**Association between poly-substance use and substance use disorder treatment non-completion admitted to multiple treatments between 2010-2019 in Chile**

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**ABSTRACT**

**Background**: Evidence on the influence of reporting polysubstance use (PSU) at admission on substance use treatment (SUT) completion is limited, especially outside the Global North. Most studies exclude patients reporting PSU, restricting their applicability to real-world settings. Therefore, determining the role of reporting PSU in treatment non-completion is crucial to improve treatment for these groups.

**Methods**: This comprehensive retrospective cohort study used adult treatment records from the Chilean National Substance Use Agency (2010–2019) of 13,317 individuals with multiple treatments (30,988 episodes). The primary outcome was SUT non-completion (vs. completion). Relative risk (RR) and 95% confidence intervals (95%CI) of non-completion by reporting PSU were obtained through Poisson general estimating equations using inverse intensity weighting and adjusting for sociodemographics, mental health and substance use patterns. Analyses were stratified by baseline treatment settings and homogeneity of associations was tested. Weights were derived from a Cox proportional hazards model of treatment visit intensity, using lagged covariates to address dependencies. Two models were conducted: for the first treatment episode (with no prior data), lagged dichotomized categorical covariates were fixed to either 0 (lag0) or 1 (lag1), and log-scaled previous days in treatment were set to 45 or 90 days, respectively. Sensitivity analyses included alternative modelling approaches and examined the role of alcohol as a secondary substance.

**Results**: The association between PSU and non-completion varied across treatment settings (Cochran's Q lag0= 14.24, p= 0.007; Cochran's Q lag1= 13.32, p= 0.010). Non-completion risk was higher in patients reporting PSU in general population intensive ambulatory (RRlag0=1.04 95%CI 1.01-1.07; RRlag1=1.04 95%CI 1.01-1.08) and in women-only residential settings (RRlag0=1.15 95%CI 1.06-1.25; RRlag1= 1.13 95%CI 1.04-1.22) vs. patients not reporting PSU. Sensitivity analyses supported these findings, although attenuated associations between PSU and treatment non-completion.

**Conclusions**: Reporting PSU was associated with a modest increase in non-completion risk, especially in specific treatment settings. This study, one of the few from outside the Global North, underscores the need for tailored interventions for patients reporting PSU. These insights can guide policies and clinical practices to address PSU complexities and improve SUT outcomes, enhancing the relevance and applicability of PSU-related research in diverse populations.

**Keywords**: Polysubstance use; Substance use; Treatment non-completion; Administrative data; Chile.

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Abstracts should be 350 words or fewer, structured into sections describing the Introduction, Methods, Results, and Conclusions. Do not include in-text citations in the abstract.

* All figures (include relevant captions) in separate files
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# INTRODUCTION

Polysubstance use (PSU) refers to the concurrent or sequential use of more than one substance, either unintentionally or intentionally (Bunting et al., 2023; Quek et al., 2013) ). People with substance use disorders (SUD) often engage in PSU during their lifetime (Connor et al., 2014). Importantly, individuals with PSU are a high-risk population due to higher mortality rates (Gjersing & Bretteville-Jensen, 2018), increased risk of relapse (Chen et al., 2019; Hassan & Le Foll, 2019), and reduced responsiveness to substance use treatment (Bonfiglio et al., 2022). They also exhibit other detrimental features such as risky sexual behavior (Daskalopoulou et al., 2014; Sewell et al., 2017), violence (Choi et al., 2022; Steele & Peralta, 2020), and psychiatric comorbidities (Mefodeva et al., 2022). Over the last three decades, evidence has shown a significant increase in the number of patients with PSU in high-income countries from North America, Europe, and Oceania (Bonfiglio et al., 2022), highlighting the relevance of studying this topic. A meta-analysis of Global North studies on cocaine use found that over 70% of cocaine users concurrently consumed alcohol, and between 38% and 64% reported concurrent marijuana use (Liu et al., 2018). However, there remains a knowledge gap regarding the prevalence of PSU in the Global South.

Moreover, evidence on the long-term consequences of reporting PSU on treatment outcomes is limited and mixed. Most studies have focused on the association between completing SUD treatment and long-term benefits, such as a lower risk of readmission to treatment (Ruiz-Tagle Maturana et al., 2023) and lower risk of relapse (Andersson et al., 2019). The lack of research on PSU is partly explained because most studies have focused on individual substances in isolation and have considered multiple substance use history as an exclusion criterion for clinical studies on treatment effectiveness (Bonfiglio et al., 2022). Regarding treatment outcomes, some studies have found a lower likelihood of treatment completion among patients reporting PSU (Andersson et al., 2021; Levola et al., 2021), while others have found no association (Andersson et al., 2018) or higher completion rates (Basu et al., 2017). Therefore, it is crucial to determine the role of reporting PSU, including the patterns of PSU (Bhondoekhan et al., 2023; Price et al., 2023), in treatment completion to improve treatment effectiveness and research translatability (Crummy et al., 2020).

Moreover, the role of PSU in treatment effectiveness should be understood in the context of a chronic condition in which a proportion of patients with SUD will transition across multiple treatments during their lifetime (Bórquez et al., 2024; Fleury et al., 2016). Patients with persistent SUD show different characteristics from those who no longer have a disorder after a single treatment or without any treatment (Beaulieu et al., 2022). The latter requires developing empirical strategies to account for explanations other than causal associations (e.g., confounding). This presents a methodological challenge, as studies on the relationship between PSU and treatment outcomes have overlooked these complex dynamics.

Additionally, these treatments are irregularly spaced but not random, as the time between treatments might be related to biopsychosocial and treatment-related factors. Hence, patients with worse outcomes in previous treatments might have different treatment intensities in the future, which may also explain treatment outcomes, such as completion or dropout (Hansen et al., 2020; Vázquez-Real et al., 2022). Observing individuals more frequently due to their specific characteristics, practices, contexts, or treatment trajectories can lead to under- or overestimation of the association between PSU and treatment outcomes. However, limited research has considered this potential bias.

Thus, this study aimed to estimate the association between having reported PSU and treatment non-completion (i.e., treatment dropouts or spelled by misconduct) among adult patients admitted to multiple SUD treatment programs in Chile from 2010 to 2019, taking advantage of a large and high-quality administrative dataset that includes all treatment episodes of people with public health insurance (~80% of the population) since its creation in 2010 up to 2022 (Mateo Pinones et al., 2022).

* 1. The Chilean context

In Chile, treatments for adults with SUD are delivered in residential, intensive ambulatory, and basic ambulatory settings. Residential settings have a planned duration of one year, and are offered from five to seven days a week with at least five weekly interventions, while intensive ambulatory have a duration of six to eight months, with weekly sessions that have a duration of six hours and up to four interventions. These also are divided into treatments for the general population and women-specific treatments (i.e., with tailored needs often directed to pregnant women or having children), but basic ambulatory settings are only available within general population programs. Like several Latin American countries and most South American nations, Chilean treatment services receive mostly patients with alcohol use disorder, disorders related to the use of cocaine and cocaine base paste, cannabis, and pharmaceutical products, with a relatively lower proportion of patients using opioids and injecting drug use (Ruiz-Tagle Maturana et al., 2023). Likewise, PSU is frequent in the Chilean population. A study conducted in a Chilean hard-to-reach population that used cocaine base paste found that 47–66% had PSU (Olivari et al., 2022). Findings from the Chilean Budgetary Office study support the need for further research to determine whether treatments effectively address characteristics such as PSU behaviors in a context where two out of three patients report PSU (DIPRES, 2017).

# MATERIAL AND METHODS

* 1. Setting and participants

A retrospective cohort study using administrative records of adult patients (+18 years old) with ongoing SUD treatments from 2010 to 2019. Censoring occurred after the date of data retrieval (November 13, 2019), after an outcome event, or when a patient left the cohort with no other outcomes. Patients with only one treatment episode were excluded (See Supplemental Section 1 for details). To account for variability by treatment setting, we stratified the analysis by baseline treatment: basic ambulatory (n=4,360), intensive ambulatory for the general population (GP) (n=4,998), GP residential (n=2,178), women-only (WO) intensive ambulatory (n=745), and WO residential (n=1,036). After excluding records of ongoing treatments and referrals outside the treatment network, 72,404 patients with 90,075 treatments were selected. In the total sample, 82% had one treatment episode, whereas 1% had more than three. We focused on patients who received more than one treatment, identifying 13,317 patients and 30,988 observations. This study was approved by the Griffith University Human Research Ethics Committee (GUHREC GU Ref. No: 2022/919).

* 1. Variables

The exposure variable was PSU at each admission, based on the presence of primary and secondary substances that met the criteria for SUD, evaluated in one or more clinical interviews (Crummy et al., 2020; Font-Mayolas & Calvo, 2022).

The outcome variable was SUD treatment outcome/non-completion (1=dropout or spelled by misconduct; 0=completed treatment). In addition, the models were adjusted for various baseline confounding variables related to substance use, demographics, and social factors.

The following covariates registered at admission to treatment were included in the model assessing the association between reported PSU and treatment non-completion status: age, birth year (to capture potential cohort effects), primary substance of the initial diagnosis (cocaine hydrochloride, cocaine base paste, marijuana, and other substances), psychiatric comorbidity (confirmed comorbidity or diagnosis unknown or under study), daily frequency of primary substance use, occupational status (inactive or unemployed), primary substance (cocaine hydrochloride, cocaine base paste, marijuana, and other substances), and biopsychosocial compromise. The biopsychosocial compromise is a holistic severity classification from clinical assessments that considers factors such as withdrawal symptoms, motivation to change, substance use patterns, social environment, and health symptoms. For further information about covariates, review Supplemental Section 2.

* 1. Missing data

Given the complex longitudinal structure of the data, a random-forest-based imputation was conducted using the *missRanger* package. Three hundred trees were set with five candidate values of predictive matching (thus aiming for plausible imputations given predictor values), with a maximum of 50 iterations per chaining step. This imputation procedure may circumvent the specification of interactions or nonparametric relationships and handle collinearity between imputation variables (Hong & Lynn, 2020; Sheetal et al., 2023).

* 1. Bivariate analyses

Differences between patients reporting and not reporting PSU at baseline were quantified using standardized mean differences (SMD). Chi-square (χ2) were employed to compare the proportion of patients by baseline treatment setting, PSU and treatment completion.

Incidence rates (IR) were calculated per 1,000 person-months to explore the crude association between reporting PSU and treatment non-completion while accounting for heterogeneous follow-up times.

* 1. Model adjustment

Marginal regression models were fitted to estimate the relative risk (RR) and 95% confidence intervals of non-completing SUD treatment among patients with or without PSU at admission using generalized estimating equations (GEE), assuming a Poisson distribution with a log-link function and an independent covariance structure (Grafféo et al., 2018). The statistical significance level was p value <0.05.

Given that data collection was based on administrative records with varying frequencies of patient admissions and follow-up periods, the irregular timing of assessments was examined (See Supplemental Section 3). To address the irregular patterns of admission to treatment and the informative differences therein, GEE models were weighted using inverse intensity weights (IIW). Intensities were measured through Cox proportional hazards model to account for the time-to-event (e.g., remaining in treatment or being readmitted) as a counting process, predicted by covariates of the previous treatment episode. For the initial treatment episode where no previous information was available, lagged dichotomized categorical predictors (through *one hot encoding*) were fixed to either 0 (*lag0*) or 1 (*lag1*), and log-scaled continuous covariates of previous days in treatment were fixed to reference values of 45 or 90 days, respectively. These fixed covariate values allowed modelling different baseline scenarios (See Supplemental Section 4 for model specification).

Heterogeneity tests were performed across treatment setting strata to examine effect measure modification in ratio metrics (Kaufman & MacLehose, 2013).

* 1. Sensitivity analyses

Sensitivity analyses were conducted through a traditional GEE model without weights. Also, to account for overdispersion of PSU reports, models with Negative Binomial distributions were tested using the Quasi-likelihood Information criterion for model selection. A third sensitivity analysis used traditional GEE model without weights, and decomposing PSU status into three groups: patients showing PSU with alcohol as their secondary substance at admission, patients with PSU without alcohol as their secondary substance, and patients without PSU (See Supplemental Sections 5 & 6).

All analyses were performed in R v. 4.1.2 (R Core Team, Vienna).

* 1. Data and code availability

Code & markdowns are available here: bit.ly/4cE8gyf.

# RESULTS

* 1. Characteristics of the study sample

Several key differences were notable among the individuals who reported PSU. In terms of demographics at baseline, patients with PSU, when compared to patients who reported single substance use, had their first admission to treatment earlier in life. In addition, a higher percentage of the participants were unemployed. Regarding substanceuse at baseline, patients with PSU were more likely to report using cocaine paste and hydrochloride cocaine instead of alcohol as the primary substances that led them to treatment. In terms of the type of initiation substance, fewer started with alcohol, whereas more began with marijuana. In terms of other health information at baseline, severe biopsychosocial compromise was more frequent among patients with PSU. These differences led to adjust for covariates to estimate the relative risk of treatment non-completion between patients who reported PSU and those who did not (Table 1).

* 1. Prevalence and incidence of PSU and treatment completion

Among patients with one treatment, 72% reported PSU, however, when examining patients with multiple treatment episodes, 91% reported PSU in at least one treatment episode. This association was also evident looking at the proportion of incomplete treatments. Specifically, 71% of patients with only one treatment did not complete it, whereas 92% of the patients with multiple treatments had at least one episode with a non-completion status. Focusing on patients with multiple treatment episodes (Figure 1), data suggest varying strength and direction of the association of PSU and treatment completion between treatment settings, indicating that a common association may be unreliable (Woolf-test χ2(4)= 13.74, p= 0.0082). Patients reporting PSU had a slightly higher proportion of non-completion compared to those without PSU. This difference was more notable among patients in women-specific residential settings (74% vs. 63%) (χ2(4)= 22.46, p< 0.001). Patients in baseline basic ambulatory settings showed the highest percentages of non-completion (80% in patients with PSU and 74% in patients with single substance use) (Post-hoc χ2 residuals= 8.07, p<0.001), followed by patients in general-population intensive ambulatory settings (Post-hoc χ2 res.= 3.61, p=0.003). In contrast, patients in general-population (Post-hoc χ2 res.= -11.07, p<0.001) and in women-specific residential (Post-hoc χ2 res.= -5.05, p<0.001) settings showed lower non-completion (χ2(4)= 177.64, p< 0.001). Also, the greatest proportion of patients with PSU was found in residential general-population (84%; Post-hoc χ2 res.= 8.78, p=0.028) and in women-specific (82% Post-hoc χ2 res.= 2.99, p=0.028). In contrast, the lowest was in basic ambulatory settings (Post-hoc χ2 res.= -12.30, p<0.001; χ2(4)= 194.31, p< 0.001).

However, a lower incidence of non-completion was observed in patients who reported PSU at admission. The incidence of at least one non-completion episode per patient followed from the first admission until the censoring date (November 2019), was lower in patients who reported PSU at admission to the first treatment (11.6 95%CI 11.3, 11.8 per 1,000 person-months) compared to patients who did not report PSU (13.2 95%CI 12.6, 13.8). Similarly, the incidence of non-completion at the first admission was lower among patients who reported PSU at admission to the first treatment (9.9 95%CI 9.7, 10.1) versus patients who did not report PSU (11.3 95%CI 10.8, 11.9). When focusing longitudinally on patients who had at least one treatment in which they reported PSU, we see that rates of at least one non-completion were lower in this group (11.6 95%CI 11.4,11.9) compared to patients who did not report any PSU (13.9; 95%CI 13.1, 14.8). This trend was also observed when looking at the incidence of non-completion at the first treatment episode alone (10.0 95%CI 9.8,10.2 versus 11.9 95%CI 11.1, 12.6) (Table 2).

* 1. Marginal longitudinal association between Polysubstance use at admission and treatment outcome

The association between polysubstance use and treatment non-completion varied significantly across treatment settings (Cochran's Qlag0 [lagged covariate values fixed at 0]= 14.24, p= 0.0066; Cochran's Qlag1 [lagged covariate values fixed at 1]= 13.32, p= 0.0098). According to Table 3, we found a modest association between polysubstance use at any admission to treatment and treatment non-completion among users in intensive ambulatory settings for the general population (RRlag0=1.04 95%CI 1.01-1.07; RRlag1=1.04 95%CI 1.01-1.08). Also, the risk was at least 13% higher for residential settings exclusive to women (RRlag0=1.15 95%CI 1.06-1.25; RRlag1= 1.13 95%CI 1.04-1.22).

* 1. Sensitivity analyses

The associations between polysubstance use (PSU) and treatment non-completion were stable across models, with intervals overlapping with the null for intensive ambulatory settings for women and residential settings for the general population. Associations without inverse intensity weights were almost equal to the main analyses in terms of direction and strength of association (Table 3). One model for basic ambulatory settings showed a modest significant association (RR=1.04 95%CI 1.01-1.07). The association weakened in general population intensive ambulatory settings, especially with marginal models with inverse intensity weights from an intensity model with stratified follow-up and lagged covariates fixed at 1 (RR=1.01 95%CI 0.98-1.05). In women-specific residential settings, only the marginal model with inverse intensity weights from an intensity model stratified by follow-up with lagged covariates fixed at 1 overlapped the null (RR= 1.09 95% CI 0.99-1.20), although both settings maintained a positive direction (See Supplemental Table S5).

Distinguishing between patients reporting PSU with and without alcohol at admission as the secondary substance of concern showed interesting results (See Supplemental Table S6). In women-only residential settings, both groups showed associations with alcohol (RR= 1.14 95%CI 1.06-1.23) and without alcohol (RR= 1.14 95%CI 1.05-1.24). Only those with alcohol use as a secondary substance showed significant associations in general population intensive (RR=1.10 95%CI 1.07-1.14) and basic ambulatory settings (RR=1.08 95%CI 1.05-1.12). Notably, in general population residential treatments, PSU with alcohol as a secondary substance had a protective role (RR=0.89 95%CI 0.83-0.94).

# DISCUSSION

Our findings revealed a significant association between reporting PSU at admission and the risk of treatment non-completion among patients admitted to SUD treatment programs in Chile between 2010 and 2019. Specifically, the risk of non-completion was modestly higher in intensive ambulatory settings for the general population and in women-only residential settings. However, this association was not consistent across all treatment settings, indicating variability in how PSU influences treatment outcomes, depending on the type of treatment program. Sensitivity analyses supported these findings, showing stability in the associations across the different model specifications and treatment settings. After comparing patients reporting PSU versus those reporting single substance use regarding treatment completion, we found notable differences in treatment outcomes. The association between reporting PSU and treatment non-completion seems robust to different model specifications, suggesting that despite their complex clinical profiles, patients with PSU are more likely to abandon treatment or be discharged due to misconduct, regardless of the episode.

A more detailed analysis distinguishing between PSU with alcohol and PSU without alcohol as a secondary substance revealed that PSU with alcohol as a secondary substance was associated with treatment noncompletion across all treatment setting at baseline, except among patients in women-specific intensive-ambulatory settings. This adds support to paying attention to alcohol use, a substance shown to be associated with adverse health outcomes, though widely accepted and normalized by social customs in Latin America (Krawczyk et al., 2021). Interestingly, among patients in general-population residential treatments having alcohol as a secondary substance, appeared to be protective against treatment non-completion. If alcohol is the secondary substance, the other groups (including the reference group) should necessarily display a higher proportion of individuals who identified alcohol as their primary substance. This finding is in line with research conducted in general population surveys in the US, where PSU with heavy drinking patterns was associated with lower negative mental, physical and social functioning outcomes (Tucker et al., 2021). Our results indicate that while PSU poses challenges, the specific context and characteristics of the treatment setting play a critical role in determining outcomes, highlighting the need for tailored interventions to forestall future negative consequences (Manning et al., 2017).

However, our findings suggest gender differences regarding the implications of alcohol for PSU. Women reporting PSU with and without alcohol as a secondary substance had greater risk of non-completion among patients in women-specific residential settings. Women in residential treatments tend to have a severe substance use profile that develops rapidly. Additionally, women with severe alcohol use disorder are prone to prolonged PSU (Stephenson et al., 2022). which in turn is associated with worse treatment outcomes, regardless of the substances used. We suspect that gender roles may help explain the observed differences, as women in the Latin American context, particularly mothers, may face heightened stigmatization for not fulfilling traditional family roles due to the legacy of colonialism and christianity (Mascayano et al., 2016).

Regarding the reasons for non-completion, a study conducted in Latin America found that the main reasons for abandonment were “not accepting the rules of the institution,” “lack of money”, and “not feeling comfortable with the facilities” (Gómez-Restrepo et al., 2017). An impact evaluation of treatment conducted in Chile found a lack of time to assist (in ambulatory treatments) and a sense of well-being (DIPRES, 2017) as the main reasons for non-completion. Patients with PSU in specific treatment settings face heightened risks, a challenge shared across the region. This concern is illustrated by the QALAT project (Quality Assurance in the Treatment of Substance Use Disorders in Latin America and the Caribbean), conducted under the UNODC [United Nations Office on Drugs and Crime] initiative with data from 385 treatment centers in Bolivia, the Dominican Republic, Ecuador, Guatemala, Mexico, and Panama. Among the key findings is the need to broaden the range of services offered, ensuring a more effective response to individuals’ needs.

Bivariate analyses highlight the various demographic and clinical characteristics that differentiate patients reporting PSU from those using a single substance. Patients with PSU tended to be younger, and were more likely to be unemployed compared to single-substance users. Additionally, the expansion of treatment supply, the broader reach of SENDA into more sectors and the healthcare network, and a gradual reduction in the stigma associated with returning to treatment could also contribute to this pattern. The primary substances leading to treatment admission differed significantly, with PSU patients reporting cocaine hydrochloride and base paste as their main substances compared with alcohol. Moreover, severe biopsychosocial compromise is more prevalent among patients with PSU, underscoring the complex clinical profiles that require tailored interventions. Despite these differences, PSU at admission was associated with a lower incidence of non-completion than single substance use, suggesting that repeated treatment engagements might influence their overall treatment trajectory. We suspect that the continuity of substance use treatments considered in our study is often overlooked in other research, which has generally reported lower treatment responsiveness among patients with PSU (Bonfiglio et al., 2022).

We focused on patients with a persistent pattern of substance use disorder rather than a transient substance use disorder. These patients are characterized by repeated treatment episodes, varying periods of abstinence, and relapses leading to the resumption of moderate or problematic substance use, as highlighted in the literature (Beaulieu et al., 2022).

Although individuals reporting PSU had a higher cumulative prevalence of dropout or administrative discharge, their incidence of these outcomes per person-month was lower than that of patients not reporting PSU. This finding suggests that the former group may have had a longer observation period in the database, which could have influenced the association. Regarding secondary analyses, we observed that accounting for irregular assessment of patients with multiple treatments (i.e., different frequency of treatments and time between treatments) through inverse intensity weighting did not substantially change the associations between reporting PSU and treatment non-completion. Interestingly, some factors that we expected to be influential, such as PSU in previous treatments, specific primary substances at admission, and certain psychiatric comorbidities (Passos & Camacho, 2000), were found to have negligible or non-significant effects on treatment return rates. We suspect adjusting for biopsychosocial compromise and stratification by treatment setting would have captured the variability attributed to these factors and substantially attenuated these associations. Future studies should explore whether a causal conclusion can be drawn from these associations by employing other advanced causal inference methods.

This study had some limitations. First, the proportional intensity model that calculates IIWs imposes a proportional hazard assumption on assessment intensity. However, this assumption is debatable. Diagnosing proportionality in a Cox model with recurrent events can be quite challenging, and statistical tools might not account for changes in intensities due to possible changes in baseline risks for cumulative events, making interpretations of nonproportionality less straightforward (Royston & Altman, 2013). Tests based on Schoenfeld residuals are insufficient because contrasting the null hypothesis for changes as a function of time may not be entirely indicative of nonproportional hazards (Dickman, 2023). Even small violations can become apparent because of sample size (Keele, 2010). Additionally, given that the intensity model has prediction purposes (i.e., readmission), it can still be used effectively even if hazards are not proportional (Jardillier et al., 2022). However, the association described here may lack causal interpretation, given that the recurrent event process might be associated with the right censoring mechanism. For example, patients admitted for treatment on dates closer to administrative censorship or in ongoing treatments might have different characteristics that may change the inverse of susceptibility to recurrent treatments (Rytgaard & van der Laan, 2024).

# CONCLUSION

Our study showed that PSU at admission was associated with higher treatment non-completion rates in specific settings, notably in intensive ambulatory and women-only residential programs. These findings underline the need for tailored interventions to address the unique challenges of PSU patients with PSU. Additionally, demographic factors such as age and birth cohort significantly influenced treatment outcomes. This study provides valuable insights for improving SUD treatment programs in Latin America, emphasizing the importance of comprehensive data collection and personalized treatment strategies to enhance patient retention and completion rates.

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