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Distinct cardiac troponin alterations in patients with cocaine and alcohol use disorders during abstinence for cardiovascular risk assessment

Óscar Porras-Perales[1,2,3], Jorge Segovia-Reyes[4,9], Ángela Crespo-Delgado[4,9], Diego Ruiz-González[4,9], María Flores-López[1,3,5], Dina Medina-Vera[1,2,4,6], Laura Sánchez-Marín[1,5], Laura Martín-Chaves[1,2,4,6], Nerea Requena-Ocaña[1,3], Ana Isabel Molina-Ramos[1,2,6], Juan Jesús Ruiz-Ruiz[7], Fernando Rodríguez de Fonseca[1,8], Manuel Jiménez-Navarro[1,2,4,6], Jorge Rodríguez-Capitán[1,2,6]✉, Francisco Javier Pavón-Morón[1,2,6]✉ & Antonia Serrano[1,5]

Cocaine use is a well-established cardiovascular risk factor, further enhanced by concurrent alcohol use. However, cardiovascular risk is poorly managed in individuals with cocaine use disorder (CUD). This observational, cross-sectional case-control study assessed cardiac troponins T (cTnT) and I (cTnI) as biomarkers of myocardial injury in patients with CUD and/or alcohol use disorder (AUD) during abstinence. Eighty-four participants were categorized by primary substance use [cocaine (CUD, with or without AUD), alcohol (AUD), and healthy controls] and further stratified by cardiovascular diagnosis [cardiovascular (CV) and non-cardiovascular (non-CV)]. After clinical assessment, blood samples were collected for high-sensitivity cTnT and cTnI assays, and for inflammatory mediators. Patients exhibited a high prevalence of psychiatric comorbidities (67.9%). The cocaine group exhibited higher cTnT levels ($p < 0.001$), while the alcohol group had higher cTnI levels ($p < 0.05$) compared to controls. The non-CV group also had elevated troponin levels, with CUD patients displaying higher cTnT levels than AUD patients. Additionally, cTnI levels were lower in the cocaine group compared to the alcohol group ($p < 0.01$), and the CV group exhibited lower cTnI levels than the non-CV group ($p = 0.001$). CUD severity correlated with cTnT levels, while AUD severity correlated with both troponins. Inflammatory mediators correlated with troponins, particularly cTnT. Results indicate distinct troponin alterations in CUD and AUD patients, even without cardiovascular diagnosis, underscoring the importance of cardiovascular risk assessment in addiction treatment.

Keywords Alcohol, Cardiovascular, Cocaine, Inflammation, Troponin, Substance use disorder

Substance use disorder is a chronic, relapsing disease characterized by persistent harmful substance use despite adverse consequences. Globally, substance use contributes to approximately 12 million deaths annually, with tobacco and alcohol use ranking second and seventh, respectively, among risk factors for premature death[1,2]. The systemic toxicity from substances results in a wide range of short-term and long-term health consequences,

[1]The Biomedical Research Institute of Málaga and Nanomedicine Platform (IBIMA Plataforma BIONAND), 29590 Málaga, Spain. [2]Cardiology and Cardiovascular Surgery Department, Virgen de la Victoria University Hospital, 29010 Málaga, Spain. [3]School of Psychology, University of Málaga, 29010 Málaga, Spain. [4]School of Medicine, University of Málaga, 29010 Málaga, Spain. [5]Mental Health Department, Regional University Hospital of Málaga, 29010 Málaga, Spain. [6]The Spanish Consortium CIBER of Cardiovascular Diseases (CIBERCV), Instituto de Salud Carlos III, 28029 Madrid, Spain. [7]Centro Provincial de Drogodependencias, Diputación Provincial de Málaga, 29010 Málaga, Spain. [8]Neurology Department, Regional University Hospital of Málaga, 29010 Málaga, Spain. [9]Jorge Segovia-Reyes, Ángela Crespo-Delgado and Diego Ruiz-González contributed equally to this work. ✉email: capijorge@hotmail.com; javier.pavon@ibima.eu

influenced by the type of substance, usage patterns, duration, sociological and environmental factors, and individual health status. Common medical complications include psychiatric disorders, neurological conditions, cancers, gastrointestinal diseases, and cardiovascular diseases[1,3], highlighting the need for effective prevention programs and comprehensive treatment[4].

Alcohol and psychostimulants, particularly cocaine and amphetamines, are among the most commonly used substances in individuals seeking treatment. Unlike alcohol, psychostimulants are frequently co-used with other substances, especially alcohol and cannabis, a pattern consistently associated with poorer treatment outcomes and higher relapse rates due to the potentiation and interference of physiological and behavioral effects[5,6]. Cocaine inhibits catecholamine reuptake, exerting acute chronotropic and inotropic effects in addition to strong vasoconstrictive properties. These cardiovascular effects increase myocardial oxygen demand while reducing coronary blood flow. As a result, cocaine use is associated with a high prevalence of self-reported chest pain. For instance, in a clinical study of treatment-seeking individuals, 52% of users reported cocaine-associated chest pain (CACP), typically described as oppressive and retrosternal, and occurring within minutes after consumption[7]. A multicenter cohort further confirmed that 32.6% of patients reported CACP, particularly among those with daily use and rapid routes of administration[8]. Alcohol enhances the euphoric effects of cocaine by altering its metabolism and promoting the formation of cocaethylene, a metabolite that prolongs and amplifies the sympathomimetic effects of cocaine[9,10]. This metabolic interaction results in heightened cardiotoxicity, which compounds the known cardiovascular risks of cocaine, including hypertension, tachycardia, malignant arrhythmias, myocardial ischemia and infarction, dilated cardiomyopathy, and heart failure[11–13]. Concomitant use with alcohol may further exacerbate these events[12,14]. While alcohol alone lacks psychostimulant properties, abrupt cessation in individuals with alcohol use disorder (AUD) often leads to a hyperadrenergic and hyperglutamatergic state, which increases cardiac workload and predisposes individuals to cardiovascular complications. A retrospective study assessing plasma brain natriuretic peptide (BNP) levels in hospitalized patients revealed significant increases by day 12 of alcohol withdrawal, suggesting the presence of withdrawal-related myocardial stress[15]. High-dose and chronic alcohol use also independently contributes to cardiomyocyte toxicity, arterial hypertension, and atherosclerosis[16,17]. In this context, tobacco smoking, frequently co-occurring in individuals with substance use disorders, also represents a major cardiovascular risk factor. In a large retrospective cohort, tobacco use disorder was associated with higher rates of cardiovascular and respiratory diseases than cocaine use alone, suggesting that smoking may be a dominant risk factor in this population[18].

Cardiomyocyte damage and necrosis lead to the release of cardiac troponin I (cTnI) and T (cTnT), isomers of proteins from the troponin–tropomyosin complex, into the bloodstream. These biomarkers are essential for detecting myocardial injury and stratifying cardiovascular risk in patients with suspected acute coronary syndromes[19]. When combined with other biomarkers, cTnI and cTnT provide independent prognostic information beyond clinical variables, and can predict outcomes such as death and the first coronary heart disease event in individuals without prior cardiovascular disease. The introduction of high-sensitivity assays has further enhanced the ability to detect even subtle troponin elevations, indicative of subclinical myocardial injury, disease progression, or increased mortality risk. In addition to their diagnostic utility in acute cardiac events, cardiac troponins may reflect subclinical myocardial stress and inflammation in patients without overt cardiovascular disease. Chronic systemic inflammation is a recognized hallmark of substance use disorders and is increasingly implicated in the pathophysiology of cardiovascular dysfunction within this population. We therefore hypothesized that elevated inflammatory mediators in abstinent individuals with cocaine use disorder (CUD) and/or AUD may be associated with altered cardiac troponin levels, providing insight into early mechanisms of cardiovascular vulnerability in this high-risk group.

The rationale for evaluating the association between cardiac troponins and inflammatory biomarkers in individuals with substance use disorder arises from accumulating evidence that chronic inflammation contributes to both psychiatric comorbidities and cardiovascular dysfunction[20,21].

In this observational study we measured plasma levels of cardiac troponins in patients with CUD and AUD during abstinence, taking into account prior cardiovascular diagnoses. All patients underwent comprehensive clinical assessments, and we further investigated potential associations between troponin alterations and key inflammatory mediators, including soluble suppression of tumorigenicity-2 (sST2), a validated biomarker for cardiovascular risk.

Results

Sociodemographic characteristics

Table 1 presents the sociodemographic characteristics of the sample ($n = 84$), divided into three groups based on the primary substance use disorder: cocaine, alcohol, and control. The sample had a median age of 52 years, median body mass index (BMI) of 28.8 kg/m^2, and a higher proportion of men (75.0%) than women (25.0%). Occupation differed significantly among participants with substance use disorder compared to controls ($p < 0.001$), with higher rates of unemployment (41.1%) and sick leave (23.2%).

Cardiac troponins and physiological variables

Correlations were analyzed between $\log_{10}$-transformed troponin concentrations and continuous physiological variables (i.e., age and BMI). While cTnT levels showed no correlation with age or BMI, cTnI levels were significantly correlated with BMI ($r = +0.301$, $p = 0.006$) in the total sample. Since the sample was categorized by lifetime substance use disorder type and cardiovascular diagnosis, we further analyzed correlations within each group. In the control group, cTnT levels correlated significantly with age ($r = -0.413$, $p = 0.015$), while cTnI levels correlated with BMI ($r = +0.632$, $p < 0.001$). In the alcohol group, cTnI levels showed a significant correlation with BMI ($r = +0.446$, $p = 0.017$). In the CV group, cTnI levels also correlated with BMI ($r = +0.545$, $p = 0.002$).

Variable		Group			p-value
		Control	Alcohol	Cocaine	
		n = 28	n = 28	n = 28	
Age (years)	Median (IQR)	54.0 (42.0–59.8)	52.5 (46.0–55.0)	49.5 (45.0–52.8)	0.439[a]
Body mass index (kg/m^2)	Median (IQR)	28.7 (26.0–29.8)	29.2 (26.5–32.3)	28.7 (26.5–34.2)	0.297[a]
Sex [*n* (%)]	Female	7 (25.0)	8 (28.6)	6 (21.4)	0.82[b]
	Male	21 (75.0)	20 (71.4)	22 (78.6)	
Marital status [*n* (%)]	Single	9 (32.1)	4 (14.3)	8 (28.6)	0.220[b]
	Married/cohabiting	13 (46.4)	10 (35.7)	13 (46.4)	
	Divorced/separated	6 (21.4)	12 (42.9)	7 (25.0)	
	Widowed	0 (0.0)	2 (7.1)	0 (0.0)	
Education [*n* (%)]	≤ Primary	6 (21.4)	14 (50.0)	9 (32.1)	0.151[b]
	Secondary	17 (60.7)	8 (28.6)	14 (50.0)	
	Higher	5 (17.9)	6 (21.4)	5 (17.9)	
Occupation [*n* (%)]	Employed	19 (67.9)	4 (14.3)	6 (21.4)	< 0.001[b]
	Sick leave	1 (3.6)	6 (21.4)	7 (25.0)	
	Unemployed	4 (14.3)	12 (42.6)	11 (39.3)	
	Retired	4 (14.3)	6 (21.4)	4 (14.3)	

Table 1. Baseline sociodemographic characteristics of the sample. [a]*P*-value calculated using the Kruskal–Wallis test; [b]*P*-value calculated using the chi-square test. *BMI* body mass index, *IQR* interquartile range, *SD* standard deviation.

We also evaluated the association between troponin levels and sex across the entire sample, finding no significant differences between men and women. Moreover, comparisons within the control and other groups showed no significant sex-based differences.

Clinical characteristics

Abstinent patients diagnosed with severe substance use disorders were recruited from primary care outpatient treatment for cocaine or alcohol. As summarized in Table 2, patients exhibited high rates of psychiatric comorbidities (67.9%, excluding other substance use disorders), current smoking (67.8%), and medical conditions, including cardiovascular diseases (53.6%) [primarily hypertension (39.3%)] as well as obesity (41.1%) and diabetes (21.4%). Cardiovascular treatments included ACE inhibitors, beta-blockers, antiarrhythmic drugs, diuretics, statins, and antiplatelet agents, tailored to specific conditions and risk factors.

Due to the recruitment strategy, the alcohol group had no additional substance use disorders, while 50% of the cocaine group had comorbid AUD. Nicotine use disorder was not considered an exclusion criterion given its high prevalence in the overall sample. The cocaine group had a median abstinence of 26 days from cocaine and alcohol, compared to 60 days of alcohol abstinence in the alcohol group. Additionally, the cocaine group exhibited a higher prevalence of psychiatric disorders, including mood, psychotic, borderline, and antisocial personality disorders, compared to the alcohol group ($p < 0.05$).

Cardiac troponins based on primary substance use disorder

Raw troponin concentrations were $\log_{10}$-transformed (Table S1) for one-way analysis of covariance (ANCOVA) by primary substance use disorder, with age, BMI, and sex as covariates. Back-transformed values are shown in Fig. 1a,b.

The analysis revealed a significant main effect of primary substance use disorder on plasma levels of cTnT ($F_{2,78}$=7.35, $p = 0.001$; Fig. 1a) and cTnI ($F_{2,78}$=3.28, $p = 0.043$; Fig. 1b), with elevated cTnT in the cocaine group ($p < 0.001$) and cTnI in the alcohol group ($p < 0.05$) compared to controls.

Cardiac troponins based on cardiovascular diagnosis

Log_{10}-transformed cTnT and cTnI concentrations were also analyzed based on cardiovascular condition diagnosis, with back-transformed values shown in Fig. 1c,d.

We found a significant main effect of cardiovascular diagnosis on plasma levels of cTnT ($F_{2,78} = 5.09$, $p = 0.008$; Fig. 1c) and cTnI ($F_{2,78} = 5.49$, $p = 0.006$; Fig. 1d). Post hoc tests showed higher cTnT and cTnI levels in the non-CV group compared to controls ($p < 0.01$ and $p < 0.05$, respectively).

Cardiac troponins based on primary substance use disorder and cardiovascular diagnosis

Although no significant differences were observed in the overall prevalence of smoking, obesity, or diabetes between the CUD and AUD groups, we further examined these cardiovascular risk factors based on cardiovascular diagnosis, given their potential influence on cardiac troponin levels. The comparison between patients with and without a cardiovascular condition revealed no statistically significant differences: current smoking was reported in 73.3% vs. 61.5% ($n = 22$ vs. $n = 16$; $p = 0.336$), obesity in 43.3% vs. 38.5% ($n = 13$ vs.

Variable		Group		p-value
		Alcohol	Cocaine	
		n = 28	n = 28	
Primary substance use disorder in treatment [n (%)]	AUD	28 (100.0)	–	–
	CUD	–	28 (100.0)	
Comorbid substance use disorders (AUD) [n (%)]	Yes	0 (0.0)	14 (50.0)	< 0.001[a]
	No	28 (100.0)	14 (50.0)	
Comorbid mental disorders [n (%)]	Yes	16 (57.1)	22 (78.6)	0.152[a]
	No	12 (42.9)	6 (21.4)	
	Mood disorders	12 (42.9)	22 (78.6)	0.013[a]
	Anxiety disorders	8 (28.6)	12 (42.9)	0.403[a]
	Psychotic disorders	0 (0.0)	6 (21.4)	0.023[a]
	Eating disorders	2 (7.1)	0 (0.0)	0.491[a]
	Personality disorders	0 (0.0)	6 (21.4)	0.023[a]
Cocaine abstinence (day)	Median (IQR)	0.0 (0.0–0.0)	25.5 (15.0–38.0)	–
Alcohol abstinence (day)	Median (IQR)	60.0 (27.0–98.0)	25.5 (7.0–38.0)	0.004[b]
Smoking [n (%)]	Yes	18 (64.3)	20 (71.4)	0.286[a]
	No	4 (14.3)	6 (21.4)	
	Ex-smoker	6 (21.4)	2 (7.1)	
Obesity [n (%)]	BMI (≥ 30)	12 (42.9)	11 (39.3)	0.999[a]
Type 2 diabetes mellitus [n (%)]	Yes	7 (25.0)	5 (17.9)	0.746[a]
	No	21 (75.0)	23 (82.1)	
Hypertension and cardiovascular conditions [n (%)]	Yes	18 (64.3)	12 (42.9)	0.180[a]
	No	10 (35.7)	16 (57.1)	
	Hypertension	14 (50.0)	8 (28.6)	0.171[a]
	Arrhythmia	6 (21.4)	6 (21.4)	0.999[a]
	Atherosclerosis	5 (17.9)	6 (21.4)	0.999[a]
	Coronary artery disease	0 (0.0)	1 (3.6)	0.999[a]

Table 2. Clinical characteristics of the cocaine and alcohol groups. [a]*P*-value calculated using the Fisher's exact test or chi-square test; [b]*P*-value calculated using the Mann–Whitney U test. *AUD* alcohol use disorder, *BMI* body mass index, *CUD* cocaine use disorder, *IQR* interquartile range, *SD* standard deviation.

$n = 10$; $p = 0.789$), and diabetes in 26.7% vs. 11.5% ($n = 8$ vs. $n = 3$; $p = 0.182$), respectively. These findings suggest that the burden of traditional cardiovascular risk factors was similar between CV and non-CV groups.

Two-way ANCOVA was conducted to elucidate the relative contribution and interaction of primary substance use disorder and cardiovascular condition on $\log_{10}$-transformed troponin concentrations. Back-transformed values with 95% confidence intervals (95% CI) are presented in Fig. 2.

Primary substance use disorder and cardiovascular diagnosis

cTnT concentrations showed a significant main effect of primary substance use disorder ($F_{1,49} = 4.90$, $p = 0.032$) and an interaction between both factors ($F_{1,49} = 5.95$, $p = 0.018$) (Fig. 2a). Patients without cardiovascular diagnosis in the cocaine group had significantly higher cTnT levels ($p < 0.001$) than those in the alcohol group, exhibiting the highest overall cTnT levels.

For cTnI concentrations, there were significant main effects of primary substance use disorder ($F_{1,49} = 9.92$, $p = 0.003$) and cardiovascular diagnosis ($F_{1,49} = 12.94$, $p = 0.001$) (Fig. 2b). Specifically, the cocaine group had lower cTnI levels than the alcohol group, and the CV group had lower cTnI levels than the non-CV group. Patients in the alcohol group without cardiovascular diagnosis showed the highest cTnI levels.

Lifetime substance use disorder without cardiovascular diagnosis

We further explored troponin concentrations in patients without cardiovascular disease, categorized by substance use disorder diagnosis (CUD and/or AUD). The CV group was excluded as no differences were found in troponin levels.

cTnT concentrations showed a significant main effect of substance use disorder diagnosis ($F_{2,20} = 6.03$, $p = 0.009$) (Fig. 2c). Pairwise comparisons indicated that cTnI levels were significantly higher in CUD patients compared to AUD patients ($p < 0.05$), with the alcohol group without cardiovascular diagnosis showing the highest cTnT levels.

Similarly, cTnI concentrations showed a significant main effect of substance use disorder diagnosis ($F_{2,20} = 4.25$, $p = 0.029$) (Fig. 2d). Unlike cTnT, cTnI levels were significantly lower in CUD patients than AUD patients ($p < 0.05$), with the highest cTnI levels in the alcohol group without cardiovascular disease.

Cardiac troponins and substance use disorder severity

Given the significant effects of lifetime substance use disorder diagnosis on troponin concentrations, we examined substance use disorder severity (DSM-5 criteria for CUD and AUD) and recent abstinence duration using correlation analyses.

Significant positive correlations were observed between DSM-5 criteria for substance use disorders and $\log_{10}$-transformed troponin concentrations (Table 3). Specifically, CUD severity correlated with cTnT ($rho = +0.39$, $p < 0.001$), while AUD severity correlated with both cTnT ($rho = +0.33$, $p < 0.01$) and cTnI ($rho = +0.40$, $p < 0.001$). No significant correlations were found between the duration of cocaine or alcohol abstinence and troponin levels.

Cardiac troponins and inflammatory mediators

We examined the relationship between troponins and inflammatory mediators [interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), chemokine C-X_3-C motif ligand 1 (CX_3CL1, fractalkine), and sST2], as both substance use disorders and cardiovascular diseases involve heightened systemic inflammation and immune dysregulation that may exacerbate cardiac injury.

Significant differences in inflammatory mediator concentrations were found across groups based on substance use disorder diagnosis, with the highest levels observed in the cocaine group (Table S2).

Correlation analysis revealed significant positive correlations between $\log_{10}$-transformed inflammatory mediators and troponins (Table 3). Specifically, IL1-β levels significantly correlated with cTnT ($r = +0.41$, $p < 0.01$) and cTnI ($r = +0.31$, $p < 0.05$); TNF-α levels correlated with cTnT ($r = +0.28$, $p < 0.05$); CX_3CL1 levels correlated with cTnT ($r = +0.40$, $p < 0.01$) and cTnI ($r = +0.32$, $p < 0.05$); and sST2 levels correlated with cTnT ($r = +0.60$, $p < 0.001$) and cTnI ($r = +0.35$, $p = 0.010$).

Discussion

This study highlights the under-management of cardiovascular risk in patients with substance use disorders, even in the absence of a formal cardiovascular diagnosis. We examined cardiac troponins as biomarkers of myocardial injury in abstinent individuals with lifetime CUD and/or AUD. A key aim was to explore whether systemic inflammation contributes to subclinical myocardial stress in this population.

In addition to their established diagnostic value in acute coronary syndromes, high-sensitivity cardiac troponin assays can detect subtle elevations indicative of reversible cardiomyocyte injury, low-grade inflammation, and autonomic imbalance. These other mechanisms are particularly relevant in substance use disorders, which are characterized by chronic systemic inflammation, psychological stress, and neuroendocrine dysregulation. Consistent with our hypothesis, we observed significant correlations between troponins and inflammatory markers, suggesting that inflammation may mediate cardiovascular vulnerability during abstinence.

Our findings reveal significant differences in troponin levels based on substance use disorder type and the presence of pre-existing cardiovascular condition. Notably, patients in the cocaine group exhibited elevated cTnT levels compared to controls, while the alcohol group showed increased cTnI levels. In patients without cardiovascular diagnosis, those with CUD had higher cTnT and lower cTnI levels than patients with AUD, suggesting distinct mechanisms of cardiac injury between cocaine and alcohol use during early abstinence.

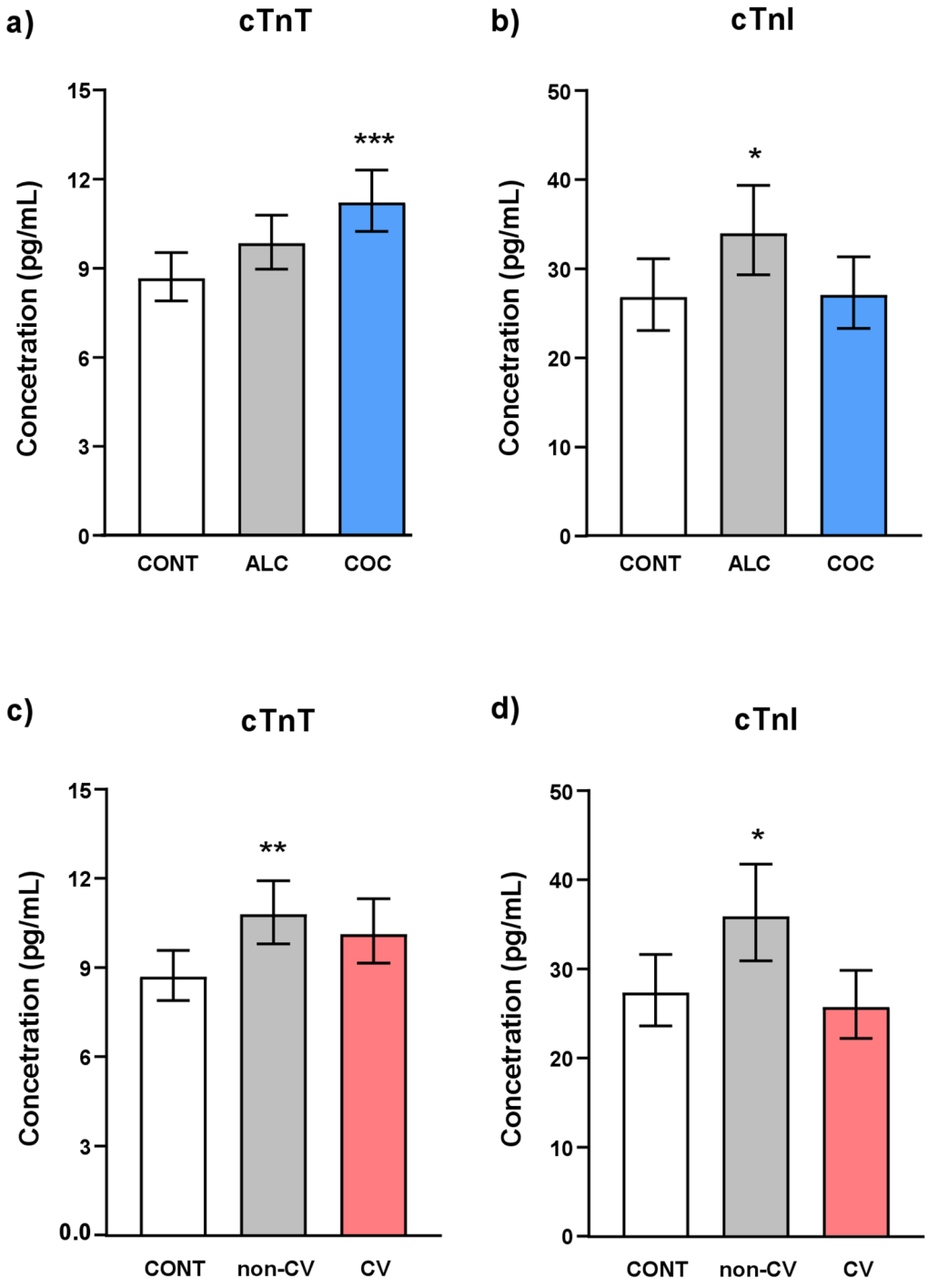
Interestingly, patients with established cardiovascular disease showed troponin levels comparable to controls and, in some cases, even lower than those without cardiovascular diagnoses. This counterintuitive result may be explained by several non-exclusive mechanisms. First, although we found no statistically significant group differences, other cardiovascular risk factors such as smoking status, obesity, and diabetes mellitus, may have influenced troponin levels[18,22,23]. These variables were not included as covariates in our models to avoid overfitting, although we acknowledge their potential impact. Second, pharmacological treatments received by patients with cardiovascular conditions (e.g., beta-blockers, ACE inhibitors, statins) may reduce myocardial stress and troponin release, as previously documented[24,25]. Third, although not specifically assessed in this cohort, opioid maintenance therapy (OMT) may also offer cardioprotective effects. Clergue-Duval et al. (2021) reported a reduced prevalence of CACP among patients receiving OMT, likely due to attenuated sympathetic tone[8].

Troponin elevations in substance use disorders may therefore reflect emotional stress, autonomic dysregulation, myocardial injury, and/or persistent systemic inflammation, particularly during abstinence[26]. This hypothesis is further supported by the significant positive correlations observed between troponin levels (especially cTnT) and inflammatory mediators such as IL-1β, TNF-α, CX_3CL1, and sST2. It is also important to note that these patients exhibited a high psychiatric comorbidity, mainly mood disorders and anxiety disorders, consistent with previous findings of elevated inflammatory mediators and psychiatric conditions in patients with substance use disorders[20,27].

Emerging evidence suggests troponin can be released during reversible cell injury without necrosis[28]as seen after intense physical exertion or in circadian fluctuation[29,30]. High-sensitivity assays have also revealed variations in cTnT and cTnI expression in contexts such as acute myocardial infarction, highlighting their potential as complementary biomarkers[31]. Our data support the notion that cTnT and cTnI may reflect different sensitivities to cardiac stress depending on the substance involved[32].

The divergent effects of cocaine and alcohol on troponin levels likely arise from their distinct impacts on cardiac physiology. cTnT may be more sensitive to diffuse, low-level cardiac injury from chronic systemic inflammation common in substance use disorder, while cTnI indicates focal myocardial damage without systemic inflammation[33,34]. This is supported by studies where cTnT associates with non-cardiovascular mortality and cTnI with acute myocardial injury[35].

In patients with CUD, elevated cTnT during cocaine withdrawal may result from residual sympathetic hyperactivity, emotional stress, persistent inflammation, and recovery from subclinical myocardial damage[36].



Notably, we found a strong correlation between cTnT levels and CUD severity. Unlike other studies involving recent users without substance use disorder diagnosis[19,37]we did not observe significant cTnI alterations, possibly due to differences in abstinence duration or diagnostic classification.

Conversely, chronic alcohol exposure can impair protein synthesis, induce oxidative stress, and promote cardiomyocyte apoptosis, leading to troponin release and diffuse myocardial damage[36]. This may explain the stronger association of cTnI with AUD in our study. Our findings are consistent with reports of elevated cTnI in chronic alcohol use in the absence of overt infarction[38,39]. We also found a positive correlation between cTnI levels and BMI, aligning with large-scale studies, such as the Trøndelag Health-HUNT Study, showing higher cTnI levels in overweight or obese individuals[22].

While some studies suggest co-use of cocaine and alcohol increases cardiac damage compared to cocaine alone[14,19]our results do not support additive or synergistic effects on cTnT or cTnI during abstinence. Cocaine

◀**Fig. 1**. Plasma concentrations of cTnT and cTnI in the sample based on primary substance use disorder or cardiovascular disease diagnosis. (**a**) Bars represent estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnT concentrations (pg/mL), based on primary substance use disorder; (**b**) Bars represent estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnI concentrations (pg/mL), based on primary substance use disorder; (**c**) Bars represent estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnT concentrations (pg/mL), based on cardiovascular disease diagnosis; (**d**) Bars represent estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnI concentrations (pg/ml), based on cardiovascular disease diagnosis. (*) indicates $p < 0.05$ compared to the control group; (**) indicates $p < 0.01$ compared to the control group; and (***) indicates $p < 0.001$ compared to the control group. (**a**) and (**b**) were analyzed using a one-way ANCOVA with primary substance use disorder as the factor, controlling for age, BMI, and sex; (**c**) and (**d**) were analyzed using a one-way ANCOVA with cardiovascular disease diagnosis as the factor, controlling for age, BMI, and sex.

users with AUD did not exhibit significant increases in either troponin, possibly reflecting reduced acute toxicity or cocaethylene-related effects during abstinence.

Our findings align with prior research showing high prevalence of subclinical cardiac injury in asymptomatic individuals with substance use disorders[40,41]. The strong correlation between troponins and inflammatory mediators underscores the role of systemic inflammation in cardiovascular damage. Similar correlations are seen in other inflammatory conditions such as COVID-19[42]. Additionally, elevated sST2 levels, particularly in patients with CUD, are clinically significant due to their prognostic value for mortality and cardiovascular diseases[23].

Limitations

This study has several limitations. First, the sample size was relatively small and composed exclusively of Caucasian participants, which limits the generalizability of the findings. Second, the cross-sectional design prevents causal interpretations. Third, although key cardiovascular risk factors such as smoking, obesity, and diabetes mellitus did not significantly differ between patients with and without a cardiovascular diagnosis, and did not appear to influence troponin levels in our analyses, their potential effects cannot be entirely ruled out. These variables were not included as covariates in the ANCOVA models to avoid overfitting, but they may still contribute to the observed variability. Moreover, unmeasured confounding factors (e.g., diet, physical activity, medication adherence, or subclinical conditions) could have influenced the results. Additionally, the exclusion of other substance use disorders and the relatively short abstinence periods may limit our understanding of long-term cardiovascular recovery in this population. Lastly, although cardiac troponins provided relevant insights into subclinical myocardial injury, future studies should incorporate broader cardiac assessments and longitudinal designs with more balanced sex representation to enhance external validity and clarify temporal relationships.

Conclusions

This study reveals distinct patterns of cardiac troponin alterations in abstinent patients with cocaine and alcohol use disorders, suggesting substance-specific mechanisms of myocardial injury. Elevated cTnT levels in individuals with CUD and increased cTnI levels in those with AUD underscore the need to assess cardiovascular risk even in the absence of clinically diagnosed heart disease. The strong correlations between troponin concentrations and inflammatory markers highlight the contribution of systemic inflammation to subclinical cardiac injury in this population. These findings emphasize the importance of incorporating cardiovascular risk evaluation into addiction treatment frameworks. Future research should aim to clarify the underlying mechanisms through longitudinal studies involving diverse populations, more comprehensive cardiac evaluations, and greater inclusion of female participants to explore potential sex-specific effects. Such efforts are essential to improve prevention strategies and optimize cardiovascular care in individuals with substance use disorders, particularly within primary care settings.

Methods

Participants and recruitment

Ninety-five Caucasian subjects were initially recruited for this observational, cross-sectional case-control study between March 2021 and June 2023. Six participants were excluded for not meeting eligibility criteria, and five dropped out before clinical assessments. A total of 84 participants (88%) completed the study and were categorized into the following sample groups: Participants from primary care outpatient treatment programs for cocaine or alcohol use at the Regional University Hospital of Málaga and the Provincial Center for Drug Dependence (Málaga, Spain) were first divided into two groups based on their primary substance use disorder: cocaine (abstinent patients undergoing treatment for CUD, $n = 28$) and alcohol (abstinent patients undergoing treatment for AUD, $n = 28$). Patients in the cocaine group could have a comorbid lifetime diagnosis of AUD, whereas those in the alcohol group did not have a comorbid lifetime diagnosis of CUD. This was a main requirement for the alcohol group based on the prevailing understanding that alcohol use is commonly associated with CUD. Subsequently, patients with CUD and/or AUD were further categorized into two groups based on their cardiovascular disease diagnosis: CV (patients previously diagnosed with and treated for cardiovascular diseases as indicated in their medical records, $n = 30$) and non-CV (patients without a medical history of cardiovascular diseases, $n = 26$).

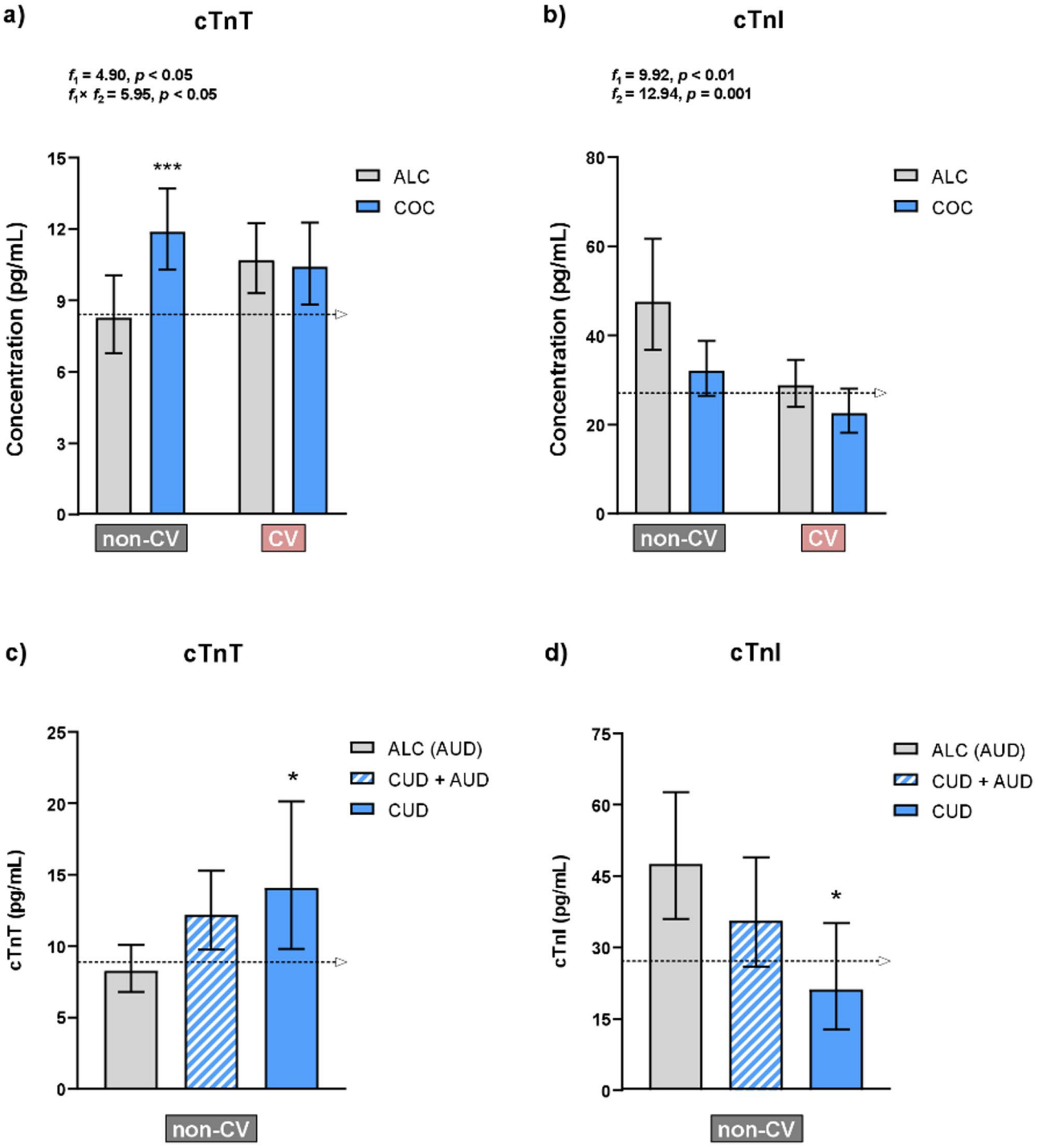


Fig. 2. Plasma concentrations of cTnT and cTnI in patients based on substance use disorder and cardiovascular disease diagnosis. (**a**) Bars represent estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnT concentrations (pg/mL), based on primary substance use disorder and cardiovascular disease diagnosis; (**b**) Bars are estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnI concentrations (pg/mL), based on primary substance use disorder and cardiovascular disease diagnosis; (**c**) Bars are estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnT concentrations (pg/ml), based on substance use disorder diagnosis in the non-CV group; (**d**) Bars are estimated marginal means and 95% CI of back-transformed values from log (10)-transformed cTnI concentrations (pg/mL), based on substance use disorder diagnosis in the non-CV group. (*) indicates $p < 0.05$ compared to the alcohol and non-CV subgroup. The dashed arrows represent concentrations for the control group. (**a**) and (**b**) were analyzed using a two-way ANCOVA with primary substance use disorder (f_1) and cardiovascular disease (f_2) as factors, controlling for age, BMI, and sex; (**c**) and (**d**) were analyzed using a one-way ANCOVA with substance use disorder diagnosis as the factor, controlling for age, BMI, and sex.

Variable	Log_{10} cTnT (pg/mL)			Log_{10} cTnI (pg/mL)		
	Correlation coefficient		*p*-value	Correlation coefficient		*p*-value
CUD severity [DSM-5 criteria (0–11)]	*rho*	+0.394	< 0.001	*rho*	− 0.044	0.710
AUD severity [DSM-5 criteria (0–11)]	*rho*	+0.327	0.004	*rho*	+0.402	< 0.001
Log_{10} IL1-β (pg/mL)	*r*	+0.412	0.002	*r*	+0.305	0.028
Log_{10} TNF-α (pg/mL)	*r*	+0.281	0.044	*r*	+0.211	0.133
Log_{10} CX_3CL1 (ng/mL)	*r*	+0.396	0.004	*r*	+0.322	0.019
Log_{10} sST2 (ng/mL)	*r*	+0.602	< 0.001	*r*	+0.348	0.010

Table 3. Correlation analysis between plasma concentrations of cardiac troponins and both DSM-5 criteria for substance use disorders and inflammatory markers. Spearman (*rho*) and Pearson (*r*) coefficient correlations. *AUD* alcohol use disorder, *CUD* cocaine use disorder, *DSM* diagnostic and statistical manual of mental disorders, *r* Pearson correlation coefficient, *rho* Spearman correlation coefficient.

A control group consisted of healthy individuals without substance use disorders and significant circulatory complications ($n = 28$). These participants were matched for age, sex, and BMI relative to patients with substance use disorders, and were recruited from a cohort of volunteers working in various capacities at the Regional University Hospital of Málaga (Málaga, Spain).

Eligibility criteria

A convenience sample was selected based on the diagnosis/type of substance use disorder (i.e., CUD and/or AUD), as well as the presence or absence of cardiovascular complications [e.g., hypertension (systolic ≥ 130 mmHg or diastolic ≥ 80 mmHg), atherosclerosis, prior stroke, coronary artery disease, aortic disease, valvular heart disease, thrombosis, arrhythmias, heart failure, and other vascular diseases]. Participants with congenital cardiovascular conditions were excluded.

Participation was voluntary, and all participants had to meet the following inclusion and exclusion criteria. Inclusion criteria included: being 18–65 years old; a diagnosis of lifetime CUD in the cocaine group; a diagnosis of lifetime AUD in the alcohol group; and no medical history of circulatory and cardiovascular diseases or problematic substance use in the control group. Exclusion criteria were: comorbid substance use disorders in the cocaine group, except for AUD; comorbid substance use disorders in the alcohol group (excluding nicotine use disorder); less than two weeks of abstinence from any drug, except for nicotine and caffeine; a medical history of chronic inflammatory diseases (excluding cardiovascular diseases) and/or infectious diseases; severe mental disorders that precluded evaluation; and pregnancy or breastfeeding. Control subjects were matched with patients in terms of age, BMI, and sex to facilitate appropriate group comparisons.

Ethics statements

Written informed consents were obtained from each participant after a complete description of the study. The experimental protocols for recruitment were approved by the Ethics Committee of the Andalusian Health Service (Portal de Ética de la Investigación Biomédica de Andalucía-PEIBA, Consejería de Salud y Familias, Junta de Andalucía) (code: 0813-N-23//PI22/01833) in accordance with the Ethical Principles for Medical Research Involving Human Subjects adopted in the World Medical Association Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and Recommendation No. R (97) 5 of the Committee of Ministers to Member States on the Protection of Medical Data (1997), and Spanish data protection act [Regulation (EU) 2016/679 of the European Parliament and of the Council 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). All collected data were assigned unique code numbers to ensure privacy and confidentiality.

Clinical assessments

Sociodemographic and clinical data pertaining to substance use disorders were gathered from the participants using various psychiatric interviews based on the characteristics of each group. Patients in the cocaine and alcohol groups underwent assessment with the Spanish version of the Psychiatric Research Interview for Substance and Mental Disorders (PRISM), a semistructured interview based on DSM-IV-TR criteria known for its strong psychometric properties in assessing substance use disorders and common comorbid psychiatric conditions in individuals with substance addiction[43,44]. The total number of DSM-IV TR criteria for substance abuse and dependence was utilized as a severity index for CUD and AUD, with adaptations made to align with DSM-5 criteria. Specifically, the legal problems criterion in DSM-IV-TR was replaced by the craving criterion in DSM-5[45].

In contrast, control subjects underwent assessment with the Spanish version of the Composite International Diagnostic Interview (CIDI) to detect of psychiatric disorders[46]along with PRISM module 1 (Overview for sociodemographic variables)[43]. All study participants were evaluated by trained and experienced psychologists.

Blood collection and plasma preparation

Blood extractions were conducted under standardized conditions by experienced nurses in the morning after and 8–12 h fast. Venous blood samples were collected into 10-mL K_2 EDTA tubes (BD, Franklin Lakes, NJ, USA), and plasma was obtained by centrifugation at 2200×g for 10 min at 4 °C. Prior to centrifugation, each blood sample underwent rapid antigen detection tests for HIV, hepatitis B, hepatitis C, and COVID-19. Infected samples were handled and excluded according to laboratory safety protocols. Plasma samples were logged and stored at – 80 °C until further analysis.

Determination of cardiac troponins

Plasma concentrations of cardiac troponins cTnT and cTnI were measured using human 96-well enzyme-linked immunosorbent assay (ELISA) kits with high sensitivity and excellent specificity: ELISA kit for Troponin T Type 2 (TNNT2) (Product No. SED232Hu 96 Tests, Cloud-Clone Corp., Katy, TX, USA) and ELISA kit for Troponin I Type 3 (TNNI3) (Product No. SEA478Hu 96 Tests, Cloud-Clone Corp., Katy, TX, USA). According to the instruction manuals, the microplates provided in these kits were pre-coated with an antibody specific to cTnT or cTnI. For each high-sensitive ELISA kit, 100 µL of standards or samples were added to the appropriate microplate wells with a biotin-conjugated antibody specific to cTnT/cTnI. Next, Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. After 3,3′,5,5′-tetramethylbenzidine (TMB) substrate solution was added, only those wells that contained cTnT/cTnI, biotin-conjugated antibody and enzyme-conjugated Avidin exhibited a change in color. The enzyme-substrate reaction was terminated by the addition of H_2SO_4 solution, and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentrations of cardiac troponins in the samples (pg/mL) were then determined by comparing the optical density (OD) of the samples to the standard curve. The spectrophotometer used was a VersaMax Tunable Micropate Reader (Molecular Devices, LLC, San José, CA, USA) and raw data were analyzed using SoftMax Pro Software 5.4 (Molecular Devices, LLC, San José, CA, USA). All samples were run in duplicate, and a standard curve was included in each ELISA microplate.

The human TNNT2 ELISA kit indicated a detection range of 15.6 to 1000 pg/mL (standard curve) and a sensitivity < 6.4 pg/mL. The human TNNI3 ELISA kit indicated a detection range of 31.2 to 2000 pg/mL (standard curve) and a sensitivity < 11.3 pg/mL. For both high-sensitive ELISA kits, the coefficients of variation for intra-assay and inter-assay were < 10% and < 12%, respectively.

Determination of inflammatory mediators

Determination of IL-β, TNF-α, and CX_3CL1

Plasma concentrations of IL-1β, TNF-α, and CX_3CL1 (fractalkine) were measured using Invitrogen ProcartaPlex Immunoassays (Thermo Fisher Scientific, Waltham, MA, USA) on a Luminex 200 Instrument System (Thermo Fisher Scientific, Waltham, MA, USA) at the Proteomics Unit of the Central Research Support Services, University of Malaga. A human 3-ProcartaPlex panel (catalog #: PPX-03, Mix & Match 96-well panel) was configured to simultaneously detect IL-1β, TNF-α, and CX_3CL1. The measurements of these analytes were conducted using 25 mL of plasma following the manufacturer's instructions. Raw data (mean fluorescence intensity) were obtained after a plate read time of 60 min. Plasma concentrations were expressed in pg/mL or ng/mL. Assay sensitivity and standard curve range for each analyte were as follows: 0.2 pg/mL and a range of 2.44 to 10,000 pg/mL for IL-1β (catalog #: EPX01A-10224-901); 0.4 pg/mL and a range of 8.54 to 35,000 pg/mL for TNF-α (catalog #: EPX01A-10223-901); and 20.5 pg/mL and a range of 2.08 to 8500 pg/mL for CX_3CL1 (catalog #: EPX01A-12121-901). The coefficients of variation for inter-assay and intra-assay were as follows: <5% and 8.9% for IL-1β; 7.1% and 6.5% for TNF-α; and 7.2% and 6.4% for CX_3CL1.

Determination of sST2

The quantitative determination of sST2 was performed in the biomedical research laboratory using a sandwich-type monoclonal immunoassay in a 96-well plate format (Presage ST2 Assay kit from Critical Diagnostics, San Diego, CA, USA). Diluted plasma samples were loaded into designated wells coated with anti-ST2 antibodies and incubated for 60 min with shaking. Subsequent steps included repeated washing with 1× wash buffer and incubation procedures after the addition of anti-ST2 biotinylated antibody reagent and working streptavidin-HRP conjugate reagent into each well. Analytes were then detected by adding TMB reagent and stop solution, with the resulting signal measured at 450 nm. The soluble ST2 assay exhibited a measurement range of 2.35–200 ng/mL with a limit of detection of 1.31 ng/mL. The coefficients of variation for inter-assay and intra-assay were 4% and < 6%, respectively.

Commercial controls for sST2 were prepared at two concentrations: one within the normal reference range (18.8–35 ng/mL) and the other within the concentration range observed in individuals with cardiac disease (65.3–105 ng/mL) (Presage ST2 Assay Control kit from Critical Diagnostics, San Diego, CA, USA). Control samples were analyzed using the same protocol as the clinical test samples.

Statistical analysis

A priori sample size calculations were conducted using G*Power 3.1.9.2 for ANCOVA (fixed effects, omnibus, one-way), targeting an effect size of f = 0.35 (moderate-to-large), α = 0.05, and power = 0.80. A minimum sample size of 84 participants was determined to detect group differences while adjusting for covariates. We also considered potential dropouts based on eligibility criteria to ensure adequate power across all comparisons.

Data in tables are presented as number and percentage [*n* (%)], mean and standard deviation (mean ± SD), or median and interquartile range [median (IQR 25–75%)] depending on variable type and distribution. For molecular determinations (i.e., cardiac troponins and inflammatory mediators), all samples were run in

duplicate. For values below the detection limit but above background, concentrations were imputed as half the minimum value interpolated from the standard curve[47,48].

Group differences in categorical variables were analyzed using the Fisher's exact test or chi-square test (χ^2 statistic). For continuous variables with non-normal distributions, comparisons were performed using the Mann–Whitney U or Kruskal–Wallis H tests.

ANCOVA (*F* statistic) was used to assess the main effects and interactions of categorical factors [i.e., primary substance use (cocaine, alcohol, and control), lifetime substance use disorder diagnosis (CUD, AUD, CUD + AUD, and control), and cardiovascular diagnosis (CV, non-CV, and control)] on plasma concentrations of cTnT and cTnI while controlling for age, BMI, and sex as covariates. Because plasma concentrations of cardiac troponins showed a positively skewed distribution, raw data were $\log_{10}$-transformed to approximate a normal distribution and to ensure statistical assumptions of the ANCOVA. The estimated marginal means and 95% CI of the $\log_{10}$-transformed troponin concentrations were back-transformed and are presented in figures. Post hoc multiple comparisons were adjusted using the Sidak's correction test.

Correlation analyses between troponin levels ($\log_{10}$-transformed data) and relevant variables (i.e., age, BMI, DSM-5 criteria for substance use disorders and abstinence duration) were performed using the correlation coefficients of Pearson (*r*) and Spearman (*rho*) with continuous and categorical variables, respectively.

All statistical analyses were performed using the GraphPad Prism version 5.04 (GraphPad Software, San Diego, CA, USA), and IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA). *p*-values with the corresponding test statistics and degrees of freedom were reported in the Results section. A two-tailed p-value < 0.05 was considered statistically significant.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

O.P.-P., M.F.-L., N.R.-O., and J.J.R.-R. recruited participants based on eligibility criteria; O.P.-P. collected blood samples; J.S.-R., A.C.-D., D.R.-G., and A.I.M.-R. performed clinical characterization and measured cardiac troponins; D.M.-V., L.S.-M., and L.M.-C. measured inflammatory mediators; O.P.-P., and F.J.P.-M. conducted statistical analyses; F.R. de F., and M.J.-N. contributed to the interpretation of results; A.S., J.R.-C., and F.J.P.-M. drafted the manuscript; A.S., J.R.-C., and F.J.P.-M. conceived and designed the study. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to J.R.-C. or F.J.P.-M.