1	Reduced Plasma IL-40 and Total IgA Levels in Patients with Substance Use Disorders:
2	Indicators of Impaired Humoral Immune Response
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19	Short Title: IL-40 and IgA levels in SUD patients
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Abstract

Background: Substance use disorders (SUDs) continue to be a public health challenge of significant importance. The immunomodulatory effects of substances of abuse have been extensively studied but there is a dearth of information on their effects on plasma interleukin-40 (IL-40) level, a biomarker of B cell activity, and its consequent effects on plasma total IgA level in patients with substance use disorders (SUD). Therefore, the plasma levels of IL-40 and total IgA in SUD patients were determined in this study.

43 Methods: Ninety adults comprising 50 SUD patients and 40 controls were enrolled into this case44 control study. The SUD patients were stratified into groups based on the number of substances
45 they abuse and plasma levels of IL-40 and IgA were determined using ELISA.

Results: Marijuana was the most abused substance (68.0%) and majority of the SUD patients (64.0%) were polydrug users. The median plasma IL-40 level was significantly lower in SUD patients compared with the controls. Similarly, the median plasma total IgA level was significantly lower in SUD patients compared with the controls. However, there were no significant differences in the plasma levels of IL-40 and IgA in SUD patients who abuse single substance, two substances, and three or more substances. The plasma IL-40 level had significant positive correlation with IgA in SUD patients.

53 **Conclusion:** Substance use disorder is associated with impaired humoral immune function, but 54 the dysregulation appears not to be influenced by poly-drug use. Studies evaluating the 55 mechanisms underlying humoral immune impairment in patients with substance use disorder and 56 its potential clinical implications are suggested.

57 Keywords: Antibodies, B cell activity, Humoral immunity, Substance abuse.

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60 Introduction

Substance use disorders (SUDs) are a global public health concern. Despite their associated morbidity and mortality, as well as existing drug laws, policies, and prevention strategies, the prevalence of drug and substance abuse continues to rise particularly among youths [1, 2]. In 2021, the estimated number of illegal drug users worldwide was around 296 million. Among these users,

65 39.5 million have a drug use disorder [3].

66 In Nigeria, drug and substance abuse is prevalent and remains a significant public health challenge.

67 According to a 2018 report by the United Nations Office on Drugs and Crime (UNODC), the past-

year prevalence of any drug use among individuals aged 15 to 64 years was 14.4%, representing

69 approximately 14.3 million people. The report also indicated that among the six geopolitical zones,

the South-West had the highest prevalence (22.4% or approximately 4.38 million users), followed

71 by the South-South, South-East, North-East, North-West, and North-Central zones [4].

72 Drugs of abuse modulate the immune system primarily through receptor-mediated mechanisms; 73 either by directly engaging receptors on immune cells or indirectly by interacting with analogous 74 receptors in the nervous system [5]. They are associated with well-characterized changes in the 75 levels of catecholamine such as dopamine, epinephrine, and norepinephrine that have both central 76 and peripheral effects on neurotransmission and neuroendocrine signaling. Due to their activating 77 effects on the sympathetic nervous system, abused stimulants may serve as potential mediators of 78 the immune response. In particular, stimulant exposure is associated with disruption of the blood 79 brain barrier and activation of the hypothalamic- pituitary- adrenal axis (HPA axis), which have 80 consequences on immune function [6, 7].

Reports continue to show that patients with SUD have compromised immunity characterised by
immunostimulation and immunosenescence [5, 8]. This immune dysfunction predisposes them to

increased risk of infection requiring hospitalization or resulting in death [9]. Acute and chronic use of substances is associated with the dysregulation of the innate and adaptive immune response such as alterations in lymphocyte numbers, changes in cytokine expression and impairments in phagocytic functions [10-13]. In addition, studies have shown that immune factor signaling is associated with neural and behavioural aspects of addiction, such as drug seeking and resilience to relapse [14].

89 Inflammatory processes, especially the cell mediated immune response, play vital roles in the 90 pathogenesis of neurological disorders associated with substance abuse [15]. However, 91 dysfunction in humoral immune response in SUD patients continues to receive little attention. In 92 1976, Bogdal et al. [16] reported that there is an association between serum levels of 93 immunoglobulins and alcohol use disorder (AUD). Similarly, elevated levels of immunoglobulin A (IgA) and IgE have been reported in SUD patients [15]. This alteration in immunoglobulin 94 95 classes has also been reported in experimental studies [17]. Currently, there is lack of information 96 on the dysregulation of cytokines involved in B cells homeostasis such as interleukin 40 (IL-40) 97 in SUD patients.

98 IL-40, also known as chromosome 17 open reading frame 99 (*C17orf99*), is a B cell-associated 99 cytokine implicated in humoral immune responses and B cell homeostasis [18-22]. An 100 experimental study showed that it affects IgA production and, has direct influence on the 101 composition of the intestinal microbiome in IL-40 knockout mice. In addition, the IL-40 knockout 102 mice exhibited abnormalities in B cell populations, indicating the role of IL-40 in B cell 103 development [18]. Although IL-40 may play a role in SUD-associated immune dysregulation, 104 there is currently no information on its plasma level in SUD patients.

105 B cells count and subsets have been reported to be altered in patients with SUDs. Piepenbrink et 106 al. [23] reported a significant, 2-fold increase in total B cells associated with increased activated 107 B cell subsets in heroin injection drug users (IDU) compared with healthy controls. They also 108 reported chronic B cell activation characterized by skewed plasma antibody profile with significant 109 elevation in total IgM level and IgG3 and IgG4 subclasses but insignificantly different IgA level 110 in heroin IDU. In addition, Wang et al. [24] reported that morphine significantly reduced IgA 111 levels in animal models. Furthermore, Molina et al. [25] reported that chronic alcohol use resulted 112 in decreased IgA secretion in the gut, contributing to systemic inflammation and liver damage. 113 These reports clearly indicate that there is broad alteration in the steady-state humoral profile of 114 patients with SUDs. Presently, information on the plasma IgA level in SUD patients is limited. 115 Due to limited information on the plasma IL-40 and IgA levels in SUD patients, this study was 116 conducted to determine the plasma levels of these biological markers in Nigerians with SUDs with 117 a view to understanding how possible alteration in their plasma levels may impact the ability of 118 SUD patients to generate optimal responses to infection. 119 120 121 122 123 124 125

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128 Materials and Methods

129 Ethical Consideration

130 Ethical approval (UI/EC/24/0455) was obtained from the University of Ibadan/University College

131 Hospital (UI/UCH) Joint Ethics Committee before the commencement of the study. Also, written

132 informed consent was obtained from the study participants and where impossible, assent was

133 obtained from the relatives or guardians.

134 *Study participants*

A total of 90 participants consisting of 50 adults with substance use disorders (SUDs) and 40 apparently healthy adults who served as controls were enrolled into this case-control study using a convenient sampling method. SUD patients were enrolled from the Psychiatry Department, University College Hospital, Ibadan, Nigeria, and the New World Specialist Hospital, Ibadan. The controls were enrolled from the Ibadan metropolis and were certified free of any form of psychiatric disorder by a Consultant Psychiatrist. The study participants were recruited between 30th July, 2024 and 30th December, 2024.

142 Sample size calculation

143 The sample size could not be calculated due to the lack of available reports on plasma levels of 144 IL-40 in patients with SUDs, to the best of our knowledge, at the time this study was conducted. 145 Therefore, a convenient sampling method was adopted and the study is thus, considered a 146 preliminary study.

147 Diagnosis of Substance Use Disorder

SUD was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition(DSM-5) criteria [26].

151 Exclusion criteria

- 152 Patients with history of schizophrenia, mood disorders and anxiety disorder were excluded from
- 153 the study. Also, patients with history of autoimmune disorders and those on steroid therapy were
- 154 excluded from the study.
- 155 Data collection
- 156 Demographic data and clinical history of the study participants were obtained using a short-
- 157 structured questionnaire.
- 158 Blood sample collection
- 159 Venous blood samples (5 ml) was obtained from each study participant and dispensed into lithium
- 160 heparinized sample bottles to obtain plasma which was stored at -20^oC until analyzed.
- 161 Laboratory Analysis
- 162 Plasma levels of IL-40 and IgA were determined using ELISA following the manufacturer's
- 163 instructions (Melsin Medical Co., China).
- 164 Data Analysis
- The Statistical Package for Social Sciences (SPSS), version 23.0 and GraphPad Prism, version 10.2.0 were used for data analysis. The data were assessed for Gaussian distribution using the Shapiro-Wilk test and Kolmogorov-Smirnov test. Thereafter, Mann Whitney *U* and Kruskal Wallis tests were used to determine differences in the median levels of IL-40 and IgA between two or more groups, respectively. Correlation between the variables was done using the Spearman rho correlation. *P*-values less than 0.05 (2-tailed) were considered as statistically significant. Results are presented as median (interquartile range).
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173 **Results**

- 174 The characteristics of the study participants are shown in the Table 1. Majority of the study
- 175 participants were observed to be abusing marijuana (68.0%) and were polydrug abusers (64%).

176 Table 1: Characteristics of the study participants

	SUD Patients $(n = 50)$	Controls $(n = 40)$
Age	28.86 ± 8.98	25.38 ± 6.01
Tunas of Substance		
abused		
Marijuana		
Vas	24(68.00%)	-
No	16 (32 0%)	
Cigarette	10 (32.070)	
Ves	18	-
No	10	
Alcohol		_
Vas	27(54%)	_
No	27(3+70) 23(46%)	
Tramadol	23 (4070)	_
	1 (8%)	-
No	46(02%)	
Heroine	40 (9270)	
Ves	2(2%)	-
No	2(270)	
Cocaine	чб (9070)	_
Ves	3(6%)	-
No	47(94%)	
Prescribed Drugs	+7 (5+70)	
Ves	1 (2%)	-
No	1(270)	
Shisha	(9070)	_
Ves	1 (2%)	_
No	49(98%)	
Codeine	(9070)	_
Ves	5 (10%)	
No	45 (90%)	
Colorado	45 (5070)	_
Ves	7 (14%)	_
No	43(86%)s	
Multiplicity of drug	45 (0070)3	
use		
<u>use</u> Monodrug abusers	18 (36%)	_
Polydrug abusers	32(64%)	_
	52 (07/0)	

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As shown in Figure 1, the median level of IL-40 was significantly lower in patients with SUD compared with the controls [146.02 pg/ml (100.51 – 237.78) vs 300.92 pg/ml (190.87 – 420.21), p-value = 0.000)]. Similarly, the median level of IgA was significantly lower in SUD patients compared with the controls [214.21 mg/ml (1370.27 – 3180.73) vs 5639.21 (3646.34 – 15577.83), P = 0.000] (Figure 2).









187 Figure 2: Plasma levels of immunoglobulin A in SUD patients and controls

- 188 Considering the number of substances abused, there were no significant differences in the median
- 189 levels of IL-40 and IgA in patients monodrug abusers and polydrug abusers (Table 2).

190 Table 2: Plasma levels of IL-40 and IgA in monodrug and polydrug abusers

	Parameters	Monodrug abusers	Two substances	Multiple substances	P-value
		(n = 18)	(n = 15)	(n = 18)	
	IL-40 (pg/ml)	120.70	181.30	146.90	0.262
		(77.53 - 166.70)	(93.31 - 229.50)	(104.20 - 324.10)	
	IgA (µg/ml)	2526.49	1825.48	1996.50	0.250
		(1491.59 - 4026.59)	(1352.28 - 2537.70)	(1185.81 - 3119.23)	
191	$\overline{\text{IL-40}} = \text{Interleukin-40}, \text{Ig}$	gA = Immunoglobulin A			
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As shown in Table 3, plasma IL-40 level had significant positive correlation with IgA in SUD

213 patients.

Table 3: Correlation between the plasma levels of IL-40 and IgA in SUD patients and controls

	SUD patients $(n = 50)$		Controls $(n = 40)$	
	r – value	P-value	r – value	P - value
IL-40 (pg/ml) vs IgA (µg/ml)	0.437	0.0012*	0.182	0.262
*Significant at p<0.05, IL-40 = Interleuking	n-40, IgA = Immunoglo	obulin A		

241 **Discussion**

242 Cannabis use disorder (CUD) is a global growing concern, with around 24% of individuals seeking 243 treatment for SUD being diagnosed with the condition [27]. In 2010, it accounted for 244 approximately 2 million disability-adjusted life years (DALYs) worldwide [28]. In this study, 245 marijuana was observed to be the most abused substance in the SUD patients. This observation is 246 in line with previous reports. In 2019, the World Drug Report showed that approximately 200 247 million people used cannabis, highlighting its widespread consumption [29]. Similarly, 248 Morcuende *et al.* [30] reported that cannabis is the most commonly used illicit drug, worldwide. 249 These reports, together with the observation from this study, showed that cannabis use is a serious 250 public health problem and thus, addressing the rising use of cannabis and its associated health 251 implications should remain a critical priority for public health interventions.

252 IL-40 is a cytokine involved in formation of B cells in the bone marrow and IgA production [31]. 253 It is a proinflammatory cytokine whose expression is upregulated in conditions characterized by 254 heightened immune activity. Reports have shown that it plays a crucial role in humoral immune 255 responses and has been implicated in various autoimmune diseases, such as rheumatoid arthritis 256 and Sjögren's syndrome [21]. The observed significant reduction in median IL-40 level in SUD 257 patients compared to controls suggests a potential link between serum IL-40 level and SUD 258 pathophysiology. Our observation could not be compared with previous reports as currently, there 259 is lack of information on IL-40 level in SUD patients. Immune system dysregulation, characterised 260 by a state of peripheral inflammation and neuroinflammation or immunosuppression, is a common 261 feature in SUD patients and plays crucial roles in the course of the disorder including drug 262 dependence and relapse [30, 32, 33]. The observed significantly low IL-40 levels observed in SUD 263 patients may suggest an impaired immune response, potentially contributing to the chronic

inflammation associated with the disorder. Alternatively, the observed significant reduction might
be a consequence of various therapies for SUD. Navrátilová *et al.* [21] reported a decrease in IL40 level following Rituximab therapy; a B cell depleting therapy. Therefore, evaluation of the
plasma IL-40 level as a potential biomarker for response to therapy in SUD patients is suggested.

268 IgA is the second most abundant immunoglobulin type found in the body. It is the principal 269 antibody protecting the mucosal surfaces in the gastrointestinal, respiratory, and genitourinary 270 tracts [34, 35]. In this study, plasma total IgA level was significantly lower in SUD patients 271 compared to controls. This finding is consistent with previous studies demonstrating that opioids 272 and alcohol impair IgA production [36, 37]. Our observation could be due to the observed 273 reduction in IL-40 level which resulted in downregualtion of IgA level. This is further buttressed 274 by the observed significant positive correlation between IL-40 and IgA in SUD patients. The report 275 of Roy and Loh [36] showed that morphine inhibits the production of cytokines that promote IgA 276 secretion. This observation further highlights the immunosuppressive effects of substance abuse 277 and could be one of the mechanisms likely contributing to the increased susceptibility of SUD 278 patients to infections and likely poor response to vaccines. The report of Wang et al. [9] showed 279 that fully vaccinated SUD patients had a significantly higher risk of COVID-19 breakthrough 280 infections compared to those without SUDs. In addition, those with breakthrough infections were 281 more likely to experience severe health outcomes, including hospitalization and death. Although 282 the observed low IgA level is hypothesized to be a consequence of low IL-40 level, it could also 283 be a consequence of the effects of therapy as hypergammaglobulinemia, particularly of IgA and 284 IgE, has been reported in SUD patients [15]. Therefore, there is the need for further studies to 285 understand the homeostasis of IL-40 in SUD patients and the possible effects of therapy on it with 286 a view to clearly delineating the observed reduction in total IgA level in SUD patients.

287 Reports on the effects of poly drug abuse on immune functions are conflicting. Pacifici and 288 colleagues [38] reported that combining opioids with other substances led to greater immune 289 suppression in heroin and morphine-treated mice. However, Friedman et al. [32] reported that the 290 specific type of drug abused often has a greater impact on immune functions than the number of 291 substances abused. The observed lack of significant differences in the plasma levels of IL-40 and 292 IgA in monodrug and polydrug abusers may indicate that drug use elicits similar 293 immunomodulatory effects irrespective of the number of substances that are abused. This 294 observation is in contrast with some studies that reported additive effects of polydrug use on 295 immune dysfunction. The findings of Rahamon *et al.* [13] revealed elevated phagocytic activity in 296 polydrug abusers compared to monodrug abusers and suggested that polydrug use has additive or 297 synergistic effects on immune dysfunction. While there are no available reports on IL-40 and IgA 298 levels in monodrug and polydrug abusers, observation from this study could suggest that there may 299 be a threshold of immune suppression beyond which additional substances do not further reduce 300 IL-40 or IgA levels. Roy and Loh [36] reported that opioids significantly suppressed IgA 301 production and modulated cytokine levels, overshadowing any additional impact of other 302 substances used. Based on the previous reports and the findings from this study, it could be 303 suggested that polydrug abuse exerts skewed immunomodulatory effects on the innate and 304 adaptive immune response.

305 It could be concluded that patients with substance use disorder exhibit impaired humoral immune 306 function, as evidenced by significant reduction in IL-40 and IgA levels. However, this 307 dysregulation does not appear to be influenced by the multiplicity of substances abused. Further 308 research is recommended to elucidate the mechanisms underlying humoral immune impairment in

- 309 SUD patients and to explore its potential clinical implications. Small sample size and inability to
- 310 enroll drug naïve SUD patients are some of the limitations in this study.

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332 Declarations

333 Availability of data and materials

All data generated during this study are included in this published article.

335 Competing interests

336 The authors have no competing interests to declare.

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339 Authors' contributions

- 340 SKR conceived and designed the study; SKR, AAS, SOB, OO and VOL collected the samples;
- 341 AAS, SOB and SKR did the laboratory analysis, SKR wrote the initial draft, SKR, AAS, SOB,
- 342 OO and VOL reviewed the final draft, SKR supervised the entire research.

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