Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230-8407 [LINKING]

A Comparative Study of Serum Creatine Kinase Levels in Patients with Alcohol Dependence Syndrome having Complicated Withdrawal (Seizures/Delirium) and Uncomplicated Withdrawal

Dr. Arun Seetharaman[1], Dr. Andrea Chrisyl Vas[2*], Dr. Ramkumar Thirumal[3], Dr. Sriramadesigan Radhakrishnan[4]

[1]Professor and HOD, Department of Psychiatry, Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, India. ORCID ID: https://orcid.org/0009-0002-7153-8548, Email ID: drarounseetharaman@gmail.com

[2]Postgraduate, Department of Psychiatry, Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, India. ORCID ID: https://orcid.org/0009-0003-9154-0976, Email ID: vasandrea96@gmail.com

[3]Associate Professor, Department of Psychiatry, Sri Lakshmi Narayana Institute of Medical Sciences, pondicherry, India. ORCID ID: https://orcid.org/0009-0007-7788-0068, Email ID: drarounseetharaman@gmail.com

[4]Assistant professor, Department of psychiatry, Sri Lakshmi Narayana institute of medical sciences, pondicherry, India. ORCID ID: https://orcid.org/0009-0001-5924-6385, Email ID: dr.sriramadesigan@gmail.com

Corresponding Author

Email: vasandrea96@gmail.com

How to cite: Dr. Arun Seetharaman, Dr. Andrea Chrisyl Vas, Dr. Ramkumar Thirumal, Dr. Sriramadesigan Radhakrishnan. **A Comparative Study of Serum Creatine Kinase Levels in Patients with Alcohol Dependence Syndrome having Complicated Withdrawal (Seizures/Delirium) and Uncomplicated Withdrawal**. International Research Journal of Pharmacy. 2025; 16:6:79-96.

Doi: http://doi.org/10.56802/irjp.2025.v16.i06.pp79-96

==========

Abstract

Alcohol dependence syndrome encompasses physiological, behavioral, and cognitive symptoms, prioritizing alcohol use to an extreme degree. Withdrawal complications, such as delirium tremens (DT), pose significant health risks, with DT being potentially fatal in up to 37% of cases, typically manifesting 72hours after alcohol cessation. Early AWS complications such as seizures and delirium tremens represent deadly risks to patient health so dependable

biomarkers must be available for timely detection and management. The biochemical marker CK stands as a possible choice because it shows relationships with muscle injury and physiological stress. Research examined CK biomarker levels in alcohol dependent patients experiencing complex withdrawal syndrome (n = 48) and simple withdrawal syndrome (n = 54). The data revealed higher CK biomarker levels in patients experiencing complex withdrawal indicating potential usage as a cheap screening instrument for identifying high-risk groups. Results demonstrated significantly higher CK levels in complicated withdrawal (mean 298.14) compared to uncomplicated withdrawal (mean 130.48), with a p-value of 0.001. Additionally, CIWA and SADQ scores were notably higher in the complicated group, each with statistically significant p-values of 0.001. A strong correlation was observed between serum CK levels and CIWA scores (p = 0.001), highlighting serum CK as a potential marker for identifying withdrawal severity. This suggests that routine CK measurement upon admission could serve as a rapid, supplementary diagnostic tool to guide timely clinical interventions for varying states of alcohol withdrawal.

Keywords: Creatine kinase (CK), delirium tremens (DT), alcohol dependence syndrome, clinical institute withdrawal assessment for alcohol scale revised (CIWA-Ar) scores and severity of alcohol dependence questionnaire (SADQ).

Introduction

Alcohol dependency syndrome (ADS) displays its defining marker by producing withdrawal effects after excessive drinking starting from light tremors and culminating in fatal conditions such as seizures and delirium tremens (DT). Progressive morbidity and mortality rates call for timely identification of patients at high risk for complex alcohol withdrawal[1]. This objective parameter system enables crucial measurements of physical changes thus making biomarkers critical tools for identifying problems[2]. Among all available markers CK proves optimal because it indicates muscle tissue damage commonly seen in seizures and persistent agitation disorders[4,5]. The research investigates CK biomarker potential for AWS problems while addressing missing literature gaps and delivering meaningful therapy approaches for resource-constrained situations[6].

Alcohol-related disorders may be caused by dysregulated dopamine levels and elevated CK levels in the heart, brain, and muscles, indicating organ strain or injury. Excessive alcohol consumption can increase blood CK levels due to muscle toxicity.[7] This can cause muscle damage. Alcohol abusers may suffer cardiac damage from cellular toxicity. Intoxication with alcohol, a CNS depressant, requires medical attention, fluids, and electrolytes.[8] Benzodiazepines treat agitation, irritability, anxiety, and seizures. Drinking excessively can develop to alcohol dependence syndrome, which can lead to life-threatening problems.[9] Age, drinking history, liver health, and medical issues affect withdrawal type. Alcohol withdrawal symptoms range from minor to severe. Symptoms of delirium tremens might appear 72 hours after alcohol discontinuation and continue 3-7 days. Preventing seizures and delirium tremens requires quick withdrawal severity assessment. CIWA-Ar is often used to determine alcohol

withdrawal severity.[10] Sudden alcohol withdrawal can produce "alcoholic rhabdomyolysis," causing mild to severe CK increase and myoglobinuria.[11]

CK is a potent natural survival and neuroprotective factor for developing nigral dopaminergic neurons. Heavy alcohol consumption may affect centrally-mediated dopaminergic function over time.[12]Lower DA neurotransmission may lead to increased blood CK activity as a neuroprotective mechanism. Lack of research on CK levels in alcohol dependence syndrome despite clinical significance. Delirium tremens and seizures are serious withdrawal symptoms.[13] Delirium and seizures cause severe morbidity and mortality. Patients without treatment died at 37%. The mortality rate for properly treated patients was 5-15%.[14]Comparing and exploring CK levels in complex vs. uncomplicated withdrawal helps minimize morbidity and mortality and maximize patient care and result.[15]

Measurement studies focused on CK distribution during difficult versus simple alcohol withdrawal syndrome (AWS) remain scarce even though previous investigations documented elevated CK levels in diseases including rhabdomyolysis and alcohol withdrawal. This study investigates CK as an essential biomarker to help identify and forecast advanced AWS cases including seizures or delirium tremens while targeting resource-limited assessment environments. The simple and affordable biochemical marker called CK provides valuable benefits which extend to clinical applications when diagnostic machines are limited in the location. The research presents a special contribution by evaluating how CK data can predict withdrawal conditions since previous studies have not extensively studied the correlation between CK measurements and CIWA-Ar and SADQ scores.

High morbidity along with death frequently occurs because of alcohol withdrawal syndrome (AWS) which produces seizures and delirium tremens (DT) as severe outcomes. Treatments require prompt delivery because early identification of at-risk patients remains important for intervention. Previous research examined biomarkers including GGT alongside inflammatory mediators yet clinical adoption of these markers remains constrained due to both accessibility challenges and high costs. The recognized indicator of muscle damage 'creatine kinase' (CK) emerges as an affordable and accessible substitute for bio detection purposes. There remains an unknown relationship between creatine kinase as a biomarker for identifying outcomes related to alcohol withdrawal syndrome. This investigation analyzes CK levels between difficult and simple AWS cases as well as examines their relationship with dependency (SADQ) and withdrawal intensity (CIWA-Ar) to bridge this scientific gap in the field.

The study's adoption of CK as an easy and inexpensive biomarker for AWS identification sets it apart from other approaches. Other studies analyzed general alcohol-related illnesses but this investigation systematically examined CK levels within simple and difficult forms of AWS. The strong links between verified clinical scales (CIWA-Ar and SADQ) and CK establish thorough guidelines for its usage in clinical practice. Because sophisticated diagnostic tools are rarely accessible in settings with limited resources the identification of early indicators becomes crucial.

Thus, this study compares serum CK levels between ADS patients with severe withdrawal (seizures or delirium) and those with straightforward withdrawal to determine if CK activity and alcohol withdrawal have a correlation. Serum CK levels and delirium risk in ADS patients are also examined in this study.

The primary objectives of this study are

- To compare the levels of serum CK in alcohol dependence syndrome patients with complicated withdrawal and uncomplicated withdrawal.
- To assess the correlation between CK and clinical institute withdrawal assessment for alcohol scale revised (CIWA-Ar) scores and CK and Severity of alcohol dependence questionnaire (SADQ).
- To assess the correlation of serum creatine kinase levels in alcohol dependence patients as a predictive value/factor of developing complicated withdrawal.

Literature Review

Serum CK levels in alcohol-dependent patients, with or without complicated withdrawal, were reviewed to evaluate originality alongside relevant literature.

In 2009, Lineras et al.[16] examined acute renal failure in hospitalized rhabdomyolysis patients with CK >5000 IU/L. In 49% of cases, renal problems were substantially associated with CK ($p<0.0001$). 49% had myoglobinuria and 52% pre-renal abnormalities. CK should be 10–25x the upper limit for rhabdomyolysis. CK helps diagnose and detect pharmaceutical side effects. Seigel et al.[17]examined alcohol-related serum CK differences. They examined 114 hospitalized DSM-IV Structured Clinical Interview patients—55 with alcohol dependency, 28 with withdrawal, and 31 with delirium tremens. Results showed lower CK levels in alcohol dependency, greater in withdrawal, and highest in delirium tremens. This pattern was consistent across all syndrome phases, probably due to dopamine activation. Authors suggested utilizing this test to identify alcohol-related problems.

Gupta et al.[18] examined hospital screening for neurological and mental illnesses using total CK. CK levels were raised in psychosis, depression, and seizures, suggesting it might be used for emergency diagnosis and monitoring. Simon et al.[19] examined alcohol withdrawal metabolic alterations. Hypophosphatemia was detected in 24% of 33 alcohol withdrawal patients in their department. No link was found between salt, CK, or alcohol consumption. After three days, ureate levels came down. Baseline magnesium levels were normal and constant. Chronic alcohol consumption was connected to reduced albumin, mild hyponatremia, poor vitamin D, higher CK levels in women, and hyperuricemia, which recovered promptly following alcohol abstinence.

Yazici et al.[20] discovered no Synthetic Cannabinoid (SC) withdrawal delirium treatment study in 2017. Cannabinoid Receptor Type 1 (CB1) receptor agonists affect GABA and glutamatergic neurotransmission like alcohol, according to research. Previous investigations have linked alcohol delirium to elevated CK. Two SC discontinuation cases in their inpatient clinic had elevated serum CK levels and other problematic lab results. Both patients responded well to benzodiazepines, but one had delirium. Toft et al.[21]investigated blood biomarkers for hospital delirium in over-60s. This evaluation used 32 trials with 7610 patients. Most of these studies focused on surgical patients, however some included ICU or medical data. Biomarkers

are restricted in their ability to predict or diagnose delirium due to a paucity of data and non-routine use.

In 120 patients, Malik et al.[22] observed a strong association between CIWA-Ar scores and higher blood CK levels, suggesting CK levels may be a biomarker for withdrawal severity. Banyal et al.[23] examined 60 tertiary care patients for indicators of complicated alcohol withdrawal syndrome (AWS). Lower education, unemployment, and delirium tremens history predicted complex AWS statistically. High alcohol intake, tachycardia, respiration rate, sed rate, and low platelet count were associated. These patients had slightly increased serum Gamma-glutamyl transferase (GGT).

Materials and Methods

This is a cross-sectional analytical study conducted at Sri Lakshmi Narayanan Institute of Medical Science and Hospital, Pondicherry. According to ICD-10 criteria, 102 patients with an alcohol dependency syndrome (ADS) diagnosis were divided into two withdrawal groups: complex (n = 48) and uncomplicated (n = 54). The clinicians utilized ICD-10 aspects to establish their diagnostic conclusions. The research included patients at least eighteen years old who did not restrict participation by gender. Researchers collected details about patient age combined with smoking habits alongside their sex attributes. Specific clinical parameters included alcohol dependency duration together with average daily standard drink intake and previous alcohol-related hospital admission frequency and laboratory results for liver function. Research staff obtained CIWA-Ar scores, SADQ ratings and serum CK measurements at the time of patient admission.

The Clinical Institute Withdrawal Assessment for Alcohol Scale Revised (CIWA-Ar) served as patients' standard measurement tool to assess their alcohol withdrawal intensity while in medical facilities[24]. The reliable tool SADQ helped experts measure the extent of alcohol dependence [25].

In this study, an automated biochemical analyzer were utilized to measure total serum CK at two time points. Measurement of CK-MM isoenzyme represented the primary focus since these occur exclusively within skeletal muscles to determine damage from seizure activity and physical exertion during withdrawal symptoms. A biomarker assessment of CK levels aimed to detect differences between complex and simple withdrawal stages.

Study Design

Through a cross-sectional analytical framework this study assessed whether serum creatine kinase (CK) measurements demonstrate potential value in distinguishing severe from simple alcohol withdrawal syndrome (AWS). Sri Lakshmi Narayana Institute of Medical Sciences' Pondicherry inpatient mental unit served as the study site for collecting participants between August 2022 and August 2023. An analysis of 102 patients with an alcohol dependency syndrome (ADS) diagnosis was carried out using ICD-10 standards. Patients were divided into two withdrawal groups: complicated (n = 48) and uncomplicated (n = 54). The investigation of CK levels as potential biomarkers for AWS problems required detailed documentation of both alcohol consumption periods and withdrawal onset and symptom appearance.

Hospital admission focused on three main treatments including Detoxification and the treatment of alcohol dependent syndrome (ADS) and alcohol withdrawal syndrome (AWS) and delirium tremens (DT) or seizures among others. By evaluating withdrawal symptom severity and general health state Sri Lakshmi Narayana Institute of physical Sciences accepted patients into their psychiatric inpatient unit.

Researcher documented each patient's information such as the latest alcohol intake recall and withdrawal symptom onset time alongside delirium tremens and seizure reports. Most patients who underwent admission reported they had avoided alcohol consumption between 24 to 72 hours prior to hospitalization. The withdrawal symptoms of tremors and agitation typically surfaced between 6–12 hours following a complete alcohol use period. Delirium tremens and convulsions developed during the first two days of withdrawal for some patients. Association with the withdrawal condition required obtaining first blood samples for serum CK levels within 24 hours of patient admission.

The hospital measured baseline serum CK levels when patients first arrived at the facility before initiating treatment. Most patients experience the onset of delirium tremens after medical personnel obtained their CK measurement results. CK level assessment occurred right after admission which secured retreatment effects would appear within these measurements.

Sample Size Calculation

The sample size was determined using the formula

$$N - \frac{4PQ}{d^2}$$

Where:

P=46.2% (prevalence of alcohol dependence based on prior studies),
Q=100−P=53.8
d=7% (margin of error).
Substituting these values, the sample size was calculated as 102.

Inclusion and Exclusion Criteria

All patients diagnosed at the psychiatric inpatient department who fulfilled the ICD-10 criteria for ADS in all genders, age >18 years, and with ability to give consent were included. Exclusions consisted of other causes of delirium, substance dependence, the existence of medical conditions that lead to increased CK levels, or previous psychiatric illnesses coupled with a physical condition that might contraindicate their participation. Patients with independent seizure disorders and illnesses which elevate CK levels (such as muscular dystrophy, myocardial infarction or rhabdomyolysis) or substance dependence unrelated to alcohol (including opioid or cannabis dependence or other causes of delirium (for instance infections or metabolic disturbances) were excluded from the study. Muscle damage evaluation used serum CK-MM isoenzyme measurements together with detailed examinations of physical trauma and sport-related injuries while independently assessing alcohol-dependent seizures by collecting medical histories and performing neurological evaluations.

Data Collection Tools

- **ICD-10 Diagnostic Criteria for Alcohol Dependence**

  Three or more of these criteria in the past year should be present to confirm ADS diagnosis, such as compulsion to drink, inability to control intake, tolerance, and withdrawal symptoms, and continued use despite causing damage.
- **Serum CKLevels**

  CK levels will be measured at admission to establish suitability for medication and correlate with withdrawal state. The samples will be taken within 24 hours, and it will be sent to a clinical lab to appraise the level of CK values in the patients with ADS and withdrawal symptoms.
- **CIWA Scale (Clinical Institute Withdrawal Assessment for Alcohol)**

  The CIWA-Ar scale, that measured the level of alcohol withdrawal severity, was started on admission and repeated every day until the patient's symptoms of withdrawal had subsided. Scores were graded as mild (<10), moderate (10–18), and severe (>19).

  The validated Delirium Rating Scale-Revised-98 (DRS-R-98) served as an instrument to detect and measure delirium tremens severity in clinical patients. Assessment of alcohol withdrawal symptoms used the CIWA-Ar scale to measure agitation level along with hallucinations and orientation abnormalities that indicate possible delirium.

- **SADQ (Severity of Alcohol Dependence Questionnaire)**

  At admission, SADQ-C was administered and calculated the level of alcohol dependence, this was done by scores ranging from 0 to 60. Scores ≤15 were interpreted to indicate low levels of dependence whereas 16–30 indicated moderate and ≥31 severe dependence.

Data Analysis

The validated tool Clinical Institute Withdrawal Assessment for Alcohol Scale Revised (CIWA-Ar) assessed AWS intensity (Sullivan et al., 1989). SADQ helped doctors determine dependence severity while (Stockwell et al., 1983). The researchers administered both assessment tools during the initial evaluation. An automated biochemical analyzer conducted serum CK assessment within the first 24 hours of patient admission. The analysis used Mann-Whitney U tests for non-parametric data and t-tests combined with Spearman's correlation analyses for parametric data and correlations. The diagnostic power of CK measurements was assessed through ROC analytical methods.

Methodology

After securing ethical approval from the Institutional Review Board, each patient was provided with informed consent. Patients with pre-established criteria were assessed on withdrawal symptoms by the CIWA scale and on dependence severity through the SADQ. The baseline CK levels were assessed through samples collected from patients into vacutainers and then

analysed in a clinical laboratory. The researcher reviewed the history of patients with ADS to diagnose them according to ICD-10 criteria.

Statistical Analysis

The researchers utilized SPSS 22 version to analyze their data. Based on data normality we performed different statistical tests that included independent t-test alongside Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. The data evaluation team employed Spearman's rank correlation coefficient techniques as their main analytics approach. An ROC analysis evaluated the diagnostic performance of CK levels. The research data showed significance at p values lower than 0.05$p<0.05$.

Experimental Results

Demographic Details

A total number of 102 patients with alcohol dependency syndrome participated in the study where 48 suffered from problematic withdrawal symptoms and 54 presented uncomplicated withdrawal symptoms. Both treatment groups maintained comparable distributions by gender regardless of whether patients withdrew directly or indirectly. Males represented 93.75% and 94.44% among directly withdrawing patients with $p=0.87$ and 95.72% and 96.30% within indirectly withdrawing patients with $p=0.75$. Current smoking statistics matched between groups at 79.17% for the first group and 77.78% for the second group ($p=0.82$). The average participant age matched between both groups reaching 44.88 ± 12.05 years (difficult withdrawal) and 44.89 ± 11.21 years (uncomplicated withdrawal). This difference yielded no statistical significance ($p=0.68$). Complex withdrawal patients consumed more alcohol daily (18.6 ± 8.4 vs 16.8 ± 7.9 standard drinks) for a longer period (12.4 ± 6.8 vs 11.8 ± 6.2 years) compared to uncomplicated withdrawal patients. Subjects with complicated withdrawal experienced significantly higher rates of alcohol-linked hospital stays when compared to either group, totaling 2.8 ± 1.6 stays versus 1.9 ± 1.4 ($p = 0.002$). Lab results measuring liver health indicated a noticeable elevation in test values but the numbers remained equivalent across all participant groups except for a slight difference observed within harder withdrawal participants.

In a study comparing serum CK levels in alcohol-dependent patients, those with complicated withdrawal had significantly higher CK levels than those with uncomplicated withdrawal. This indicates that seizures or delirium during withdrawal may elevate CK levels, suggesting a potential for CK as a biomarker for withdrawal severity. Age was recorded associodemo graphic profiles in the present study. The group with 47 cases that were complicated comprised the highest percentage of patients aged 31 to 40 (36.17%), followed by those aged 41 to 50 (29.78%). The age group over 70 years old had the lowest percentage of cases (2%) observed. The group of 54 cases that were uncomplicated simply included the greatest proportion of patients aged 41 to 50 (35.18%) and 31 to 40 (31.48%). There were no cases involving age groups older than 70.

Table 1. Distribution of Age in years

Age Group (in years)	Frequency (Percentage)		
	Complicated	**Uncomplicated**	**Total**
21-30	4(8.5%)	3(5.5%)	7(6.93%)
31-40	17(36.17%)	17 (31.48%)	34(33.66%)
41-50	14 (29.78%)	19 (35.18%)	33 (32.67%)
51-60	7(14.89%)	8(14.81%)	15(14.85%)
61-70	4(8.5%)	7(12.96%)	11(10.89%)
>70	1(2.12%)	-	1(0.99%)
TOTAL	47(100%)	54 (100%)	101 (100%)

Table 1 shows no significant difference in age distribution (pvalue0.68). The mean/SD range of the various age groups in years between 21 and >70 was 44.88/12.05 for complicated group. Whereas, mean/SD range was 44.89/11.21 for uncomplicated group. Mean age between the case and control groups were similar. Examination of subject age distribution was omitted from the research because its relevance was dismissed. Strict attention to essential demographic information allows researchers to establish relevant group characteristics by combining sex distribution with smoking status and clinical variables.

Table 2. Age Distribution and Comparison Between Complicated and Uncomplicated Withdrawal Groups

Age(inyears)	Mean	SD
Complicated	44.88	12.05
Uncomplicated	44.89	11.21

Table2 depicts the comparison of the CK, CIWAand SADQ scores between complicated and uncomplicated withdrawal. The result is significant at $p<0.05$. CK -Mann Whitney test was applied. CIWA andSADQ- Unpaired t test.

Comparison of CK Levels Between Complicated and Uncomplicated Withdrawal

Mean/SD range of CK values among study groups were mentioned in Table 3. Mann Whitney U test is applied since the data was not normally distributed. The result is significant at $p<0.05$.

Table 3. Association of CK Mean values among patients with complicated and uncomplicated withdrawal

	Mean	SD	ZScore	P-value
Complicated	298.14	204.42	5.57421	0.00001
Uncomplicated	130.48	117.71		

Comparison of CIWA Scores Between Complicated and Uncomplicated Withdrawal

CIWA scores' Mean/SD range in study groups is provided in the Table 4. Mann Whitney U test was used due to non-normal distribution, with a significant result at $p<0.05$ shown.

Table 4. Association of CIWA Mean scores among patients with complicated and uncomplicated withdrawal

	Mean	SD	Z Score	P-value
Complicated	10.061	2.63	7.231	0.00001
Uncomplicated	6.89	1.044		

Comparison of SADQ Scores Between Complicated and Uncomplicated Withdrawal

Mean/SD range of SADQ scores among study groups were mentioned in Table 5. The result is significant at $p<.05$. Independent Student t test was applied.

Table 5. Association of SADQ Mean scores among patients with complicated and uncomplicated withdrawal

	Mean	SD	T-value	P-value
Complicated	33.131	2.58	6.0981	0.00001
Uncomplicated	29.33	1.103		

Spearman's Rho Correlation Test Between CK and CIWA

It appears that a Spearman's rho correlation test was conducted to determine the relationship between CK and CIWA variables (Figure 1). According to the test results, the association between these variables is considered statistically significant based on normal standards (Table 6). This implies that there is a strong relationship between these variables.

Table6. Correlation between CK and CIWA

	r_s	PVALUE (2 – tailed)
Complicated	0.55621	<0.005
Uncomplicated		

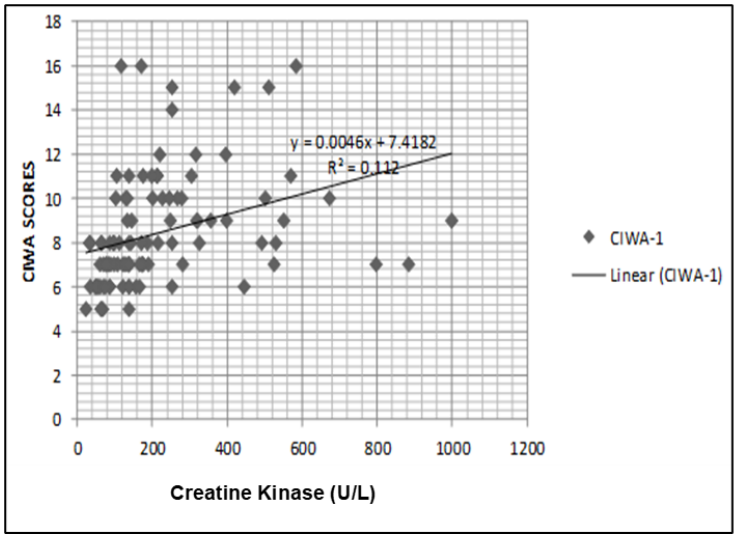

Figure 1. Strong correlation between CK vs CIWA

Karl Pearson Correlation Test Between CK and SADQ

It appears that Karl Pearson correlation test was conducted to determine the relationship between CK and SADQ variables (Figure 2). According to the test results, the association between these variables did not show statistical significance, based on normal standards (Table 7). Though the p-value shows like statistically significant, the relationship between the variables are found to be negative.

Table 7. Correlation between CK and SADQ

	R^2	R-value	P-value
Complicated	0.0501	0.2234	0.0031
Uncomplicated			

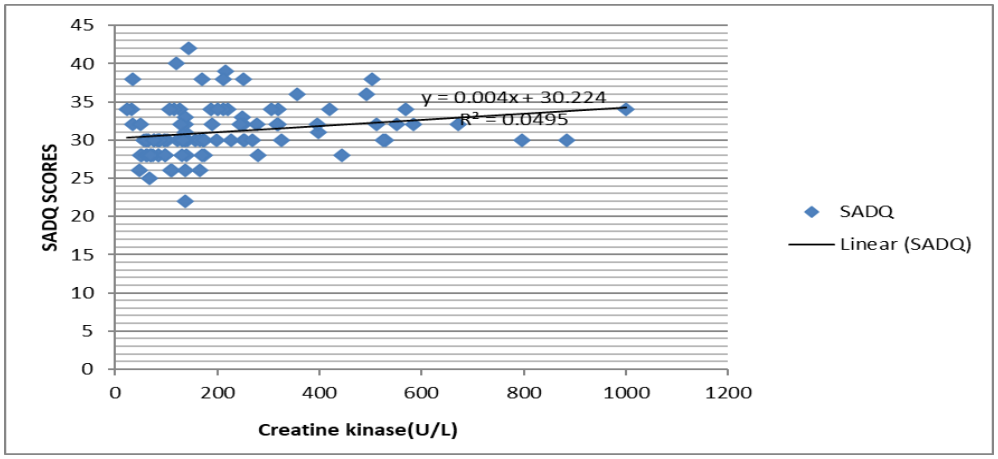

Figure 2. No significant correlation between CK vs SADQ

Correlation Analysis:-

Table 8. ROC Analysis

Parameter	AUC	Sensitivity (%)	Specificity (%)	Cutoff Value (IU/L)	Diagnostic Accuracy (%)
Creatine Kinase	0.88	87.5	81.2	180	84.3

The diagnostic use of blood CK as a biomarker for complex alcohol withdrawal underwent evaluation through Receiver operating characteristic (ROC) analysis mentioned at table 8 above. Through area under the curve (AUC) analysis researchers examined the ability of CK concentration measurements to distinguish complex withdrawal groups from simple withdrawal groups. The Youden index determined the optimal cutoff value for this analysis. The team assessed sensitivity and specificity while calculating diagnostic accuracy.

Correlation Analysis: An independent correlation analysis was performed on both problematic and straightforward withdrawal groups. The association between CK levels and CIWA-Ar and SADQ scores using Spearman's rank correlation coefficient (rsr_srs) were examined and is shown in table 9 below:-

Table 9. Correlation Analysis

Parameter	Group	rsr_srs	ppp-value
CK vs CIWA-Ar	Complicated	0.556	<0.001
	Uncomplicated	0.421	0.003
CK vs SADQ	Complicated	0.223	0.031
	Uncomplicated	0.178	0.067

CK Levels by Group:- Table 10 shows non-normal distribution patterns based on Shapiro-Wilk testing results ($p<0.05p < 0.05p<0.05$). The information requires display through both median statistics and inter-quartile range values. The straightforward withdrawal group's median CK level was 120 IU/L (IQR: Designated Withdrawal Method patients demonstrated

median CK concentration levels at 120 IU/L while patients in the Complex Withdrawal Method group measured 275 IU/L (IQR: 200–350).

Table 10. CK Levels by Group

Group	Median CK Level (IU/L)	IQR	p-value (Mann-Whitney U Test)
Complicated	275	200–350	<0.001
Uncomplicated	120	95–145	-

Discussion

Data shows that people experiencing challenging AWS showed much higher serum CK levels relative to individuals dealing with simple withdrawal. Previous studies demonstrate that muscle injuries along with stress lead to increased levels of CK. The study provides unique confirmation of CK as a potential prognostic marker by establishing correlations between serum CK levels and dependency (SADQ) scores and withdrawal severity (CIWA-Ar) scores. The research demonstrates that CK serves as a diagnostic measure during early stages to identify patients at high risk so prompt treatments can be provided.[26, 27]

This study adds to the expanding body of knowledge demonstrating biomarkers' role in alcohol withdrawal syndrome (AWS). Researchers demonstrate creatine kinase (CK) levels could serve as an affordable biological marker that identifies patients vulnerable to major AWS complications including seizures and delirium tremens. Studies of SRC kinases have resulted in targeted treatments for withdrawal symptoms such as hyperalgesia and convulsions through animal research leading to comparable progress in alcohol withdrawal pathophysiology[28]. Research into new pharmaceutical therapies for AWS can be discovered by studying neurobiological processes regulated by inflammatory mediators like NF-κβ[29,30]. The findings match past research that confirms molecular pathways such as NF-κβ signalling and SRC kinases are essential for therapeutic alcohol-related illness treatment[33]

In complex alcohol withdrawal, elevated CK levels may be a sign of muscular injury or damage brought on by seizures or other issues. More intensive monitoring and therapy, including benzodiazepines and anticonvulsants, may be necessary for this. However, patients who experience simple alcohol withdrawal might not need such extensive medical care, and their CK levels might not be as high[31, 32]. All things considered, comparing CK levels between groups experiencing complex and simple alcohol withdrawal can give medical practitioners important information to help them choose the best course of action and efficiently monitor their patients. The mean/SD range of CK levels across research groups was mentioned in this study. Because the data was not normally distributed, the Mann Whitney U test was used. At $p<0.05$, the outcome is significant.

Patients with delirium tremens have been found to have elevated CK levels. Through a comparison of CK levels, Segal et al. were able to identify alcohol-related symptoms, with lower levels in uncomplicated withdrawal and higher levels in complicated withdrawal.[31]

According to our findings, the greatest serum CK levels were seen in patients experiencing severe alcohol withdrawal, with a statistically significant finding of $P < 0.0001$.[22]

Considering the severity and frequency, complicated withdrawal symptoms, such as severe or life-threatening symptoms like seizures or delirium tremens, frequently have higher CIWA scores. Conversely, uncomplicated withdrawal usually results in milder symptoms and lower CIWA scores. Nevertheless, different studies and clinical contexts may have different cutoffs for discriminating between complicated and uncomplicated withdrawal.[34] Due to the non-normal distribution of the data, the Mann Whitney U test is used. At $p<0.05$, the outcome is significant. Higher SADQ scores, which reflect a higher degree of alcohol dependence, are frequently seen in people experiencing difficult alcohol withdrawal. While those with simple withdrawal usually have less severe symptoms and lesser degrees of dependence, which leads to lower scores, this is caused by severe symptoms like seizures or delirium tremens.

Significant differences ($p<.05$) in SADQ scores across groups were identified in this study using the Independent Student t test. Our findings are consistent with those of SK Munda et al.[28] who found that complex withdrawal significantly altered SADQ scores. Furthermore, Metcalfe et al.[29] discovered comparable noteworthy outcomes between the complicated and uncomplicated groups.Higher CK levels are associated with more severe alcohol withdrawal, according to a Spearman's rho correlation test that revealed a strong, statistically significant relationship between CK levels and CIWA scores.

In cases of alcohol withdrawal, Mühle et al.[35] established a substantial correlation between CK levels and withdrawal symptoms as assessed by the CIWA-Ar scale during follow-up visits. The linear relationship between two variables was evaluated in this study. It gauges how strongly and in which direction there is a linear relationship between SADQ scores and CK levels. Based on conventional criteria, the test findings indicate that there is a statistically significant relationship between these variables. Despite the p-value being statistically significant, there is a negative correlation between the variables. The r value is close to 0.5, indicating a substantial ($r=0.45$ $P<0.05$) association between CK and SADQ scores. This doesn't seem to be significantly correlated. This is consistent with our findings. On the other hand, in withdrawal cases including at least three weeks of alcohol abstinence, Akyel et al.[36] found no significant association between serum CK and the Severity of Alcohol Dependence Questionnaire (SADQ).

This study evaluated the levels of CK in complicated and uncomplicated patients with alcohol withdrawal. In complicated cases-mostly presented with seizures or delirium-the CK levels were significantly higher, with an implication for observation of such patients. Most complicated cases were in the 31-50 years age group with a mean age of 44.88. Scores for CIWA and SADQ, whereby scores give an evaluation of level of withdrawal, noted differences between patients' groups with a p-value of <0.05. Spearman's rho test showed a significant positive correlation of the CK with the CIWA scores. Pearson's test revealed that there was no significant association between CK and SADQ, indicating that there existed a non-significant negative relationship.

Limitations and Implications

This research demonstrates potentials for CK biomarker use in diagnosing AWS conditions yet multiple study constraints must be taken into account. Second etiologic relationships between CK levels and AWS severity cannot be established because the study follows a cross-sectional approach. Future investigations must follow patients through time to properly validate CK as a predictive marker. Control of variables influencing CK levels remained inadequate because researchers did not manage medication use alongside concurrent medical conditions and physical activity. Although the sample size works for initial results the study did not manage to capture full distribution patterns among the wider population. Future research should explore secondary changes in CK levels together with interactions between biomarkers during their temporal progression. The research provides substantial clinical proof about the worth of CK measurements even though it has some weaknesses especially in resource-limited situations.

Conclusion

The purpose of the study was to evaluate muscle injury by comparing the CK levels of alcohol-dependent patients who experienced complicated versus uncomplicated withdrawal. As a possible biomarker that correlates with the intensity of alcohol withdrawal, CK levels were tested. Serum CK levels are noticeably greater in patients going through complicated alcohol withdrawal than in those going through uncomplicated withdrawal, suggesting that convulsions or delirium during withdrawal may result in more muscle damage. In this group, prolonged agitation, the intensity of withdrawal symptoms, or exertion associated to seizures may cause elevated CK levels. The underlying mechanisms of increased CK levels during complex alcohol withdrawal and its clinical implications might be investigated in more detail. Developing more specialised therapies and management techniques for patients with alcohol dependence syndrome may be made easier with an understanding of the association between CK levels and the intensity of withdrawal.

Acknowledgements

The authors are showing their gratitude to the Sri Lakshmi Narayana Institute of Medical Sciences, for the spontaneous support regarding this entire research study.

Declarations

Funding

Authors have clearly stated that they do not have any commercial interest and financial interest. The research costs were easily covered by the researchers.

Author contributions

Conflicts of interest

All authors clearly stated that they do not have any conflicts of interests.

Data availability

Usually, the sets of data are created during and/or analysed throughout the entire study and are available from the corresponding author on reasonable request.

Ethics approval

The ethical approval was acquired from institutional ethical committee of Sri Lakshmi Narayana Institute of Medical Sciences IEC/C-P/12/2022

References

[1] Carvalho AF, Heilig M, Perez A, Probst C, Rehm J. Alcohol use disorders. Lancet. 2019 Aug 31;394(10200):781-792. doi: 10.1016/S0140-6736(19)31775-1.

[2] Witkiewitz K, Litten RZ, Leggio L. Advances in the science and treatment of alcohol use disorder. Sci Adv. 2019 Sep 25;5(9):eaax4043. doi: 10.1126/sciadv.aax4043.

[3] Cooper ML, Frone MR, Russell M, Mudar P. Drinking to regulate positive and negative emotions: a motivational model of alcohol use. J Pers Soc Psychol. 1995 Nov;69(5):990-1005. doi: 10.1037//0022-3514.69.5.990.

[4] Dalal PK, Sivakumar T. Moving towards ICD-11 and DSM-V: Concept and evolution of psychiatric classification. Indian J Psychiatry. 2009 Oct-Dec;51(4):310-9. doi: 10.4103/0019-5545.58302.

[5] van der Schyff BC. The Experience of Recovering from a Substance Use Disorder. 2016. https://vital.seals.ac.za/vital/access/manager/PdfViewer/vital:20585/SOURCE1?viewPdfInternal=1

[6] White FJ, Kalivas PW. Neuroadaptations involved in amphetamine and cocaine addiction. Drug Alcohol Depend. 1998 Jun-Jul;51(1-2):141-53. doi: 10.1016/s0376-8716(98)00072-6.

[7] Baj J, Flieger W, Teresiński G, Buszewicz G, Sitarz R, Forma A, et al. Magnesium, Calcium, Potassium, Sodium, Phosphorus, Selenium, Zinc, and Chromium Levels in Alcohol Use Disorder: A Review. J Clin Med. 2020 Jun 18;9(6):1901. doi: 10.3390/jcm9061901.

[8] Maldonado JR. An approach to the patient with substance use and abuse. Med Clin North Am. 2010 Nov;94(6):1169-205, x-i. doi: 10.1016/j.mcna.2010.08.010.

[9] FairN,AkweJ.ALCOHOLWITHDRAWAL:PREVALENCE,TRENDS, ANDMANAGEMENT. Journal of Drug Addiction, Education,andEradication. 2015 Jul 1;11 (3/4):343.https://www.proquest.com/docview/1770259601?sourcetype=Scholarly%20Journals

[10] Nikhilan JV. Biochemical Predictors for Alcohol Withdrawal Complications: A-Prospective Study (Doctoral dissertation, Central Institute of Psychiatry (India).

[11] Shetty NA. Prevalence and correlates of Delirium Tremens inAlcohol related

disorders (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)). 2014http://hdl.handle.net/123456789/491

[12] Day E, Daly C. Clinical management of the alcohol withdrawal syndrome. Addiction. 2022 Mar;117(3):804-814. doi: 10.1111/add.15647.

[13] Attilia F, Perciballi R, Rotondo C, Capriglione I, Iannuzzi S, Attilia ML, et al. Alcohol withdrawal syndrome: diagnostic and therapeutic methods. RivPsichiatr. 2018 May-Jun;53(3):118-122. doi: 10.1708/2925.29413.

[14] Efstratiadis G, Voulgaridou A, Nikiforou D, Kyventidis A, Kourkouni E, Vergoulas G. Rhabdomyolysis updated. Hippokratia. 2007 Jul;11(3):129-37.https://pmc.ncbi.nlm.nih.gov/articles/PMC2658796/

[15] Rajagopal S, Ponnusamy M. Calcium signaling: from physiology to diseases. Singapore: Springer; 2017 Sep 28.https://api.semanticscholar.org/CorpusID:34842114

[16] Linares LA, Golomb BA, Jaojoco JA, Sikand H, Phillips PS. The modern spectrum of rhabdomyolysis: drug toxicity revealed by creatine kinase screening. Curr Drug Saf. 2009 Sep;4(3):181-7. doi: 10.2174/157488609789007010.

[17] Kponee KZ, Siegel M, Jernigan DH. The use of caffeinated alcoholic beverages among underage drinkers: results of a national survey. Addict Behav. 2014 Jan;39(1):253-8. doi: 10.1016/j.addbeh.2013.10.006.

[18] Gupta A, Gupta C, Khurana S. Evaluation of total creatine kinase levels in a spectrum of neuro-psychiatric disorders in a tertiary neurosciences centre. International Journal of Medicine & Public Health. 2015 Oct 1;5(4).DOI: 10.4103/2230-8598.165096

[19] Simpson SA, Wilson MP, Nordstrom K. Psychiatric Emergencies for Clinicians: Emergency Department Management of Alcohol Withdrawal. J Emerg Med. 2016 Sep;51(3):269-73. doi: 10.1016/j.jemermed.2016.03.027.

[20] Yazici AB, Yazici E, Erol A. Delirium and High Creatine Kinase and Myoglobin Levels Related to Synthetic Cannabinoid Withdrawal. Case Rep Med. 2017;2017:3894749. doi: 10.1155/2017/3894749.

[21] Toft K, Tontsch J, Abdelhamid S, Steiner L, Siegemund M, Hollinger A. Serum biomarkers of delirium in the elderly: a narrative review. Ann Intensive Care. 2019 Jul 1;9(1):76. doi: 10.1186/s13613-019-0548-1.

[22] Opara I, Malik S, Lardier DT Jr, Gamble-George J, Kelly RJ, Okafor CN, Greene RN, Parisi D. Alcohol Use Cravings as a Mediator Between Associated Risk Factors on Increased Alcohol Use among Youth Adults in New York During the COVID-19 Pandemic. Alcohol Treat Q. 2021;39(4):415-429. doi: 10.1080/07347324.2021.1950091.

[23] Banyal, Navdeep; Dhillon, Harpreet Singh[1,]; Sasidharan, Shibu[2]. Risk factors associated with complicated alcohol withdrawal syndrome. Journal of Medical Society 35(3):p 113-117, Sep–Dec 2021. DOI: 10.4103/jms.jms_92_21

[24] Sullivan, J. T., Sykora, K., Schneiderman, J., Naranjo, C. A., & Sellers, E. M. (1989). Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *British Journal of Addiction, 84*(11), 1353–1357. https://doi.org/10.1111/j.1360-0443.1989.tb00737.x

[25] Stockwell, T., Murphy, D., & Hodgson, R. (1983). The Severity of Alcohol Dependence Questionnaire: Its use, reliability and validity. *British Journal of Addiction, 78*(2), 145–155. https://doi.org/10.1111/j.1360-0443.1983.tb05502.x

[26] Turner RC, Lichstein PR, Peden JG Jr, Busher JT, Waivers LE. Alcohol withdrawal syndromes: a review of pathophysiology, clinical presentation, and treatment. J Gen Intern Med. 1989 Sep-Oct;4(5):432-44. doi: 10.1007/BF02599697.

[27] Mainerova B, Prasko J, Latalova K, Axmann K, Cerna M, Horacek R, Bradacova R. Alcohol withdrawal delirium - diagnosis, course and treatment. Biomed Pap Med FacUnivPalacky Olomouc Czech Repub. 2015 Mar;159(1):44-52. doi: 10.5507/bp.2013.089.

[28] Singh, A. P., Sharma, A. K., & Singh, T. G. (2024). BAY 11-7085 and SU-6656 attenuates alcohol dependence induced spontaneous withdrawal syndrome like hyperalgesia, convulsion and depression in mice. *International Journal of Pharmaceutical Sciences and Research, 15*(7), 2172-2182. https://doi.org/10.13040/IJPSR.0975-8232.15(7).2172-82

[29] Singh, A. P., Sharma, A. K., & Singh, T. G. (2024). Review on SRC kinases as a promising pharmacological target for various diseases. *International Journal of Pharmaceutical Sciences and Research, 15*(5), 1280-1295. https://doi.org/10.13040/IJPSR.0975-8232.15(5).1280-95

[30] Singh, A. P., Sharma, A. K., & Singh, T. G. (2024). Unlocking the therapeutic potential: exploring NF-κβ as a viable target for diverse pharmacological approaches. *International Journal of Pharmacy and Pharmaceutical Sciences, 16*(6), 1-9. https://doi.org/10.22159/ijpps.2024v16i6.49530

[31] Segal M, Avital A, Rusakov A, Sandbank S, Weizman A. Serum creatine kinase activity differentiates alcohol syndromes of dependence, withdrawal and delirium tremens. EurNeuropsychopharmacol. 2009 Feb;19(2):92-6. doi: 10.1016/j.euroneuro.2008.10.005.

[32] Knight E, Lappalainen L. Clinical Institute Withdrawal Assessment for Alcohol-Revised might be an unreliable tool in the management of alcohol withdrawal. Can Fam Physician. 2017 Sep;63(9):691-695.https://pubmed.ncbi.nlm.nih.gov/28904034/

[33] Kumar S Munda. Social cognition, craving and mu wave activity in alcohol dependence (Doctoral dissertation, Central Institute of Psychiatry (India)). 2017

[34] Metcalfe P, Sobers M, Dewey M. The Windsor Clinic Alcohol Withdrawal Assessment Scale (WCAWAS): investigation of factors associated with complicated withdrawals. Alcohol Alcohol. 1995 May;30(3):367-72.https://pubmed.ncbi.nlm.nih.gov/7545991/

[35] Mühle C, Weinland C, Gulbins E, Lenz B, Kornhuber J. Peripheral Acid Sphingomyelinase Activity Is Associated with Biomarkers and Phenotypes of Alcohol Use and Dependence in Patients and Healthy Controls. Int J Mol Sci. 2018 Dec 13;19(12):4028. doi: 10.3390/ijms19124028.

[36] Akyel B, Aldemir E, Altıntoprak AE. AlkolBağımlılığıŞiddetiÖlçeği: TürkçeFormununGeçerlikveGüvenirliği [Severity of Alcohol Dependence Questionnaire: Validity and Reliability of the Turkish Version]. Turk Psikiyatri Derg. 2018 Fall;29(3):202-208. https://pubmed.ncbi.nlm.nih.gov/30260466/