attributed to an increase in dopamine levels. The rebound activity of glutamatergic transmission during alcohol withdrawal further induces excitotoxicity, which is exacerbated by elevated levels of homocysteine.[56,58]

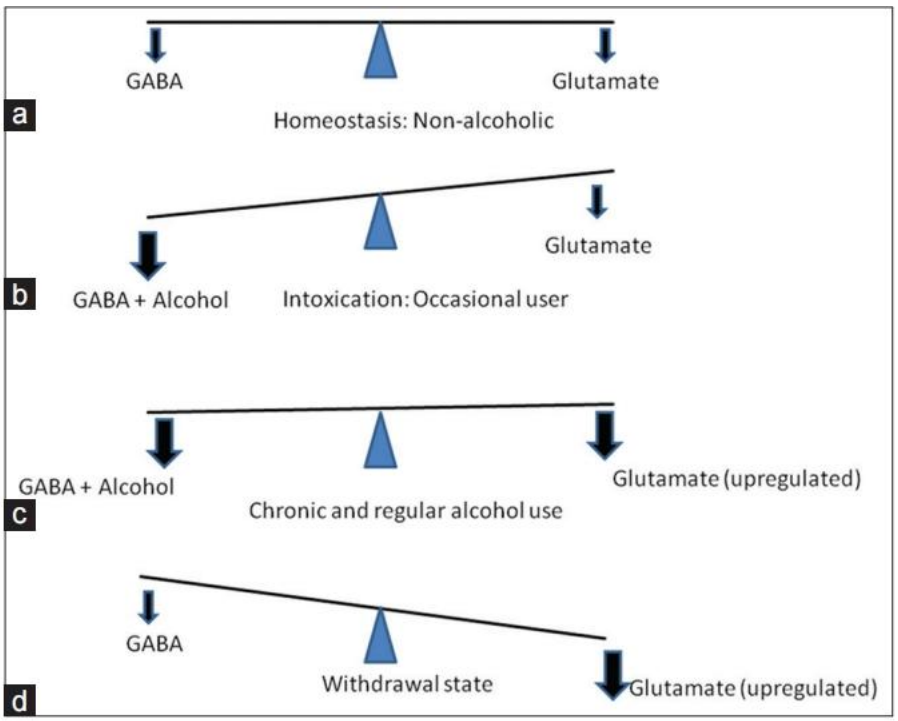


Figure 1: Neurochemistry of alcohol withdrawal

Definition of alcohol withdrawal syndrome:

Alcohol Withdrawal Syndrome (AWS): Alcohol withdrawal syndrome (AWS) refers to "a set of symptoms that occur when an individual abruptly stops or significantly reduces heavy and prolonged alcohol consumption. This syndrome typically manifests within hours to a few days after cessation of alcohol use and is characterized by a range of

physical and psychological symptoms, which can vary in severity from mild discomfort to life-threatening complications."[14]

DSM 5 CRITERIA FOR ALCOHOL WITHDRAWAL [14]

"All 4 criteria must be present to diagnose alcohol withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged

B. Two (or more) of the following, developing within several hours to a few days after cessation of (or reduction in) alcohol use described in criterion A:

1. autonomic hyperactivity (e.g. sweating or pulse rate greater than 100 b.p.m)

2. increased hand tremor

3. insomnia

4. nausea or vomiting

5. transient visual, tactile or auditory hallucinations or illusions

6. psychomotor agitation

7. anxiety

8. generalized tonic–clonic seizures

C. The signs and symptoms in criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another medical disorder, including intoxication, or withdrawal from another substance"

Alcohol withdrawal seizure

"Typically, the generalized tonic–clonic type, characterized by rhythmic, yet jerking movement, especially of the limbs"

Delirium

The DSM-5 criteria for delirium are:

A. "A disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment)

B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of day

C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language

visuospatial ability or perception)

D. The disturbances in criteria A and C are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of severely reduced level of arousal, such as coma

E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse or to a medication), or exposure to a toxin, or is because of multiple aetiologies."

The diagnosis of alcohol withdrawal syndrome is contingent upon the fulfillment of two prerequisites:

1. Recent Cessation or Reduction: There must be clear evidence of recent cessation or reduction of alcohol consumption following prolonged and/or high-dose usage that is typically repeated.
2. Exhibiting Withdrawal Symptoms: The patient must exhibit symptoms of alcohol withdrawal that cannot be attributed to any other medical, mental, or behavioral disorder.

To make an accurate diagnosis, it is crucial to gather detailed information about the patient's history of alcohol consumption, including the amount and frequency of intake, and to establish a clear relationship between the cessation of alcohol use and the onset of withdrawal symptoms.[60]

Alcohol Withdrawal Symptoms Assessment Using the CIWA-Ar Scale

The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale is a cornerstone tool in the assessment and management of alcohol withdrawal syndrome

(AWS). Developed in 1989 by Sullivan et al., it provides a standardized and objective approach to evaluating the severity of withdrawal symptoms, making it highly valuable for both clinical practice and research.

Functions of the scale.

The CIWA-Ar is a clinician-administered, 10-item questionnaire designed to assess the current severity of AWS in individuals who are dependent on alcohol and are abruptly stopping or reducing their intake. Each item is scored on a scale ranging from 0 (no symptoms) to 7 (most severe symptoms), with a total possible score of 67. Higher scores indicate greater withdrawal severity and a higher risk of developing complications such as seizures and delirium tremens.[53]

Components and Scoring [53]

The CIWA-Ar assesses the following areas of withdrawal:

Central Nervous System (CNS):

- Tremor (0-7)
- Nausea and Vomiting (0-7)
- Auditory Disturbances (0-7) (e.g., tinnitus)
- Visual Disturbances (0-7) (e.g., hallucinations)
- Tactile Disturbances (0-7) (e.g., formication)

Autonomic:

- Heart Rate (0-2) (increased rate)
- Blood Pressure (0-2) (systolic or diastolic)
- Sweating (0-7)

Mental Status:

- Anxiety (0-7)
- Headache (0-7)
- Clouding of Sensorium (0-4) (confusion)

Benefits of CIWA-Ar Scale for Clinical Practice and Research

- Standardized: Provides a consistent and objective method for assessing AWS, improving communication and collaboration between healthcare professionals.
- Clinically Useful: Guides treatment decisions based on withdrawal severity. Scores of <8 suggest minimal withdrawal, 8-15 indicate moderate withdrawal, and >15 suggest severe withdrawal, potentially requiring more intensive intervention.
- Reliable and Valid: Extensive research has established the CIWA-Ar's reliability and validity in measuring AWS severity.
- Quick and Efficient: Takes approximately 2 minutes to administer, facilitating routine assessment and monitoring.

The CIWA-Ar scale's comprehensive and systematic approach ensures effective management of AWS by enabling healthcare providers to promptly identify and address withdrawal symptoms, thereby reducing the risk of complications.53

If an individual experiences withdrawal-like symptoms or delirium more than two weeks after they have completely stopped drinking alcohol, it is no longer considered a diagnosis of alcohol withdrawal syndrome (AWS) or delirium tremens, regardless of the amount of alcohol they consumed. Instead, other potential causes for these symptoms should be investigated.[60]

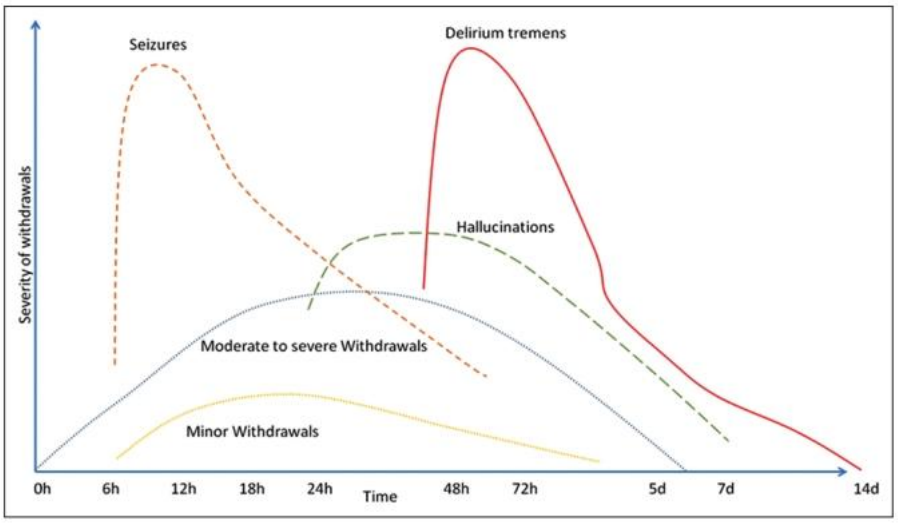


Figure 2: Graph depicting the time course of alcohol withdrawal symptoms (based on clinical information gathered in Table 2; adaptation from Haber *et al.*[7])

Clinical Descriptions of Alcohol Withdrawal Syndromes by Severity[52]

Mild Alcohol Withdrawal

- Symptoms: Anxiety, insomnia, gastrointestinal upset, headache, palpitations, and mild tremors.
- Onset: Symptoms typically begin within 6-24 hours after the last drink.
- Duration: Symptoms usually peak at 24-48 hours and may last up to 5 days.

Moderate Alcohol Withdrawal

- Symptoms: Increased anxiety, insomnia, gastrointestinal upset, headache, palpitations, moderate tremors, sweating, and elevated blood pressure.
- Onset: Symptoms usually start within 6-24 hours after cessation of alcohol.
- Duration: Symptoms peak at 24-48 hours and can persist for up to 5-7 days.

Severe Alcohol Withdrawal

- Symptoms: Severe tremors, sweating, fever, tachycardia, hypertension, agitation, hallucinations (visual, auditory, or tactile), and seizures.
- Onset: Severe symptoms typically begin within 48-72 hours after the last drink but can start as early as 24 hours.
- Duration: Symptoms can last from 4 to 12 days.

- Complications: Delirium tremens (DT) is a severe and potentially life-threatening complication of alcohol withdrawal syndrome, typically occurring 48 to 96 hours after abrupt cessation of heavy and prolonged alcohol use. It is characterized by profound confusion, visual hallucinations, severe agitation, coarse tremors, and autonomic instability including tachycardia, hypertension, and fever. Without prompt medical intervention, DT poses risks of cardiovascular collapse, seizures, and death. Treatment involves urgent administration of benzodiazepines such as diazepam or lorazepam to control symptoms and prevent seizures, along with meticulous supportive care to stabilize vital signs, manage fluid and electrolyte imbalances, provide nutritional support, and offer psychosocial reassurance. Early recognition and management are crucial for improving outcomes and reducing mortality associated with DT.[62]

Prolonged Withdrawal Symptoms

- Symptoms: Persistent anxiety, insomnia, fatigue, and mood disturbances.
- Onset: These symptoms can appear weeks to months after acute withdrawal has resolved.
- Duration: Can last several weeks to months and may require long-term management.

Recognizing and accurately assessing the severity of alcohol withdrawal is crucial for effective management and treatment. Early intervention can mitigate the risk of complications, including seizures and delirium tremens.

Management of alcohol withdrawal syndrome

Detoxification

Detoxification is a critical process aimed at safely reducing an individual's dependence on a psychoactive substance, either by gradually tapering the substance itself or substituting it with a pharmacologically cross-tolerant agent. This method helps minimize withdrawal

symptoms, prevent complications, and facilitate a smoother transition to abstinence. By stabilizing individuals physically and psychologically, detoxification prepares them for further addiction treatment and recovery efforts. It serves as an essential initial step in comprehensive addiction care offered in diverse settings such as inpatient and op facilities. [62]

General supportive care

Patients experiencing alcohol withdrawal should ideally be managed in a quiet environment with minimal stimulation and subdued lighting to reduce agitation and sensory overload. For those presenting with seizures or Delirium tremens (DT), immediate access to intravenous benzodiazepines and fluids is essential. Intramuscular lorazepam is commonly used to prevent additional seizures and provide sedation. It is crucial to administer sedation promptly to calm the patient and prevent harm from agitation, with physical restraints used if necessary. Prompt correction of fluid and electrolyte imbalances is critical, and ensuring adequate nutrition while avoiding aspiration in heavily sedated patients is important. Supplementation with vitamin B is necessary to prevent Wernicke's encephalopathy, a severe neurological disorder associated with thiamine deficiency often seen in chronic alcohol users. [52]

Drug of choice in detoxification:

In 1969, a seminal study by Kaim et al. conclusively demonstrated that chlordiazepoxide, a benzodiazepine, was significantly more effective than chlorpromazine, hydroxyzine, thiamine, or placebo in preventing seizures and delirium tremens (DT) in patients undergoing alcohol withdrawal.[63] This evidence strongly supports the use of benzodiazepines as the preferred treatment for alcohol withdrawal states, effectively reducing the risk of severe symptoms such as seizures or DT. Chlordiazepoxide specifically has shown a slight advantage over other benzodiazepines and anticonvulsants in managing alcohol withdrawal symptoms.[58]

While anticonvulsants may be considered in milder withdrawal cases owing to their lower sedative effects and potential for lower dependence or abuse, they have not been proven to be more effective than benzodiazepines in preventing seizures or DT during

severe alcohol withdrawal. Therefore, they are not recommended for use in severe withdrawal states where benzodiazepines remain the standard of care.[65]

To calculate an estimate of alcohol consumption in grams (g), the following formula is used:

{Alcohol (in g)} = \{Volume of liquor (ml)} \times 0.008 \times \{Ethanol content (%)}

Here's how each variable in the formula is defined:

- Volume of liquor (ml): The amount of alcoholic beverage consumed, measured in (ml).
- Ethanol content (%): Percentage of ethanol (alcohol) by weight/volume in the liquor. For example, if the liquor is 40% alcohol by volume (ABV), the ethanol content would be 40%.

Supportive management in AWS:

Thiamine (vitamin B1) plays a critical role in supportive care for individuals undergoing alcohol withdrawal. It is essential in preventing neurological complications such as Wernicke's encephalopathy (WE) and Korsakoff's syndrome, which can result from thiamine deficiency exacerbated by alcohol use. Alongside thiamine, comprehensive supportive care includes addressing electrolyte imbalances, correcting dietary deficiencies, and managing fluid balance, all of which are crucial for optimizing patient outcomes during alcohol detoxification. Upon admission, patients with Alcohol Withdrawal Syndrome (AWS) typically receive an initial bolus dose of thiamine, commonly 100 mg administered intravenously, to prevent acute episodes of Wernicke's encephalopathy. Maintenance doses are then provided to sustain adequate thiamine levels and mitigate further deficiency-related risks. This proactive approach helps safeguard against severe neurological complications and supports the overall recovery process for individuals undergoing alcohol detoxification. [67]

Individuals undergoing alcohol withdrawal management require comprehensive supportive care to address various aspects of their health affected by chronic alcohol use and withdrawal symptoms. This includes providing nutritional support through multivitamins, mineral packs, and specifically thiamine (vitamin B1) to address

deficiencies and aid in healing. Thiamine can be administered intramuscularly or orally daily for a period to replenish depleted stores and mitigate the risk of neurological complications like Wernicke's encephalopathy.[68]

Supportive care is crucial for managing dehydration and electrolyte imbalances that often occur due to symptoms such as vomiting, diarrhea, and increased urine production associated with Alcohol Withdrawal Syndrome (AWS). Regular monitoring of electrolyte levels and ensuring adequate hydration are essential components of supportive care to maintain overall health and prevent complications during alcohol withdrawal management. This comprehensive approach helps stabilize patients physically, supports their recovery process, and reduces the risk of serious medical complications related to alcohol withdrawal.[66,68]

MAGNESIUM

It is the second most common mineral in the intracellular fluid of the body, second only to potassium, and among cations it is the fourth abundant one. It plays a crucial role in various physiological processes and serves as a catalyst in numerous reactions involved in carbohydrate metabolism.The magnesium has a range of 1.7 to 2.3 mEq/L.[69].

Magnesium regulates many physiological systems, including mitochondrial activity, immunological defense, myocardial excitability, neural regulation, vasomotor tone, and BP. Carbohydrate metabolism regulates the flow of magnesium ions both inside and outside the cell. Positive beta anions leave the cell, whereas insulin, vitamin D, and vitamin B6 help magnesium ions enter the cells.[70]

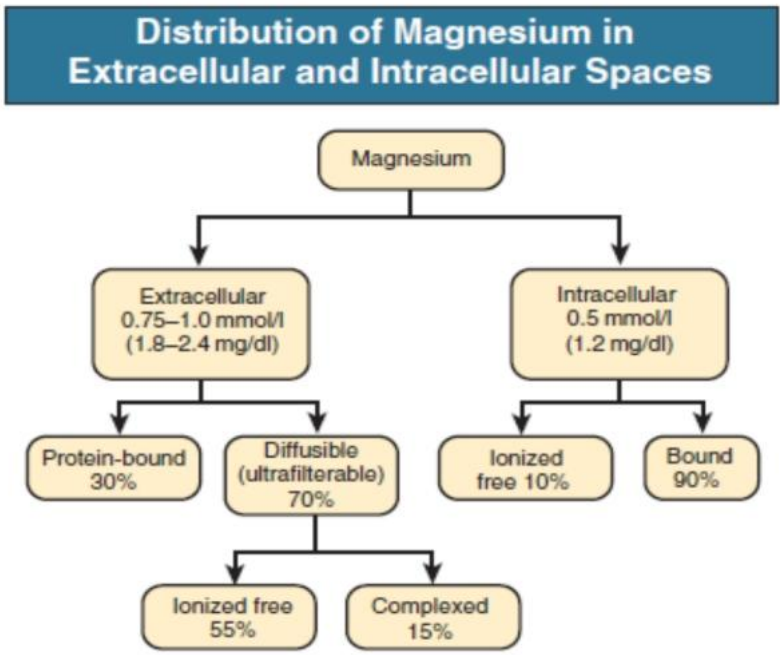


FIGURE 3 : Distribution of magnesium in extracellular spaces

Magnesium from the food sources are reabsorbed primarily from the distal part of small intestine and colon through a combination of passive transport and a saturable mechanism. The majority of intestinal magnesium uptake is attributed to Proximal convuluted tubules , which accounts for 80–90% of the process. This mode of transport will not occur in places devoid of tight junction proteins that bind claudins. Additionally, transport of transcellular magnesium occurs via two major channels the TRM6 and the TRM7 channel.[70]

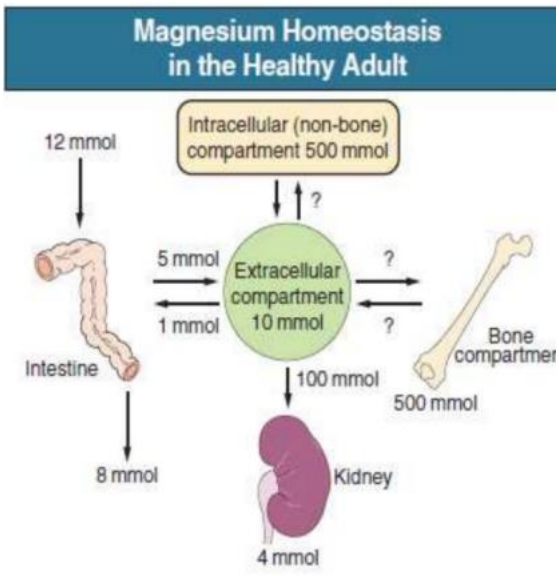


Figure 4: magnesium homeostasis in adults.

The kidneys are largely responsible for Mg elimination from the body, with lower quantities removed by intestinal secretion and perspiration. The kidneys filter around 80% of extracellular magnesium, with just 5% being eliminated in urine. Magnesium is transported transcellularly by TRPM6 and TRPM7 channels, which do not need tight cell connections.[69]

Two conditions must be satisfied in order for magnesium to be absorbed at the thick ascending limb of the Henle loop. First, an electrical lumen positive gradient must be created, which is triggered by salt reabsorption. This gradient provides a driving factor for divalent cation reabsorption. The second requirement is the development of claudins-16 and [19], which create selective tight junctions to aid magnesium transport. Transcellular transport is the primary mode of Mg reabsorption in the distal tubule. This occurs in the presence of an upward electrochemical gradient. Magnesium ion reabsorption occurs in the renal tubules, with the proximal tubule accounting for 25%, the thick ascending limb accounting for up to 65%, and the distal tubule accounting for 5%. Thus, the thick ascending limb of the Henle loop is the primary site for the reabsorption of magnesium. [71]

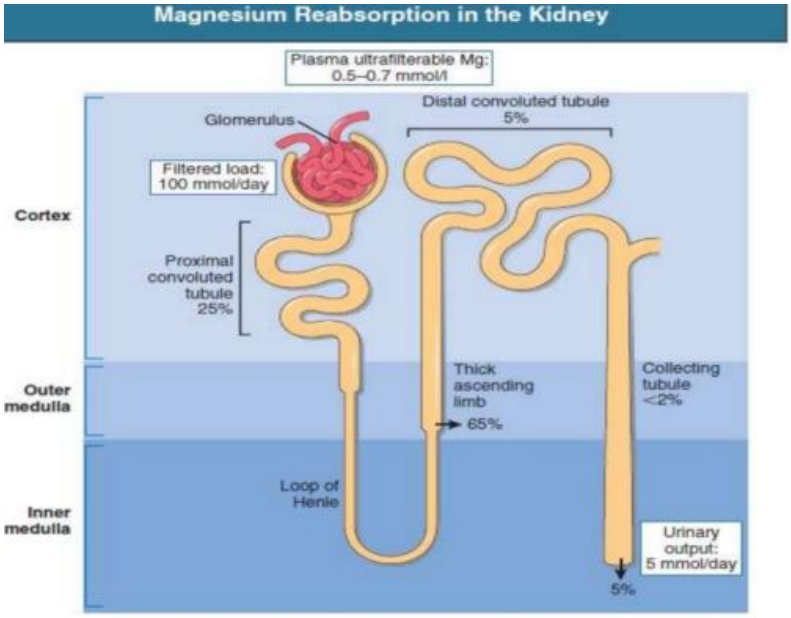


figure 5: Magnesium reabsorption in kidney

Increased serum magnesium and calcium levels can hinder magnesium transport. Additionally, Extracellular fluid volume expansion can reduce the proximal tubular reabsorption of sodium, calcium, and magnesium. Vasopressin, calcitonin, glucagon, and PTH all have the ability to promote urinary magnesium excretion via the paracellular route. Acetyl choline, bradykinin, and ANP, on the other hand, can promote magnesium release via the same mechanism. [72]

Loop and thiazide diuretics can produce hypomagnesaemia by altering the electrochemical gradient for entry of mg and increasing the distal sodium supply, resulting in decreased magnesium entry. It is vital to remember that 30% of the extracellular magnesium is intracellular, whereas 27% is found in the serum. The paracellular route activates vasopressin, calcitonin, glucagon, and PTH, whereas acetylcholine, bradykinin, and ANP enhance urinary magnesium excretion. Loop diuretics and thiazide diuretics cause hypomagnesemia by disrupting the electrochemical gradient for magnesium entry and boosting distal delivery of sodium.[72]

The transport of magnesium in the serum can be impaired by an increase in magnesium or calcium levels. The Extracellular fluid volume expansion has the effect of decreasing reabsorption of sodium, calcium, and magnesium in the kidney. Vasopressin, calcitonin, glucagon, and PTH stimulate urinary magnesium excretion via the paracellular pathway.

Acetyl choline, bradykinin, and ANP also stimulate urinary magnesium excretion. Drugs that can cause hypomagnesaemia include thiazide diuretics and loop diuretics, which disrupt the electrochemical gradient for mg entry by increasing the distal delivery of sodium. [73].

Hypomagnesaemia

Hypomagnesemia refers to a decrease in the total body magnesium levels. The incidence of hypomagnesemia is significant in critical care units. The etiology of hypomagnesemia is typically related to gastrointestinal (GI) diseases, particularly malabsorption syndromes. Proton pump inhibitors (PPIs) are also implicated in the selective impairment of intestinal magnesium absorption. Magnesium is primarily present in the body in two forms: 50% is present in the bone, and 28% is protein-bound. [69,71]

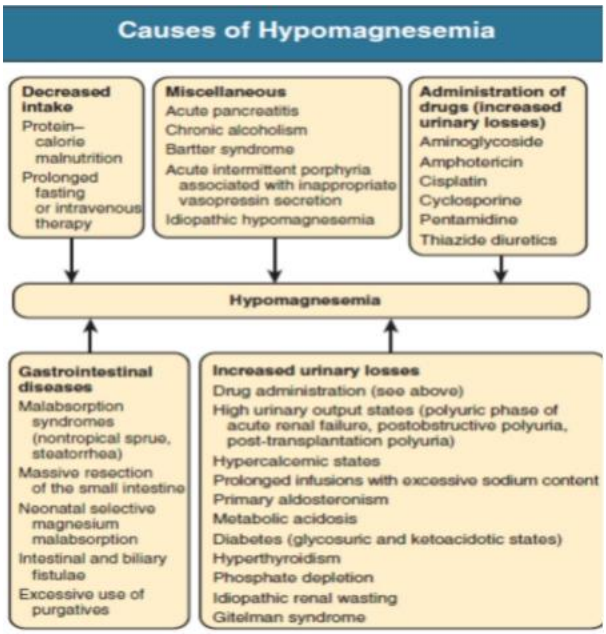


Figure 6: causes of hypomagnesemia.

Hypomagnesemia is a medical disorder defined by generalised weakness, neuromuscular hyperexcitability, seizures, and tremors. The ECG may show a prolonged QT interval with ST segment depression. This illness is characterised by a magnesium deficiency, which results in hypocalcemia and hypokalemia. Patients are commonly treated with intravenous magnesium sulphate, oral magnesium oxide or hydroxide tablets, or a combination of the two.[71]

How magnesium deficiency affects the patients with alcohol withdrawal syndrome

Consumption of alcohol is a significant cause of magnesium deficiency in adults, as it contains no calories and is a poor source of magnesium. Magnesium deficiency in alcoholics arises mainly due to the malabsorption of magnesium ions from the gastrointestinal tract, as well as alcohol's interference with the tubular reabsorption of magnesium [74].

This deficit can cause delirium tremors, which is thought to be the cause of the disorder. Magnesium insufficiency can produce muscular twitching, tremors, and convulsions, as initially reported by Hirshfeder and Haury [75].

Magnesium sulphate has been used successfully to treat delirium tremens, with the main mechanism being that extracellular magnesium exerts inhibitory control over the NMDA receptors on which the excitatory neurotransmitter glutamate works. In the withdrawal state, glutaminergic activity increases, and when combined with magnesium insufficiency, the central nervous system's excitement intensifies. As a result, magnesium's disinhibition of NMDA receptors results in a state of neuronal hyperexcitability and increased risk of seizures, anxiety, and other withdrawal symptoms [76].

Studies done in the past about relationship between serum mg levels and alcohol withdrawal state.

Thompson, R., Thomas, R., et al. (2018).

A double-blind, randomized controlled trial was conducted on 100 individuals experiencing alcohol withdrawal. Participants were divided into two groups: one received intravenous magnesium sulfate alongside standard care, while the other group received only standard care. The findings indicated that the group receiving magnesium supplementation showed a marked reduction in both the severity and duration of withdrawal symptoms. Additionally, this group experienced fewer seizures and demonstrated better overall recovery compared to the control group.[77]

Patel, M., Desai, S., et al. (2019).

In another RCT conducted to evaluate the efficacy of oral versus intravenous magnesium supplementation in treating alcohol withdrawal symptoms. A total of 80 patients

experiencing alcohol withdrawal were randomly assigned to two groups: one receiving oral magnesium supplementation and the other intravenous supplementation, in addition to standard withdrawal management. Both groups exhibited higher serum magnesium levels and a decrease in withdrawal symptoms. However, the intravenous group demonstrated a faster clinical improvement, indicating a more immediate advantage of this mode of administration. [78]

Sandhya, M., Anusha, R., et al. (2017).

- To determine the prevalence of electrolyte imbalances, including hypomagnesemia, in patients admitted for alcohol withdrawal, an observational study was conducted on 200 individuals exhibiting alcohol withdrawal symptoms. The serum magnesium levels of the patients were assessed upon admission. The results indicated that 56% of the patients had hypomagnesemia, and those experiencing severe withdrawal symptoms exhibited significantly lower magnesium levels, underscoring the necessity of monitoring and addressing magnesium deficiency in this particular population [79].

Verma, A., Biswas, A., et al. (2015).

- The relationship between serum magnesium levels and the intensity of alcohol withdrawal symptoms was examined in a study that included 150 individuals who were admitted for alcohol withdrawal. The severity of symptoms was assessed using the Clinical Institute Withdrawal Assessment for Alcohol scale, and it was found that there was a negative correlation between serum magnesium levels and withdrawal severity. This suggests that lower levels of magnesium are associated with more severe withdrawal symptoms [80.]

Zhang, Y., Wang, J., et al. (2020).

A descriptive study done to investigate the mechanisms through which magnesium exerts neuroprotective effects during alcohol withdrawal, an animal model study was conducted to analyze the influence of magnesium on NMDA receptor activity and neuronal damage during this period. The results demonstrated that magnesium modulates NMDA receptor activity, thereby reducing excitotoxicity and neuronal damage. These findings imply that

magnesium has a neuroprotective function that could be useful in managing alcohol withdrawal.[81]

Meta analysis done by Nguyen, T., Smith, H., ***et al. (2021)*** [9]

The findings are as follows

Magnesium supplementation significantly reduced the overall severity of alcohol withdrawal symptoms. This was measured using standardized scales for withdrawal symptoms.

The incidence of seizures and delirium tremens, which are severe complications of alcohol withdrawal, was notably lower in patients receiving magnesium supplementation.

Patients who received magnesium supplementation experienced a shorter duration of withdrawal symptoms compared to those who did not receive supplementation.

Hence this study supports the routine assessment of serum magnesium levels in patients undergoing alcohol withdrawal. Magnesium supplementation should be considered as an integral part of the management protocol for alcohol withdrawal to improve patient outcomes.

Hallack et.al

Hallak et al. has done an investigation into the effects of magnesium on alcohol withdrawal symptoms and discovered that individuals receiving magnesium supplementation experienced fewer and less severe symptoms as compared to the control group

[82] As American society of addiction medicine (ASAM) 2019 guidelines emphasizes the importance of monitoring and correcting electrolyte imbalances, particularly hypomagnesemia, in individuals experiencing alcohol withdrawal. The guidelines recommend magnesium supplementation for patients with documented deficiency or severe withdrawal symptoms.

Helsinki et al., in collaboration with the Finnish Foundation for Alcohol Studies, conducted a randomized controlled trial to examine the differences in serum GGT, AST, and ALT levels between two groups. The study revealed that the decrease in serum AST levels was more pronounced in the group that received magnesium supplements, potentially indicating a protective effect against alcoholic liver damage.

Ernst Beroz, MD, Peter Conran, MD, and Robert W. Banchard, has done a study on 50 male patients admitted for alcohol withdrawal and concluded that parenteral magnesium is useful in the treatment of severe acute brain syndrome related to alcohol.

Parenteral magnesium in the prophylaxis and treatment of delirum tremens.

Magnesium supplementation has been found to enhance metabolic variables and muscle strength in individuals with a history of alcohol abuse, as per a study conducted by Lars gullestad and associates. The study involved 52 individuals, aged 57 on average, with a history of alcohol abuse for at least a decade, who were randomly assigned to receive oral magnesium supplementation or a placebo. The results indicated that muscle strength increased in the group receiving magnesium supplementation, while baseline blood pressure and heart rate remained unchanged throughout the study.

Academic literature posits that a deficiency in magnesium may exacerbate withdrawal symptoms and that supplementation could be beneficial in certain situations. Nevertheless, it is essential to exercise caution when administering intravenous magnesium infusions, as this may result in iatrogenic hypermagnesemia and other adverse effects [9]. Determining the existence of a deficiency is crucial before resorting to parenteral administration and considering oral supplementation or dietary modifications [82].

Contrary findings or noteworthy information arise when contemplating the broader context of alcohol withdrawal therapy. For example, although magnesium supplementation can address particular deficiencies, extensive treatment plans typically emphasize the use of benzodiazepines and other pharmacological agents, such as carbamazepine and valproic acid, which have demonstrated effectiveness in managing withdrawal symptoms[69].

Furthermore, the significance of magnesium in the context of anxiety, which is often a withdrawal-related aspect, implies that the provision of supplementation could lead to a calming influence on the nervous system [84]. However, the efficacy of magnesium supplementation as a standalone treatment for withdrawal symptoms is not well-established and requires research.

In summary, while magnesium deficiency is a recognized concern in chronic alcoholism and may contribute to withdrawal symptoms, the decision to supplement should be based on a confirmed deficiency and tailored to the individual's needs. Oral supplementation and dietary changes are preferred over parenteral administration unless clinically indicated 85.

Treatment for alcohol withdrawal should adhere to established guidelines that may incorporate a variety of pharmacological interventions [35]. Further investigation is necessary to clarify the role of mg supplementation in the treatment of alcohol withdrawal and its potential benefits in addressing accompanying anxiety. [84].

MATERIALS AND METHODS

Source of Data

This study was conducted in a tertiary care hospital, specifically the psychiatry outpatient and inpatient departments of KLE's Dr. Prabhaker Kore Charitable Hospital, Belagavi.

Study Design

The study design is a cross-sectional study.

Study Period

The study was conducted over a period of one year, from 1st September 2022 to 31st August 2023.

Place

The study took place in the Department of Psychiatry at KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research Centre, Belagavi, Karnataka.

Sample Size

A total of 100 patients experiencing alcohol withdrawal were included in the study.

Sampling Technique

The study utilized purposive sampling to select participants.

Sample size estimation:

Prevalence taken as 50%

q= 50%,

d=20% of p=10

n=4pq/d2

4(50*50)/10*10

n=100

Inclusion Criteria

1. Patients exhibiting signs of alcohol withdrawal.
2. Patients aged over 18 years.

Exclusion Criteria

1. Patients with a history of seizure disorders.
2. Patients with neurological conditions that may cause tremors, nausea, or vomiting.
3. Patients with a history of substance abuse other than nicotine.
4. Patients with known psychiatric comorbidities.
5. Patients with malabsorption syndrome or chronic renal failure.
6. Patients taking diuretics.
7. Patients on magnesium supplements.

Ethical Clearance

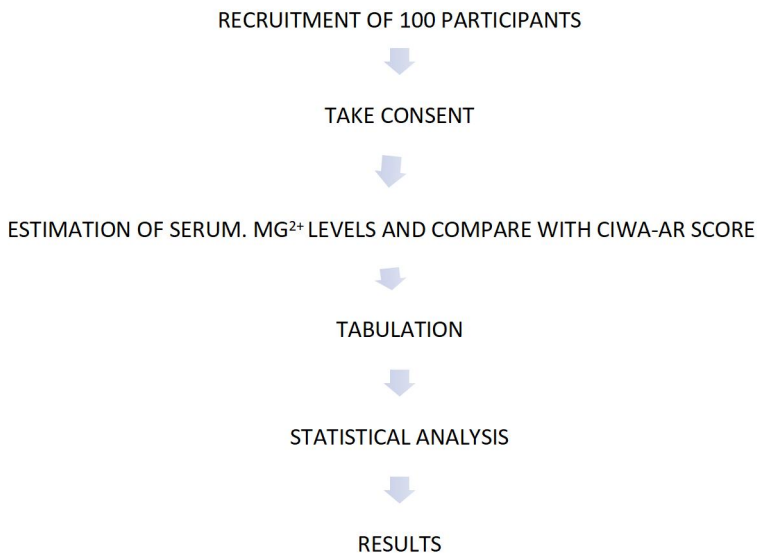
The study received ethical approval from the Institutional Ethics Committee at Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

Participants who met the inclusion criteria were briefed about the study, and informed written consent was obtained in their native language before the study began. For those unable to provide consent due to delirium, consent was obtained from accompanying relatives after explaining the study's nature.

Study Protocol and Data Collection Procedure

After obtaining approval from the Institutional Ethics Committee, 100 patients were selected based on the inclusion and exclusion criteria. Venous blood samples (2 milliliters) were collected from each patient after informed consent was obtained. Serum magnesium levels were measured using the colorimetric endpoint method batch of test (08058016) and were then correlated with the severity of alcohol withdrawal as assessed by the CIWA-Ar score.



Data Analysis

The collected data were organized and tabulated using Microsoft Excel. Descriptive statistics were presented as percentages, means, and standard deviations to summarize the socio-demographic data. The Kruskal-Wallis test was used to calculate the p-value for qualitative data to assess the strength of associations. Spearman correlation analysis was employed to determine the correlation (r) between serum magnesium levels and other variables. Statistical significance was defined as a p-value less than 0.05.

OBSERVATION AND RESULTS

A total number of 100 participants were recruited and serum magnesium was assessed upon admission and alcohol withdrawal severity was assessed using CIWA-Ar scale. The following table shows the mean and median of socio demographic details of the participants and the clinical variables.

Table 1. summary of sociodemographic details and clinical variables of Participants

(N=100)

	MEAN || MEDIAN
Age (Years)	41.88 ± 10.86 || 41.00 (35.00-51.00)
Gender (Male)	100 (100.0%)
Religion	(n)
Hindu	86 (86.0%)
Muslim	6 (6.0%)
Christian	8 (8.0%)
Marital Status	(n)
Married	86 (86.0%)
Unmarried	10 (10.0%)
Widowed/separated	4 (4.0%)
Educational Status	
Graduate	14 (14.0%)
Primary	9 (9.0%)
Middle School	9 (9.0%)
Illiterate	2 (2.0%)
Occupation	(n)
Unskilled Worker	58 (58.0%)
Semi-Skilled Worker	26 (26.0%)
Skilled Worker	8 (8.0%)
Un employed	8 (8.0 %)
Comorbidity	(n)
Nicotine use	57 (57.0%)
Hypertension	28 (28%)
Diabetes	13 (13%)

Table 1 describes the summary of socio demographic details and clinical variables of participants . The mean age of the participants was 41.88 years with a standard deviation of 10.86 years. All 100 participants were male. Regarding religion, the majority were Hindu, followed by Christian and Muslims. In terms of marital status, the majority of the participants were married, few were unmarried, and minority were widowed. For educational status, 66% had completed SSLC, 9% had primary education, 9% had middle school education, 14% were graduates, and 2% were illiterate. Regarding occupation majority of participants were unskilled workers followed by semi-skilled, skilled workers and a few participants were not employed during the time of study.

Table 2. pattern of alcohol use among participants (N=100)

Alcohol Use	Mean ± SD || Median (IQR)
Duration Of Alcohol Intake (Years)	|| 10.00 (6.00-12.25)
Time Since Last Drink (Hours)	|| 24.00 (24.00-48.00)
CIWA - AR Score	23.70 ± 11.99 ||

Table 2 describes the pattern of alcohol use such as total duration of alcohol intake in years and the time since last drink (hours). And the median values of those are tabulated, since the data was not normally distributed, for ciwa scores the mean value was taken since the data was normally distributed.

The median duration of alcohol intake among participants was 10.00 years, with an interquartile range (IQR) of 6 to 12.25 years, and it ranged from 1 to 30 years. The data exhibited a skewness of 0.82, indicating a positive skew and suggesting the data was not normally distributed. For the duration of abstinence, the median was 24.00 hours with an IQR of 24 to 48 hours, ranging from 12 to 96 hours.

The CIWA-Ar scores had a mean of 23.70 with a standard deviation of 11.99. The skewness of 0.4 and kurtosis of -0.78 indicated that the CIWA-Ar score data was normally distributed.

Table3. summary of biochemical parameters of participants: (N=100)

Levels	Median (IQR)	Min - Max
Serum Mg (mg/dL)	1.20 (0.80-1.60)	0.4 - 2.3
Serum Potassium (mEq/L)	3.50 (3.00-3.92)	1.9 - 5.1
Serum Sodium (mEq/L)	136.00 (131.00-139.00)	127.0 - 145.0
Serum Urea (mg/dL)	42.00 (28.00-52.25)	16.0 - 98.0
Serum Creatinine (mg/dL)	0.80 (0.58-1.20)	0.4 - 3.5

Table 3 describes the summary of biochemichal parameters of the participants since the data was non parametric the median (IQR) was tabulted , the median serum mg level of participants was 1.20 with an IQR of (0.80 to 1.60), serum potassium had median of 3.50 IQR (3.00-3.92). For Serum Sodium (mEq/L), the median (IQR) was 136.00 (131-139), and the median of Serum Urea (mg/dL) was 42.00, IQR (28-52.25). The median (IQR) of Serum Urea (mg/dL) was 42.00 (28-52.25), Similarly, Serum Creatinine (mg/dL) had a median (IQR) of 0.80 (0.58-1.2)

Figure 8 distribution of magnesium

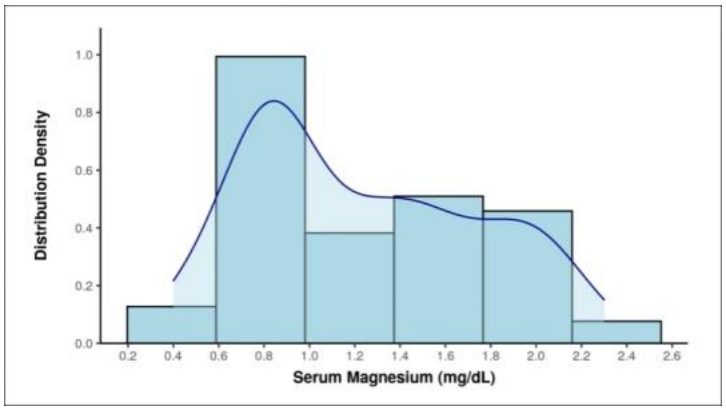
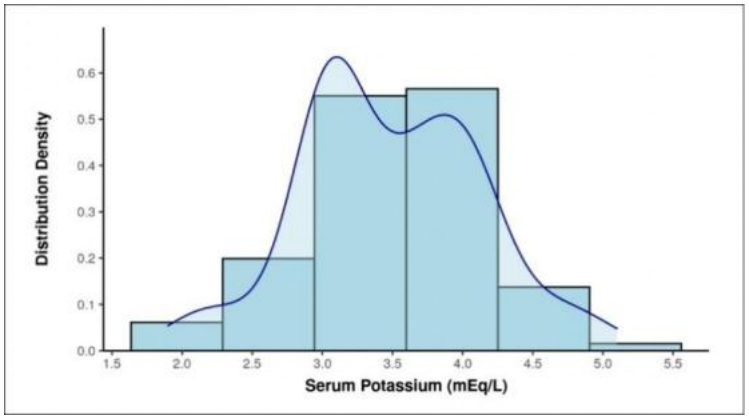


figure 9 Distribution of pottasium



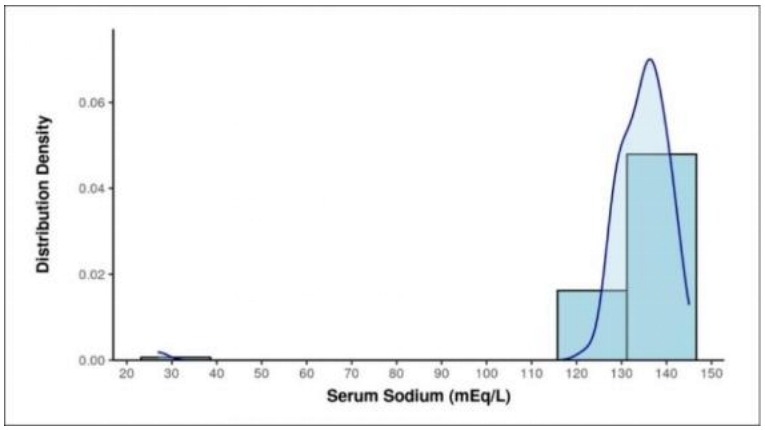


Figure 10. Distribution of sodium

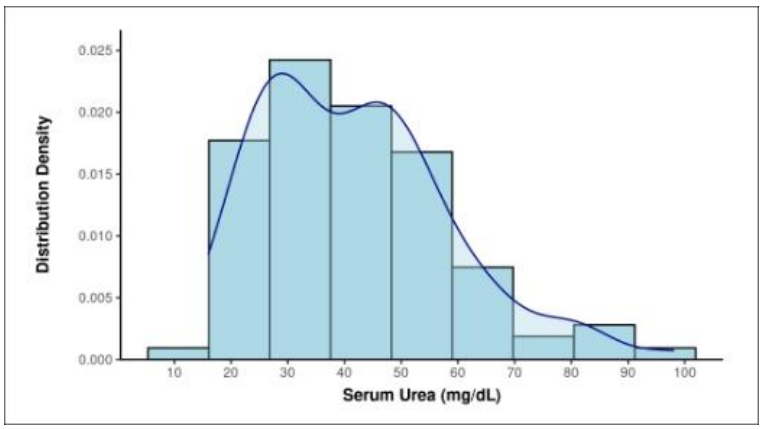


Figure 11. Distribution of urea

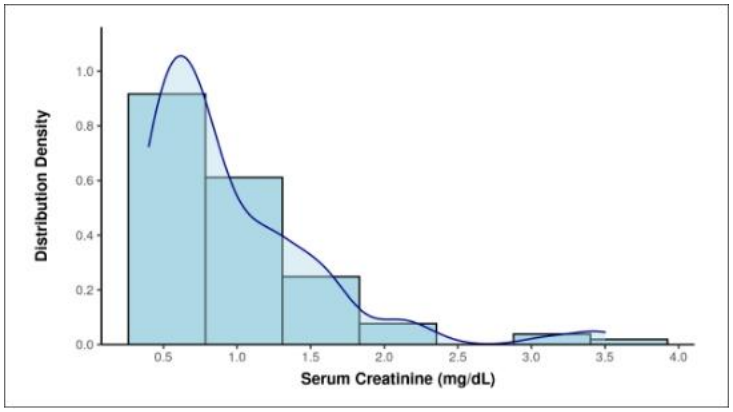


Figure 12. Distribution of creatinine

Analysis of Biochemical Parameters

The data for Serum Magnesium, Serum Potassium, Serum Sodium, Serum Urea, and Serum Creatinine did not follow a normal distribution based on their multimodal patterns, significant skewness, high kurtosis, and the results of the Shapiro-Wilk test. These findings are crucial for understanding the statistical properties of the biochemical parameters analyzed in the study.

In our study we were able to correlate between duration of alcohol use with CIWA Ar score which is positively correlated that means withdrawal symptoms worsens with increase in duration of alcohol intake, while the relationship between age and ciwa score shows positive correlation but the strength of association is very weak.

Table 4. summary of correlation between CIWA Ar scores and clinical variables of participants (N=100)

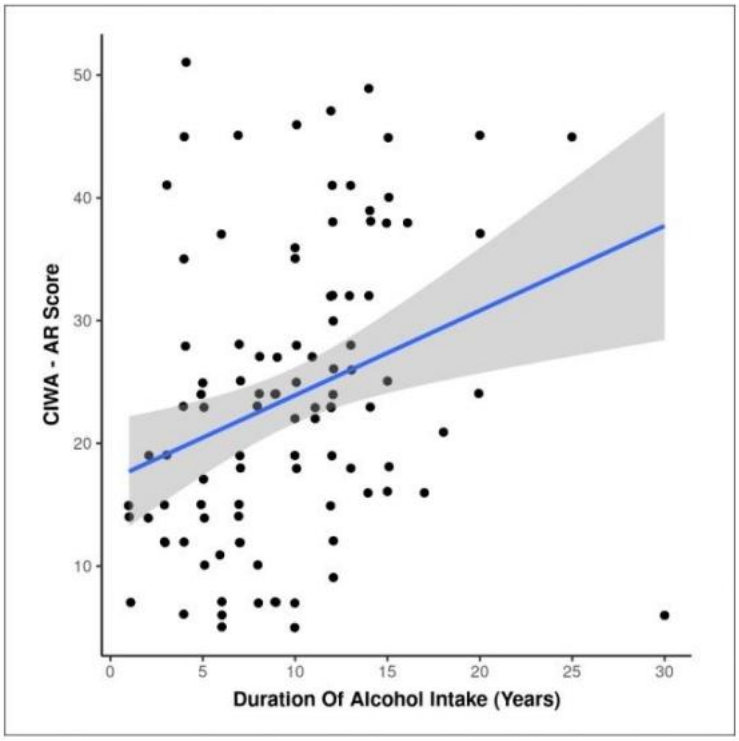
Parameters	CIWA - AR Score	p value
Age (Years)	Correlation Coefficient (rho) = 0.19	0.064
Duration Of Alcohol Intake (Years)* **	(rho) = 0.36	<0.001
Time Since Last Drink (Hours)	(rho) = -0.05	0.656
Serum Magnesium (mg/dL) * **	(rho) = -0.81	<0.001
Serum Potassium (mEq/L) * **	(rho) = -0.62	<0.001
Serum Sodium (mEq/L)	(rho) = -0.09	0.373

***Significant at p<0.01

Table 4 describes the correlation between CIWA-Ar scores and clinical variables of participants .The correlation between age and CIWA- Ar score yielded a Pearson's correlation coefficient of 0.2. This indicates a weak positive correlation, which implies that as age increases, CIWA-AR scores tend to rise slightly, but the relationship is not strong. The p-value for this correlation was found to be 0.064, suggesting that the relationship between age and CIWA-AR scores is not statistically significant.

In our study we have found that there is positive correlation between alcohol intake and CIWA-Ar score, and the values are statistically significant.

Figure 13. Correlation between CIWA-AR Score and duration of alcohol intake

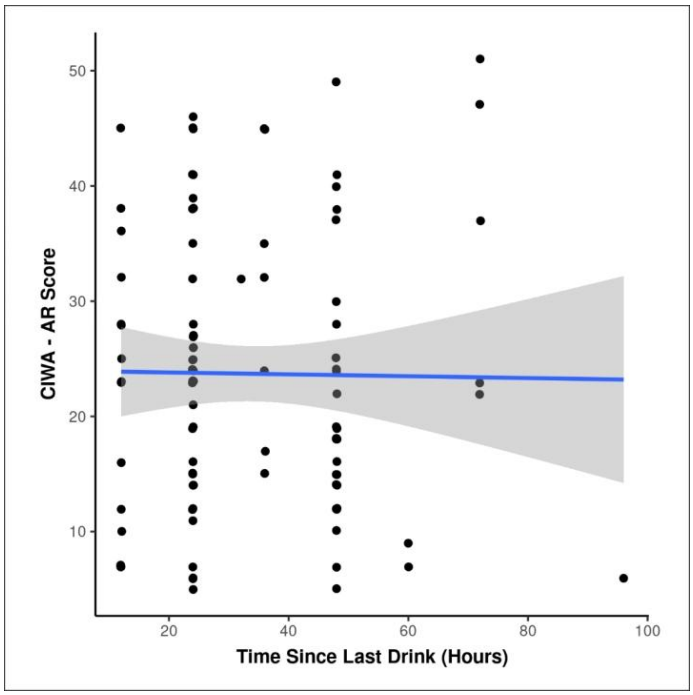


Correlation	Spearman Correlation Coefficient	P Value
Duration Of Alcohol Intake (Years) vs CIWA - AR Score	0.36 (95%CI: 0.17 to 0.54)	<0.001

scatter plot depiciting correlation between CIWA Ar score and duration of alcohol intake , each dots points a single case and x-axis represent CIWA Ar score and y axis- the duration of alcohol intake

In our study we could find no significant correlation between time since last drink and CIWA-Ar scores, suggesting that there is no meaningful association between the amount of time since the last drink and the severity of alcohol withdrawal but there was no stastistical significance for this finding.

FIGURE 14. Correlation between time since last drink (hours) and CIWA- Ar score



Correlation	Spearman Correlation Coefficient	P Value
Time Since Last Drink (Hours) vs CIWA - AR Score	-0.05 (95%CI: -0.25 to 0.15)	0.656

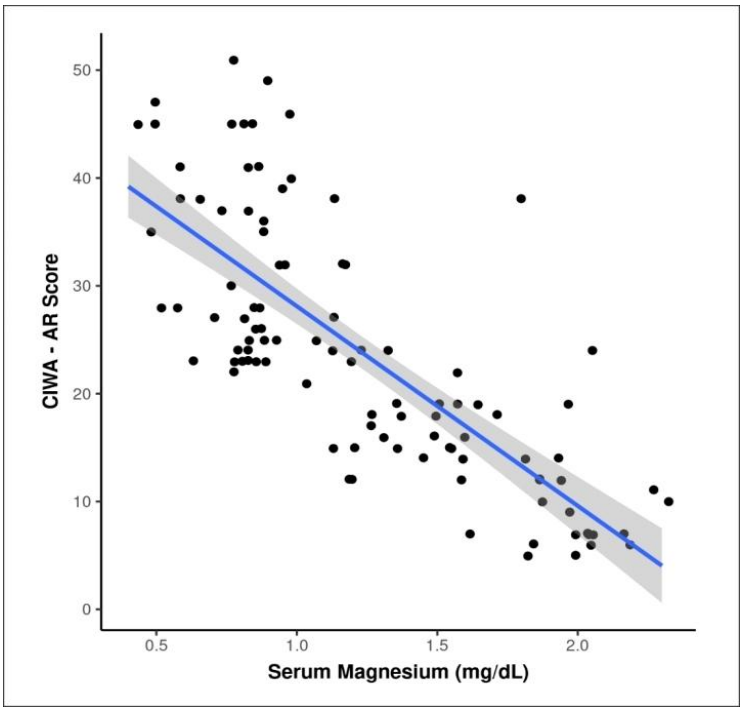
Scatter plot depiciting correlation between CIWA Ar score and time since last drink , each dots points a single case and x-axis represent CIWA Ar score and y axis- the time since last drink

The scatterplot depicts the relationship between Time Since Last Drink (Hours) and CIWA-AR Score. Each data point shows a single case, with Time Since Last Drink on the x-axis and CIWA-AR Score on the y-axis. The blue line indicates the general connection between the two variables, while the grey area around it represents the 95% confidence interval. The non-parametric test, Spearman correlation, was used to investigate the relationship between the variables due to the non-normal distribution of at least one variable.

In our study we have found strong negative correlation between Serum Magnesium (mg/dL) and CIWA-AR Score (rho = -0.81, $p < 0.001$), indicating that lower levels of serum magnesium are associated with more severe alcohol withdrawal symptoms. These

findings highlight the importance of monitoring and addressing magnesium levels in the management of alcohol withdrawal syndrome.

Figure 15. Correlation between 'Serum Magnesium (mg/dL)' and 'CIWA - AR Score'



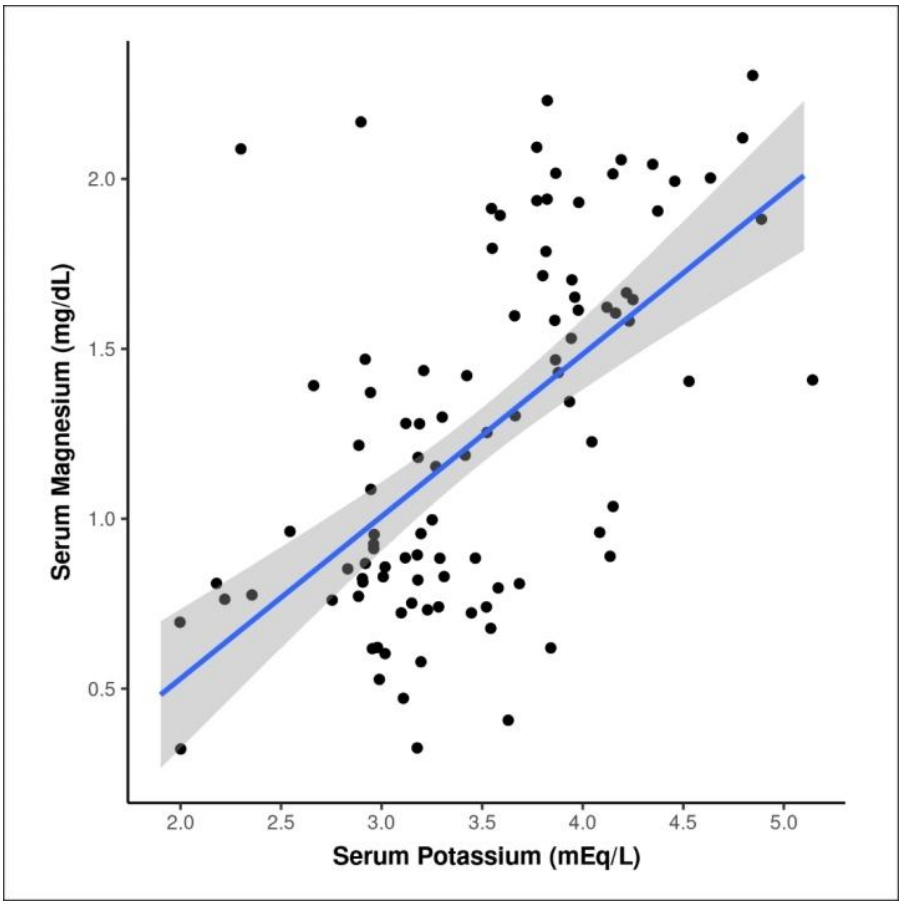
Correlation	Spearman Correlation Coefficient	P Value
Serum Magnesium (mg/dL) vs CIWA - AR Score	-0.81 (95%CI: -0.87 to -0.72)	<0.001 ***Significant at p<0.01

scatter plot depiciting correlation between CIWA Ar score and serum magnesium level , each dots points a single case and x-axis represent CIWA Ar score and y axis- serum magnesium level.

The plot above shows a scatter plot of Serum Magnesium (mg/dL) and CIWA-AR Score, with each point representing an individual case. The correlation between these two variables is depicted by the blue trendline, while the 95% confidence interval is shown in shaded grey. Non-parametric tests were used for analysis due to the non-normal distribution of at least one variable.

In our study we have also found a strong positive correlation between the two variables, and the correlation is statistically significant. As per this analysis, when serum potassium levels decreases, serum magnesium levels are also likely to decrease.

FIGURE 16 Correlation between 'Serum Potassium (mEq/L)' and 'Serum Magnesium (mg/dL)'



Correlation	Spearman Correlation Coefficient	P Value
Serum Potassium (mEq/L) vs Serum Magnesium (mg/dL)	0.6 (95%CI: 0.45 to 0.73)	<0.001 ***Significant at p<0.01

scatter plot depiciting correlation between serum magnesium and serum potassium levels , each dots points a single case and x-axis represent serum magnesium and y axis-serum potassium level.

The analysis of the correlation between serum potassium levels (measured in mEq/L) and serum magnesium levels (measured in mg/dL) was conducted using Spearman's correlation coefficient. The result yielded a Spearman correlation coefficient of 0.6, along with
a p-value of less than 0.001.

DISCUSSION

Demographics and Participant Characteristics (Refer to Table 1)

Table 1 shows the mean age of participants was 41.88 years, with a weak positive correlation (Pearson's r = 0.2, p = 0.064) between age and CIWA-AR scores, indicating that older participants tend to have slightly higher withdrawal severity. This finding aligns with several studies that have explored the relationship of age with severity of alcohol withdrawal. Sullivan et al. (2014) and Daeppen et al. (2002) reported that older age groups exhibited more severe withdrawal symptoms due to longer exposure to alcohol and possibly more significant physiological deterioration [53,86]. These studies suggest that cumulative damage from prolonged alcohol use contributes to more severe withdrawal symptoms in older individuals.

Trevisan et al. has done a comprehensive review of factors influencing alcohol withdrawal and found that age was a significant determinant of withdrawal severity. Their findings indicate that older adults, particularly those with a long history of heavy drinking, are at a higher risk for severe withdrawal symptoms [87]. This is attributed to the 7 cumulative toxic effects of alcohol on the nervous system and other organs over time. Kraemer et al. investigated predictors of alcohol withdrawal severity in a large cohort and found that age was one of the key factors associated with increased withdrawal severity[88].

Their study highlighted that older adults often have comorbid conditions and decreased physiological resilience, which exacerbates withdrawal symptoms.

Muzyk et al. examined the clinical factors influencing the severity of alcohol withdrawal in hospitalized patients. They reported a significant positive correlation between age and withdrawal severity, noting that older patients experienced more severe symptoms [89]. Their findings emphasize the need for age-specific management strategies to mitigate withdrawal symptoms in older adults.

Bayard et al. has done a study on the clinical management of alcohol withdrawal and identified age as a critical factor in determining the course and severity of withdrawal [60]. Their research supports the notion that older individuals are more susceptible to severe withdrawal, necessitating careful monitoring and intervention.

In contrast, Brower et al. has found no significant correlation between age and withdrawal severity in their study of alcohol-dependent patients. They suggested that individual variability in alcohol use patterns and overall health status might influence the relationship between age and withdrawal severity, potentially masking the impact of age alone [90].

Berggren et al. examined withdrawal symptoms in an outpatient setting and found that while older patients reported more severe symptoms, the differences were not statistically significant [91]. They hypothesized that the variation in findings across studies might be due to differences in study populations and settings.

Duration of Alcohol Intake and CIWA-Ar Score (Refer to Table 2 and 3)

Our study has found a moderate positive correlation between the duration of alcohol intake and CIWA-Ar scores ($r = 0.4$, $p < 0.001$), suggesting that longer alcohol consumption is associated with higher severity of withdrawal symptoms . It is consistent with existing literature that highlights the cumulative effects of prolonged alcohol use on the central nervous system, leading to more severe withdrawal manifestations. The Kruskal-Wallis test further supported this association, showing significant differences in CIWA-Ar scores across different durations of alcohol intake, with the highest scores observed in participants with 20 to 25 years of intake. This underscores the significance of considering the duration of alcohol use in the clinical assessment and management of withdrawal symptoms.

Schuckit et al. identified a direct relationship between chronic alcohol use and withdrawal severity. Their research demonstrated that individuals with longer histories of alcohol use experienced more intense withdrawal symptoms, likely due to greater neurochemical and structural change in the brain associated with prolonged exposure of alcohol [92]. Saitz et al has done a study on predictors of severe alcohol withdrawal and found that the duration of alcohol consumption was a significant predictor of withdrawal severity [54]. Their findings indicated that individuals with longer alcohol use histories required more intensive medical intervention during the withdrawal phase.

Haber et al. examined the severity of alcohol withdrawal in a clinical sample and found that the duration of alcohol dependence was positively correlated with the severity of withdrawal symptoms. They noted that patients with longer histories of alcohol use were more likely to experience complications such as delirium tremens and seizures [93]. Victor and Adams in their seminal work on the natural history of alcoholism, observed that chronic alcoholics with longer drinking histories had more severe withdrawal syndromes. They attributed this to the cumulative effects of alcohol on the brain and other organ systems [8].

Raimo and Schuckit explored the clinical course of alcohol severity of withdrawal and found that the length of alcohol consumption was a strong determinant of withdrawal severity [94]. Their study highlighted that prolonged alcohol exposure leads to more pronounced physiological dependence, resulting in more severe withdrawal symptoms upon cessation.

Brown et al. has done a longitudinal study on the progression of alcohol dependence and its withdrawal symptoms. They reported that the duration of alcohol use was a critical factor influencing the intensity of withdrawal symptoms, with longer use leading to more severe and prolonged withdrawal phases [95].

Chan et al. studied the biochemical and clinical aspects of alcohol withdrawal and found that individuals with longer drinking durations had higher levels of withdrawal-related biochemical markers [96]. Their research supports the notion that chronic alcohol use leads to more severe physiological withdrawal responses.

Bayard et al. in their review of alcohol withdrawal management, emphasized that the duration of alcohol consumption is an important factor in determining the severity of withdrawal symptoms [60.] They recommended that patients with long-term alcohol use histories be closely monitored for severe withdrawal symptoms and provided with appropriate medical interventions.

Duration of Abstinence and CIWA-Ar Score (Refer to table 4)

The duration of abstinence (time since the last drink) , table 4 shows a very weak negative correlation (Spearman's $\rho = -0.1$, $p = 0.656$) with CIWA-Ar scores, however the association was not statistically significant.. Rybakowski et al. suggested

that withdrawal symptoms peak within 24-48 hours after the last drink, a period typically characterized by the most severe symptoms. However, the variability in abstinence periods (12 to 96 hours) in present study may account for the weak correlation observed.

Mayo-Smith conducted a comprehensive review and found that the most severe withdrawal symptoms generally occur within the first 48 hours after cessation of alcohol intake [61]. This aligns with Rybakowski et al. but contrasts with our findings. Swift RM highlighted that withdrawal severity typically peaks within 24-48 hours and gradually diminishes thereafter. This pattern of symptom progression underscores the critical time frame immediately following the last drink, a factor that might be masked by the broader range of abstinence periods in present study. Schuckit MA also reported that withdrawal symptoms are most severe within the first 48 hours and suggested that early intervention during this peak period is crucial for managing withdrawal effectively [92].

Saitz R et al. observed that the timing of symptom onset and peak can vary depending on individual factors, including the duration and intensity of alcohol use [54]. This variability might explain why present study, with its broad range of abstinence periods, showed a weaker correlation between abstinence duration and withdrawal severity. Victor M, Adams RD provided an early characterization of alcohol withdrawal, noting that symptoms typically peak within the first two days [8]. Their foundational work supports the general consensus that withdrawal severity is closely tied to the time since the last drink. Jauhar P, Anderson JM explored the clinical features of alcohol withdrawal and confirmed that the most intense symptoms usually appear within 24-48 hours. This aligns with the bulk of the literature, emphasizing the critical early period post-abstinence.

Kosten TR, O'Connor PG discussed the medical management of alcohol withdrawal, highlighting that symptom severity often peaks within the first two days [97]. Their findings are consistent with the majority of studies but differ from our results, which showed a weak correlation possibly due to study-specific factors. Wetterling T et al. examined predictors of alcohol withdrawal severity and found that the timing of the last drink was a significant predictor of symptom intensity,

with the most severe symptoms occurring within 24-48 hours [98]. This further corroborates the general understanding of withdrawal timelines. Gossop M emphasized that withdrawal symptoms and their severity are highly individualized, which can result in variations that might obscure broader patterns, as observed in present study.

Serum Magnesium Levels and Withdrawal Severity (Refer to Table 4 and figure 15)

The present study unveiled a robust negative correlation between serum magnesium levels and CIWA-Ar scores, as indicated by Spearman's ρ ($\rho = -0.8$, $p < 0.001$). This suggests that lower serum magnesium levels are associated with higher CIWA-Ar scores, indicating more severe withdrawal symptoms, in line with several studies that have investigated the role of magnesium in alcohol withdrawal symptoms.

A significant proportion of alcohol withdrawal patients are reported to experience hypomagnesemia (low magnesium levels). In one such study by Ayirolimeethal et al. (2018), 20% of participants with withdrawal symptoms were found to have low magnesium levels [99].

Research suggests a possible relationship between magnesium levels and the severity of delirium tremens, the most severe form of alcohol withdrawal. However, the findings are not entirely conclusive. While Enadle et al. (2004) reported no significant difference in magnesium levels between mild and moderate withdrawal, Ayirolimeethal et al. (2018) found a correlation between lower magnesium levels and higher delirium scores [99].

Studies indicate that addressing magnesium deficiency during withdrawal can enhance outcomes. For example, research by Zhang et al. (2020) showed that magnesium supplementation along with standard treatment may be associated with lower mortality rates in patients with severe withdrawal [81].

Addolorato et al. demonstrated that magnesium supplementation could reduce withdrawal symptoms, highlighting magnesium's role in modulating neurological

function and mitigating excitatory neurotransmitter release during withdrawal phases [35]. More research is needed to definitively establish a link between magnesium levels and the severity of delirium tremens.

Hallak et al. has done a investigation into the effects of magnesium on alcohol withdrawal symptoms and discovered that individuals receiving magnesium supplementation experienced fewer and less severe symptoms as compared to the control group [8]. Their findings lend support to the notion that magnesium plays a critical role in alleviating withdrawal symptoms. Ebel et al. conducted a study to determine serum magnesium levels in patients undergoing alcohol withdrawal and observed that lower magnesium levels were associated with more severe withdrawal symptoms. Their research underscores the importance of maintaining adequate magnesium levels to mitigate the severity of withdrawal.

According to Victor and Adams one of the earlier studies on magnesium deficiency in alcoholics revealed several crucial findings. The researchers discovered that a significant portion of alcoholics suffered from magnesium deficiency, which often manifested in symptoms such as tremors, convulsions, and confusion. The deficiency was attributed to factors like inadequate dietary intake, increased urinary excretion of magnesium, and gastrointestinal losses. The study emphasized the importance of considering magnesium deficiency in the management of alcoholic patients, particularly those experiencing withdrawal symptoms.

Flink has done a a comprehensive review of the biochemical and clinical aspects of magnesium deficiency in alcoholism and highlighted the importance of magnesium in preventing severe withdrawal symptoms [100]. Flink's review reinforces the findings of this study, emphasizing the protective role of magnesium. Nguyen et al. (2010) has done a clinical trial to evaluate the effects of intravenous magnesium sulfate on alcohol withdrawal symptoms and reported a significant reduction in symptom severity among patients treated with magnesium [79]. Their study provides robust evidence for the therapeutic use of magnesium in managing withdrawal.

According to Yolken and Torrey magnesium demonstrates neuroprotective properties that can alleviate the excitotoxicity related to alcohol withdrawal. Their findings

align with the inverse relationship observed in this study between serum magnesium levels and withdrawal severity. Hammell et al. examined the link between electrolyte imbalances and alcohol withdrawal, revealing that hypomagnesemia was a prevalent condition among severe withdrawal patients. They suggested regular monitoring and correcting magnesium levels as a means of managing withdrawal symptoms.

Romero et al. investigated the role of magnesium in the central nervous system and found that magnesium deficiency can exacerbate neuropsychiatric symptoms, including those observed in alcohol withdrawal. Their research further supports the importance of maintaining adequate magnesium levels in managing withdrawal symptoms.

Paradis et al. assessed the use of magnesium in treating alcohol dependence and withdrawal, concluding that magnesium supplementation can be considered part of standard care for patients undergoing withdrawal, given its significant benefits in reducing symptom severity.

Comorbid Conditions and CIWA-Ar Scores (Refer to table 1)

The presence of comorbid conditions such as nicotine use, diabetes, and hypertension was also examined. This study found that 57% of participants used nicotine, 13% had diabetes, and 28% had hypertension. Hughes (1992) reported that nicotine dependence is a significant factor that can worsen the severity of alcohol withdrawal symptoms. Nicotine has been shown to increase the release of neurotransmitters that can heighten the excitability of the nervous system, thus exacerbating withdrawal symptoms.

Sutherland et al. found that smokers experienced more severe withdrawal symptoms compared to non-smokers, likely due to the additional withdrawal effects of nicotine. Their findings align with the high prevalence of nicotine use in present study and its potential impact on withdrawal severity. Falk et al. noted that the simultaneous withdrawal from both alcohol and nicotine can lead to more severe symptoms and complicate the management of withdrawal. They suggested

that addressing nicotine dependence concurrently with alcohol withdrawal could help in reducing the overall severity of symptoms.

In present study, 13% of participants had diabetes. The influence of diabetes on alcohol withdrawal severity remains less clear, and further investigation is warranted. Saitz et al. indicated that diabetic patients might experience altered withdrawal symptoms due to the metabolic complications associated with diabetes. However, they noted that more research is needed to understand this relationship fully. Heffner et al. explored the interactions between diabetes and alcohol use disorders and found that diabetic patients might have more severe withdrawal symptoms due to their overall compromised health status. This study supports the notion that comorbid diabetes could potentially influence withdrawal severity, although more specific data is required.

Schmidt et al. suggested that the presence of diabetes might complicate the clinical management of withdrawal due to the potential for fluctuating blood glucose levels and other metabolic disturbances. Their findings highlight the need for specialized care in diabetic patients undergoing alcohol withdrawal. This study found that 28% of participants had hypertension. The relationship between hypertension and alcohol withdrawal severity is less well-documented and warrants further exploration.

Peters et al. discussed the potential for hypertension to exacerbate withdrawal symptoms due to the additional cardiovascular strain found that hypertensive patients might experience more severe symptoms but noted that further studies are needed to confirm this association. Bayard et al. indicated that hypertensive patients might be at higher risk for severe withdrawal symptoms due to the stress on the cardiovascular system during withdrawal. Their findings suggest a potential link between hypertension and withdrawal severity, though more focused research is necessary.

Wetterling et al. found that hypertension could be a predictor of severe withdrawal symptoms, particularly in patients with long-term alcohol dependence. Their study supports the need for careful monitoring of hypertensive patients during withdrawal.

Leung et al. explored the broader impacts of cardiovascular comorbidities on alcohol withdrawal and found that patients with hypertension often had more severe symptoms, likely due to the compounded stress on their cardiovascular system. This aligns with the higher prevalence of hypertension in present study and its potential impact on withdrawal severity.

Relationship Between Alcohol Withdrawal (CIWA) and Potassium Levels

(Refer to table 4)

The study revealed an interesting relationship between serum potassium levels and CIWA-AR scores, indicating that lower potassium levels are associated with higher CIW A-AR scores.

. Raut et al reported that hypokalemia and hyponatremia were the most common electrolyte imbalances found among patients with alcohol withdrawal syndrome [79]. In our study though only, hypokalemia seemed to be significant

This finding aligns with previous research suggesting that electrolyte imbalances, particularly hypokalaemia, can exacerbate the severity of alcohol withdrawal symptoms. Low potassium levels can affect cardiac function and neuromuscular excitability, potentially worsening withdrawal symptoms such as tremors, seizures, and arrhythmias. Electrolyte disturbances are common in chronic alcohol users due to poor dietary intake, vomiting, diarrheal, and the diuretic effects of alcohol. These disturbances need to be corrected to mitigate withdrawal severity and prevent complications.

Studies such as those by Saitz et al. and Kosten and O'Connor have emphasized the importance of monitoring and correcting electrolyte imbalances during alcohol withdrawal. They found that managing hypokalaemia could significantly reduce the risk of severe withdrawal symptoms and improve patient outcomes [54,97].

The present study's findings underscore the need for routine electrolyte monitoring and supplementation, including potassium, as part of a comprehensive alcohol withdrawal management protocol. Further supporting evidence comes from the study

by Schuckit et al. which highlighted that chronic alcoholics often suffer from multiple electrolyte imbalances, including hypokalaemia, contributing to the severity of withdrawal symptoms [92]. Similarly, Wetterling et al. observed that correcting hypokalaemia in alcohol-dependent patients significantly reduced the incidence of withdrawal-related complications such as cardiac arrhythmias and severe tremors [98]. Moreover, the study by Ebel et al. found that patients with severe alcohol withdrawal had significantly lower serum potassium levels compared to those with milder symptoms, reinforcing the need for potassium supplementation in managing withdrawal symptoms. Flink also emphasized the role of potassium in maintaining neuromuscular function and suggested that hypokalaemia should be promptly addressed in patients undergoing alcohol withdrawal to prevent severe complications[100].

Relationship Between Serum Magnesium and Potassium Levels (Refer to figure 16)

The study highlighted a significant relationship between serum magnesium and potassium levels, demonstrating the interconnected nature of these electrolytes. Magnesium and potassium homeostasis are closely related, and deficiencies in one often lead to disturbances in the other. Hypomagnesemia can impair potassium reabsorption in the kidneys, leading to hypokalemia. Conversely, correcting magnesium deficiency can help restore normal potassium levels. Magnesium and potassium are essential electrolytes that play critical roles in various physiological processes, including neuromuscular function and cardiovascular stability [79]. Both hypomagnesemia and hypokalemia are common in chronic alcohol users due to factors such as poor nutritional intake, gastrointestinal losses (vomiting and diarrheal), and renal excretion. These deficiencies can exacerbate withdrawal symptoms, including tremors, seizures, and cardiac arrhythmias, making their management crucial during alcohol withdrawal.

Several studies have demonstrated the importance of magnesium in the context of alcohol withdrawal. Hallak et al. conducted a study on the effects of magnesium sulfate on alcohol withdrawal symptoms and found that patients receiving magnesium supplementation experienced significantly fewer and less severe

symptoms compared to the control group [101]. This finding suggests that magnesium supplementation helps mitigate the severity of withdrawal symptoms by maintaining neuromuscular stability and preventing excitatory neurotransmitter release.

Nguyen et al. conducted a clinical trial on the effects of intravenous magnesium sulfate on alcohol withdrawal symptoms. They reported a significant reduction in symptom severity among patients treated with magnesium. Their study provides strong evidence for the therapeutic use of magnesium in managing alcohol withdrawal. By stabilizing magnesium levels, potassium levels are also positively affected, reducing the overall severity of withdrawal symptoms [102].

Ebel et al. investigated the levels of serum magnesium in patients undergoing alcohol withdrawal and discovered that lower magnesium levels were associated with more severe withdrawal symptoms. This finding highlights the significance of ensuring adequate magnesium levels to alleviate the severity of withdrawal symptoms and prevent complications [103].

Similarly, Flink (1986) emphasized the role of magnesium in neuromuscular function and recommended that magnesium deficiency should be promptly addressed in patients undergoing alcohol withdrawal to avert severe complications. Evidence supporting the importance of magnesium in alcohol withdrawal comes from studies on the association between hypomagnesemia and hypokalemia [100].

Further evidence came from Hallak et al. (2001) and Nguyen et al. (2010), who demonstrated that maintaining adequate magnesium levels can help stabilize potassium levels, thereby lessening the overall severity of withdrawal symptoms [101,102]

All the participants included in our study were treated with benzodiazepines for management of withdrawal state and thiamine supplementation was given as per guidelines. With respect to hypomagnesemia and hypokalemia reference was taken from the medicine department and were treated accordingly.

CONCLUSION

Our study on the correlation between serum magnesium levels and alcohol withdrawal severity revealed several key findings: a high prevalence (72%) of magnesium deficiency among chronic alcoholics, particularly those with higher CIWA-Ar scores, underscoring the need for routine magnesium screening. Hypokalemia emerged as a significant confounding factor, indicating the necessity of monitoring both potassium and magnesium levels. Although an inverse relationship was observed between serum sodium levels and CIWA-Ar scores, the correlation was not significant to deem hyponatremia a significant risk factor. Serum urea levels showed no significant correlation with withdrawal severity. The duration of alcohol intake was a significant risk factor for severe withdrawal symptoms, with longer periods associated with higher CIWA-Ar scores, while the period of abstinence before assessment did not significantly affect withdrawal severity. These findings highlight the critical role of maintaining adequate magnesium levels in managing alcohol withdrawal and suggest that monitoring magnesium and potassium levels could improve patient outcomes, warranting further research on magnesium supplementation's impact on withdrawal severity.

Limitations of the study

The study's participant pool consists exclusively of males, which may introduce gender bias into the findings. As a result, the conclusions drawn may not accurately reflect the experiences or perspectives of females.

The research is based on a relatively small sample size, limiting the ability to generalize the results to a broader population.

Moreover, the Ciwa Ar scale includes self-reported components, which may lead to inaccurate measurement of withdrawal severity if participants over-report or under-report their symptoms.

SUMMARY

The descriptive study conducted at KLE's Dr. Prabhakar Kore Hospital focused on investigating the correlation between serum magnesium levels and the severity of alcohol withdrawal symptoms in patients admitted for alcohol dependence syndrome. This detailed investigation was carried out to understand whether magnesium levels could predict the severity of withdrawal symptoms and if managing these levels could improve patient outcomes.

In this prospective observational study, a cohort of patients admitted with alcohol dependence syndrome was selected. These patients were closely monitored from the time of their admission. The severity of alcohol withdrawal symptoms was assessed using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale, a widely recognized tool for quantifying the severity of withdrawal symptoms such as tremors, sweating, nausea, and anxiety.

Upon admission, serum magnesium levels were measured for each patient. This biochemical data was then correlated with the CIWA-Ar scores to determine if there was a significant relationship between magnesium levels and the severity of withdrawal symptoms .In the mean time treatment for alcohol withdrawal and correction of electrolyte imbalances were also done during the course of treatment.

The findings of the study revealed a significant inverse correlation between serum magnesium levels and the severity of alcohol withdrawal symptoms. Specifically, patients who had lower serum magnesium levels tended to exhibit higher CIWA-Ar scores, indicating that they experienced more severe withdrawal symptoms. This result highlighted a clear link between magnesium deficiency and the exacerbation of withdrawal symptoms.

Furthermore, the study identified that a substantial proportion of the patients had hypomagnesemia (low magnesium levels) at the time of admission. This prevalence of magnesium deficiency among the patients suggested that it is a common issue in individuals with alcohol dependence.

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ANNEXURE 1

TEST PRINCIPLE OF COLOIMETRIC END POINT METHOD

Test principle of colorimetric end point method:

The colorimetric end-point method using Xylidyl Blue is a biochemical assay used to measure the concentration of magnesium in serum. The principle behind this method is based on the formation of a colored complex between magnesium ions (Mg^{2+}) and the dye Xylidyl Blue. The intensity of the color produced is directly proportional to the concentration of magnesium in the sample.

Reaction:

In a test tube or cuvette, mix a specific volume of serum (typically 10-20 microliters) with the Xylidyl Blue reagent. The magnesium in the serum reacts with Xylidyl Blue to form a colored complex, while the buffer in the reagent ensures optimal pH for the reaction, usually around pH 11.

Incubation:

Allow the mixture to develop fully by incubating it for a specified period, usually at room temperature for about 5-10 minutes**.**

Measurement:

Measure the absorbance of the colored complex at a specific wavelength (usually around 600-660 nm) using a spectrophotometer. The absorbance value, which indicates the intensity of the color, is directly proportional to the magnesium concentration in the sample.

Calculation:

Determine the concentration of magnesium in the serum sample by comparing the absorbance to a standard curve prepared using known concentrations of magnesium.

The utilisation of absorbance readings enables the calculation of magnesium concentration through the standard curve. The measurement units for the results are generally milligrams per deciliter or millimoles per liter.

ANNEXURE 2

MAGNESIUM DIRECT COLORIMETRIC METHOD REAGENTS INFORMATION

00080590161902c503V4.0

MG2

Magnesium Gen.2

cobas®

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08058016 190	Magnesium Gen.2 (**690 tests**)	System-ID 2089 001	Roche/Hitachi **cobas c** 503

Materials required (but not provided)

10759350 190	Calibrator f.a.s. (**12 x 3 mL**)	Code 20401
10759350 360	Calibrator f.a.s. (**12 x 3 mL, for USA**)	Code 20401
05117003 190	PreciControl ClinChem **Multi 1 (20 x 5 mL)**	Code 20391
05947626 190	PreciControl ClinChem **Multi 1 (4 x 5 mL)**	Code 20391
05947626 160	PreciControl ClinChem **Multi 1 (4 x 5 mL**, for USA)	Code 20391
05117216 190	PreciControl ClinChem **Multi 2 (20 x 5 mL)**	Code 20392
05947774 190	PreciControl ClinChem **Multi 2** (4 x 5 mL)	Code 20392
05947774 160	PreciControl ClinChem **Multi 2** (4 x 5 mL, for USA)	Code 20392
08063494 190	Diluent NaCl 9 % (**123 mL**)	System-ID 2906 001

English

System information

MG2: ACN 20890 (Serum/plasma)

MG2U: ACN 20891 (Urine)

Intended use

In vitro test for the quantitative determination of magnesium in human serum, plasma and urine on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4,5]

Magnesium along with potassium is a major intracellular cation. Mg^{2+} is a cofactor of many enzyme systems. Thus, all ATP-dependent enzymatic reactions require Mg^{2+} as a cofactor in the ATP-magnesium complex. Approximately 69 % of magnesium ions are stored in bone. The rest are part of the intermediary metabolism, about 70 % being present in free form while the other 30 % is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The Mg^{2+} serum level is kept constant within very narrow limits (0.65-1.05 mmol/L). Regulation takes place mainly via the kidneys, especially via the ascending loop of Henle.

This assay is used for diagnosing and monitoring hypomagnesemia (magnesium deficiency) and hypermagnesemia (magnesium excess). Numerous studies have shown a correlation between magnesium deficiency and changes in calcium-, potassium- and phosphate-homeostasis which are associated with cardiac disorders such as ventricular arrhythmias that cannot be treated by conventional therapy, increased sensitivity to digoxin, coronary artery spasms, and sudden death. Additional concurrent symptoms include neuromuscular and neuropsychiatric disorders. Hypermagnesemia is found in acute and chronic renal failure, magnesium excess, and magnesium release from the intracellular space.

In addition to atomic absorption spectrometry (AAS), complexometric methods can also be used to determine magnesium.

The method described here is based on the reaction of magnesium with xylidyl blue in alkaline solution containing EGTA to mask the calcium in the sample.

Urine magnesium levels are determined in magnesium depletion tests.

Test principle[5]

Colorimetric endpoint method

- Sample and addition of R1
- Addition of R2 and start of reaction:

  In alkaline solution, magnesium forms a purple complex with xylidyl blue, diazonium salt. The magnesium concentration is measured photometrically via the decrease in the xylidyl blue absorbance.

Reagents - working solutions

R1 TRIS[a]/6-aminocaproic acid buffer: 500 mmol/L, pH 11.25; EGTA: 129 µmol/L; preservative

R3 Xylidyl blue: 0.28 mmol/L; detergent; preservative

a) TRIS = Tris(hydroxymethyl)-aminomethane

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste

Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:

Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H315	Causes skin irritation.
H319	Causes serious eye irritation.

Prevention:

P264	Wash skin thoroughly after handling.
P280	Wear protective gloves/ eye protection/ face protection.

Response:

P302 + P352	IF ON SKIN: Wash with plenty of water.
P332 + P313	If skin irritation occurs: Get medical advice/attention.
P337 + P313	If eye irritation persists: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590, USA: 1-800-428-2336

Reagent handling

Ready for use

Storage and stability

Shelf life at 15-25 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	26 weeks

ANNEXURE 3

CIWA -AR SCALE

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Patient:_____ **Date:** _____ **Time:** _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute:_____ **Blood pressure:**_____

NAUSEA AND VOMITING -- Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES -- Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

TREMOR -- Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

AUDITORY DISTURBANCES -- Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

PAROXYSMAL SWEATS -- Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

VISUAL DISTURBANCES -- Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

ANXIETY -- Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mild anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

HEADACHE, FULLNESS IN HEAD -- Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

AGITATION -- Observation.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM -- Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place/or person

Total **CIWA-Ar** Score _____
Rater's Initials _____
Maximum Possible Score 67

*The **CIWA-Ar** is not* copyrighted and may be reproduced freely. This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal.

Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (**CIWA-Ar**). *British Journal of Addiction* 84:1353-1357, 1989.

ANNEXURE 4

CONSENT STATEMENTS

Consent form format

KAHERs JNMC
BELAGAVI
INFORMED CONSENT FORM

ASSESMENT OF SERUM MAGNESIUM LEVELS IN ALCOHOL USE DISORDER AND ITS CORELATION WITH SEVERITY OF ALCOHOL WITHDRAWAL STATE: A CROSS SECTIONAL DESCRIPTIVE HOSPITAL BASED STUDY

PG Student, Department of psychiatry,

J.N. Medical College, KAHER, Belagavi -590010

Objective: Estimation of serum magnesium level and comparing it with severity of alcohol withdrawal state as per CIWA Ar scale.

Introduction: Magnesium deficiency has been found to be very common among chronic alcoholics. There are limited study available in our country to establish the role of magnesium in alcohol withdrawal state . This is a one year study to assess the serum magnesium level in alcohol withdrawal state

Explanation of procedure: In this study Serum magnesium levels will be estimated by collecting Two ml of venous blood from you and the levels will be estimated using xylidyl blue technique and compared with the severity of symptoms as outlined by the CIWA Ar scale. If you agree to participate, the required information will be collected.

Cost of serum magnesium estimation will be borne by the principle investigator .

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no potential risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: post graduate student department of psychiatry JNMC, Belgavi phone number:8838981531 mail:anshonantony@gmail.com If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "ASSESMENT OF SERUM MAGNESIUM LEVELS IN ALCOHOL WITHDRAWAL STATE: A CROSS SECTIONAL DESCRIPTIVE HOSPITAL BASED STUDY".

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ಕಾಹೇರ್ಸ್ ಜೆ ಎನ್ ಎಂ ಸಿ

ಬೆಳಗಾವಿ

ತಿಳುವಳಿಕೆಯುಳ್ಳ ಒಪ್ಪಿಗೆ ಪತ್ರ

"ಆಲ್ಕೋಹಾಲ್ ಬಳಕೆಯ ಅಸ್ವಸ್ಥತೆಯಲ್ಲಿನ ಸೀರಮ್ ಮೆಗ್ನೀಸಿಯಮ್ ಮಟ್ಟಗಳ ಮೌಲ್ಯಮಾಪನ ಮತ್ತು ಆಲ್ಕೋಹಾಲ್ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವ ಸ್ಥಿತಿಯ ತೀವ್ರತೆಯೊಂದಿಗೆ ಅದರ ಸಂಬಂಧ: ಕ್ರಾಸ್ ಸೆಕ್ಷನಲ್ ಡಿಸ್ಕ್ರಿಪ್ಟಿವ್ ಆಸ್ಪತ್ರೆ ಆಧಾರಿತ ಅಧ್ಯಯನ".

ಪರಿಚಯ:

ದೀರ್ಘಕಾಲದ ಆಲ್ಕೊಹಾಲ್ಯುಕ್ತರಲ್ಲಿ ಮೆಗ್ನೀಸಿಯಮ್ ಕೊರತೆಯು ತುಂಬಾ ಸಾಮಾನ್ಯವಾಗಿದೆ ಎಂದು ಕಂಡುಬಂದಿದೆ. ಆಲ್ಕೋಹಾಲ್ ಿಂತೆಗೆದುಕೊಳ್ಳುವ ಸ್ಥಿತಿಯಲ್ಲಿ ಮೆಗ್ನೀಸಿಯಮ್ ಪಾತ್ರವನ್ನು ಸ್ಥಾಪಿಸಲು ನಮ್ಮ ದೇಶದಲ್ಲಿ ಸೀಮಿತ ಅಧ್ಯಯನಗಳು ಲಭ್ಯವಿದೆ. ಆಲ್ಕೋಹಾಲ್ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವ ಸ್ಥಿತಿಯಲ್ಲಿ ಸೀರಮ್ ಮೆಗ್ನೀಸಿಯಮ್ ಮಟ್ಟವನ್ನು ನಿರ್ಣಯಿಸಲು ಇದು ಒಂದು ವರ್ಷದ ಅಧ್ಯಯನವಾಗಿದೆ.

ಕಾರ್ಯವಿಧಾನದ ವಿವರಣೆ:

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮಿಂದ ಎರಡು ಮಿಲಿ ಸಿರೆಯ ರಕ್ತವನ್ನು ಸಂಗ್ರಹಿಸುವ ಮೂಲಕ ಸೀರಮ್ ಮೆಗ್ನೀಸಿಯಮ್ ಮಟ್ಟವನ್ನು ಅಂದಾಜು ಮಾಡಲಾಗುತ್ತದೆ ಮತ್ತು ಕ್ಸಿಲಿಡಿಲ್ ಬ್ಲೂ ತಂತ್ರವನ್ನು ಬಳಸಿಕೊಂಡು ಮಟ್ಟವನ್ನು ಅಂದಾಜು ಮಾಡಲಾಗುತ್ತದೆ ಮತ್ತು ಸಿ ಐಡಬ್ಲ್ಯೂ ಎ ಎ ಆರ್ ಮಾಪಕದಿಂದ ವಿವರಿಸಿರುವ ರೋಗಲಕ್ಷಣಗಳ ತೀವ್ರತೆಗೆ ಹೋಲಿಸಲಾಗುತ್ತದೆ. ನೀವು ಭಾಗವಹಿಸಲು ಒಪ್ಪಿದರೆ, ಅಗತ್ಯವಿರುವ ಮಾಹಿತಿಯನ್ನು ಸಂಗ್ರಹಿಸಲಾಗುತ್ತದೆ.

ಸೀರಮ್ ಮೆಗ್ನೀಸಿಯಮ್ ಅಂದಾಜು ವೆಚ್ಚವನ್ನು ತತ್ಸ ತನಿಖಾಧಿಕಾರಿ ಭರಿಸುತ್ತಾರೆ.

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯಿಂದ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವಿಕೆ :

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯು ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ. ಒಮ್ಮೆ ದಾಖಲಾದ ನಂತರ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಬೇಕೆ ಅಥವಾ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಮುಂದುವರಿಸಬೇಕೆ ಎಂದು ನಿರ್ಧರಿಸಲು ನೀವು ಸ್ವತಂತ್ರರಾಗಿರುತ್ತೀರಿ. ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಹಿಂತೆಗೆದುಕೊಳ್ಳಲು ನೀವು ನಿರ್ಧರಿಸಿದರೆ, ಹಾಗೆ ಮಾಡಲು ನೀವು ಸ್ವತಂತ್ರರು. ಆದಾಗ್ಯೂ, ದಯವಿಟ್ಟು ನಿರ್ಧಾರವನ್ನು ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿಗೆ ತಿಳಿಸಿ.

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಸಂಭವನೀಯ ಪ್ರಯೋಜನಗಳು :

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವ ಮೂಲಕ ನೀವು ಯಾವುದೇ ಪ್ರಯೋಜನಗಳನ್ನು ಹೊಂದಿರುವುದಿಲ್ಲ ಅಥವಾ ಪಡೆಯುವುದಿಲ್ಲ. ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯು ಜನಸಂಖ್ಯೆಗೆ ದೊಡ್ಡ ಪ್ರಮಾಣದಲ್ಲಿ ಸಹಾಯ ಮಾಡುತ್ತದೆ.

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಸಂಭವನೀಯ ಅಪಾಯಗಳು :

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಯಾವುದೇ ಅಪಾಯಗಳಿಲ್ಲ.

ಗೌಪ್ಯತೆ

ಯಾವುದೇ ವ್ಯಕ್ತಿ ನಿಮ್ಮನ್ನು ಗುರುತಿಸದಂತೆ ತಡೆಯಲು ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಕೋಡ್ ಮಾಡಲಾಗುತ್ತದೆ. ನಿಮ್ಮ ಗುರುತನ್ನು ಎಂದಿಗೂ ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಡೇಟಾವನ್ನು ಗೌಪ್ಯವಾಗಿ ಇರಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಪ್ರಕ್ರಿಯೆಗೊಳಿಸಿದ ಅಥವಾ ಒಟ್ಟುಗೂಡಿದ ಡೇಟಾವನ್ನು ಮಾತ್ರ ಪ್ರಕಟಣೆಗಾಗಿ ಬಳಸಲಾಗುತ್ತದೆ.

ಆರ್ಥಿಕ ಪ್ರೋತ್ಸಾಹಗಳು : ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಿದ್ದಕ್ಕಾಗಿ ನೀವು ಯಾವುದೇ ಪಾವತಿಯನ್ನು ಸ್ವೀಕರಿಸುವುದಿಲ್ಲ.

ಒಟ್ಟುಗೂಡಿದ ಡೇಟಾದ ಪ್ರಕಟಣೆಗೆ ಅಧಿಕಾರ :

ಒಟ್ಟುಗೂಡಿದ ಡೇಟಾವನ್ನು ಪ್ರಕ್ರಿಯೆಗೊಳಿಸಿದ ನಂತರ ಪಡೆದ ಫಲಿತಾಂಶಗಳನ್ನು ವೈಜ್ಞಾನಿಕ ಉದ್ದೇಶಗಳಿಗಾಗಿ ಪ್ರಕಟಿಸಲಾಗುತ್ತದೆ ಅಥವಾ ವೈಜ್ಞಾನಿಕ ಗುಂಪುಗಳಿಗೆ ಪ್ರಸ್ತುತಪಡಿಸಲಾಗುತ್ತದೆ. ಆದಾಗ್ಯೂ, ನಿಮ್ಮ ಗುರುತನ್ನು ಎಂದಿಗೂ ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ

ಪ್ರಶ್ನೆಗಳು

ಈ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳಿದ್ದಲ್ಲಿ, ನೀವು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿರುತ್ತೀರಿ: ಡಾ. ಅಂಶೋನ್ ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ ಮನೋವೈದ್ಯಶಾಸ್ತ್ರ ವಿಭಾಗ ಜೆಎನ್ ಎಂ ಸಿ , ಬೆಳಗಾವಿ ದೂರವಾಣಿ ಸಂಖ್ಯೆ: 8838981531 , mail: anshonantony@gmail.com ನಿಮ್ಮ ಹಕ್ಕಿನ ಕುರಿತು ನೀವು ಯಾವುದೇ ಪ್ರಶ್ನೆ ಅಥವಾ ದೂರುಗಳನ್ನು ಹೊಂದಿದ್ದರೆ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವವರನ್ನು ನೀವು ಸಂಪರ್ಕಿಸಬಹುದು ಡಾ. ಹರ್ಷ ಹೆಗಡೆ, ಅಧ್ಯಕ್ಷರು, ಜೆಎನ್ಎಂಸಿ ನೈತಿಕ ಸಮಿತಿ, 0831-2473777 ವಿಸ್ತರಣೆ 4052.

ಕಾನೂನು ಹಕ್ಕುಗಳು :

ಈ ಸಮ್ಮತಿಯ ನಮೂನೆಗೆ ಸಹಿ ಮಾಡುವ ಮೂಲಕ, ನಿಮ್ಮ ಯಾವುದೇ ಕಾನೂನು ಹಕ್ಕುಗಳನ್ನು ನಾವು ಕೈ ಬೀಸಿ ಕರೆಯುತ್ತಿಲ್ಲ.

ಸಮ್ಮತಿ ಹೇಳಿಕೆ

ನಾನು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಸ್ವಯಂಪ್ರೇರಿತ ನಿರ್ಧಾರವನ್ನು ಮಾಡುತ್ತಿದ್ದೇನೆ "ಆಲ್ಕೋಹಾಲ್ ಬಳಕೆಯ ಅಸ್ವಸ್ಥತೆಯಲ್ಲಿನ ಸೀರಮ್ ಮೆಗ್ನೀಸಿಯಮ್ ಮಟ್ಟಗಳ ಮೌಲ್ಯಮಾಪನ ಮತ್ತು ಆಲ್ಕೋಹಾಲ್ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವ ಸ್ಥಿತಿಯ ತೀವ್ರತೆಯೊಂದಿಗೆ ಅದರ ಸಂಬಂಧ: ಕ್ರಾಸ್ ಸೆಕ್ಷನಲ್ ಡಿಸ್ಕ್ರಿಪ್ಟಿವ್ ಆಸ್ಪತ್ರೆ ಆಧಾರಿತ ಅಧ್ಯಯನ". . ಕೆಳಗಿನ ನನ್ನ ಸಹಿಯು ನಾನು ಭಾಗವಹಿಸಲು ನಿರ್ಧರಿಸಿದ್ದೇನೆ ಮತ್ತು ನಾನು ಮೇಲೆ ಒದಗಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಓದಿದ್ದೇನೆ ಅಥವಾ ಮೇಲೆ ಒದಗಿಸಿದ ಮಾಹಿತಿಯನ್ನು ನನಗೆ ಚೆನ್ನಾಗಿ ಅರ್ಥವಾಗುವ ಭಾಷೆಯಲ್ಲಿ ಓದಲಾಗಿದೆ ಎಂದು ಸೂಚಿಸುತ್ತದೆ. ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶವನ್ನು ನೀಡಲಾಯಿತು ಮತ್ತು ಅವುಗಳಿಗೆ ನನ್ನ ತೃಪ್ತಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ.

ಭಾಗವಹಿಸುವವರ ಹೆಸರು:

ಭಾಗವಹಿಸುವವರ ಸಹಿ ಅಥವಾ ಎಡ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು:

ಸಾಕ್ಷಿಯ ಹೆಸರು:

ಸಾಕ್ಷಿಯ ಸಹಿ ಅಥವಾ ಎಡ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು:

ತನಿಖಾಧಿಕಾರಿಯ ಹೆಸರು:

ತನಿಖಾಧಿಕಾರಿಯ ಸಹಿ:

काहेरचे जे एन एम सी

बेलागावी

माहितीपूर्ण संमती पत्र

"असेसमेंट ऑफ सीरम मॅग्नेशियम लेव्हल्स इन अल्कोहोल यूज डिसऑर्डर आणि अल्कोहोल विथड्रॉवल स्टेटच्या तीव्रतेशी त्याचा संबंध: एक क्रॉस सेक्शनल वर्णनात्मक हॉस्पिटल आधारित अभ्यास".

परिचय:

दीर्घकाळ मद्यपान करणाऱ्यांमध्ये मॅग्नेशियमची कमतरता खूप सामान्य असल्याचे आढळून आले आहे. अल्कोहोल काढण्याच्या स्थितीत मॅग्नेशियमची भूमिका स्थापित करण्यासाठी आपल्या देशात मर्यादित अभ्यास उपलब्ध आहेत. अल्कोहोल काढण्याच्या स्थितीत सीरम मॅग्नेशियम पातळीचे मूल्यांकन करण्यासाठी हा एक वर्षाचा अभ्यास आहे.

प्रक्रियेचे स्पष्टीकरण:

या अभ्यासात तुमच्याकडून दोन मिली शिरासंबंधी रक्त गोळा करून सीरम मॅग्नेशियमच्या पातळीचा अंदाज लावला जाईल आणि जेलीडायल ब्लू तंत्राचा वापर करून पातळीचा अंदाज लावला जाईल आणि आय डब्ल्यू ए ए आर स्केलने वर्णन केलेल्या लक्षणांच्या तीव्रतेशी तुलना केली जाईल. आपण सहभागी होण्यास सहमत असल्यास, आवश्यक माहिती गोळा केली जाईल.

सीरम मॅग्नेशियमच्या अंदाजाची किंमत तत्त्व अन्वेषकाद्वारे वहन केली जाईल.

अभ्यासातील सहभागातून माघार घेणे :

या अभ्यासात सहभाग ऐच्छिक आहे. या अभ्यासात भाग घ्यायचा की नावनोंदणी झाल्यावर सहभाग सुरू ठेवायचा हे ठरवण्यासाठी तुम्ही मोकळे असाल. तुम्ही तुमचा सहभाग मागे घेण्याचा निर्णय घेतल्यास, तुम्ही तसे करण्यास मोकळे आहात. तथापि, कृपया मुख्य अन्वेषकांना निर्णय कळवा.

अभ्यासात सहभागी होण्याचे संभाव्य फायदे :

या अभ्यासात सहभागी होऊन तुम्हाला कोणतेही फायदे मिळणार/नाही किंवा मिळणार नाहीत. गोळा केलेला डेटा मोठ्या प्रमाणावर लोकसंख्येला मदत करेल.

अभ्यासात सहभागी होण्याचे संभाव्य धोके : या अभ्यासात सहभागी होण्यात कोणतेही धोके नाहीत.

गोपनीयता

कोणत्याही व्यक्तीला तुमची ओळख पटवण्यापासून रोखण्यासाठी तुमच्याकडून गोळा केलेली माहिती कोड केली जाईल. तुमची ओळख कधीच उघड होणार नाही. तुमच्याकडून गोळा केलेला डेटा गोपनीय ठेवला जाईल आणि केवळ प्रक्रिया केलेला किंवा एकत्रित केलेला डेटा प्रकाशनासाठी वापरला जाईल.

आर्थिक प्रोत्साहन : या अभ्यासात सहभागी होण्यासाठी तुम्हाला कोणतेही पेमेंट मिळणार नाही.

एकत्रित डेटाच्या प्रकाशनासाठी अधिकृतता :

एकत्रित डेटाच्या प्रक्रियेनंतर प्राप्त झालेले परिणाम वैज्ञानिक हेतूंसाठी प्रकाशित केले जातील आणि किंवा वैज्ञानिक गटांना सादर केले जातील. मात्र, तुमची ओळख कधीही उघड होणार नाही.

प्रश्नावळ:

या अभ्यासाबाबत काही प्रश्न असल्यास, तुम्ही मोकळेपणे संपर्क साधू शकता: डॉ. अंशोन पदव्युत्तर विद्यार्थी मानसोपचार विभाग जे एन एम सी, बेळगावी फोन नंबर: 8838981531 mail:anshonantony@gmail.com.

: तुम्हाला तुमच्या अधिकाराबाबत काही प्रश्न किंवा तक्रारी असल्यास अभ्यासात सहभागी म्हणून तुम्ही डॉ. हर्षा हेगडे, अध्यक्षा, जे एन एमसी च्या नैतिक समिती, 0831-2473777 विस्तार 4052 यांच्याशी संपर्क साधू शकता.

कायदेशीर अधिकार :

या संमती फॉर्मवर स्वाक्षरी करून, आम्ही तुमचे कोणतेही कायदेशीर अधिकार सोडत नाही.

संमती विधान

मी अभ्यासात सहभागी होण्याचा ऐच्छिक निर्णय घेत आहे "असेसमेंट ऑफ सीरम मॅग्नेशियम लेव्हल्स इन अल्कोहोल यूज डिसऑर्डर आणि अल्कोहोल विथड्रॉवल स्टेटच्या तीव्रतेशी त्याचा संबंध: एक क्रॉस सेक्शनल वर्णनात्मक हॉस्पिटल आधारित अभ्यास" . .खाली दिलेली माझी स्वाक्षरी सूचित करते की मी सहभागी होण्याचा निर्णय घेतला आहे आणि मी वर दिलेली माहिती वाचली आहे किंवा वर दिलेली माहिती मला चांगल्या प्रकारे समजत असलेल्या भाषेत वाचण्यात आली आहे. मला प्रश्न विचारण्याची संधी देण्यात आली आणि त्यांना माझ्या समाधानासाठी उत्तरे देण्यात आली .

सहभागीचे नाव:

सहभागीची सही किंवा डाव्या अंगठ्याचा ठसा:

साक्षीदाराचे नाव:

साक्षीदाराची सही किंवा डाव्या अंगठ्याचा ठसा:

तपासकर्त्याचे नाव:

अन्वेषकाची स्वाक्षरी:

ANNEXURE 5 PERFORMA

ASSESMENT OF SERUM MAGNESIUM LEVELS IN ALCOHOL WITHDRAWAL STATE: A CROSS SECTIONAL DESCRIPTIVE HOSPITAL BASED STUDY

NAME:

AGE/ SEX:

OP/IP NO:

OCCUPATION:

ADDRESS:

CONTACT NUMBER:

SYMPTOMS:

Autonomic hyperactivity

Worsening tremor

Insomnia

Vomiting and nausea

Hallucinations

Psychomotor agitation

Anxiety

Generalised tonic-clonic seizures

CIWA Ar score:

PAST HISTORY:

History of similar complaints in the past

History of any other co morbid illness

PERSONAL HISTORY:

History of alcohol intake: type of alcohol, quantity and duration

History of last consumption of alcohol

History of other substance abuse

GENERAL EXAMINATION:

Consciousness, orientation to time, place and person

Pallor/ Icterus / Cyanosis / Clubbing / Pedal edema / lymphadenopathy

VITALS: Blood pressure / Pulse rate / respiratory rate / Temperature

SYSTEMIC EXAMINATION:

Cardiovascular system:

Respiratory system

Per abdomen:

Central nervous system:

INVESTIGATIONS:

Complete blood count

Renal function test

Liver function test

Serum magnesium levels

S. Number	Age (Years)	Gender	Religion	Marital Status	Educational Status	Occupation	Type Of Alcohol Currently	Duration Of Alcohol Intake (Years)	Time Since Last Drink (Hours)	Nicotine	Diabetes	Hypertension	CIWA - AR Score	Serum Magnesium (mg/dL)	Serum Potassium (mEq/L)	Serum Sodium (mEq/L)	Serum Urea (mg/dL)	Serum Creatinine (mg/dL)		
1	40	1	1	1	1	2	1	20	24	1	0	0	24	1.2	3.1	132	35	0.7		
2	56	1	1	1	2	1	1	25	36	0	0	0	45	0.8	3.2	136	25	0.6		
3	55	1	1	1	1	2	2	30	96	0	1	0	6	2.1	2.9	130	49	1.6		
4	53	1	1	1	1	2	2	12	60	1	0	1	9	1.9	3.7	140	54	1.4		
5	48	1	1	1	1	2	2	14	12	1	0	0	38	0.6	3.8	139	42	1.8		
6	35	1	1	1	5	2	1	10	72	1	0	0	22	1.6	4	144	16	0.5		
7	42	1	1	1	1	2	2	15	48	1	1	0	18	1.3	3	131	49	1.1		
8	25	1	2	2	3	2	3	3	24	0	0	0	15	1.6	4.1	136	24	0.6		
9	41	1	1	2	1	3	1	12	36	1	0	0	24	0.8	3.1	141	31	0.7		
10	40	1	1	1	1	2	2	9	48	1	0	0	7	2	4.6	139	44	0.8		
11	33	1	2	3	1	2	3	2	24	0	0	0	14	1.9	4.8	136	54	0.8		
12	30	1	1	1	1	2	2	12	24	1	0	0	26	0.8	2.8	129	21	0.4		
13	29	1	1	1	1	3	1	4	24	1	0	0	35	0.9	2.9	128	28	0.7		
14	47	1	1	1	2	2	1	6	24	1	0	0	11	2.2	3.9	138	54	0.9		
15	39	1	1	1	4	3	1	8	12	0	1	1	23	0.8	3	134	84	2.1		
16	51	1	1	1	4	4	2	14	12	1	0	1	16	1.4	2.6	129	49	1.6		
17	43	1	1	1	2	2	1	13	24	1	0	0	41	0.8	3.1	131	98	1.2		
18	28	1	1	2	1	2	1	11	24	0	0	0	23	1.2	3.3	133	24	0.8		
19	30	1	1	1	1	2	2	7	24	1	0	0	19	1.4	3.5	138	18	0.5		
20	25	1	3	2	4	4	2	1	48	0	0	0	15	1.3	4.1	137	35	0.8		
21	48	1	1	3	1	2	2	12	72	0	0	1	47	0.4	2.1	130	49	1.5		
22	52	1	1	1	2	3	2	6	24	0	0	0	6	2.1	3.8	131	44	0.9		
23	41	1	1	1	4	2	2	10	60	1	0	0	7	2	3.9	136	17	0.5		
24	35	1	3	3	1	2	2	4	48	0	0	0	28	0.6	3	136	21	0.6		
25	57	1	1	1	1	1	2	7	48	1	1	1	12	1.1	3.2	139	63	1.6		
26	35	1	1	1	1	1	1	7	36	1	0	0	15	1.2	3.5	141	44	0.8		
27	40	1	1	1	1	3	1	10	36	1	0	0	35	0.4	3.1	142	25	0.6		
28	38	1	1	1	1	3	3	6	24	1	0	0	5	1.9	4.3	144	35	0.7		
29	24	1	1	2	1	2	1	6	12	1	0	0	7	2	4.1	138	21	0.5		
30	34	1	1	2	4	3	1	9	24	0	0	1	24	1.3	4	142	36	1.2		
31	27	1	1	1	1	3	2	4	36	0	0	0	45	0.8	3	139	31	0.5		
32	44	1	2	1	4	4	4	4	48	0	0	0	12	1.9	3.5	137	45	0.8		
33	38	1	1	1	1	2	2	7	48	0	0	0	18	1.4	4.6	138	44	0.7		
34	45	1	1	1	4	3	2	12	32	0	0	1	32	0.9	3.2	130	54	0.9		
35	43	1	1	1	1	2	2	11	24	0	0	0	27	1.2	3.2	129	32	0.5		
36	25	1	2	1	1	2	1	3	48	0	0	0	41	0.9	3	136	25	0.6		
37	29	1	1	1	4	3	2	6	48	1	0	0	37	0.7	3.1	137	32	0.7		
38	36	1	1	1	1	2	2	7	48	1	0	0	12	1.5	3.9	132	35	0.4		
39	50	1	1	1	5	2	2	12	72	1	0	1	23	0.9	4	133	64	2.3		
40	39	1	1	1	1	2	2	4	72	0	0	0	51	0.7	1.9	132	29	0.5		
41	26	1	3	2	1	2	2	5	48	0	0	0	24	1.4	3.2	132	34	0.7		
42	52	1	1	1	1	2	1	12	48	0	0	1	30	0.8	2.9	129	68	1.3		
43	45	1	1	1	1	3	2	5	48	1	1	1	10	1.8	3.9	139	78	1.7		
44	46	1	1	1	1	3	2	10	48	1	0	1	5	2	4.3	130	56	1.3		
45	53	1	1	1	1	1	4	9	48	1	1	0	24	2.1	2.4	128	45	1		
46	49	1	1	1	1	2	1	13	24	1	1	1	26	0.9	3.1	133	53	1.6		
47	36	1	1	1	1	3	1	14	48	0	0	0	49	0.8	2.2	27	28	1.2		
48	37	1	1	1	1	3	2	12	24	0	0	1	12	1.9	4.5	138	45	1.3		
49	52	1	1	1	1	3	2	20	72	0	0	1	37	0.8	3	135	24	0.8		
50	35	1	1	1	1	2	2	4	24	0	0	0	23	0.6	3.6	136	28	0.5		
51	58	1	1	1	1	3	2	15	24	0	1	1	45	0.5	3.2	140	56	3.4		
52	36	1	1	1	1	2	1	12	24	0	0	1	23	0.8	3.6	142	34	1.2		
53	20	1	1	2	1	1	1	1	48	0	0	0	14	1.6	4	143	24	0.4		
54	36	1	1	1	1	3	2	14	12	1	0	0	23	0.9	4.1	143	28	0.4		
55	22	1	3	2	4	4	3	2	48	1	0	0	19	1.5	5.1	138	25	0.6		
56	39	1	1	1	1	2	2	16	24	1	0	0	38	1.1	2.9	132	48	0.4		
57	44	1	1	1	1	2	2	5	24	0	1	0	23	0.9	2.1	128	42	1		
58	51	1	1	1	1	2	1	8	24	0	0	0	27	0.8	3.6	135	59	1.5		
59	48	1	1	1	1	2	1	10	24	1	0	0	25	0.8	3.2	136	64	0.8		
60	52	1	3	1	1	2	2	12	24	1	0	1	38	0.7	2.3	141	81	2.1		
61	56	1	1	1	1	2	2	17	48	1	0	1	16	1.5	3.6	135	69	1.7		
62	37	1	3	1	4	2	4	5	36	0	0	0	17	1.3	3.7	138	19	0.5		
63	43	1	1	1	3	3	2	10	12	1	0	0	36	0.8	3.1	134	29	0.6		
64	32	1	1	1	1	2	1	5	12	1	0	0	25	0.9	3.4	133	45	0.7		
65	29	1	1	1	3	3	2	3	48	1	0	0	19	1.6	4.2	141	25	0.4		
66	37	1	1	1	1	2	2	7	12	0	0	0	28	0.8	2.9	129	44	0.8		
67	45	1	1	1	1	2	1	8	24	1	0	1	24	0.7	3	128	47	1.3		
68	52	1	1	1	2	2	1	11	48	1	0	0	22	0.8	3.2	135	60	1.4		
69	45	1	1	1	1	2	2	10	24	1	1	1	46	0.9	2.6	137	54	1.5		
70	53	1	1	1	3	3	2	15	24	1	0	0	16	1.6	4.2	139	62	1		
71	67	1	1	3	3	2	1	12	48	1	0	1	19	1.6	4	134	40	0.4		
72	49	1	1	1	1	2	1	7	24	1	0	0	45	0.4	3.2	141	35	1.2		
73	40	1	1	1	2	2	2	12	12	0	0	0	32	0.9	3.4	136	38	1.2		
74	56	1	1	1	4	4	1	18	24	1	0	0	21	1	3.2	134	48	1		
75	62	1	1	1	2	1	2	20	12	1	0	1	45	0.9	3.1	141	38	2.1		

76	25	1	1	1	1	2	2	5	48	1	0	0	15	1.4	3.9	136	50	0.4		
77	34	1	1	1	1	2	2	13	48	1	0	0	18	1.7	4	141	32	0.5		
78	56	1	1	1	1	2	2	15	24	1	0	1	25	1	4.2	136	45	1.2		
79	49	1	1	1	3	3	1	12	24	1	0	0	15	1.5	4.3	145	44	1		
80	48	1	3	1	1	2	1	10	48	1	0	0	18	1.4	3	129	53	0.6		
81	32	1	1	1	1	2	1	3	12	0	0	0	12	1.1	3.2	127	23	0.5		
82	41	1	1	1	1	2	4	8	12	0	0	0	10	2.3	4.9	130	42	0.5		
83	57	1	1	1	3	2	1	9	12	0	1	0	7	2.2	4.8	129	52	0.9		
84	45	1	1	1	1	2	2	10	24	0	0	0	19	2	4.1	133	34	0.5		
85	52	1	1	1	1	2	1	12	24	1	0	0	41	0.5	3.7	132	28	0.7		
86	61	1	1	1	2	2	2	15	48	0	1	1	38	1.7	3.9	122	74	3.1		
87	21	1	1	1	1	2	2	3	24	0	0	0	12	1.9	3.6	133	26	0.7		
88	26	1	3	1	1	3	2	7	24	0	0	0	14	1.8	3.6	135	18	0.6		
89	36	1	1	1	4	4	2	4	24	0	0	0	6	1.9	3.9	136	28	0.5		
90	54	1	1	1	4	4	2	8	24	0	1	1	7	1.7	4.1	136	64	3.5		
91	62	1	1	1	1	1	1	15	48	0	0	0	40	0.9	2.9	128	45	0.5		
92	65	1	1	1	1	1	2	13	24	0	0	1	32	1.2	3.6	139	81	1.5		
93	41	1	1	1	3	2	1	10	12	1	0	0	28	0.6	3	141	52	1.1		
94	37	1	1	1	1	2	1	14	36	1	0	0	32	1.2	2.89	126	28	0.7		
95	26	1	1	2	1	3	3	5	48	1	0	0	14	1.4	3.8	128	26	0.4		
96	36	1	1	1	2	2	2	7	48	1	0	0	25	0.9	3.1	127	28	0.8		
97	41	1	1	1	1	3	2	9	24	1	0	0	27	0.7	3.5	135	33	0.7		
98	52	1	2	1	1	3	1	14	24	1	0	1	39	0.9	3.7	137	53	0.7		
99	47	1	1	1	3	3	2	13	24	1	0	1	28	0.9	2.9	140	45	0.4		
100	34	1	2	1	4	4	1	1	12	1	0	0	7	2.1	3.9	132	28	0.7		