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Original Research Article

Red cell distribution width may help to discriminate synthetic cannabinoid users in the emergency department

Utku Murat Kalafat*, Serkan Dogan

Department of Emergency Medicine, University of Health Sciences, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey

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***Correspondence:**
Dr. Utku Murat Kalafat,
E-mail: utkumuratk@yahoo.com

ABSTRACT

Background: Differentiating bonsai users from the suspected users is problematic. The aim was to determine whether bonsai using men and the others can be distinguished via the hemogram parameters such as mean corpuscular volume (MCV), mean platelet volume (MPV), red cell distribution width (RDW) and Plateletcrit (PCT).
Methods: In this retrospective case-control study, a total of 138 men admitted to ED were investigated in Kanuni Sultan Suleyman Hospital, Istanbul, Turkey in 2014. The patients were divided into 2 groups which were the first group had included bonsai users whereas the second group was consist of men not using bonsai. Complete blood count tests were performed on all patients.
Results: Among the suspected bonsai users, 68 were diagnosed to use bonsai. It was found that MCV, RDW and PCT levels were significantly higher in bonsai users compared to controls while MPV levels were lower in the users. Author put all these parameters to logistic regression analysis model using enter method. RDW (OR: 3.98, 95%CI:2.180-7.266, p<0.0001), MPV (OR:0.526, 95%CI:0.373-0.742, p<0.0001) and PCT (OR:<0.0001, 95%CI:0.000-0.058, p=0.007) were independent variables to discriminate bonsai users from that of suspected users. The most promising parameter to differentiate bonsai users from suspected users was RDW (AUC: 0.748, 95%CI: 0.668-0.828, p:<0.0001). The optimal cut-off value was found as 10.8 for RDW with a sensitivity, specificity, +LR and -LR as 66.2%, 64.3%, 1.85, 0.53, respectively.
Conclusions: RDW marker can be a reliable parameter to discriminate bonsai users from that of suspected users with moderate sensitivity and specificity.

Keywords: Bonsai, Diagnosis, Illicit drug, Plateletcrit, Red cell distribution width

INTRODUCTION

Natural cannabis (delta9-tetrahydrocannabinol (Δ9-THC)) is obtained from the plant called *Cannabis sativa*.[1] The process first started with isolation of Δ9-THC in 1964.[2] This caused production of many cannabinoid receptor antagonists for therapeutic purposes after discovery of cannabinoid receptors (CB1 and CB2) in 1980s. Synthetic cannabinoids (SCs) are obtained by the researching of these compounds in the time.[3] SCs have metabolic and cardiovascular effects on human.[4] Furthermore, evidences for anti-inflammatory and neuroprotective effects of cannabinoids were detected through immunosuppressive efficiency of cannabis.[5] However, illegal use of these agents became widespread by observation of side effects on cognitive functions and reached out an uncontrolled and undesired state. The difficulty to analyze SCs in the blood made this agent more attractive for illegal use. Although some SCs may be detected in the blood, all chemical substances cannot be analyzed. Therefore, no simple drug screening tests exist for the patients with the suspicion of SC abuse who

refer to emergency department. The most significant tests to help diagnosis for emergency medicine practitioners include the symptoms, clinical evaluation and routine laboratory tests. Therefore, detection of the cases using SC is very important for forensic medicine as well as clinical monitoring.

Red blood cell distribution width (RDW) is simply measurement of dimensional distribution of the red blood cells and may be easily calculated by dividing the mean corpuscular volume to the standard deviation. RDW is reported as an inflammatory biomarker. The mechanism between inflammation and RDW was not clarified yet, however, it is considered that high RDW levels are caused by inflammation and cardiovascular abnormalities.[6] The aim of the present study was to search whether complete blood count parameters including RDW would help the emergency medicine specialists to identify the cases with SC abuse within a short period.

METHODS

The present retrospective study was performed between January 2014 to December 2014 by approval no. 2018-01-11 of the Ethical Commitee of Bakirkoy Dr.Sadi Konuk Education and Research Hospital on 08/01/2018. It is a governmental referral hospital with 60 stretchers and 628.640 annual visits in İstanbul, Turkey. An informed consent form was obtained from each participant.

The male patients (n=239) with any suspicion of drug abuse who do not have exclusion criteria were enrolled into the study. The patients with diabetes mellitus (n=5), anemia (n=4), congestive heart failure (n=2), lower glomerular filtration rate (n=7), hemoglobinopathy (n=3), infectious disease (n=5) and hypertension (n=9) which may affect hemogram parameters were excluded from the study. Patients were included if both the patients and their close relatives and/or friends declare the use of the illicit drug (n=68). Thus, 31 patients whose relatives declared no SC use, 24 patients who declared no use of SC and 11 patients who mentioned use of any other drug were excluded from both drug user and control groups.

The patients (n=70) who entered ED with the same symptoms with drug users but were diagnosed with major depressive attack and conversion during emergency medicine monitoring whose SC use was excluded through both self-statement and statement by the relatives were enrolled in the control group (Figure 1). Female patients were also excluded as their number were insufficient to make a conclusion for statistical methods. It was later confirmed from hospital records and statements that the patients in the control group have never used SC. SC drugs can cause anxiety or panic attack and opposing effects like repressed anxiety. Therefore, psychiatric diagnosis of the patients in the control group supports the methodology of the present study.

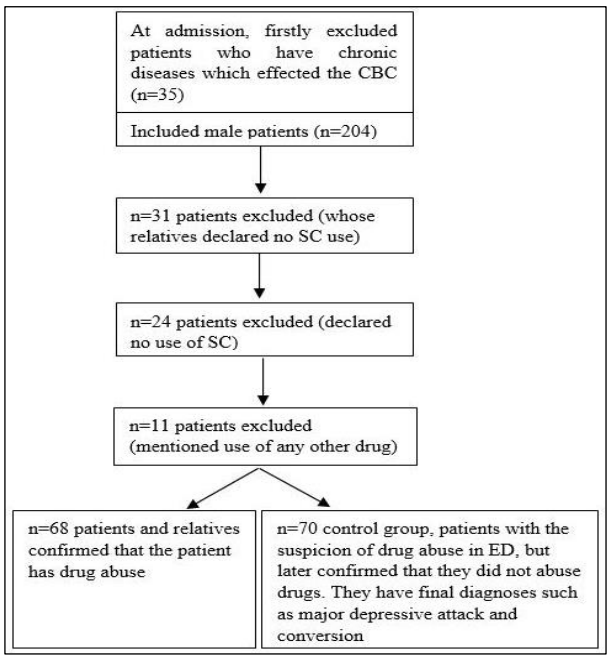

Figure 1: Flow chart of the patients and controls included.

Demographic data such as age, gender and hemogram parameters (lymphocyte, neutrophils, eosinophils, basophile, mean platelet volume (MPV), mean corpuscular volume (MCV), RDW and platelet) analyzed from venous blood samples at referral, arterial blood gas analyses (lactate) and C-reactive protein (CRP) levels were recorded. The blood samples obtained were analyzed by Abbott CELL DYN 3700 (USA) in the biochemistry laboratory.

The following reference ranges were used in the laboratory; leukocyte (WBC), 3.7-910.1x103/uL, red blood cell (RBC), 4.06-5.58x106/uL, hemoglobin (HGB), 12.9-15.9g/dl, hematocrite (HCT), %39-49, platelet (PLT), 155-366x103/uL, MCV, 81.1-96fL; mean corpuscular hemoglobin (MCH), 27.0-31.2pg, mean corpuscular hemoglobin concentration (MCHC), 31.8-35.4g/dl, MPV, 6.9-10.6fL, RDW, 11.5%-14.5%, plateletcrit (PCT), 0.0%-9.99%, CRP, <5mg/dl and lactate, <1mmol/L. Complete blood count was measured by Cobas Integra 400 Plus, Roche which daily calibrating.

SPSS for Windows statistical package version 22 (SPSS Inc., Chicago, IL, United States) was used for all statistical analyses. Author gave ±SD for mean values. Chi-squared test was used to compare percentages while Mann-Whitney U test was used to assess difference. A logistic regression analysis to define bonsai users among suspected abusers was conducted after the first compartment analyses. In the first analyses (Table 1), RBC, MPV, RDW and Plateletcrit levels were

statistically different between groups. Author excluded RBC while designing logistic regression as RBC was affected by many other illnesses and situations and as RBC and RDW in the same logistic regression analysis may disrupt the independency.

Table 1: Laboratory Parameters.

Parameters	Bonsai (n=68)	Control (n=70)	P value
WBC	11.2±4.1	10.5±3.8	0.554
RBC	5.0±0.4	5.3±0.5	0.004
Hb	14.7±1.6	15.1±1.3	0.102
Hct	43.1±4.1	43.6±3.3	0.425
Plt	256.1±70	240.2±76	0.203
MCV	85.7±5.4	82.0±10.1	0.007
MCH	29.3±2.2	28.8±1.9	0.175
MCHC	34.7±4.2	34.8±1.6	0.880
MPV	6.5±1.3	8.0±2.1	<0.0001
RDW	11.4±1.3	10.3±1.0	<0.0001
Neutrophil	7.6±3.5	6.9±3.8	0.309
Lymphocyte	2.6±1.8	2.5±1.1	0.705
Monocyte	0.9±1.2	0.8±0.3	0.289
Eosinophil	0.1±0.1	0.2±0.3	0.086
Basophile	0.1±0.1	0.1±0.5	0.100
PCT	0.2±0.06	0.15±0.06	<0.0001
Lactate	2.3±1.8	0.7±0.0	0.391
CRP	13.0±52.1	0.1±0.0	0.809
Neutrophil/ lymphocyte ratio	4.03±3.14	3.76±4.17	0.673

WBC: White blood cell, RBC: Red blood cell, Hb: Hemoglobin, Hct: Hematocrite, Plt: Platelet, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MPV: Mean platelet Volume, RDW: Red cell distribution width, PCT: Plateletcrit, CRP: C-reactive Protein.

Later logistic regression analyses with enter method showed that MPV, RDW and plateletcrit were independent significant different parameters between groups. Thus, author analyzed area under the curve measures of RDW, PCT and MPV. Last, as RDW had the higher AUC value. Author analyzed cut off values for RDW.

RESULTS

A total of 138 men who were suspected to use bonsai were enrolled. Their complaints were tachycardia (86%), tachypnea (90%), dyspnea (70%), agitation (94%), nausea and vomiting (82%). Of them, 68 were diagnosed to use bonsai. There was no difference between mean ages of the groups (26.1±6.8 in bonsai group vs 25.5±3 in the controls, p=0.549). The differences in complete blood count and arterial blood parameters were analyzed in Table 1. Mean MCV, RDW and PCT levels were significantly higher in bonsai users compared to controls while mean MPV levels were lower in the users (Table 1). Author put all these significantly different parameters to logistic regression analysis model using enter method. RDW (OR:3.98, 95%CI:2.180-7.266, p<0.0001), MPV (OR:0.526, 95%CI:0.373-0.742, p<0.0001) and PCT (OR:<0.0001, 95%CI:0.000-0.058, p=0.007) were independent variables to discriminate bonsai users from that of suspected users (Table 2).

The AUC analyses of MPV, RDW and PCT were demonstrated in Table 3 and Figure 2. The most promising parameter to differentiate bonsai users from suspected users was RDW (AUC:0.748, 95%CI:0.668-0.828, p:<0.0001). The optimal cut-off value was found as 10.8 for RDW with a sensitivity, specificity, +LR and -LR as 66.2%, 64.3%, 1.85, 0.53, respectively (Table 4). There were no differences in terms of arterial blood gas analyses (pH, PCO2, PO2, COHb, HCO3, and calcium) between bonsai users and controls.

Table 2: Logistic regression analysis to define bonsai users among suspected abusers.

Parameter	B	S.E.	Wald	P	OR	95%CI for OR
MCV	0.032	0.043	0.549	0.459	1.033	0.949-1.124
MPV	-0.642	0.175	13.407	<0.0001	0.526	0.373-0.742
RDW	1.381	0.307	20.233	<0.0001	3.98	2.180-7.266
Plateletcrit	-10.464	3.887	7.248	0.007	<0.0001	0.000-0.058

MCV: Mean corpuscular volume, MPV: Mean platelet volume, RDW: Red cell distribution width, B: Coefficient, S.E.: Standard error, OR: odds ratio, CI: Confidence interval.

Table 3: Area under the curve measures of the parameters.

Parameter	AUC	95% of AUC	Std error	P
RDW	0.748	0.668-0.828	0.041	<0.0001
Pct	0.340	0.249-0.430	0.34	0.001
MPV	0.284	0.200-0.369	0.043	<0.0001

RDW: Red cell distribution width, Pct: Platelet Crit, MPV: Mean platelet volume, AUC: Area under curve.

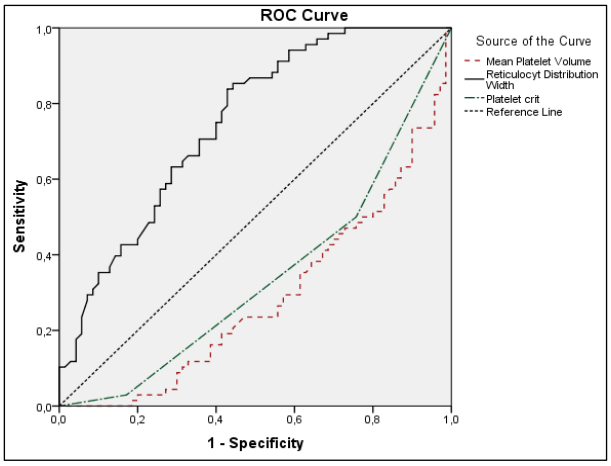

Figure 2: ROC curve analyses of CBC parameters to define bonsai users among suspected patients.

Table 4: Cut-off values for RDW to define bonsai users among suspected ones.

Cut-off for RDW	Sensitivity (%)	Specificity (%)	+LR	-LR
10	94.1	40	1.57	0.15
10.8	66.2	64.3	1.85	0.53
11.5	35.3	87.1	2.75	0.74
12	17.6	95.7	4.12	0.86

RDW: Red cell distribution width, LR: Likelihood ratio

DISCUSSION

In the present study, author showed for the first time that RDW as one of the laboratory parameters used routinely in the emergency department may be moderately effective to identify SC users. Production of different SC types through chemical reactions makes identification with standardized methods difficult. New types are actively released before standardization of type-specific tests and this makes the physicians vulnerable to misdiagnosis. These drugs may cause misdiagnoses since the use of such agents may cause cognitive function losses with an acute onset and gradual worsening as well as cardiac disorders.

Author designed the present study to determine whether complete blood count parameters which provide the fastest result in emergency medicine practice would guide the clinician to detect SC use for seeking a marker, test or method with rapid result. Author could not detect any study investigating the association between acute toxicity and complete blood count parameters of the patients with SC abuse in the literature.

However, MCV, RDW and Plateletcrit levels of the bonsai users were detected significantly higher than the control group (Table 1). Logistic regression analysis of these parameters revealed RDW, MPV and Plateletcrit levels were independent variables to differentiate the patients with suspicion of drug abuse from bonsai users (Table 2). PCT stands for plateletcrit. It is defined as percent volume of the blood occupied by the platelets. It reflects the number and size of the platelets (packed platelet volume). PCT-plateletcrit (normal 0.108-0.282), the proportion (%) of whole blood occupied by the platelets. The parameter yielding the most significant results among these independent variables were RDW (AUC: 0.748, 95%CI: 0.668-0.828, p:<0.0001) (Table 3).

The optimal cut-off value was found as 10.8 for RDW with sensitivity, specificity, +LR and -LR as 66.2%, 64.3%, 1.85, 0.53, respectively (Table 4). In this study, conducted by Guzel D et al, RDW, MCV and MCH values were detected significantly higher and MPV values were detected significantly lower in the SC group.

The results of this study are consistent with the literature.[7] RDW changes were observed in various diseases. Increased RDW levels were identified as independent predictors of the increase in left ventricular myocardial index, decrease in glomerular filtration rate values and correlated with 24-h systolic blood pressure.[8]

The most frequent cardiovascular effects of SC include hypertension and tachycardia. However, effects such as bradycardia and hypotension were also reported.[9,10] Therefore, these cardiovascular changes caused by bonsai use may lead abnormal RDW values in the patients. RDW also reflects vascular thrombosis or embolism. In the study conducted by Demir R et al, RDW levels of the patients diagnosed with cerebral venous sinus thrombosis were detected significantly higher among the patients referred to emergency department because of headache.[11]

Kisaoglu A et al, reported in their study that RDW would help to diagnose the patients who refer due to abdominal pain with acute mesenteric ischemia.[12] SCs are known to affect cardiovascular effects through activation of sympathetic nervous system by inhibition of autonomic parasympathetic nervous system.[4] Thus, this can be another mechanism for the RDW increase in the patients.

There are studies suggesting that RDW elevation reflects the degree of systemic inflammatory response beyond acute pathologies.[13] In acute conditions, RDW can also be used as a predictor for mortality among patients with acute pancreatitis, acute dyspnea during an ED visit, out-of-hospital cardiac arrest and critical illness in ICU setting.[14-17]

SCs play a role in inflammation by suppressing the pro-inflammatory cytokine response and increasing the anti-inflammatory cytokine response through effect of CB2 receptors.[18-20] Another mechanism clarifying the RDW elevation in SC users may be the effects of SC on hematopoietic system. As known, cannabinoid receptors exist in hematopoietic system. Immature erythrocytes released from the bone marrow to circulation may cause RDW elevation. Effect of endocannabinoid system both on hematopoietic stem and progenitor cells supports this

hypothesis.[21] In another study, chronic use of cannabinoids was associated with an increase in inflammatory cells and it was mentioned that this immune activity may cause high RDW values.[7] SC use is more common among younger population. Hoyte CO et al, reported the age average of the cases as 22.5±8.86.[22] In a study carried out in alcohol and substance addiction treatment and training center in Turkey, age average was reported as 26.1±7.1.[23]

Similarly, the age average of the bonsai users was found 26.1±6.8 in the present study. In the whole world, this illicit drug abuse is commonly seen in younger population. This situation may detract to obtain false positive results for RDW values as some diseases such as chronic heart failure, acute myocardial infarction and pulmonary embolism causing RDW elevation are generally observed during advanced ages.

Author should accept that the present study has some limitations. The study was conducted on a small case series and since there is no chromatographic diagnostic tests for bonsai use in the hospital, patient inclusion was depended on medical history obtained from the patient or patient attendants. It is not known from the literature that if RDW increases during use of other illicit drugs. Such addicts may use many different substances together. Although this issue was addressed during medical history investigation, they might have declared inaccurately. Male users generally referred to emergency department and female users were almost none. Therefore, conducting the present study on male cases may be considered as a limitation.

CONCLUSION

The clinicians should consider the gradually increasing trend for SC use to diagnose the patients referring with unclear toxidromes. The individuals using SC may have severe clinical manifestations including death. Author suggest that monitoring the laboratory values such as RDW as well as clinical manifestations may ensure valuable contributions not only for helping us as clinicians but also in reducing the mortality rates in this patient group.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Bakirkoy Dr. Sadi Konuk Education and Research Hospital (2018-01-11)

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