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Treatment outcome and readmission risk among women in women-only versus mixed-gender drug treatment programs in Chile

--Manuscript Draft--

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Abstract:	Introduction: Traditional treatment programs for substance use disorder (SUD) tend to be male-dominated environments, which can negatively affect women's access to treatment and related outcomes. Women's specific treatment needs have led some providers to develop women-only SUD treatment programs in several countries. In Chile, women-only programs were only fully implemented in 2010. We compared treatment outcomes and readmission risk for adult women admitted to state-funded women-only versus mixed-gender SUD treatment programs in Chile. Methods: We used a registry-based retrospective cohort design of adult women in women-only (N= 8,200) and mixed-gender (N= 13,178) SUD treatment programs from 2010 to 2019. The study obtained data from the National Drug and Alcohol Service from Chile. We used a multistate model to estimate the probabilities of experiencing treatment completion, discharge without completion (i.e., patient-initiated discharge and administrative discharge), or readmission, as well as the likelihood of being readmitted, conditioned on prior treatment outcome. We adjusted models for multiple baseline characteristics (e.g., substance use, socioeconomic). Results: Overall, 24% of women completed treatment and 54% dropped out of treatment. The proportion of patient-initiated discharges within the first three month was larger in women-only than in mixed-gender programs (19% vs. 12%). In both programs, women who completed treatment were more likely to experience readmission at three months, and one and three years. In the long term, women in the women-only programs were more likely to complete treatment than women in mixed-gender programs (34% vs. 23%, respectively). The readmission probability was higher among women who previously completed treatment than those who had a discharge without completion (40% vs 21% among women in women-only programs; 38% vs. 19% among women in mixed-gender programs, respectively); no differences occurred in the risk of readmission between women-only and mixed-gender programs. Conclusions: In terms of treatment outcomes and readmission risk, women-only programs had similar results to mixed-gender programs in Chile. The added value of these specialized programs should be addressed in further research.
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Response to Reviewers:	Dr. Castillo-Carniglia: With assistance from two external reviewers, I have reached a decision to request a major revision of your manuscript JOSAT-D21-00326. Please resubmit within 30 days so that we can finalize the special issue. If you cannot resubmit within 30 days please withdraw your manuscript from the review process. I strongly support the reviewers' recommendations to clarify the terminology used to describe the types of discharge using terms like "treatment completed", "patient initiated discharge" and "discharged without completion". The introduction is relatively unfocused. Retain the first paragraph, delete the second, third and fourth paragraphs and continue with paragraph five "In Chile, ..." A table of the study variables and values will make the methods section more concise. Review 2 also suggests including details on how gender specific and co-ed services vary. Note also Reviewer 1's recommendations for restructuring the results section and changing the analysis. Comments from Review 1 follow. Review 2 is an attachment. Sincerely, Dennis McCarty co-editor JSAT international special issue Response Thank you for giving us the opportunity to revise our paper. In order to clarify the terminology used to describe the types of discharge, we decided to replace the term “therapeutic discharge” with “treatment completion” and the term “discharge without clinical advice” with “discharge without completion” as suggested by Reviewer #1. In this major revision, we reorganized the introduction according to reviewer’s suggestions, and concisely present relevant information on the characteristics of women with SUD within the broader literature. As suggested by reviewer #2, we also added more detailed information on gender-specific and co-educational services provided in publicly funded SUD treatment programs (page 6, paragraph 1). “The SUD treatment programs system implemented in Chile provides professionalized therapeutic interventions and services, including social support, psychotherapy (individual and in group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks the promotion of a safe and empathic therapeutic environment to address gender-specific content and develops social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997). In addition, the distinctive activities considered in women-only programs in Chile include co-educational services to enhance parental skills development, and the acquisition of skills to generate income. Women-only programs also play an

important role in coordinating with other social services (e.g., legal system, primary health care services) that are critical to the recovery and social integration of women with SUD (Consejo Nacional para el Control de Estupefacientes, 2007; Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol y Ministerio de Salud de Chile, 2018).
Finally, we also revised the methods and results sections to have a more clear and concise description of the variables, analyses and results.
A point-by-point response to reviewers comments is presented below.

Reviewer #1

Summary:

Below are some specific comments/questions for the authors which I have separated by section for clarity and organization.

General Feedback:
I would reconsider some of the terms used for the 3 categories -
"Therapeutic discharge" has a different meaning to me and may be confusing to readers though it is defined in the methods later on. It may be helpful to come up with a different term for the category of patients who completed their treatment course. Perhaps "treatment completion" of "planned discharge" (reference: Taylor JB, Beach SR, Kontos N. "The therapeutic discharge: An approach to dealing with deceptive patients." General Hospital Psychiatry 2017)

I would also reconsider the term "drop-out" as perhaps these patients had a reason for them that necessitated leaving treatment early though they may be wanted to continue (a sick child that needed to be cared for). I have seen the term "patient-initiated discharge" being used more which I think would be appropriate (as opposed to "against medical advice" - AMA). I think the term "discharged without clinical advice" used throughout the manuscript may be a translation attempt at "against medical advice" but as stated earlier would prefer the term "patient-initiated discharge" be used. Could also say "prior to treatment completion" as a way to distinguish between those that did complete treatment.

Response
As suggested and in order to clarify the terminology used to describe the types of discharge, we decided to replace the term “therapeutic discharge” with “treatment completion”, the term “discharge without clinical advice” for “discharge without completion”, and “drop-out” for “patient-initiated discharge”.

Reviewer comment
Highlights
Given the above general feedback I would rephrase these first 3 highlights.

Response
Highlights were re-written according to the new terms used throughout the manuscript (i.e., treatment completion and discharge without completion)

Reviewer comment
Abstract
No additional comments other than incorporating general feedback above

Response
Terminology was also updated in the abstract and throughout the manuscript.

Reviewer comment
Introduction
Overall, I think the introduction is well-written and organized and provides excellent context for the history and development of women only SUD treatment programs specifically in Latin America. I do think it would be helpful in this section to include background on the intersectional risk environment (micro and macro environment) and

experiences such as trauma, and sexual violence/intimate partner violence women who use drugs face. This will provide added context to why women who use drugs (WWUD) may prefer women-only spaces. This background could be incorporated on page 6 in the paragraph starting with "In Chile,…" as this includes information about rationale for women-only programs.

Some references to consider including/adding to the introduction:
- Ait-Daoud, N et al "Women and Addiction: An Update" Medical Clinics of North America 2019.
- Agabio R et al "Sex differences in substance use disorders: focus on side effects" Addiction Biology 2016.
- Collins AB et al "The Intersectional Risk Environment for People Who Use Drugs" Social Science and Medicine 2019.

Response
As suggested by the editor and reviewers, we modified the introduction and added background on risk environments and experiences of women who use drugs in Chile. New paragraphs (page 5, paragraphs 1 and 2) include evidence on the macro and micro level risk environments and experiences of women with substance use disorders in Chile (Collins AB et al., 2019).
“Under a risk environment perspective (Rhodes, 2009; Collins et al., 2019), social vulnerability of women with SUD is a product of a range of macro (economic, political, and social milieus) and micro-level environments (drug trafficking neighborhoods, intimate-partner violence, sex trade participation) that intersect with disadvantaged social locations producing increased risk (Collins et al., 2019).
Data from Chilean SUD treatment programs depicts the disadvantaged position of women with SUD, expressed in the lack of economic autonomy (i.e., income generation), housing instability, food insecurity, trauma/violence exposure, and stigmatization due to difficulties in accomplishing Latin American traditional gender roles, in which women are expected to be affectionate, submissive and a faithful spouse, mother and family caregiver, in contrast to the independent, polygamous and dominant role of the Chilean macho man (Cianelli et al, 2008; Hawkins et al., 2017). Accordingly, 45% of women admitted to public treatment programs reported being unemployed, and 29% reported unpaid work. Among women with co-occurring mental health problems, 70% reported being victims of interpersonal violence from their partners or other family members (Valencia-Recabarren, 2015). Results from a RDS-study on people who use cocaine base paste in Chile may be indicative of how structural environment and situated contexts in Chile affect women with SUD. For example, women from this study reported a total monthly income of USD$150 (USD$68 under the poverty line in Chile), which was 50% lower than the income reported by men (Instituto de Sociología de la Pontificia Universidad Católica de Chile, 2015). Women also reported more insecure housing conditions, and lower levels of education (Instituto de Sociología de la Pontificia Universidad Católica de Chile, 2015). In this context, the implementation of gender-specific services in Chile represents an effort to provide a therapeutic alternative that may better suit the needs of women with SUD”

Reviewer comment
Specific Feedback:
On page 4 "The 'telescoping phenomenon' in the course of SUD in women is well supported by evidence showing that, compared to men, women experience a faster progression from substance use to SUD than men (Becker et al., 2017; Keyes et al., 2010), and report health problems of greater severity such as trauma and psychiatric comorbidities (Becker et al., 2016)." I think the second half of this sentence is incorrectly phrased. Women have greater rates and severity of trauma and psychiatric comorbidities which increase their risk of developing SUD. I don't think Becker, 2016 is the best reference for health problems. I would recommend Ait-Daoud which discusses more rapid development of severe medical consequences such as alcohol related complications - alcohol-related liver disease, cardiac complications, etc. Agabio R. et al, is also an excellent reference to include here.

Response
As suggested by the editor and reviewers, we rewrote and reorganized the introduction, and removed the reference to the 'telescoping phenomenon' from the

paper. To characterize the distinctive characteristics of women's course of illness and related health problems we added a more detailed description based on the paper by Ait-Daoud et al, and Agabio et al (page 4 paragraph 2)
"Overall, women are less likely than men to use illicit drugs, tend to initiate substance use later in life, but experience a faster progression from substance use to dependence or abuse, and consequently to first treatment entry. This accelerated progression to SUDs is usually associated with more severe SUD-related problems (Ait-Daoud et al., 2019; Agabio et al., 2019). Over the last three decades though, the increased recognition of sex and gender differences in SUDs led to the implementation of women-only treatment programs in many countries (Schleifer & Pol, 2017)."

Reviewer comment
Some additional clarity on what is meant by treatment outcome would be helpful in the last paragraph or later on in the methods. Is this completion of treatment or does it include other outcome measures of interest like return to substance use, retention in outpatient treatment, etc.

Response
We use the term "treatment outcome" to refer to completion/end of treatment, which has two possible categories: "treatment completion" and "discharge without completion", which groups patient-initiated discharges and administrative discharges. This was clarified in the method section. We also use as study outcome treatment readmissions, though we do not refer to readmission as "treatment outcome". It is important to mention that substance use alone is not a sufficient cause for readmission, but it is a requirement to be readmitted to a treatment program. In the modeling process we use other relevant measures, such as time in treatment and time outside treatment. We are aware that other relevant measures could be of interest (e.g., physical and mental health outcomes, family functioning), but due to data availability and simplicity we only used treatment outcomes and readmissions. The latter was recognized as a potential limitation of our study (page 16, paragraph 3):
"Our analytic approach allows capturing only a part of a highly complex phenomenon which is influenced by several factors and that has multiple relevant outcomes apart from type of discharge and treatment readmission (i.e., social functioning, criminal offending, return to substance use, among others) that could not be considered in the analysis. In line with this, research on other intersecting dimensions, such as life experiences of gender-based violence and economic dependence, may contribute to the characterization of risk environments that may lead to treatment readmission"

Reviewer comment
Methods
Overall, after reading the supplemental information, I would consider pulling slightly more of what is in the appendix into the methods. The supplemental info is very well written and can help provide more information on model selection, parts of which do belong in the methods.

Response
We appreciate the reviewer's note regarding the utility of the supplemental material. As both reviewers requested, we incorporated several changes in the method section. These included an explanation of the encryption algorithm, how the registries on patient's admissions were collected, definition of referrals and right censoring for external referrals, tests for proportional hazards assumption, how we tested the violation of markovianity assumption, how we balanced the criteria used to choose each transition, the criteria used to determine the time points chosen, and the steps considered in the analysis (i.e., cumulative hazards, transition probabilities, expected lengths of stay).
A detailed description of each of these points is presented in our responses below.

Reviewer comment
Study design
What is an MD5 algorithm?

Response:
To clarify this we added the following sentence in section 2.1 (page 7 paragraph 1):
"All patient identification information was encrypted using an MD5 (Message Digest 5)

algorithm. The MD5 algorithm is widely used in security protocols to encrypt information, such as a personal identification number, into a 128-bits hash code (Jayawickrama, 2008)."

-Jayawickrama, W. (2008). Chapter 3 - An Introduction To Cryptography. In J. Liu, D., Caceres, M., Robichaux, T., Forte, D.V., Seagren, E.S., Ganger, D.L., Smith, B., Jayawickrama, W., Stokes, C. & Kanclirz (Eds.), Next Generation SSH2 Implementation: Securing Data in Motion (1st ed., pp. 41–64). Rockland, MA: Syngress Publishing. https://books.google.cl/books?id=4GVjngEACAAJ

Reviewer comment
I would move the sentence on complete data to your missing data section, unless you elaborate here what you mean re: complete data

Response
Indeed, the term "complete" was ambiguous and confusing. We decided to delete the following phrase: "with complete data", because we were meaning "imputed" data. Details of the imputation can be found after Figure S1 in the Supplemental Material.

Reviewer comment
Measures
Unclear what you mean for referrals here- referrals to treatment?

Response
We added the words "to another SUD treatment" to specify the type of referrals that were collapsed in the database and clarified that not every referral was collapsed. Additionally, we provided some examples of treatment transfers and external referrals outside SENDA's network in the first paragraph of section 2.2 (page 8):
"Referrals to another SUD treatment (i.e., treatment transfers) within the same treatment network (often suggested by the professional team of the center due to change of address, change of the treatment plan, or other justified reason) with fewer than 45 days of difference (...) Referrals outside SENDA's network such as primary or secondary health care facilities (e.g., psychiatric units, other health centers)..."

Reviewer comment
It would be helpful for international audiences to know more about the data collection- can you expand on what you mean by routine? Is this information that is excellently collected for every patient, or is this on a piece of paper, entered into computer systems later, and not always done? Or is there variation by center?

Response
We appreciate the opportunity to clarify data collection information. Centers are mandated to enter patients' information at admission, throughout the treatment process and discharge into an electronic system (SISTRAT); SENDA pays treatments only if they have complete data at admission and at least one therapeutic activity during the month. Most of SISTRAT's fields are required, otherwise the system is not allowed to save the information. The information filled in the SISTRAT is obtained through a baseline assessment interview. The clinical information (e.g., psychiatric comorbidity) is the result of a clinical appraisal of the treatment team, which includes an interview with a psychiatrist or physician with mental health experience, after one or more interviews with the patient. Electronic records do not replace the clinical chart, usually kept in paper. There may be a variation by center regarding the personnel in charge of filling the electronic records, or the timing at which this information is entered into the system, but centers have to routinely collect the data to proceed to payment.
Considering the above mentioned, we modified the start of the first paragraph in the section 2.2 (page 8, paragraph 1):
"All clients of a state-funded SUD treatment programs in Chile are interviewed at admission by treatment center professionals. Through this interview, the center's professionals gather information on the client's sociodemographic characteristics, health status, substance use patterns, among others, which are entered into the SISTRAT system. Clinical information stems from the appraisal from the treatment team and consultation with a psychiatrist or physician with mental health experience, if necessary. Centers must collect the data to proceed to payment."

Reviewer comment
You include a definition for therapeutic discharge- is this a definition you created for the analysis or is this determined by center staff? If done at the center, maybe describe how the definitions are actualized.

Response
This category —now called “treatment completion”— is determined by the center therapeutic team and registered in SISTRAT. We rephrased the third paragraph of section 2.2 (page 8) to make this clearer.
“According to SENDA’s guidelines, treatment completion is defined as a discharge after achieving the goals defined in the patient's individual treatment plan developed by the therapeutic team at admission”

Reviewer comment
I would take the categories for patient characteristics and either put them in a table describing what was in the survey, which would be helpful in an appendix, or put in paragraph form.

Response
As suggested, we put the variables used in paragraph form and added a Supplemental Table with a detailed description of each one: The new paragraph in section 2.2 reads (page 9, paragraph 1):
“We compared patient-level sociodemographic, substance use, health, and treatment characteristics of women in mixed-gender and women-only programs (i.e., age, educational attainment, have children, housing, biopsychosocial status, primary substance at admission, frequency of use of primary substance, co-occurring SUD, treatment duration, and treatment modality). See supplemental Table S1 for a detailed description of these variables.”
We situated the table in the supplemental material to not exceed the maximum number of tables/figures permitted in the journal’s author guidelines.

Reviewer comment
This does not need to go into the paper, but I'm curious why you didn't leave your continuous variables continuous (e.g. age)

Response
With the exception of age, SENDA registers patient’s information in predefined categories to minimize error when filling data into the SISTRAT records. For example, the frequency of use of the primary substance in the last 30 days is registered in predefined categories (from “No use/Less than 1 day per week” to “Daily”). We grouped ages into categories to be consistent with the age ranges generated by SENDA in their annual reports, making them more locally relevant and accessible to policy makers.

Reviewer comment
Appreciate the inclusion of evaluation of missing data here. Would be sure to clarify that the low rate of missing data is not because you only included people with complete data.

Response
We appreciate the opportunity to clarify this point. We used imputation methods to address missing data concerns, and used this imputed data in our analyses. As discussed in response to reviewer #1, we decided to delete the words "with complete data" in the first paragraph of the Section 2.1, hoping that this modification clarifies that the percentages of missing data shown did not correspond to people with only complete data, and instead are records reflected imputed data, as described.

Reviewer comment
It's really great to see the use of multistate model here to answer your research question- I think this is a real strength of this paper. It would be helpful to have more information about your decisions around model fit- I see that you chose a parametric model based on AIC- can you talk more about how you balanced AIC with visual inspection and extrapolation?

Response
We appreciate the positive feedback. As suggested, we expanded on the selection of parametric models for each transition in the Supplemental material, by adding a measure of root mean squared error (RMSE) of the differences between the smoothed hazard function and parametric models (Table S3), replacing Figure S1 for the comparison of hazard curves, and including a paragraph on how the different criteria was combined to select the best parametric model for each transition after the Table S3 (page 10, paragraph 1 and 2, in Supplemental Material).
“We chose the Gompertz distribution for the first and second transition, because this distribution provided a more reasonable extrapolation at 11 years, resembling most to the hazard curve, as seen in Figure S3, despite the Gompertz distribution showed the fifth and second best fit, respectively (AIC= 24,884 and AIC= 31,787). Considering that Generalized F & Generalized Gamma distributions showed convergence issues in the model that controlled for covariates, we selected the Log-normal distribution (AIC= 6,242).
Visual differences may seem difficult to appreciate for the fourth and fifth transitions. However, and despite this distribution was fourth in the AIC (but with negligible differences between the first six distributions), we chose Generalized gamma (AIC= 7,440) for the fourth transition because of the lower mean RMSE of both programs (see Table S3), and lower observed differences with smoothed hazard function. For the fifth transition, we chose Log-normal distribution despite being the third with lower AICs (AIC= 22,841) because of lower mean RMSE of both programs and lower observed differences with smoothed hazard function.”
In the manuscript we included the following sentence in the fourth paragraph of the section 2.3 (page 10, paragraph 3):
“The Kaplan-Meier survival curves and simple survival model were calculated using the survival package (Therneau T., 2021). The smoothed hazard function was estimated through the muhaz package (Hess & Gentleman, 2019).

Reviewer comment
For the transition probabilities- why not extrapolate from the adjusted models? Would just add a sentence here on why you chose to use intercept only models here (or consider adjusting). I would also just state here

Response
Intercept-only models were only used to determine the distribution for each transition, not to estimate the study results. Adjusted multistate models were used to calculate cumulative hazards for each transition, transition probabilities and lengths of stay in each state (results presented in section 3.1.1, 3.1.2 and 3.1.3 sections). In order to clarify this, we added a sentence in the third paragraph of the section 2.3 (page 10 paragraph 2):
“We checked whether the time spent in the previous state played an important role for intermediate states. As treatment duration (i.e., time in the baseline state) could affect the likelihood of readmissions, we used a semi-Markov multistate model that included the time spent in treatment (years in treatment). This multistate model is the result of the combination of the selected distributions for each of the transitions. These models were adjusted for all covariates listed in section 2.2 and detailed in Table S1 in the Supplemental Material. Based on two hypothetical patients, we first obtained the patient-specific instantaneous cumulative hazards of progressing from one state to another”

Reviewer comment
Really love the Markov approach here.

Response
Thank you.

Reviewer comment
Mention somewhere why you chose 3 months, 1 year and 3 years as your time points.

Response
The time-points used in our analysis were defined based on a consensus discussed between our research team and SENDA’s team professionals that are responsible for

treatment programs design and functioning in Chile.
The three months time-point was chosen based on empirical evidence suggesting that after three months under treatment, patients drastically increase their chances of completing treatment (Brorson et al 2013). The second time-point was chosen based on the expected average treatment duration (therefore, it's the time-point in which we expected to find the greater number of patients completing treatment), which is one year. Three years after treatment admission was also defined as a relevant time-point considering that this is the maximum expected treatment duration defined by SENDA's team professionals.
To clarify this, we added the following sentence in the manuscript (page 10, paragraph 1):
"We considered these three time points based on a consensus established between our research team and SENDA's team professionals that are responsible for treatment programs design and functioning in Chile."

Reviewer comment
Need discussion somewhere of model validation

Response
In our study, we are looking at events that occur in the treatment process, which include treatment outcomes and readmissions. Given that, we used the most parsimonious version as a starting point to guide future research. It is a way to implement a more complex modeling process beyond the time to a specific event of a standard survival model, allowing scaling other events and processes beyond a readmission. To this end, we tested for non-markovianity, proportional hazards assumption, adding the following sentence in the second paragraph of the section 2.3 (page 9 paragraph 3):
"The proportional hazards assumption in the Cox models was assessed visually and through a chi-squared goodness-of-fit test (more details in the Supplemental Material)."
Considering the above mentioned, we added a paragraph and a figure in the Supplemental Material to give a more detailed description of the decision to use standard parametric models instead of multistate models based on cox regressions (page 6, paragraph 1, in Supplemental Material):
"As seen in Figure S2, we did not see parallel trends in every transition, and the test indicated a significant deviation from expected proportionality in Admission to Treatment without completion ($X^2(df=1)=226.67$, $p<0.001$), Treatment completion to Readmission ($X^2(df=1)=10.34$, $p=0.001$), and Treatment without completion to Readmission ($X^2(df=1)=34.26$, $p<0.001$). Hence, we decided to select standard parametric distributions for each transition that do not solely rely on this proportionality assumption (Williams et al., 2016)"
Additionally, we tested multiple distributions (9) for each transition. In an effort to address another of your observations related to the lack of explanation in the methods section, we added more details about these procedures. Specifically, we added the following sentence in the third paragraph of the section 2.3 (page 10, paragraph 1):
"We checked whether the time spent in the previous state played an important role for intermediate states."
- Gray, J., Sullivan, T., Latimer, N. R., Salter, A., Sorich, M. J., Ward, R. L., & Karnon, J. (2020). Extrapolation of Survival Curves Using Standard Parametric Models and Flexible Parametric Spline Models: Comparisons in Large Registry Cohorts with Advanced Cancer. Medical Decision Making, 0272989X2097895. doi:10.1177/0272989x20978958
- Gibson, E. J., Begum, N., Koblbauer, I., Dranitsaris, G., Liew, D., McEwan, P., … Pritchard, C. (2019). Cohort versus patient level simulation for the economic evaluation of single versus combination immuno-oncology therapies in metastatic melanoma. Journal of Medical Economics, 1–1. doi:10.1080/13696998.2019.1569446

Results
Reviewer comment
Overall, this is strong. I would suggest cleaning up the results section to more clearly match the methods section, prespecifying analyses so they are not a surprise in the results and tightening up language.
I would try to make the writing in overall results section more clear- it's fairly wordy and complicated for conveying the least complicated part of the analysis

Reviewer comment
Transition intensities- not sure why using this terminology here.

Response
We made several changes to the results section, including a revision of the writing, changing subheading/terminology (e.g., replaced “3.1.1 Transition intensities” for “3.1.1 Cumulative hazards”), and made clear the correspondence with the steps described in the Method section.

Reviewer comment
Sentence "There were 21,378 women at admission"- when you refer to women who stayed in the same state, are these women who remain in treatment? Or women who were not in treatment?

Response
The 21,378 women encompass the whole sample, that is, with at least one treatment admission during the follow-up period. We modified the following sentence to avoid confusion about this (page 12, paragraph 1):
“There were 21,378 women with at least one treatment admission during any time point between January 1st, 2010 and November 13th, 2019; 16.4% (n= 3,516) remained in the same states up until the end of the follow-up period, mostly those admitted in 2018-2019, since they had a shorter follow-up period and thus a lower chance of completing their treatment, 56.1% had a discharge without completion, 24% completed treatment and 3.5% transitioned directly from admission to readmission”

Reviewer comment
I think overall, the results need to be reorganized. I would talk about the basic demographics, then the model transition probabilities, and then the estimates/outcomes- so for example would move the paragraph "As seen in Figure 2" to later after model transition probabilities. Though it's just a step in this analysis, the transition probabilities themselves are important information.

Response
We thank the reviewer for this important suggestion. We have edited the text so that the methods section now clearly matches the results section across statistical procedures. For example, we structured the results by first introducing the main characteristics of the sample, followed by the description of the transitions in terms of observed counts and percentages in each state. Then, we reported the adjusted cumulative hazards, the predicted probability of moving from one state into another (transition probabilities) and the predicted average time spent in a state (length of stay). We presented the results in this order for clarity and to be consistent with the step followed in the analysis.
We added the following sentence in the third paragraph of methods section 2.3, to introduce the reader into the main analyses (page 10, paragraph 1):
“Based on two hypothetical patients, we first obtained the patient-specific instantaneous cumulative hazards of progressing from one state to another”
Then, in the results, section 3.1.1, we added an introductory paragraph (page 12, paragraph 2).
“We computed the adjusted hazards of transitioning from one state to another based on a set of the most frequent categories of each covariate, also known as patient-specific transitions (Putter, Fiocco & Geskus, 2007).”
We also added a paragraph after the section 3.1.2 (page 12, paragraph 3):
“By incorporating these patient-specific cumulative hazards as an input, we estimated the probability of transitioning from one state to another, and the predicted average time spent in a state for the three follow-up periods considered (3 months, 1 year and 3 years).”

Reviewer comment
Marginal probabilities- what you really want here are marginal effects. The approach of defaulting to estimating margins with a patient who essential is the mode of the dataset needs justification if not doing marginal effects instead (oddly, Stata's margin command actually accomplishes this versus extrapolating with mode). If you choose to not update, will definitely need further explanation why you chose this approach. The difference is looking at the most common type of patient (current approach) which

ignores all other patients, versus, looking at the distribution of all patients, at different states of the covariate of interest (marginal effect).

Response
We appreciate this comment. Our approximation is fairly similar to what the reviewer is proposing, in the sense that our multistate model is composed of standard parametric survival models in which we adjusted for patient characteristics. In effect, we could have used the term "conditional probabilities", since they were estimated while fixing covariate at specific values. Despite acknowledging that there may be several strategies such as inverse probability treatment weighting, g-computation or marginal structural models, Gran, Lie, Øyeflaten, Borgan & Aalen (2015) found that predicting from average covariate values can be a valid approach for multistate models if covariates follow an additive structure (if there are no time-varying covariates or interactions between them), such as in our case. In fact, this approximation has been used previously to descriptively compare the trajectories or progression of different treatment arms or strategies within the possibilities of the “mstate” R package (Putter, Fiocco, & Geskus, 2007).
We added the following note to the second figure, to clarify this approach to the reader (page 31):
“Note. Dashed line: Women-only program. Solid line: Mixed-gender program. Both lines represent hazards for average covariate values, which are woman aged 30-39, who completed high school or less, reported alcohol as the primary substance at admission, had a daily consumption frequency, moderate biopsychosocial status (i.e., multidimensional clinical appraisal of SUD severity made by the professional team), stayed temporarily with a relative, had co-occurring SUD (i.e., diagnosis of abuse or dependence of one additional substance), had more than one child, and were in a residential treatment modality.”
Additionally, we modified the final sentence in the Limitations section to recognize that it is possible to generate other models that incorporate more complex data structures and dynamics, such as time-varying covariates and interactions (page 17, paragraph 2):
“Finally, due to the novel methodological framework we used, we recognize that often model structures influence conclusions (Cranmer et al., 2020), there is still room for modeling improvements (e.g., more flexible transition probability distributions) and more complex structures, including other states in the treatment outcome (early vs. late drop-out), second or third treatment readmissions, time-varying confounders or interaction terms (Gran et al., 2015).”
- Putter, H., Fiocco, M., & Geskus, R. B. (2007). Tutorial in biostatistics: competing risks and multi-state models. Statistics in Medicine, 26(11), 2389–2430. doi:10.1002/sim.2712
- Gran, J. M., Lie, S. A., Øyeflaten, I., Borgan, Ø., & Aalen, O. O. (2015). Causal inference in multi-state models-sickness absence and work for 1145 participants after work rehabilitation. BMC public health, 15, 1082. https://doi.org/10.1186/s12889-015-2408-8

Reviewer comment
It would be better to formally test your hypothesis with contrast than extrapolating via confidence intervals. I would also include any tests you decide to do in methods as either prespecified or post-hoc analyses. It reads now like you looked at the transition probabilities and then thought some might be different and then looked at confidence intervals and decided they are significantly different. Also, are the final transition probabilities from the adjusted models or from the intercept only models?

Response
Transition probabilities presented in Table 2 were estimated from the adjusted models. Intercept-only models were only used to select transition probability distribution for the parametric model. Regarding hypothesis testing, the msstate package in R does not allow for formal hypothesis testing between groups. We were not able to store results and estimate differences across each bootstrap resampling. Still, the comparison of transition probabilities based on bootstrap confidence intervals is widely used as a conservative assessment for observing differences (MacGregor-Fors & Payton, 2013).
We added the following sentence to the Discussion section (page 16, paragraph 2):
“Future studies should formally test differences in transition probabilities.”

	- MacGregor-Fors I, Payton ME (2013) Contrasting Diversity Values: Statistical Inferences Based on Overlapping Confidence Intervals. PLOS ONE 8(2): e56794. https://doi.org/10.1371/journal.pone.0056794 Reviewer comment Discussion How did you all handle patients that completed residential and transitioned to outpatient treatment? Was this considered a treatment completion and then readmission? Response Indeed, we did not distinguish by the type of treatment program or modality at readmission. Women who completed residential treatment and subsequently entered to an outpatient treatment were considered as having a treatment completion and one readmission. Reviewer comment You reference Brady & Ashley 2005 that facilities that allow women to participate with their children had higher levels of treatment completion but was this looked at in the treatment programs in Chile? Do any of the programs offer on-site child-care or allow/encourage women to participate with their children? Also would be helpful to note which, if any, provide pregnancy/perinatal support during addiction treatment. Response The Brady & Ashley paper does not look at Chilean treatment programs, though women-only treatments in Chile are similar to those described in that paper. One of the features of women-only programs in Chile is that they provide on-site childcare and pre/postnatal support. We added more detailed information on women-only program characteristics in the Introduction section (page 6, paragraph 1). “The SUD treatment programs system implemented in Chile provides professionalized therapeutic interventions and services, including social support, psychotherapy (individual and in group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks the promotion of a safe and empathic therapeutic environment to address gender-specific content and develops social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997).” Reviewer comment I am not sure what this sentence is trying to say and would recommend rewording it - "To adequately interpret these results, discussion over phenomena that may explain the nature or causes of readmissions remained necessary." Response We agreed. In the process of rewriting and editing the manuscript and the discussion section we decided to delete that sentence. Reviewer comment On page 16 please exchange the term "relapse" with "return to use" - Saitz R, et al "Recommended Use of Terminology in Addiction Medicine" Journal of Addiction Medicine 2020. Response We changed the term “relapse” to “return to use” throughout the manuscript. Reviewer comment In the conclusion, I would also add more research is needed exploring the experiences of patients with women-only vs. mixed-gender services as some of the benefits may

not be easily measured quantitatively (may be better assessed qualitatively). I'd also recommend reviewing this commentary by Grella, CE "What Do Women with Substance Use Disorder Want?" in Addiction 2018 which may provide some additional insights for a more nuanced discussion and conclusion.

Response
To enhance our conclusion we added a paragraph indicating that more research is needed to capture other dimensions of the studied phenomenon. We specified that qualitative research may be an appropriate approach to study other relevant factors such as how the construct of 'gender' within SUD treatment centers influence and inform women's SUD treatment preferences (page 17, paragraph 3).
"Overall, our findings suggest that women-only programs have similar results in terms of treatment outcomes and readmission risk than mixed-gender programs. Future research on the added value of specialized SUD treatment programs and their effectiveness should incorporate other dimensions of analysis to better capture the complexity of this phenomenon. For example, information on trauma histories, economic dependence, gender-based violence experiences, social support networks, and other services utilization (i.e., primary care services and hospitalizations) are relevant factors that may influence treatment success and readmission risk. Women's preferences regarding SUD treatment and how the construct of 'gender' held within treatment centers may affect women's recovery process have been pointed out as critical dimensions that remain necessary to address (Grella, 2018; Neale et al., 2018). Qualitative research may be a better methodological approach to address these and other dimensions."

Reviewer #2

Date: June 13, 2021
Journal: JOSAT – D-21-00326
Article Title: "Treatment outcome and readmission risk among women in women-only versus mixed gender drug treatment programs in Chile."
Reviewer comment
General
This study is, according to the authors, the first to examine large data sets of treatment admission and discharge records for women seeking substance use treatment in Chile, for the purpose of examining trajectories between women in women-only vs mixed-gender programs. This is an important contribution to the literature and of potential value and interest to stakeholders outside the treatment community, such as policy makers who provide public funding in Chile. That said, there are some revisions the authors could make for clarity and scope that would improve the quality of this report.

Response
Thanks for the positive feedback

Reviewer comment
Below are some specific comments:
Title
Title seems appropriate and descriptive.

Abstract
Abstract is descriptive, but the definitions of "therapeutic discharge" should be included as it is, briefly, for "discharge without clinical advice."

Response
We thank the reviewer for this comment, in line with Reviewer 1's recommendation. In this revision, we decided to change the term "therapeutic discharge" for "treatment completion" and the term "discharge without clinical advice" for "discharge without completion" throughout the manuscript.

Reviewer comment
Highlights
Highlights are clear.
Introduction
1. Paragraph 1: "National institute on drug abuse" should be capitalized.

Response
We incorporated this edit into the revision.

Reviewer comment
Methods
1. Section 2.1: Please define “MD5 algorithm”

Response
In order to respond to the observations made by the reviewers, we added the following sentence (page 7, paragraph 1):
“All patient identification information was encrypted using an MD5 (Message Digest 5) algorithm, which is widely used in security protocols to encrypt information, such as a personal identification number, into a 128-bits hash code (Jayawickrama, 2008).”
-Jayawickrama, W. (2008). Chapter 3 - An Introduction To Cryptography. In J. Liu, D., Caceres, M., Robichaux, T., Forte, D.V., Seagren, E.S., Ganger, D.L., Smith, B., Jayawickrama, W., Stokes, C. & Kanclirz (Eds.), Next Generation SSH2 Implementation: Securing Data in Motion (1st ed., pp. 41–64). Rockland, MA: Syngress Publishing. https://books.google.cl/books?id=4GVjngEACAAJ

Reviewer comment
2. Section 2.1: The difference between SISTRAT and SENDA is somewhat confusing to the reader because authors refer to data coming from both. Please review for places to make this more clear.

Response
SENDA stands for the National Service for Prevention and Rehabilitation of Drug and Alcohol Consumption of Chile. SISTRAT, on the other hand, refers to the digital registration system for people in treatment funded by SENDA. We clarified this by deleting those sentences that may confuse readers such as “data were obtained from SENDA”.

Reviewer comment
3. Section 2.2: “Referrals within the same treatment network were collapsed and treated as one treatment; referrals outside SENDA’s network were treated as censored.” Please clarify this sentence: assuming this means that referrals to additional treatments within this SUD network were coded as one treatment episode, explain the rationale. Similarly, what does “censored” mean and why would these referrals be coded differently?

Response
We appreciate this important observation. Referrals outside SENDA’s network were (right) censored, meaning that there was no treatment information about those women. We used this term since it is the standard terminology in multistate model and traditional survival analysis. To make this clear we added the following sentence in the first paragraph of section 2.2 (page 8, paragraph 1)
“[...] that did not experience a readmission within the study period were treated as right censored, because the follow-up period ended before any of the treatment outcomes occurred (Jepsen et al., 2015).”
Referrals within SENDA’s network were collapsed and treated as one treatment episode if the time span between them was <45 days. This time span was defined in agreement with SENDA’s treatment experts as a way to distinguish between a referral from a readmission, since they both appear as a new data entry in the SISTRAT dataset. In order to clarify this, we added the following sentence in page 8, paragraph 1:
“These can be conceived as consecutive episodes provided by one or more providers.”
- Jepsen, P., Vilstrup, H., & Andersen, P. K. (2015). The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology (Baltimore, Md.), 62(1), 292–302. https://doi.org/10.1002/hep.27598

Reviewer comment
4. Section 2.2: Remove the bullet formatting. Use section headers to denote domains of patient characteristic (Sociodemographics, Substance Use, etc) and describe the definitions of selected variables via text.

Response
As suggested by reviewer #1 and #2, we put the variables used in paragraph form and added a Supplemental Table (to not exceed the maximum number of Tables/Figures allowed by the journal) with a detailed description of each one: The new paragraph in section 2.2 reads (page 9, paragraph 1):
“We compared patient-level sociodemographic, substance use, health, and treatment characteristics of women in mixed-gender and women-only programs (i.e., age, educational attainment, have children, housing, biopsychosocial status, primary substance at admission, frequency of use of primary substance, co-occurring SUD, treatment duration, and treatment modality). See supplemental Table S1 for a detailed description of these variables.”

Reviewer comment
5. Section 2.2. Biopsychosocial Status: is this a variable already entered into the registry by the treatment program, or is it a variable created by the study authors?

Response
Biopsychosocial status is already included into the registry of public funded SUD treatment programs in Chile. It specifically refers to a clinical appreciation to evaluate the extent to which negative consequences of SUD affects different areas of subjects with SUD (e.g., social functioning, physical disability, social support networks). We clarify the nature of the variable description in Supplemental Table S1.

Reviewer comment
6. Section 2.2 Co-Occurring SUD: specify whether this is at intake, or at some other point in the treatment episode.

Response
The co-occurring SUD variable refers to concurrent SUDs at admission, which is diagnosed after one clinical interview with clients. We clarify this in the variable description in Supplemental Table S1.

Reviewer comment
In general, at the start of the description of variables used, please provide a sentence or two orienting the reader to this data. When is it collected for each participant, by who, who enters, is the data standardized across treatment programs, and so on.

Response
To clarify this, we added a sentence indicating how data was collected, in page 8, paragraph 1:
“All clients of a state-funded SUD treatment program in Chile are interviewed at admission by treatment center professionals. Through this interview, the center’s professionals gather information on the client's sociodemographic characteristics, ‘health status, substance use patterns, among others, which are entered into the SISTRAT system.”

Reviewer comment
Also, please explain the rationale behind the three follow-up time points; why 3-months, 1 yr and 3 yrs?

Response
As noted in response to Reviewer 1, the time-points used in our analysis were defined based on a consensus established between our research team and SENDA’s team professionals that are responsible for treatment programs design and functioning in Chile.
The three months time-point was chosen based on empirical evidence suggesting that after three months under treatment, patients increase their chances of completing treatment (Brorson et al 2013).
The second time-point was chosen based on the average treatment duration (therefore, it’s the time-point in which we expected to find the greater number of patients completing treatment), which is one year according to SENDA. Three years after treatment admission was also defined as relevant time-point considering that this is the maximum expected treatment duration.

Reviewer comment
Results

1. Section 3.0: Women in women-only programs were younger, less residentially stable, sicker, used more drugs, and were more likely to be admitted to residential treatment. This finding is interesting and should be acknowledged and addressed in the Discussion. I.e. it appears that the women referred to women-only treatment were qualitatively different in important ways. It would help the reader to understand how these treatment referrals are made, and see clear statements about how these differences were taken into account in the analyses.

Response
In general, women with more complex profiles (i.e., having children, being pregnant, housing instability, exposure to intimate-partner violence, and severe drug use pattern) were prioritized to enter in the women-only program. However, in Chile, women-only treatment admission is largely constrained by availability, since there are fewer women-only programs than mixed-gender programs, usually concentrated in large urban centers.
As a consequence of criteria for prioritizing women-only treatment admission, women in the mixed-gender program may be characterized by less complex profiles compared to women in the women-only program.
Since our study is based on multistate regression modelling, variables exhibiting significant differences between both programs (see Supplemental Material) were incorporated into the model as covariables, thus adjusting their potential confounding effect.
We now added information on how we handled these differences in section 2.3 (page 10, paragraph 1)
“This multistate model is the result of the combination of the selected distributions for each of the transitions. These models were adjusted for all covariates listed in section 2.2 and detailed in Table S1 in the Supplemental Material.”

Reviewer comment
2. Section 3.1.1: “There were 21,378 women at admission, 16.4% stayed in the same states (mostly those admitted in 2018-2019)…” Please address in the Discussion why the results might vary for 2018-2019.

Response
Women admitted in 2018-2019 had a shorter follow-up period and thus a lower chance of completing their treatment. We extended the phrase that was in the parenthesis with information regarding treatment duration (page 12, paragraph 1)
“...mostly those admitted in 2018-2019, since they had a shorter follow-up period and thus a lower chance of completing their treatment...”

Reviewer comment
3. Section 3.1.2: “However, we noticed that women-only programs were more likely to transition from admission to therapeutic discharge than discharge without clinical advice. This difference is statistically significant only at three years (34%; 95% CI: 28-40% vs. 23%; 95%CI: 20-26%). In contrast, mixed-gender programs had a slightly greater transition probability from admission to discharge without clinical advice. Still, these differences were not statistically significant at any time point measured.”
Although it is interesting that women-only programs might be associated with greater rates of treatment completion, the fact that all but the 3-year follow-up timepoints are not statistically significant makes me question the value of reporting them here, even though the lack of significance is appropriately acknowledged.

Response
In general, we used significance testing and non-overlapping confidence intervals as a reference to guide the interpretation and discussion of our results, but we do not believe it should be the sole criteria to report or interpret results. To that end, we decided to keep that sentence, though we defer to editorial discretion.
Also, we think that this finding is very relevant if we are taking into account the fact that 3 years is the maximum expected treatment duration defined by SENDA’s team

professionals. Considering that 20,3% of the respondents were 366 days or more in treatment, three years is a time point that allows us to capture the transition probabilities of every patient admitted in the initial years of the cohort.

Discussion/Limitations

Reviewer comment
1. Please expand on the topic of single gender vs mixed gender treatment programs in Chile. In what ways are these programs similar or different, in terms of treatment providers, settings, and program content? This may be better addressed in Methods, but currently is only alluded to in the Discussion.

Response
As suggested, we added more detailed information on the characteristics and services that are exclusively offered in the women-only treatment program (in contrast to the traditional mixed-gender program) in the introduction (page 6, paragraph 1)
"The SUD treatment programs system implemented in Chile provides professionalized therapeutic interventions and services, including social support, psychotherapy (individual and in group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks the promotion of a safe and empathic therapeutic environment to address gender-specific content and develops social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997). In addition, the distinctive activities considered in women-only programs in Chile include co-educational services to enhance parental skills development, and the acquisition of skills to generate income. Women-only programs also play an important role in coordinating with other social services (e.g., legal system, primary health care services) that are critical to the recovery and social integration of women with SUD (Consejo Nacional para el Control de Estupefacientes, 2007; Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol y Ministerio de Salud de Chile, 2018)."

Reviewer comment
2. Authors should comment on how the demographic differences between the women-only treatment group vs the mixed-gender treatment group might have influenced the study's findings. In what ways would factors such as addiction and mental health severity/complexity, housing stability and age influence treatment completion, discharge, etc.?

Response
This is an important issue. In our study we adjusted for several covariates that have seemed to be associated with SUD treatment progression such as age, educational attainment, primary substance of use, etc. In this sense, we were concerned about this issue and incorporated some of those differences in the modeling process. However, there may be unobserved differences that still may be affecting our results estimates (e.g., gender-based violence, economic dependence, lack of social networks and support). We added a sentence acknowledging the existence of potential unmeasured confounding effects in the first paragraph of the Limitations section (page 17, paragraph 2):
"We acknowledge that the existence of these and other unmeasured variables may lead to residual confounding when comparing women-only and mixed-gender treatment programs. Other key measured variables may be variable in quality or completeness, such as psychiatric comorbidity"

Reviewer comment
3. The authors are right to be cautious about how these data may be interpreted because they may be used inappropriately to justify funding or de-funding certain programs. The authors might consider enhancing their discussion of additional factors that could not be assessed in this study with existing data, but that are nevertheless

	critical to consider in overall treatment success (treatment access, childcare, mental health, source of income, engagement in or reliance on transactional sex, trauma history, qualitative differences in the content of SUD programming in women-only vs mixed-gender settings, burden of caregiving for others, and so on). There are many outcomes for treatment success beyond completion and discharge status, and whether one is re-admitted to treatment. Data such as these were not available for this study, but the authors should be judicious in not over-simplifying the picture for SUD treatment for women in Chile. Response We thank the reviewer for this comment. Our results should not be interpreted to support de-funding of women-only treatment programs in Chile. We also agree that there are several treatment outcomes that would be necessary to incorporate in order to assess the women-only treatment program. These ideas were incorporated in the Discussion section (page 16, paragraph 3) “Our analytic approach allows capturing only a part of a highly complex phenomenon which is influenced by several factors and that has multiple relevant outcomes apart from type of discharge and treatment readmission (i.e., social functioning, criminal offending, return to substance use, among others) that could not be considered in the analysis. In line with this, research on other intersecting dimensions, such as life experiences of gender-based violence and economic dependence, may be an important contribution to characterize risk environments that may lead to treatment readmission. For example, in Chile, women previously admitted to SUD treatment may prefer being readmitted due to the lack of resources to maintain stable housing conditions and food security. Specially in residential modalities, treatment readmission may also be seen as an alternative to avoid intimate-partner violence, which has been shown to be highly prevalent among women with SUD.” Reviewer comment Tables/Figures Tables 1 and 2: Please add indicators of statistical significance across groups. Response We added indicators of statistical significance across groups in the first table. However, we could not add them in the semi-markov multistate transition probabilities, because the significance in this case is provided by simulating state histories of individuals (in our case, 100,000 trajectories), as well as obtaining confidence intervals for transition probabilities (by 10,000 resamples, recommended by Williams et al., 2017, and Jackson, et al., 2016). As explained above, the comparisons between them was based on whether the transition probabilities overlapped its confidence intervals with different states along the matrix. - Williams, C., Lewsey, J. D., Briggs, A. H., & Mackay, D. F. (2017). Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial. Med Decis Making, 37(4), 340-352. https://doi.org/10.1177/0272989X16651869 - Jackson, C. H. (2016). flexsurv: A Platform for Parametric Survival Modeling in R. J Stat Softw, 70. https://doi.org/10.18637/jss.v070.i08

Dear Dr. McCarty
Thank you for your interest in our paper and your constructive comments and recommendations. We believe that this new version is greatly improved thanks to the review process. We have made substantial changes throughout the manuscript (marked in red) and included a point-by-point response to your and reviewers' comments.

If you have further comments, please do not hesitate to contact me.
Sincerely
Alvaro Castillo-Carniglia, PhD
Associate Professor and corresponding author

Dr. Castillo-Carniglia:
With assistance from two external reviewers, I have reached a decision to request a major revision of your manuscript JOSAT-D21-00326.
Please resubmit within 30 days so that we can finalize the special issue. If you cannot resubmit within 30 days please withdraw your manuscript from the review process.

I strongly support the reviewers' recommendations to clarify the terminology used to describe the types of discharge using terms like "treatment completed", "patient initiated discharge" and "discharged without completion". The introduction is relatively unfocused. Retain the first paragraph, delete the second, third and fourth paragraphs and continue with paragraph five "In Chile, ..." A table of the study variables and values will make the methods section more concise. Review 2 also suggests including details on how gender specific and co-ed services vary. Note also Reviewer 1's recommendations for restructuring the results section and changing the analysis. Comments from Review 1 follow. Review 2 is an attachment.
Sincerely,
Dennis McCarty
co-editor JSAT international special issue

Response
Thank you for giving us the opportunity to revise our paper. In order to clarify the terminology used to describe the types of discharge, we decided to replace the term “therapeutic discharge” with “treatment completion” and the term “discharge without clinical advice” with “discharge without completion” as suggested by Reviewer #1.
In this major revision, we reorganized the introduction according to reviewer’s suggestions, and concisely present relevant information on the characteristics of women with SUD within the broader literature.

As suggested by reviewer #2, we also added more detailed information on gender-specific and co-educational services provided in publicly funded SUD treatment programs (page 6, paragraph 1).

> “The SUD treatment programs system implemented in Chile provides professionalized therapeutic interventions and services, including social support, psychotherapy (individual and in group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks the promotion of a safe and empathic therapeutic environment to address gender-specific content and develops social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997). In addition, the distinctive activities considered in women-only programs in Chile include co-educational services to enhance parental skills development, and the acquisition of skills to generate income. Women-only programs also play an important role in coordinating with other social services (e.g., legal system, primary

health care services) that are critical to the recovery and social integration of women with SUD (Consejo Nacional para el Control de Estupefacientes, 2007; Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol y Ministerio de Salud de Chile, 2018).

Finally, we also revised the methods and results sections to have a more clear and concise description of the variables, analyses and results.

A point-by-point response to reviewers comments is presented below.

Reviewer #1

Summary:

Below are some specific comments/questions for the authors which I have separated by section for clarity and organization.

General Feedback:

I would reconsider some of the terms used for the 3 categories -
"Therapeutic discharge" has a different meaning to me and may be confusing to readers though it is defined in the methods later on. It may be helpful to come up with a different term for the category of patients who completed their treatment course. Perhaps "treatment completion" of "planned discharge" (reference: Taylor JB, Beach SR, Kontos N. "The therapeutic discharge: An approach to dealing with deceptive patients." General Hospital Psychiatry 2017)

I would also reconsider the term "drop-out" as perhaps these patients had a reason for them that necessitated leaving treatment early though they may be wanted to continue (a sick child that needed to be cared for). I have seen the term "patient-initiated discharge" being used more which I think would be appropriate (as opposed to "against medical advice" - AMA). I think the term "discharged without clinical advice" used throughout the manuscript may be a translation attempt at "against medical advice" but as stated earlier would prefer the term "patient-initiated discharge" be used. Could also say "prior to treatment completion" as a way to distinguish between those that did complete treatment.

Response

As suggested and in order to clarify the terminology used to describe the types of discharge, we decided to replace the term “therapeutic discharge” with “treatment completion”, the term “discharge without clinical advice” for “discharge without completion”, and “drop-out” for “patient-initiated discharge”.

Reviewer comment

Highlights

Given the above general feedback I would rephrase these first 3 highlights.

Response

Highlights were re-written according to the new terms used throughout the manuscript (i.e., treatment completion and discharge without completion)

Reviewer comment
Abstract
No additional comments other than incorporating general feedback above

Response
Terminology was also updated in the abstract and throughout the manuscript.

Reviewer comment
Introduction
Overall, I think the introduction is well-written and organized and provides excellent context for the history and development of women only SUD treatment programs specifically in Latin America. I do think it would be helpful in this section to include background on the intersectional risk environment (micro and macro environment) and experiences such as trauma, and sexual violence/intimate partner violence women who use drugs face. This will provide added context to why women who use drugs (WWUD) may prefer women-only spaces. This background could be incorporated on page 6 in the paragraph starting with "In Chile,…" as this includes information about rationale for women-only programs.

Some references to consider including/adding to the introduction:
- Ait-Daoud, N et al "Women and Addiction: An Update" Medical Clinics of North America 2019.
- Agabio R et al "Sex differences in substance use disorders: focus on side effects" Addiction Biology 2016.
- Collins AB et al "The Intersectional Risk Environment for People Who Use Drugs" Social Science and Medicine 2019.

Response
As suggested by the editor and reviewers, we modified the introduction and added background on risk environments and experiences of women who use drugs in Chile. New paragraphs (page 5, paragraphs 1 and 2) include evidence on the macro and micro level risk environments and experiences of women with substance use disorders in Chile (Collins AB et al., 2019).

> "Under a risk environment perspective (Rhodes, 2009; Collins et al., 2019), social vulnerability of women with SUD is a product of a range of macro (economic, political, and social milieus) and micro-level environments (drug trafficking neighborhoods, intimate-partner violence, sex trade participation) that intersect with disadvantaged social locations producing increased risk (Collins et al., 2019).
> Data from Chilean SUD treatment programs depicts the disadvantaged position of women with SUD, expressed in the lack of economic autonomy (i.e., income generation), housing instability, food insecurity, trauma/violence exposure, and stigmatization due to difficulties in accomplishing Latin American traditional gender roles, in which women are expected to be affectionate, submissive and a faithful spouse, mother and family caregiver, in contrast to the independent, polygamous and dominant role of the Chilean *macho* man (Cianelli et al, 2008; Hawkins et al., 2017). Accordingly, 45% of women admitted to public treatment programs reported being unemployed, and 29% reported unpaid work. Among women with co-occurring mental health problems, 70% reported being victims of interpersonal violence from their

partners or other family members (Valencia-Recabarren, 2015). Results from a RDS-study on people who use cocaine base paste in Chile may be indicative of how structural environment and situated contexts in Chile affect women with SUD. For example, women from this study reported a total monthly income of USD$150 (USD$68 under the poverty line in Chile), which was 50% lower than the income reported by men (Instituto de Sociología de la Pontificia Universidad Católica de Chile, 2015). Women also reported more insecure housing conditions, and lower levels of education (Instituto de Sociología de la Pontificia Universidad Católica de Chile, 2015). In this context, the implementation of gender-specific services in Chile represents an effort to provide a therapeutic alternative that may better suit the needs of women with SUD"

Reviewer comment

Specific Feedback:
On page 4 "The 'telescoping phenomenon' in the course of SUD in women is well supported by evidence showing that, compared to men, women experience a faster progression from substance use to SUD than men (Becker et al., 2017; Keyes et al., 2010), and report health problems of greater severity such as trauma and psychiatric comorbidities (Becker et al., 2016)." I think the second half of this sentence is incorrectly phrased. Women have greater rates and severity of trauma and psychiatric comorbidities which increase their risk of developing SUD. I don't think Becker, 2016 is the best reference for health problems. I would recommend Ait-Daoud which discusses more rapid development of severe medical consequences such as alcohol related complications - alcohol-related liver disease, cardiac complications, etc. Agabio R. et al, is also an excellent reference to include here.

Response

As suggested by the editor and reviewers, we rewrote and reorganized the introduction, and removed the reference to the 'telescoping phenomenon' from the paper. To characterize the distinctive characteristics of women's course of illness and related health problems we added a more detailed description based on the paper by Ait-Daoud et al, and Agabio et al (page 4 paragraph 2)

"Overall, women are less likely than men to use illicit drugs, tend to initiate substance use later in life, but experience a faster progression from substance use to dependence or abuse, and consequently to first treatment entry. This accelerated progression to SUDs is usually associated with more severe SUD-related problems (Ait-Daoud et al., 2019; Agabio et al., 2019). Over the last three decades though, the increased recognition of sex and gender differences in SUDs led to the implementation of women-only treatment programs in many countries (Schleifer & Pol, 2017)."

Reviewer comment

Some additional clarity on what is meant by treatment outcome would be helpful in the last paragraph or later on in the methods. Is this completion of treatment or does it include other outcome measures of interest like return to substance use, retention in outpatient treatment, etc.

Response

We use the term "treatment outcome" to refer to completion/end of treatment, which has two possible categories: "treatment completion" and "discharge without completion", which

groups patient-initiated discharges and administrative discharges. This was clarified in the method section. We also use as study outcome treatment readmissions, though we do not refer to readmission as "treatment outcome". It is important to mention that substance use alone is not a sufficient cause for readmission, but it is a requirement to be readmitted to a treatment program. In the modeling process we use other relevant measures, such as time in treatment and time outside treatment. We are aware that other relevant measures could be of interest (e.g., physical and mental health outcomes, family functioning), but due to data availability and simplicity we only used treatment outcomes and readmissions. The latter was recognized as a potential limitation of our study (page 16, paragraph 3):

> "Our analytic approach allows capturing only a part of a highly complex phenomenon which is influenced by several factors and that has multiple relevant outcomes apart from type of discharge and treatment readmission (i.e., social functioning, criminal offending, return to substance use, among others) that could not be considered in the analysis. In line with this, research on other intersecting dimensions, such as life experiences of gender-based violence and economic dependence, may contribute to the characterization of risk environments that may lead to treatment readmission"

Reviewer comment

Methods

Overall, after reading the supplemental information, I would consider pulling slightly more of what is in the appendix into the methods. The supplemental info is very well written and can help provide more information on model selection, parts of which do belong in the methods.

Response

We appreciate the reviewer's note regarding the utility of the supplemental material. As both reviewers requested, we incorporated several changes in the method section. These included an explanation of the encryption algorithm, how the registries on patient's admissions were collected, definition of referrals and right censoring for external referrals, tests for proportional hazards assumption, how we tested the violation of markovianity assumption, how we balanced the criteria used to choose each transition, the criteria used to determine the time points chosen, and the steps considered in the analysis (i.e., cumulative hazards, transition probabilities, expected lengths of stay).

A detailed description of each of these points is presented in our responses below.

Reviewer comment

Study design

What is an MD5 algorithm?

Response:

To clarify this we added the following sentence in section 2.1 (page 7 paragraph 1):

> "All patient identification information was encrypted using an MD5 (Message Digest 5) algorithm. The MD5 algorithm is widely used in security protocols to encrypt information, such as a personal identification number, into a 128-bits hash code (Jayawickrama, 2008)."

- Jayawickrama, W. (2008). Chapter 3 - An Introduction To Cryptography. In J. Liu, D., Caceres, M., Robichaux, T., Forte, D.V., Seagren, E.S., Ganger, D.L., Smith, B., Jayawickrama, W., Stokes, C. & Kanclirz (Eds.), Next Generation SSH2

Implementation: Securing Data in Motion (1st ed., pp. 41–64). Rockland, MA: Syngress Publishing. https://books.google.cl/books?id=4GVjngEACAAJ

Reviewer comment

I would move the sentence on complete data to your missing data section, unless you elaborate here what you mean re: complete data

Response

Indeed, the term “complete” was ambiguous and confusing. We decided to delete the following phrase: "with complete data", because we were meaning "imputed" data. Details of the imputation can be found after Figure S1 in the Supplemental Material.

Reviewer comment

Measures

Unclear what you mean for referrals here- referrals to treatment?

Response

We added the words “to another SUD treatment” to specify the type of referrals that were collapsed in the database and clarified that not every referral was collapsed. Additionally, we provided some examples of treatment transfers and external referrals outside SENDA’s network in the first paragraph of section 2.2 (page 8):

> “Referrals to another SUD treatment (i.e., treatment transfers) within the same treatment network (often suggested by the professional team of the center due to change of address, change of the treatment plan, or other justified reason) with fewer than 45 days of difference (...) Referrals outside SENDA’s network such as primary or secondary health care facilities (e.g., psychiatric units, other health centers)...”

Reviewer comment

It would be helpful for international audiences to know more about the data collection- can you expand on what you mean by routine? Is this information that is excellently collected for every patient, or is this on a piece of paper, entered into computer systems later, and not always done? Or is there variation by center?

Response

We appreciate the opportunity to clarify data collection information. Centers are mandated to enter patients’ information at admission, throughout the treatment process and discharge into an electronic system (SISTRAT); SENDA pays treatments only if they have complete data at admission and at least one therapeutic activity during the month. Most of SISTRAT’s fields are required, otherwise the system is not allowed to save the information. The information filled in the SISTRAT is obtained through a baseline assessment interview. The clinical information (e.g., psychiatric comorbidity) is the result of a clinical appraisal of the treatment team, which includes an interview with a psychiatrist or physician with mental health experience, after one or more interviews with the patient. Electronic records do not replace the clinical chart, usually kept in paper. There may be a variation by center regarding the personnel in charge of filling the electronic records, or the timing at which this information is entered into the system, but centers have to routinely collect the data to proceed to payment.

Considering the above mentioned, we modified the start of the first paragraph in the section 2.2 (page 8, paragraph 1):

> "All clients of a state-funded SUD treatment programs in Chile are interviewed at admission by treatment center professionals. Through this interview, the center's professionals gather information on the client's sociodemographic characteristics, health status, substance use patterns, among others, which are entered into the SISTRAT system. Clinical information stems from the appraisal from the treatment team and consultation with a psychiatrist or physician with mental health experience, if necessary. Centers must collect the data to proceed to payment."

Reviewer comment

You include a definition for therapeutic discharge- is this a definition you created for the analysis or is this determined by center staff? If done at the center, maybe describe how the definitions are actualized.

Response

This category —now called "treatment completion"— is determined by the center therapeutic team and registered in SISTRAT. We rephrased the third paragraph of section 2.2 (page 8) to make this clearer.

> "According to SENDA's guidelines, treatment completion is defined as a discharge after achieving the goals defined in the patient's individual treatment plan developed by the therapeutic team at admission"

Reviewer comment

I would take the categories for patient characteristics and either put them in a table describing what was in the survey, which would be helpful in an appendix, or put in paragraph form.

Response

As suggested, we put the variables used in paragraph form and added a Supplemental Table with a detailed description of each one: The new paragraph in section 2.2 reads (page 9, paragraph 1):

> "We compared patient-level sociodemographic, substance use, health, and treatment characteristics of women in mixed-gender and women-only programs (i.e., age, educational attainment, have children, housing, biopsychosocial status, primary substance at admission, frequency of use of primary substance, co-occurring SUD, treatment duration, and treatment modality). See supplemental Table S1 for a detailed description of these variables."

We situated the table in the supplemental material to not exceed the maximum number of tables/figures permitted in the journal's author guidelines.

Reviewer comment

This does not need to go into the paper, but I'm curious why you didn't leave your continuous variables continuous (e.g. age)

Response

With the exception of age, SENDA registers patient's information in predefined categories to minimize error when filling data into the SISTRAT records. For example, the frequency of

use of the primary substance in the last 30 days is registered in predefined categories (from “No use/Less than 1 day per week” to “Daily”). We grouped ages into categories to be consistent with the age ranges generated by SENDA in their annual reports, making them more locally relevant and accessible to policy makers.

Reviewer comment
Appreciate the inclusion of evaluation of missing data here. Would be sure to clarify that the low rate of missing data is not because you only included people with complete data.

Response
We appreciate the opportunity to clarify this point. We used imputation methods to address missing data concerns, and used this imputed data in our analyses. As discussed in response to reviewer #1, we decided to delete the words "with complete data" in the first paragraph of the Section 2.1, hoping that this modification clarifies that the percentages of missing data shown did not correspond to people with only complete data, and instead are records reflected imputed data, as described.

Reviewer comment
It's really great to see the use of multistate model here to answer your research question- I think this is a real strength of this paper. It would be helpful to have more information about your decisions around model fit- I see that you chose a parametric model based on AIC- can you talk more about how you balanced AIC with visual inspection and extrapolation?

Response
We appreciate the positive feedback. As suggested, we expanded on the selection of parametric models for each transition in the Supplemental material, by adding a measure of root mean squared error (RMSE) of the differences between the smoothed hazard function and parametric models (Table S3), replacing Figure S1 for the comparison of hazard curves, and including a paragraph on how the different criteria was combined to select the best parametric model for each transition after the Table S3 (page 10, paragraph 1 and 2, in Supplemental Material).

> “We chose the Gompertz distribution for the first and second transition, because this distribution provided a more reasonable extrapolation at 11 years, resembling most to the hazard curve, as seen in Figure S3, despite the Gompertz distribution showed the fifth and second best fit, respectively (AIC= 24,884 and AIC= 31,787). Considering that Generalized F & Generalized Gamma distributions showed convergence issues in the model that controlled for covariates, we selected the Log-normal distribution (AIC= 6,242).
>
> Visual differences may seem difficult to appreciate for the fourth and fifth transitions. However, and despite this distribution was fourth in the AIC (but with negligible differences between the first six distributions), we chose Generalized gamma (AIC= 7,440) for the fourth transition because of the lower mean RMSE of both programs (see Table S3), and lower observed differences with smoothed hazard function. For the fifth transition, we chose Log-normal distribution despite being the third with lower AICs (AIC= 22,841) because of lower mean RMSE of both programs and lower observed differences with smoothed hazard function.”

In the manuscript we included the following sentence in the fourth paragraph of the section 2.3 (page 10, paragraph 3):

"The Kaplan-Meier survival curves and simple survival model were calculated using the *survival* package (Therneau T., 2021). The smoothed hazard function was estimated through the *muhaz* package (Hess & Gentleman, 2019).

Reviewer comment
For the transition probabilities- why not extrapolate from the adjusted models? Would just add a sentence here on why you chose to use intercept only models here (or consider adjusting). I would also just state here

Response
Intercept-only models were only used to determine the distribution for each transition, not to estimate the study results. Adjusted multistate models were used to calculate cumulative hazards for each transition, transition probabilities and lengths of stay in each state (results presented in section 3.1.1, 3.1.2 and 3.1.3 sections). In order to clarify this, we added a sentence in the third paragraph of the section 2.3 (page 10 paragraph 2):

"We checked whether the time spent in the previous state played an important role for intermediate states. As treatment duration (i.e., time in the baseline state) could affect the likelihood of readmissions, we used a semi-Markov multistate model that included the time spent in treatment (years in treatment). This multistate model is the result of the combination of the selected distributions for each of the transitions. These models were adjusted for all covariates listed in section 2.2 and detailed in Table S1 in the Supplemental Material. Based on two hypothetical patients, we first obtained the patient-specific instantaneous cumulative hazards of progressing from one state to another"

Reviewer comment
Really love the Markov approach here.

Response
Thank you.

Reviewer comment
Mention somewhere why you chose 3 months, 1 year and 3 years as your time points.

Response
The time-points used in our analysis were defined based on a consensus discussed between our research team and SENDA's team professionals that are responsible for treatment programs design and functioning in Chile.
The three months time-point was chosen based on empirical evidence suggesting that after three months under treatment, patients drastically increase their chances of completing treatment (Brorson et al 2013). The second time-point was chosen based on the expected average treatment duration (therefore, it's the time-point in which we expected to find the greater number of patients completing treatment), which is one year. Three years after treatment admission was also defined as a relevant time-point considering that this is the maximum expected treatment duration defined by SENDA's team professionals.
To clarify this, we added the following sentence in the manuscript (page 10, paragraph 1):

"We considered these three time points based on a consensus established between our research team and SENDA's team professionals that are responsible for treatment programs design and functioning in Chile."

Reviewer comment

Need discussion somewhere of model validation

Response

In our study, we are looking at events that occur in the treatment process, which include treatment outcomes and readmissions. Given that, we used the most parsimonious version as a starting point to guide future research. It is a way to implement a more complex modeling process beyond the time to a specific event of a standard survival model, allowing scaling other events and processes beyond a readmission. To this end, we tested for non-markovianity, proportional hazards assumption, adding the following sentence in the second paragraph of the section 2.3 (page 9 paragraph 3):

"The proportional hazards assumption in the Cox models was assessed visually and through a chi-squared goodness-of-fit test (more details in the Supplemental Material)."

Considering the above mentioned, we added a paragraph and a figure in the Supplemental Material to give a more detailed description of the decision to use standard parametric models instead of multistate models based on cox regressions (page 6, paragraph 1, in Supplemental Material):

"As seen in Figure S2, we did not see parallel trends in every transition, and the test indicated a significant deviation from expected proportionality in Admission to Treatment without completion ($X^2(df=1)=226.67$, $p<0.001$), Treatment completion to Readmission ($X^2(df=1)=10.34$, $p=0.001$), and Treatment without completion to Readmission ($X^2(df=1)=34.26$, $p<0.001$). Hence, we decided to select standard parametric distributions for each transition that do not solely rely on this proportionality assumption (Williams et al., 2016)"

Additionally, we tested multiple distributions (9) for each transition. In an effort to address another of your observations related to the lack of explanation in the methods section, we added more details about these procedures. Specifically, we added the following sentence in the third paragraph of the section 2.3 (page 10, paragraph 1):

"We checked whether the time spent in the previous state played an important role for intermediate states."

- Gray, J., Sullivan, T., Latimer, N. R., Salter, A., Sorich, M. J., Ward, R. L., & Karnon, J. (2020). Extrapolation of Survival Curves Using Standard Parametric Models and Flexible Parametric Spline Models: Comparisons in Large Registry Cohorts with Advanced Cancer. Medical Decision Making, 0272989X2097895. doi:10.1177/0272989x20978958
- Gibson, E. J., Begum, N., Koblbauer, I., Dranitsaris, G., Liew, D., McEwan, P., … Pritchard, C. (2019). Cohort versus patient level simulation for the economic evaluation of single versus combination immuno-oncology therapies in metastatic melanoma. Journal of Medical Economics, 1–1. doi:10.1080/13696998.2019.1569446

Results

Reviewer comment

Overall, this is strong. I would suggest cleaning up the results section to more clearly match the methods section, prespecifying analyses so they are not a surprise in the results and tightening up language.
I would try to make the writing in overall results section more clear- it's fairly wordy and complicated for conveying the least complicated part of the analysis

Reviewer comment
Transition intensities- not sure why using this terminology here.

Response
We made several changes to the results section, including a revision of the writing, changing subheading/terminology (e.g., replaced “3.1.1 Transition intensities” for “3.1.1 Cumulative hazards”), and made clear the correspondence with the steps described in the Method section.

Reviewer comment
Sentence "There were 21,378 women at admission"- when you refer to women who stayed in the same state, are these women who remain in treatment? Or women who were not in treatment?

Response
The 21,378 women encompass the whole sample, that is, with at least one treatment admission during the follow-up period. We modified the following sentence to avoid confusion about this (page 12, paragraph 1):

> “There were 21,378 women with at least one treatment admission during any time point between January 1st, 2010 and November 13th, 2019; 16.4% (n= 3,516) remained in the same states up until the end of the follow-up period, mostly those admitted in 2018-2019, since they had a shorter follow-up period and thus a lower chance of completing their treatment, 56.1% had a discharge without completion, 24% completed treatment and 3.5% transitioned directly from admission to readmission”

Reviewer comment
I think overall, the results need to be reorganized. I would talk about the basic demographics, then the model transition probabilities, and then the estimates/outcomes- so for example would move the paragraph "As seen in Figure 2" to later after model transition probabilities. Though it's just a step in this analysis, the transition probabilities themselves are important information.

Response
We thank the reviewer for this important suggestion. We have edited the text so that the methods section now clearly matches the results section across statistical procedures. For example, we structured the results by first introducing the main characteristics of the sample, followed by the description of the transitions in terms of observed counts and percentages in each state. Then, we reported the adjusted cumulative hazards, the predicted probability of moving from one state into another (transition probabilities) and the predicted average time spent in a state (length of stay). We presented the results in this order for clarity and to be consistent with the step followed in the analysis.

We added the following sentence in the third paragraph of methods section 2.3, to introduce the reader into the main analyses (page 10, paragraph 1):

> "Based on two hypothetical patients, we first obtained the patient-specific instantaneous cumulative hazards of progressing from one state to another"

Then, in the results, section 3.1.1, we added an introductory paragraph (page 12, paragraph 2).

> "We computed the adjusted hazards of transitioning from one state to another based on a set of the most frequent categories of each covariate, also known as patient-specific transitions (Putter, Fiocco & Geskus, 2007)."

We also added a paragraph after the section 3.1.2 (page 12, paragraph 3):

> "By incorporating these patient-specific cumulative hazards as an input, we estimated the probability of transitioning from one state to another, and the predicted average time spent in a state for the three follow-up periods considered (3 months, 1 year and 3 years)."

Reviewer comment

Marginal probabilities- what you really want here are marginal effects. The approach of defaulting to estimating margins with a patient who essential is the mode of the dataset needs justification if not doing marginal effects instead (oddly, Stata's margin command actually accomplishes this versus extrapolating with mode). If you choose to not update, will definitely need further explanation why you chose this approach. The difference is looking at the most common type of patient (current approach) which ignores all other patients, versus, looking at the distribution of all patients, at different states of the covariate of interest (marginal effect).

Response

We appreciate this comment. Our approximation is fairly similar to what the reviewer is proposing, in the sense that our multistate model is composed of standard parametric survival models in which we adjusted for patient characteristics. In effect, we could have used the term "conditional probabilities", since they were estimated while fixing covariate at specific values. Despite acknowledging that there may be several strategies such as inverse probability treatment weighting, g-computation or marginal structural models, Gran, Lie, Øyeflaten, Borgan & Aalen (2015) found that predicting from average covariate values can be a valid approach for multistate models if covariates follow an additive structure (if there are no time-varying covariates or interactions between them), such as in our case. In fact, this approximation has been used previously to descriptively compare the trajectories or progression of different treatment arms or strategies within the possibilities of the "mstate" R package (Putter, Fiocco, & Geskus, 2007).

We added the following note to the second figure, to clarify this approach to the reader (page 31):

> "Note. Dashed line: Women-only program. Solid line: Mixed-gender program. Both lines represent hazards for average covariate values, which are woman aged 30-39, who completed high school or less, reported alcohol as the primary substance at admission, had a daily consumption frequency, moderate biopsychosocial status (i.e., multidimensional clinical appraisal of SUD severity made by the professional team), stayed temporarily with a relative, had co-occurring SUD (i.e., diagnosis of

abuse or dependence of one additional substance), had more than one child, and were in a residential treatment modality."

Additionally, we modified the final sentence in the Limitations section to recognize that it is possible to generate other models that incorporate more complex data structures and dynamics, such as time-varying covariates and interactions (page 17, paragraph 2):

"Finally, due to the novel methodological framework we used, we recognize that often model structures influence conclusions (Cranmer et al., 2020), there is still room for modeling improvements (e.g., more flexible transition probability distributions) and more complex structures, including other states in the treatment outcome (early vs. late drop-out), second or third treatment readmissions, time-varying confounders or interaction terms (Gran et al., 2015)."

- Putter, H., Fiocco, M., & Geskus, R. B. (2007). Tutorial in biostatistics: competing risks and multi-state models. Statistics in Medicine, 26(11), 2389–2430. doi:10.1002/sim.2712
- Gran, J. M., Lie, S. A., Øyeflaten, I., Borgan, Ø., & Aalen, O. O. (2015). Causal inference in multi-state models-sickness absence and work for 1145 participants after work rehabilitation. BMC public health, 15, 1082. https://doi.org/10.1186/s12889-015-2408-8

Reviewer comment

It would be better to formally test your hypothesis with contrast than extrapolating via confidence intervals. I would also include any tests you decide to do in methods as either prespecified or post-hoc analyses. It reads now like you looked at the transition probabilities and then thought some might be different and then looked at confidence intervals and decided they are significantly different. Also, are the final transition probabilities from the adjusted models or from the intercept only models?

Response

Transition probabilities presented in Table 2 were estimated from the adjusted models. Intercept-only models were only used to select transition probability distribution for the parametric model. Regarding hypothesis testing, the msstate package in R does not allow for formal hypothesis testing between groups. We were not able to store results and estimate differences across each bootstrap resampling. Still, the comparison of transition probabilities based on bootstrap confidence intervals is widely used as a conservative assessment for observing differences (MacGregor-Fors & Payton, 2013). We added the following sentence to the Discussion section (page 16, paragraph 2):

"Future studies should formally test differences in transition probabilities."

- MacGregor-Fors I, Payton ME (2013) Contrasting Diversity Values: Statistical Inferences Based on Overlapping Confidence Intervals. PLOS ONE 8(2): e56794. https://doi.org/10.1371/journal.pone.0056794

Reviewer comment

Discussion

How did you all handle patients that completed residential and transitioned to outpatient treatment? Was this considered a treatment completion and then readmission?

Response

Indeed, we did not distinguish by the type of treatment program or modality at readmission. Women who completed residential treatment and subsequently entered to an outpatient treatment were considered as having a treatment completion and one readmission.

Reviewer comment

You reference Brady & Ashley 2005 that facilities that allow women to participate with their children had higher levels of treatment completion but was this looked at in the treatment programs in Chile? Do any of the programs offer on-site child-care or allow/encourage women to participate with their children? Also would be helpful to note which, if any, provide pregnancy/perinatal support during addiction treatment.

Response

The Brady & Ashley paper does not look at Chilean treatment programs, though women-only treatments in Chile are similar to those described in that paper. One of the features of women-only programs in Chile is that they provide on-site childcare and pre/postnatal support.

We added more detailed information on women-only program characteristics in the Introduction section (page 6, paragraph 1).

> "The SUD treatment programs system implemented in Chile provides professionalized therapeutic interventions and services, including social support, psychotherapy (individual and in group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks the promotion of a safe and empathic therapeutic environment to address gender-specific content and develops social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997)."

Reviewer comment

I am not sure what this sentence is trying to say and would recommend rewording it - "To adequately interpret these results, discussion over phenomena that may explain the nature or causes of readmissions remained necessary."

Response

We agreed. In the process of rewriting and editing the manuscript and the discussion section we decided to delete that sentence.

Reviewer comment

On page 16 please exchange the term "relapse" with "return to use" - Saitz R, et al "Recommended Use of Terminology in Addiction Medicine" Journal of Addiction Medicine 2020.

Response

We changed the term "relapse" to "return to use" throughout the manuscript.

Reviewer comment

In the conclusion, I would also add more research is needed exploring the experiences of patients with women-only vs. mixed-gender services as some of the benefits may not be easily measured quantitatively (may be better assessed qualitatively). I'd also recommend reviewing this commentary by Grella, CE "What Do Women with Substance Use Disorder Want?" in Addiction 2018 which may provide some additional insights for a more nuanced discussion and conclusion.

Response
To enhance our conclusion we added a paragraph indicating that more research is needed to capture other dimensions of the studied phenomenon. We specified that qualitative research may be an appropriate approach to study other relevant factors such as how the construct of 'gender' within SUD treatment centers influence and inform women's SUD treatment preferences (page 17, paragraph 3).

> "Overall, our findings suggest that women-only programs have similar results in terms of treatment outcomes and readmission risk than mixed-gender programs. Future research on the added value of specialized SUD treatment programs and their effectiveness should incorporate other dimensions of analysis to better capture the complexity of this phenomenon. For example, information on trauma histories, economic dependence, gender-based violence experiences, social support networks, and other services utilization (i.e., primary care services and hospitalizations) are relevant factors that may influence treatment success and readmission risk. Women's preferences regarding SUD treatment and how the construct of 'gender' held within treatment centers may affect women's recovery process have been pointed out as critical dimensions that remain necessary to address (Grella, 2018; Neale et al., 2018). Qualitative research may be a better methodological approach to address these and other dimensions."

Reviewer #2

Date: June 13, 2021

Journal: JOSAT – D-21-00326

Article Title: "Treatment outcome and readmission risk among women in women-only versus mixed gender drug treatment programs in Chile."

Reviewer comment
General

This study is, according to the authors, the first to examine large data sets of treatment admission and discharge records for women seeking substance use treatment in Chile, for the purpose of examining trajectories between women in women-only vs mixed-gender programs. This is an important contribution to the literature and of potential value and interest to stakeholders outside the treatment community, such as policy makers who provide public funding in Chile. That said, there are some revisions the authors could make for clarity and scope that would improve the quality of this report.

Response

Thanks for the positive feedback

Reviewer comment
Below are some specific comments:
Title
Title seems appropriate and descriptive.

Abstract
Abstract is descriptive, but the definitions of “therapeutic discharge” should be included as it is, briefly, for “discharge without clinical advice.”

Response
We thank the reviewer for this comment, in line with Reviewer 1’s recommendation. In this revision, we decided to change the term “therapeutic discharge” for “treatment completion” and the term “discharge without clinical advice” for “discharge without completion” throughout the manuscript.

Reviewer comment
Highlights
Highlights are clear.
Introduction
1. Paragraph 1: “National institute on drug abuse” should be capitalized.

Response
We incorporated this edit into the revision.

Reviewer comment
Methods
1. Section 2.1: Please define “MD5 algorithm”

Response
In order to respond to the observations made by the reviewers, we added the following sentence (page 7, paragraph 1):

> “All patient identification information was encrypted using an MD5 (Message Digest 5) algorithm, which is widely used in security protocols to encrypt information, such as a personal identification number, into a 128-bits hash code (Jayawickrama, 2008).”

- Jayawickrama, W. (2008). Chapter 3 - An Introduction To Cryptography. In J. Liu, D., Caceres, M., Robichaux, T., Forte, D.V., Seagren, E.S., Ganger, D.L., Smith, B., Jayawickrama, W., Stokes, C. & Kanclirz (Eds.), Next Generation SSH2 Implementation: Securing Data in Motion (1st ed., pp. 41–64). Rockland, MA: Syngress Publishing. https://books.google.cl/books?id=4GVjngEACAAJ

Reviewer comment
2. Section 2.1: The difference between SISTRAT and SENDA is somewhat confusing to the reader because authors refer to data coming from both. Please review for places to make this more clear.

Response

SENDA stands for the National Service for Prevention and Rehabilitation of Drug and Alcohol Consumption of Chile. SISTRAT, on the other hand, refers to the digital registration system for people in treatment funded by SENDA. We clarified this by deleting those sentences that may confuse readers such as “data were obtained from SENDA”.

Reviewer comment

3. Section 2.2: “Referrals within the same treatment network were collapsed and treated as one treatment; referrals outside SENDA’s network were treated as censored.” Please clarify this sentence: assuming this means that referrals to additional treatments within this SUD network were coded as one treatment episode, explain the rationale. Similarly, what does “censored” mean and why would these referrals be coded differently?

Response

We appreciate this important observation. Referrals outside SENDA’s network were (right) censored, meaning that there was no treatment information about those women. We used this term since it is the standard terminology in multistate model and traditional survival analysis. To make this clear we added the following sentence in the first paragraph of section 2.2 (page 8, paragraph 1)

> “[...] that did not experience a readmission within the study period were treated as right censored, because the follow-up period ended before any of the treatment outcomes occurred (Jepsen et al., 2015).”

Referrals within SENDA’s network were collapsed and treated as one treatment episode if the time span between them was <45 days. This time span was defined in agreement with SENDA’s treatment experts as a way to distinguish between a referral from a readmission, since they both appear as a new data entry in the SISTRAT dataset. In order to clarify this, we added the following sentence in page 8, paragraph 1:

> “These can be conceived as consecutive episodes provided by one or more providers.”

- Jepsen, P., Vilstrup, H., & Andersen, P. K. (2015). The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology (Baltimore, Md.), 62(1), 292–302. https://doi.org/10.1002/hep.27598

Reviewer comment

4. Section 2.2: Remove the bullet formatting. Use section headers to denote domains of patient characteristic (Sociodemographics, Substance Use, etc) and describe the definitions of selected variables via text.

Response

As suggested by reviewer #1 and #2, we put the variables used in paragraph form and added a Supplemental Table (to not exceed the maximum number of Tables/Figures allowed by the journal) with a detailed description of each one: The new paragraph in section 2.2 reads (page 9, paragraph 1):

> “We compared patient-level sociodemographic, substance use, health, and treatment characteristics of women in mixed-gender and women-only programs (i.e., age, educational attainment, have children, housing, biopsychosocial status, primary substance at admission, frequency of use of primary substance, co-occurring SUD, treatment duration, and treatment modality). See supplemental Table S1 for a detailed description of these variables.”

Reviewer comment

5. Section 2.2. Biopsychosocial Status: is this a variable already entered into the registry by the treatment program, or is it a variable created by the study authors?

Response

Biopsychosocial status is already included into the registry of public funded SUD treatment programs in Chile. It specifically refers to a clinical appreciation to evaluate the extent to which negative consequences of SUD affects different areas of subjects with SUD (e.g., social functioning, physical disability, social support networks). We clarify the nature of the variable description in Supplemental Table S1.

Reviewer comment

6. Section 2.2 Co-Occurring SUD: specify whether this is at intake, or at some other point in the treatment episode.

Response

The co-occurring SUD variable refers to concurrent SUDs at admission, which is diagnosed after one clinical interview with clients. We clarify this in the variable description in Supplemental Table S1.

Reviewer comment

In general, at the start of the description of variables used, please provide a sentence or two orienting the reader to this data. When is it collected for each participant, by who, who enters, is the data standardized across treatment programs, and so on.

Response

To clarify this, we added a sentence indicating how data was collected, in page 8, paragraph 1:

> "All clients of a state-funded SUD treatment program in Chile are interviewed at admission by treatment center professionals. Through this interview, the center's professionals gather information on the client's sociodemographic characteristics, 'health status, substance use patterns, among others, which are entered into the SISTRAT system."

Reviewer comment

Also, please explain the rationale behind the three follow-up time points; why 3-months, 1 yr and 3 yrs?

Response

As noted in response to Reviewer 1, the time-points used in our analysis were defined based on a consensus established between our research team and SENDA's team professionals that are responsible for treatment programs design and functioning in Chile.

The three months time-point was chosen based on empirical evidence suggesting that after three months under treatment, patients increase their chances of completing treatment (Brorson et al 2013).

The second time-point was chosen based on the average treatment duration (therefore, it's the time-point in which we expected to find the greater number of patients completing treatment), which is one year according to SENDA. Three years after treatment admission

was also defined as relevant time-point considering that this is the maximum expected treatment duration.

Reviewer comment
Results

1. Section 3.0: Women in women-only programs were younger, less residentially stable, sicker, used more drugs, and were more likely to be admitted to residential treatment. This finding is interesting and should be acknowledged and addressed in the Discussion. I.e. it appears that the women referred to women-only treatment were qualitatively different in important ways. It would help the reader to understand how these treatment referrals are made, and see clear statements about how these differences were taken into account in the analyses.

Response
In general, women with more complex profiles (i.e., having children, being pregnant, housing instability, exposure to intimate-partner violence, and severe drug use pattern) were prioritized to enter in the women-only program. However, in Chile, women-only treatment admission is largely constrained by availability, since there are fewer women-only programs than mixed-gender programs, usually concentrated in large urban centers.
As a consequence of criteria for prioritizing women-only treatment admission, women in the mixed-gender program may be characterized by less complex profiles compared to women in the women-only program.
Since our study is based on multistate regression modelling, variables exhibiting significant differences between both programs (see Supplemental Material) were incorporated into the model as covariables, thus adjusting their potential confounding effect.
We now added information on how we handled these differences in section 2.3 (page 10, paragraph 1)

> "This multistate model is the result of the combination of the selected distributions for each of the transitions. These models were adjusted for all covariates listed in section 2.2 and detailed in Table S1 in the Supplemental Material."

Reviewer comment
2. Section 3.1.1: "There were 21,378 women at admission, 16.4% stayed in the same states (mostly those admitted in 2018-2019)…" Please address in the Discussion why the results might vary for 2018-2019.

Response
Women admitted in 2018-2019 had a shorter follow-up period and thus a lower chance of completing their treatment. We extended the phrase that was in the parenthesis with information regarding treatment duration (page 12, paragraph 1)

> "...mostly those admitted in 2018-2019, since they had a shorter follow-up period and thus a lower chance of completing their treatment..."

Reviewer comment
3. Section 3.1.2: "However, we noticed that women-only programs were more likely to transition from admission to therapeutic discharge than discharge without clinical advice.

This difference is statistically significant only at three years (34%; 95% CI: 28-40% vs. 23%; 95%CI: 20-26%). In contrast, mixed-gender programs had a slightly greater transition probability from admission to discharge without clinical advice. Still, these differences were not statistically significant at any time point measured." Although it is interesting that women-only programs might be associated with greater rates of treatment completion, the fact that all but the 3-year follow-up timepoints are not statistically significant makes me question the value of reporting them here, even though the lack of significance is appropriately acknowledged.

Response
In general, we used significance testing and non-overlapping confidence intervals as a reference to guide the interpretation and discussion of our results, but we do not believe it should be the sole criteria to report or interpret results. To that end, we decided to keep that sentence, though we defer to editorial discretion.
Also, we think that this finding is very relevant if we are taking into account the fact that 3 years is the maximum expected treatment duration defined by SENDA's team professionals. Considering that 20,3% of the respondents were 366 days or more in treatment, three years is a time point that allows us to capture the transition probabilities of every patient admitted in the initial years of the cohort.

Discussion/Limitations

Reviewer comment
1. Please expand on the topic of single gender vs mixed gender treatment programs in Chile. In what ways are these programs similar or different, in terms of treatment providers, settings, and program content? This may be better addressed in Methods, but currently is only alluded to in the Discussion.

Response
As suggested, we added more detailed information on the characteristics and services that are exclusively offered in the women-only treatment program (in contrast to the traditional mixed-gender program) in the introduction (page 6, paragraph 1)

> "The SUD treatment programs system implemented in Chile provides professionalized therapeutic interventions and services, including social support, psychotherapy (individual and in group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks the promotion of a safe and empathic therapeutic environment to address gender-specific content and develops social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997). In addition, the distinctive activities considered in women-only programs in Chile include co-educational services to enhance parental skills development, and the acquisition of skills to generate income. Women-only programs also play an important role in coordinating with other social services (e.g., legal system, primary

health care services) that are critical to the recovery and social integration of women with SUD (Consejo Nacional para el Control de Estupefacientes, 2007; Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol y Ministerio de Salud de Chile, 2018)."

Reviewer comment

2. Authors should comment on how the demographic differences between the women-only treatment group vs the mixed-gender treatment group might have influenced the study's findings. In what ways would factors such as addiction and mental health severity/complexity, housing stability and age influence treatment completion, discharge, etc.?

Response

This is an important issue. In our study we adjusted for several covariates that have seemed to be associated with SUD treatment progression such as age, educational attainment, primary substance of use, etc. In this sense, we were concerned about this issue and incorporated some of those differences in the modeling process. However, there may be unobserved differences that still may be affecting our results estimates (e.g., gender-based violence, economic dependence, lack of social networks and support). We added a sentence acknowledging the existence of potential unmeasured confounding effects in the first paragraph of the Limitations section (page 17, paragraph 2):

"We acknowledge that the existence of these and other unmeasured variables may lead to residual confounding when comparing women-only and mixed-gender treatment programs. Other key measured variables may be variable in quality or completeness, such as psychiatric comorbidity"

Reviewer comment

3**.** The authors are right to be cautious about how these data may be interpreted because they may be used inappropriately to justify funding or de-funding certain programs. The authors might consider enhancing their discussion of additional factors that could not be assessed in this study with existing data, but that are nevertheless critical to consider in overall treatment success (treatment access, childcare, mental health, source of income, engagement in or reliance on transactional sex, trauma history, qualitative differences in the content of SUD programming in women-only vs mixed-gender settings, burden of caregiving for others, and so on).

There are many outcomes for treatment success beyond completion and discharge status, and whether one is re-admitted to treatment. Data such as these were not available for this study, but the authors should be judicious in not over-simplifying the picture for SUD treatment for women in Chile.

Response

We thank the reviewer for this comment. Our results should not be interpreted to support de-funding of women-only treatment programs in Chile. We also agree that there are several treatment outcomes that would be necessary to incorporate in order to assess the women-only treatment program. These ideas were incorporated in the Discussion section (page 16, paragraph 3)

"Our analytic approach allows capturing only a part of a highly complex phenomenon which is influenced by several factors and that has multiple relevant outcomes apart

from type of discharge and treatment readmission (i.e., social functioning, criminal offending, return to substance use, among others) that could not be considered in the analysis. In line with this, research on other intersecting dimensions, such as life experiences of gender-based violence and economic dependence, may be an important contribution to characterize risk environments that may lead to treatment readmission. For example, in Chile, women previously admitted to SUD treatment may prefer being readmitted due to the lack of resources to maintain stable housing conditions and food security. Specially in residential modalities, treatment readmission may also be seen as an alternative to avoid intimate-partner violence, which has been shown to be highly prevalent among women with SUD."

Reviewer comment

Tables/Figures

Tables 1 and 2: Please add indicators of statistical significance across groups.

Response

We added indicators of statistical significance across groups in the first table. However, we could not add them in the semi-markov multistate transition probabilities, because the significance in this case is provided by simulating state histories of individuals (in our case, 100,000 trajectories), as well as obtaining confidence intervals for transition probabilities (by 10,000 resamples, recommended by Williams et al., 2017, and Jackson, et al., 2016). As explained above, the comparisons between them was based on whether the transition probabilities overlapped its confidence intervals with different states along the matrix.

- Williams, C., Lewsey, J. D., Briggs, A. H., & Mackay, D. F. (2017). Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial. Med Decis Making, 37(4), 340-352. https://doi.org/10.1177/0272989X16651869
- Jackson, C. H. (2016). flexsurv: A Platform for Parametric Survival Modeling in R. J Stat Softw, 70. https://doi.org/10.18637/jss.v070.i08

Highlights

- More than 50% of treatment ended with a patient-initiated discharge.
- Patient-initiated discharge was more frequent in women-only program.
- Readmission risk was higher among women that completed their treatment.
- Women-only and mixed-gender programs had similar treatment readmission risk.

Abstract

Introduction: Traditional treatment programs for substance use disorder (SUD) tend to be male-dominated environments, which can negatively affect women's access to treatment and related outcomes. Women's specific treatment needs have led some providers to develop women-only SUD treatment programs in several countries. In Chile, women-only programs were only fully implemented in 2010. We compared treatment outcomes and readmission risk for adult women admitted to state-funded women-only versus mixed-gender SUD treatment programs in Chile.

Methods: We used a registry-based retrospective cohort design of adult women in women-only (N= 8,200) and mixed-gender (N= 13,178) SUD treatment programs from 2010 to 2019. The study obtained data from the National Drug and Alcohol Service from Chile. We used a multistate model to estimate the probabilities of experiencing treatment completion, discharge without completion (i.e., patient-initiated discharge and administrative discharge), or readmission, as well as the likelihood of being readmitted, conditioned on prior treatment outcome. We adjusted models for multiple baseline characteristics (e.g., substance use, socioeconomic).

Results: Overall, 24% of women completed treatment and 54% dropped out of treatment. The proportion of patient-initiated discharges within the first three month was larger in women-only than in mixed-gender programs (19% vs. 12%). In both programs, women who completed treatment were more likely to experience readmission at three months, and one and three years. In the long term, women in the women-only programs were more likely to complete treatment than women in mixed-gender programs (34% vs. 23%, respectively). The readmission probability was higher among women who previously completed treatment than those who had a discharge without completion (40% vs 21%

among women in women-only programs; 38% vs. 19% among women in mixed-gender programs, respectively); no differences occurred in the risk of readmission between women-only and mixed-gender programs.

Conclusions: In terms of treatment outcomes and readmission risk, women-only programs had similar results to mixed-gender programs in Chile. The added value of these specialized programs should be addressed in further research.

Treatment outcome and readmission risk among women in women-only versus mixed-gender drug treatment programs in Chile

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Abstract

Introduction: Traditional treatment programs for substance use disorder (SUD) tend to be male-dominated environments, which can negatively affect women's access to treatment and related outcomes. Women's specific treatment needs have led some providers to develop women-only SUD treatment programs in several countries. In Chile, women-only programs were only fully implemented in 2010. We compared treatment outcomes and readmission risk for adult women admitted to state-funded women-only versus mixed-gender SUD treatment programs in Chile.

Methods: We used a registry-based retrospective cohort design of adult women in women-only (N= 8,200) and mixed-gender (N= 13,178) SUD treatment programs from 2010 to 2019. The study obtained data from the National Drug and Alcohol Service from Chile. We used a multistate model to estimate the probabilities of experiencing treatment completion, discharge without completion (i.e., patient-initiated discharge and administrative discharge), or readmission, as well as the likelihood of being readmitted, conditioned on prior treatment outcome. We adjusted models for multiple baseline characteristics (e.g., substance use, socioeconomic).

Results: Overall, 24% of women completed treatment and 54% dropped out of treatment. The proportion of patient-initiated discharges within the first three month was larger in women-only than in mixed-gender programs (19% vs. 12%). In both programs, women who completed treatment were more likely to experience readmission at three months, and one and three years. In the long term, women in the women-only programs were more likely to complete treatment than women in mixed-gender programs (34% vs. 23%, respectively). The readmission probability was higher among women who previously completed treatment than those who had a discharge without completion (40% vs 21% among women in women-only programs; 38% vs. 19% among women in mixed-gender programs, respectively); no

differences occurred in the risk of readmission between women-only and mixed-gender programs.

Conclusions: In terms of treatment outcomes and readmission risk, women-only programs had similar results to mixed-gender programs in Chile. The added value of these specialized programs should be addressed in further research.

Keywords: Substance use disorder; Treatment; Gender; Chile

1. Introduction

In residential or outpatient settings, substance use disorder (SUD) treatment interventions usually occur in mixed-gender group format (U.S. Department of Health and Human Services & General, 2016), where group interventions can be a powerful therapeutic tool for addressing SUDs (National institute on drug abuse, 2020). If well guided, group treatment can direct groups to foster healthy attachments, provide positive peer reinforcement, strengthen self- expression, and help individuals to develop new social skills (U.S. Department of Health and Human Services & General, 2016). However, research has criticized the group approach as insensitive to gender-related dynamics (Greenfield et al., 2010). Evidence shows that while women with SUD seek treatment in mental health services, men are more likely to access specialized SUD treatment programs. This divide can lead to a male-dominated therapeutic environment, as males can be overrepresented in these settings (McHugh et al., 2018; Tuchman, 2010). In this context, interactional styles in group interventions may better suit hierarchical and confrontational "male cultural norms" (McHugh et al., 2018).

Overall, women are less likely than men to use illicit drugs and tend to initiate substance use later in life than men, but women experience a faster progression from substance use to dependence or abuse, and consequently a faster progression to first treatment entry. This accelerated progression to SUDs is usually associated with more severe SUD-related problems (Ait-Daoud et al., 2019; Agabio et al., 2019). Over the last three decades, though, the increased recognition of sex and gender differences in SUDs has led to the implementation of women-only treatment programs in many countries (Schleifer & Pol, 2017).

In Chile, women-only programs were fully established at a national level in 2010 under the technical support and funding of the National Service for Prevention and

Rehabilitation of Drug and Alcohol Consumption of Chile (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol y Ministerio de Salud de Chile, 2018). This program was designed to improve treatment access and address the vulnerabilities that Chilean women with SUD face.

From a risk environment perspective (Rhodes, 2009; Collins et al., 2019), social vulnerability of women with SUD experience social vulnerabilities as a result of a range of macro- (economic, political, and social milieus) and micro-level environments (drug trafficking neighborhoods, intimate-partner violence, sex trade participation) that intersect with disadvantaged social locations to produce increased risk (Collins et al., 2019).

Data from Chilean SUD treatment programs depict the disadvantaged position of women with SUD, expressed in their lack of economic autonomy (i.e., income generation), housing instability, food insecurity, trauma/violence exposure, and stigmatization due to difficulties in accomplishing Latin American traditional gender roles, in which women are expected to be affectionate, submissive, and a faithful spouse; mother and family caregiver, in contrast to the independent, polygamous, and dominant Chilean *macho* man (Cianelli et al, 2008; Hawkins et al., 2017). Accordingly, 45% of women admitted to public treatment programs reported being unemployed, and 29% reported unpaid work. Among women with co-occurring mental health problems, 70% reported being victims of interpersonal violence from their partners or other family members (Valencia-Recabarren, 2015). Results from an RDS study of people who use cocaine base paste in Chile may be indicative of how the structural environment and situated contexts in Chile affect women with SUD. For example, women from this study reported a total monthly income of USD$150 (USD$68 under the poverty line in Chile), which was 50% lower than the income that men reported (Instituto de Sociología de la Pontificia Universidad Católica de Chile, 2015). Women also reported more

insecure housing conditions and lower levels of education (Instituto de Sociología de la Pontificia Universidad Católica de Chile, 2015).

Hence, the implementation of gender-specific services in Chile represents an effort to provide a therapeutic alternative that may better suit the needs of women with SUD.
The SUD treatment programs system implemented in Chile provides professional therapeutic interventions and services, including social support, psychotherapy (individual and group format), mental health counseling, and basic pharmacological support, among others (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, & Ministerio de Salud de Chile, 2012). In contrast to the general population program, the women-only program also includes gender-sensitive services such as childcare facilities, peri/postnatal care (i.e., adequate infrastructure and trained staff), and transportation services. Based on a gender-relational perspective, this program seeks to provide a safe and empathic therapeutic environment to address gender-specific needs and develop social skills such as validation, empowerment, and empathy, which have been considered critical for attachment and recovery in groups of women (Greenfield et al., 2013; Covington & Surrey, 1997). In addition, women-only programs in Chile include co-educational services to enhance parental skills development and the acquisition of skills to generate income. Women-only programs also play an important role in coordinating with other social services (e.g., legal system, primary health care services) that are critical to the recovery and social integration of women with SUDs (Consejo Nacional para el Control de Estupefacientes, 2007; Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol y Ministerio de Salud de Chile, 2018).

In several Latin American countries, a critical limitation for research and program management has been the lack of centralized data systems. However, in Chile, this difficulty has been overcome due to the implementation of a centralized data registry system,

SISTRAT, since 2010 (Centro de Estudios Justicia y Sociedad & Pontificia Universidad Católica de Chile, 2020). This data system registers all patients admitted to adult SUD treatment programs in centers affiliated with SENDA's network, and contains relevant patient information (i.e., sociodemographics, health status, and substance use history). In this context, the implementation of women-only programs and SISTRAT data offers us a unique opportunity to analyze the outcomes of women-only SUD treatment options in a Latin American context.

Given the scarce evidence on treatment quality and outcomes of state-funded women-only treatments in Chile (Centro de Estudios Justicia y Sociedad & Pontificia Universidad Católica de Chile, 2020; Valencia-Recabarren, 2015), this study aimed to compare treatment outcomes and readmission risk between adult women admitted to state-funded women-only treatment programs and those admitted to mixed-gender SUD treatment programs in Chile.

2. Methods

2.1. Study design

We conducted a retrospective analysis of 21,378 records in SISTRAT for women in residential and outpatient SUD treatments between 2010 and the third quarter of 2019. All patient identification information was encrypted using an MD5 (Message Digest 5) algorithm, which is widely used in security protocols to encrypt information, such as a personal identification number, into a 128-bits hash code (Jayawickrama, 2008). The selected data encompass admissions and discharges for SUD treatment. The eligibility criteria included women of 18+ years of age admitted at least once to a women-only or mixed-gender SUD treatment program funded by SENDA between 2010 and 2019.

The Ethics Committee of Universidad Mayor, Chile, reviewed and approved this study (No. 260/2019).

2.2. Measures

A treatment center professional interview all clients of state-funded SUD treatment programs in Chile upon admission. Through this interview, the center's professionals gather information on the client's sociodemographic characteristics, health status, substance use patterns, among other factors, which they then enter into the SISTRAT system. Clinical information stems from the appraisal of the treatment team in consultation with a psychiatrist or physician with mental health experience, if necessary. Centers must collect the data to proceed to payment.

Treatment outcomes considered in our study were registered at discharge, with two possible categories: treatment completion and discharge without completion. This study collapsed and treated as one treatment referrals to another SUD treatment (i.e., treatment transfers) within the same treatment network (often suggested by the professional team of the center due to change of address, change of the treatment plan, or other justified reason) with fewer than 45 days of difference. These can be conceived as consecutive episodes provided by one or more providers. Referrals outside of SENDA's network (e.g., mental and other health centers) that did not experience a readmission within the study period were treated as right censored, because the follow-up period ended before any of the treatment outcomes occurred (Jepsen et al., 2015).

SENDA's guidelines define treatment completion as a discharge after achieving the goals determined in the patient's individual treatment plan developed by the therapeutic team at admission. We grouped patient-initiated discharges (i.e., drop-outs) and administrative discharges (i.e., discharges due to serious misconduct against treatment norms) into one category called "discharge without completion" (Guerrero et al., 2013).

The study defined readmissions as having a second entry to a treatment program within SENDA's network (Moon & Lee, 2020). If more than one readmission was recorded,

we considered only the first in the multistate analysis. We based this decision on the fact that among readmitted women, 72% registered only one admission.

We compared patient-level sociodemographic, substance use, health, and treatment characteristics of women in mixed-gender and women-only programs (i.e., age, educational attainment, have children, housing, biopsychosocial status, primary substance at admission, frequency of use of primary substance, co-occurring SUD, treatment duration, and treatment modality). See supplemental Table S1 for a detailed description of these variables.

2.3. Analysis

After applying exclusion criteria (<18 years of age and men) and data cleaning processes, missing data ranged from 0% to ~4.4% across the covariates. We implemented multivariate imputation by chained equations using the Amelia package (Honaker et al., 2011; Zhang, 2016), assuming data were missing at random (see the Supplemental Material for additional details).

Since we studied concatenated events (admission-discharge-readmission), we implemented a multistate approach to incorporate all data in a single modeling process. Multistate models are an extension of competing-risk regression models that allow us to analyze event history data (Castañeda & Gerritse, 2010; Kulkarni et al., 2017). We specified a model of four states, starting with the initial admission as the first state, followed by treatment completion and discharge without completion as intermediate competing states, ending with readmission as the sole absorbing state (see the Supplemental Material for additional information). The study assessed the proportional hazards assumption in the Cox models visually and through a chi-squared goodness-of-fit test (more details in the Supplemental Material). We chose the parametric model that best fit the data for each transition according to Akaike information criterion (Akaike, 1976), visual inspection, and

extrapolation up to 15 years. We compared intercept-only models to select the standard parametric models across each of the transitions. The best-fitted models included Gompertz distributions for transitions from admission to treatment completion and admission to discharge without completion. The study team chose log-normal distribution for the transition from admission to readmission. Generalized-Gamma and log-normal distributions, respectively, provided the most reasonable fit for the transitions from treatment completion and discharge without completion. Additional information on the modeling process is available in the Supplemental Material.

We checked whether the time spent in a previous state played an important role for intermediate states. As treatment duration (i.e., time in the baseline state) could affect the likelihood of readmissions, we used a semi-Markov multistate model that included the time spent in treatment (years in treatment). This multistate model is the result of the combination of the selected distributions for each of the transitions. The study adjusted these models for all covariates listed in section 2.2 and detailed in Table S1 in the Supplemental Material. Based on two hypothetical patients, we first obtained the patient-specific instantaneous cumulative hazards of progressing from one state to another. From the adjusted models, we calculated transition probabilities (i.e., the probability that a patient would change from a state to another at a certain time), and length of stay in each state by simulating patients' trajectories and transitions at three months, and 1 and 3 years, modeling at the individual patient level, which generated two hypothetical patients with the same average covariate characteristics, except for being exposed to different type of programs (Crowther MJ & Lambert PC, 2017; Jackson, 2016; Williams et al., 2017). We considered these three time points based on a consensus established between our research team and SENDA's team professionals who are responsible for treatment program design and functioning in Chile.

The study calculated the Kaplan-Meier survival curves and simple survival model using the *survival* package (Therneau T., 2021). The study estimated the smoothed hazard function through the *muhaz* package (Hess & Gentleman, 2019). The multistate semi-Markov models were fitted using the *mstate* (de Wreede et al., 2011), *flexsurv* (Jackson, 2016), and *survival* packages. The research team completed all of the analyses in R statistical software version 4.0.2. (R Core Team, 2020).

Data and markdown with all software codes and outputs are available at https://bit.ly/34uGjbv.

3. Results

Table 1 summarizes demographic and substance use data comparing baseline characteristics of women attending women-only and mixed-gender treatment programs between 2010 and 2019. Samples differ from one another in several characteristics. The women-only programs had a larger proportion of women between 18 and 29 years old (41%) than the mixed-gender programs (34.3%); the proportion of women in women-only treatment who reported living in their own house was 19% lower than women in mixed-gender programs; and women in women-only programs were 1.28 times more likely to be staying temporarily with relatives than those in mixed-gender programs. A larger proportion of severe biopsychosocial status occurred in women in the women-only programs (57.4% vs. 30.6%). A greater proportion of women in women-only treatment declared using one or more drugs as secondary substances compared to patients in the mixed-gender program (79% vs. 66,7%). Finally, women in the women-only programs were 8.8 times more likely to be admitted to residential treatment settings than women in the mixed-gender programs.

The incidence rate of treatment readmission was approximately 85 per 1,000 patients-year among women admitted to women-only treatment at baseline vs. 55 per 1,000 patients-

year among women admitted to mixed-gender programs. Additionally, the incidence rate of readmission among patients with a discharge without completion was approximately 83 vs. 63 per 1,000 patients-year in patients with treatment completion at admission.

3.1. Multistate model

As Figure 1 shows, this model estimates the adjusted probability of 5 possible transitions. There were 21,378 women with at least one treatment admission during any time point between January 1, 2010, and November 13, 2019; 16.4% (n=3,516) remained in the same states up until the end of the follow-up period, mostly those admitted in 2018–2019, since they had a shorter follow-up period and thus a lower chance of completing their treatment; 56.1% had a discharge without completion; 24% completed treatment; and 3.5% transitioned directly from admission to readmission. The latter corresponds to women referred to treatments outside SENDA's network who were then readmitted to treatment.

3.1.1 Cumulative hazards

We computed the adjusted hazards of transitioning from one state to another based on a set of the most frequent categories of each covariate, also known as patient-specific transitions (Putter et al., 2007). As Figure 2, panel A shows, women in women-only programs have higher adjusted hazards of treatment completion compared to women in mixed-gender programs. Women-only programs showed slightly lower rates from admission to discharge without completion. For the transitions admission-readmission, discharge without completion-readmission, and treatment completion-readmission, differences between women-only and mixed-gender were negligible, with slightly greater rates for women-only programs.

By incorporating these patient-specific cumulative hazards as input, we estimated the probability of transitioning from one state to another, and the predicted average time spent for the three follow-up periods considered (3 months, 1 year, and 3 years).

3.1.2. Transition probabilities

Table 2 shows that the probability of experiencing readmission was significantly greater for those patients with treatment completion at every time point for both types of programs. The estimated state transition probabilities for the sets of covariates do not differ much between program types. However, we noticed that women-only programs were more likely to transition from admission to treatment completion than to discharge without completion. This difference is statistically significant only at 3 years (34%; 95% CI: 28–40% vs. 23%; 95% CI: 20–26%). In contrast, mixed-gender programs had a slightly greater transition probability from admission to discharge without completion. Still, these differences were not statistically significant at any time point that the study measured. The readmission probability was higher among women who previously experienced treatment completion than those who experienced a discharge without completion (40% vs 21% among women in women-only programs; 38% vs. 19% among women in mixed-gender programs, respectively); no differences existed in the probability of readmission between women-only and mixed-gender programs.

3.1.3. Expected length of stay

The study found no significant differences between women-only and mixed-gender programs in the length they stayed in each state (e.g., average time between treatment discharge and readmission) at any time point reported (3 months, 1 year, and 3 years). However, for women-only programs, after one year of observation, those who were

discharged without completion were expected to remain in that state on average for 0.92 (95% CI: 0.90–0.95) years vs. 0.82 (95% CI: 0.75–0.88) for those who experienced treatment completion. For women in mixed-gender programs, those who were discharged without completion remain in that state on average for 0.93 (95% CI: 0.91–0.95) years vs. 0.83 (95% CI: 0.75–0.89) for those who had treatment completion. The relative difference between those discharged without completion and those with a treatment completion is the same at 3 years (see the Supplemental Material).

4. Discussion

Our study examined treatment outcomes for women in women-only versus mixed-gender SUD treatment programs using data of 21,378 adult women admitted to publicly funded SUD treatments from 2010 to 2019 in Chile. We found that patients admitted to women-only programs had a slightly higher probability of treatment completion than those admitted to mixed-gender programs. However, we observed no difference in the probability of being discharged without completion or in the probability of being readmitted to treatment. Overall, about one quarter of patients had completed treatment and a little less than half had a patient-initiated discharge (15% within the first 3 months). More women in women-only programs had a patient-initiated discharge within the first 3 months of treatment (19%) compared to women in mixed-gender programs (12%); the former were younger, reported using cocaine base paste daily in a larger proportion, and had a more severe biopsychosocial status.

Based on the available literature, the comparative effectiveness of women-only and mixed-gender programs remains unclear, with several studies showing mixed results. However, as expected under the rationale of gender-oriented programs, our results show that women in the women-only programs had a greater probability of completing treatment than

those in the mixed-gender program, which research has been indicated as one of the most critical factors to obtaining treatment benefits overall (Brorson et al., 2013). This finding is also in line with previous evidence indicating that women in women-only programs had greater likelihood of staying longer in treatment relative to women in mixed-gender programs (Greenfield et al., 2007). In line with this, higher levels of treatment completion in programs have been associated with the availability of facilities that allow women to participate with their children, which research has identified as a critical barrier to treatment access for women (Brady & Ashley, 2005).

The negligible differences of readmission probabilities between programs are consistent with evidence showing no significant associations between the type of program (i.e., women-only or mixed-gender) and better long-term treatment outcomes (Hser et al., 2011; Kaskutas et al., 2005). For example, a randomized clinical trial that compared outcomes of women-only outpatient programs to mixed-gender programs (N=122) found no significant differences in psychiatric or social problem severity at any of the follow-up points (6- and 12-months post-treatment). Similarly, the study found no significant differences in drug use abstinence between the two groups (Kaskutas et al., 2005). One of the unique contributions of this study is that it relies on a large population-based dataset. Additionally, to our knowledge, no previous studies on this topic have taken advantage of multistate modeling to look simultaneously at sequential events in SUD treatments. Our findings add valuable information on women-only treatments in the Latin American context, where little research has been published on women-only treatments' comparative effectiveness (Zilberman et al., 2003b).

Research has had an ongoing debate (Hansen et al., 2020; Hser et al., 2011) about readmission as a treatment outcome—its advantages and disadvantages, and its different interpretations. For example, Hansen et al. argue that readmission overcomes the difficulties

of using measures based on self-reported data such as the definition of treatment goals and experiencing return to substance use (Hansen et al., 2020). Other authors have proposed nuances for interpreting readmission that can certainly apply to our results (Hornack & Yates, 2017; Hser et al., 2011). Readmission may be interpreted as a positive event if the readmission results from a woman's increased awareness of her need to minimize drug exposure and skills development that has resulted in efficiently using health care services (Almeida et al., 2018; Vazquez et al., 2015). Women at risk of returning to substance use might have been able to seek counseling in primary care services as the first preventive action. If primary care support could not prevent return to use, then treatment readmission may have been needed as part of therapeutic planning. Thus, network coordination between primary care services and specialized services can maximize resources and ensure care continuity (Pan American Health Organization, 2010; Vazquez et al., 2009).

In contrast, if readmissions are the result of the existence of a "captive" population of specialized services, then readmission may be interpreted as a health system failure, one that has failed to offer care continuity in services of lower complexity (Pan American Health Organization, 2010), which are expected to be an important point of support for those with chronic illnesses such as SUDs.

In light of these interpretations, the negligible differences between women-only and mixed-gender programs do not allow us to assert that women admitted to women-only programs had a lower readmission risk after treatment completion than women in mixed-gender programs. Future studies should formally test differences in transition probabilities.

Our analytic approach allows us to capture only a part of a highly complex phenomenon that is influenced by several factors and that has multiple relevant outcomes apart from type of discharge and treatment readmission (i.e., social functioning, criminal offending, return to substance use, among others) that we could not consider in the analysis.

Other intersecting dimensions, such as experiences of gender-based violence and economic dependence, may characterize risk environments that may lead to treatment readmission. For example, in Chile, women previously admitted to SUD treatment may prefer readmission because they lack the resources to maintain stable housing and food security. Especially in residential settings, individuals may see treatment readmission as a way to avoid intimate-partner violence, which research has shown to be highly prevalent among women with SUD.

Beyond evidence of the effectiveness of women-only or mixed-gender programs, women-only programs are likely to be more sensitive to gender-specific needs (e.g., intimate partner violence, pregnancy) than mixed-gender programs and could enhance treatment access for women (Holzhauer et al., 2020).

4.1 Limitations

While our study used a large administrative dataset that had many advantages, the study also has limitations. For example, some relevant clinical information is not registered in SISTRAT, such as stage of change, traumatic experiences, or addiction severity. We acknowledge that the existence of these and other unmeasured variables may lead to residual confounding when comparing women-only and mixed-gender treatment programs. Other key variables that this study measured may vary in quality or completeness, such as psychiatric comorbidity. We did not have other information that could enhance our ability to describe complex trajectories of women outside SUD treatment programs. Data on mortality, hospitalizations, and incarceration could complement the analysis and point to potential milestones before readmission. Finally, due to the novel methodological framework that we used, we recognize that model structures influence conclusions (Cranmer et al., 2020), and that there is room for modeling improvements (e.g., more flexible transition probability distributions) and more complex structures, including other states in the treatment outcome

(early vs. late dropout), second or third treatment readmissions, and time-varying confounders or interaction terms (Gran et al., 2015).

5. Conclusions

Overall, our findings suggest that women-only programs have similar results in terms of treatment outcomes and readmission risk to mixed-gender programs. Future research on the added value of specialized SUD treatment programs and their effectiveness should incorporate other dimensions of analysis to better capture the complexity of this phenomenon. For example, information on trauma histories, economic dependence, gender-based violence experiences, social support networks, and other services utilization (i.e., primary care services and hospitalizations) are relevant factors that may influence treatment success and readmission risk. Women's preferences regarding SUD treatment and how the construct of "gender" held within treatment centers may affect women's recovery process have been pointed out as critical dimensions that remain necessary to address (Grella, 2018; Neale et al., 2018). Qualitative research may be a better methodological approach to address these and other dimensions.

A multistate framework may be an adequate analytic approximation to jointly capture SUD treatment utilization as well as other health services utilization that the integrated health care network implemented in Chile has provided.

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Table1. Characteristics of women admitted to women-only and mixed-gender treatment programs, Chile 2010-2019

	Women-only (N=8200)	Mixed-gender (N= 13178)	Statistic	p value
Age in years at admission to treatment. N (%)			X^2 [a](3)=185.38	<0.001
18-29	3364 (41.0)	4522 (34.3)		
30-39	2754 (33.6)	4277 (32.5)		
40-49	1382 (16.9)	2651 (20.1)		
50+	700 (8.5)	1728 (13.1)		
Educational attainment. N (%)			X^2 [a](2)=7.55	0.023
Completed primary school or less	2655 (32.4)	4360 (33.1)		
Completed high school or less	4281 (52.2)	6645 (50.4)		
More than high school	1264 (15.4)	2173 (16.5)		
Primary substance at admission. N (%)			X^2 [a](4)=722.05	<0.001
Alcohol	1903 (23.2)	4843 (36.8)		
Cocaine hydrochloride	1435 (17.5)	2526 (19.2)		
Cocaine base paste	4116 (50.2)	4304 (32.7)		
Marijuana	474 (5.8)	943 (7.2)		
Other	272 (3.3)	562 (4.3)		
Consumption frequency of primary substance. N (%)			X^2 [a](4)=814.09	<0.001
Less than 1 day per week	218 (2.7)	842 (6.4)		
1 day per week	295 (3.6)	1045 (7.9)		
2 to 3 days per week	1680 (20.5)	3891 (29.5)		
4 to 6 days per week	1175 (14.3)	2052 (15.6)		
Daily	4832 (58.9)	5348 (40.6)		
Biopsychosocial status. N (%)			X^2 [a](2)=1,703.06	<0.001
Mild	163 (2.0)	1329 (10.1)		
Moderate	3334 (40.7)	7823 (59.4)		
Severe	4703 (57.4)	4026 (30.6)		
Tenure status of households. N (%)			X^2 [a](4)=258.47	<0.001
Illegal Settlement	146 (1.8)	180 (1.4)		
Owner/Transferred dwellings/Pays dividends	2498 (30.5)	4936 (37.5)		
Renting	1355 (16.5)	2725 (20.7)		
Stays temporarily with a relative	3978 (48.5)	4994 (37.9)		
Others	223 (2.7)	343 (2.6)		
Co-occurring SUD. N (%)			X^2 [a](2)=432.20	<0.001
No additional SUD	1727 (21.1)	4397 (33.4)		
One additional SUD	3215 (39.2)	4898 (37.2)		
More than one additional SUD	3258 (39.7)	3883 (29.5)		
Has children = Yes. N (%)	7287 (88.9)	11522 (87.4)	X^2 [a](1)=9.67	<0.001
Treatment outcome. N (%)			X^2(5)=249.34	<0.001
Administrative discharge	744 (9.1)	994 (7.5)		
Early Drop-out	1522 (18.6)	1638 (12.4)		
Late Drop-out	2313 (28.2)	4784 (36.3)		
Ongoing treatment	573 (7.0)	1026 (7.8)		
Referral to another treatment	1042 (12.7)	1628 (12.4)		

Treatment Completion	2006 (24.5)	3108 (23.6)		
Days in treatment. Mean (SD)	221.48 (190.78)	247.57 (198.18)	t [b]=9.58	<0.001
Treatment modality = Residential. N (%)	3323 (40.5)	603 (4.6)	X^2 [a](1)=4,354.71	<0.001

Note: Days in treatment with missing dates of discharge were calculated based on the difference between admission date and 2019-11-13

[a] Chi-square test for independence.

[b] t-statistic difference of means.

Table 2. Probability of remaining or transitioning to any of the four states, Chile 2010-2019.

Actual state	Women-only				Mixed-gender			
	ADM	**TC**	**DWC**	**READM**	**ADM**	**TC**	**DWC**	**READM**
At 3 months								
Admission	0.79 [0.77-0.81]	0.10 [0.09-0.12]	0.09 [0.08-0.10]	0.01 [0.01-0.02]	0.81 [0.79-0.83]	0.08 [0.07-0.10]	0.10 [0.09-0.11]	0.01 [0.01-0.02]
Treatment completion	-	0.86 [0.81-0.91]	-	0.14 [0.09-0.19]	-	0.87 [0.81-0.92]	-	0.13 [0.08-0.19]
Discharge without completion	-	-	0.95 [0.93-0.96]	0.05 [0.04-0.07]	-	-	0.95 [0.93-0.97]	0.05 [0.03-0.07]
At 1 year								
Admission	0.45 [0.40-0.48]	0.26 [0.22-0.30]	0.20 [0.18-0.23]	0.09 [0.07-0.12]	0.49 [0.45-0.53]	0.21 [0.18-0.25]	0.22 [0.20-0.25]	0.08 [0.06-0.10]
Treatment completion	-	0.74 [0.64-0.82]	-	0.26 [0.18-0.36]	-	0.75 [0.66-0.83]	-	0.25 [0.17-0.34]
Discharge without completion	-	-	0.88 [0.84-0.91]	0.12 [0.09-0.16]	-	-	0.89 [0.86-0.92]	0.11 [0.08-0.14]
At 3 years								
Admission	0.17 [0.13-0.20]	0.34 [0.28-0.40]	0.23 [0.20-0.26]	0.26 [0.21-0.32]	0.22 [0.17-0.26]	0.30 [0.25-0.36]	0.26 [0.23-0.29]	0.23 [0.18-0.28]
Treatment completion	-	0.60 [0.50-0.70]	-	0.40 [0.30-0.50]	-	0.62 [0.50-0.73]	-	0.38 [0.27-0.50]
Discharge without completion	-	-	0.79 [0.74-0.83]	0.21 [0.17-0.26]	-	-	0.81 [0.76-0.85]	0.19 [0.15-0.24]

Note. Removed Readmission rows because it was an absorbing state. ADM = Admission; TC = Treatment completion; DWC= Discharge without completion; READM = Readmission. Cells with "-" describe unallowed transitions.

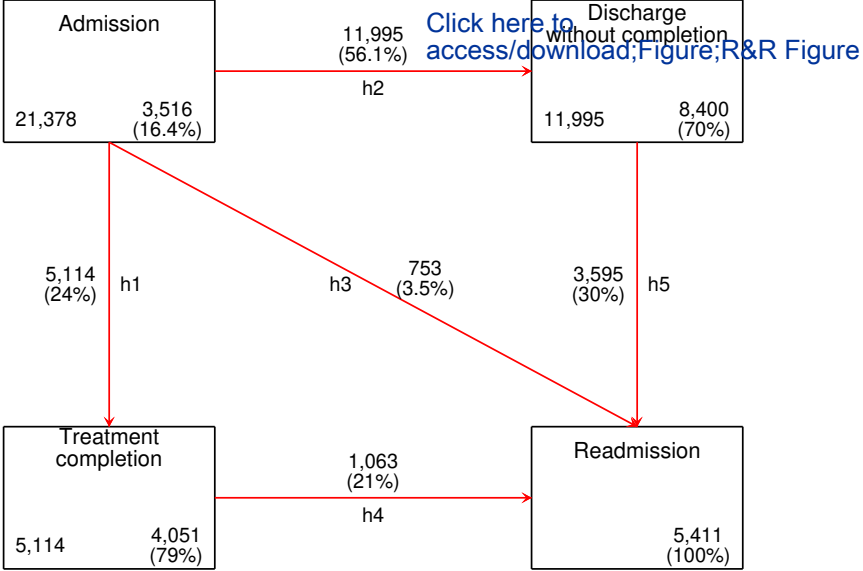
Figure 1. Graphical representation of four states model

Note. The number in the bottom-left corner depicts the number of cases that passed through the state; the number in the bottom-right corner shows no other events or subjects remaining in the same state; "h" stands for transitions. The 3,516 users who remained in the Admission state had an ongoing treatment at baseline or were referred to other treatments but did not experience readmission.

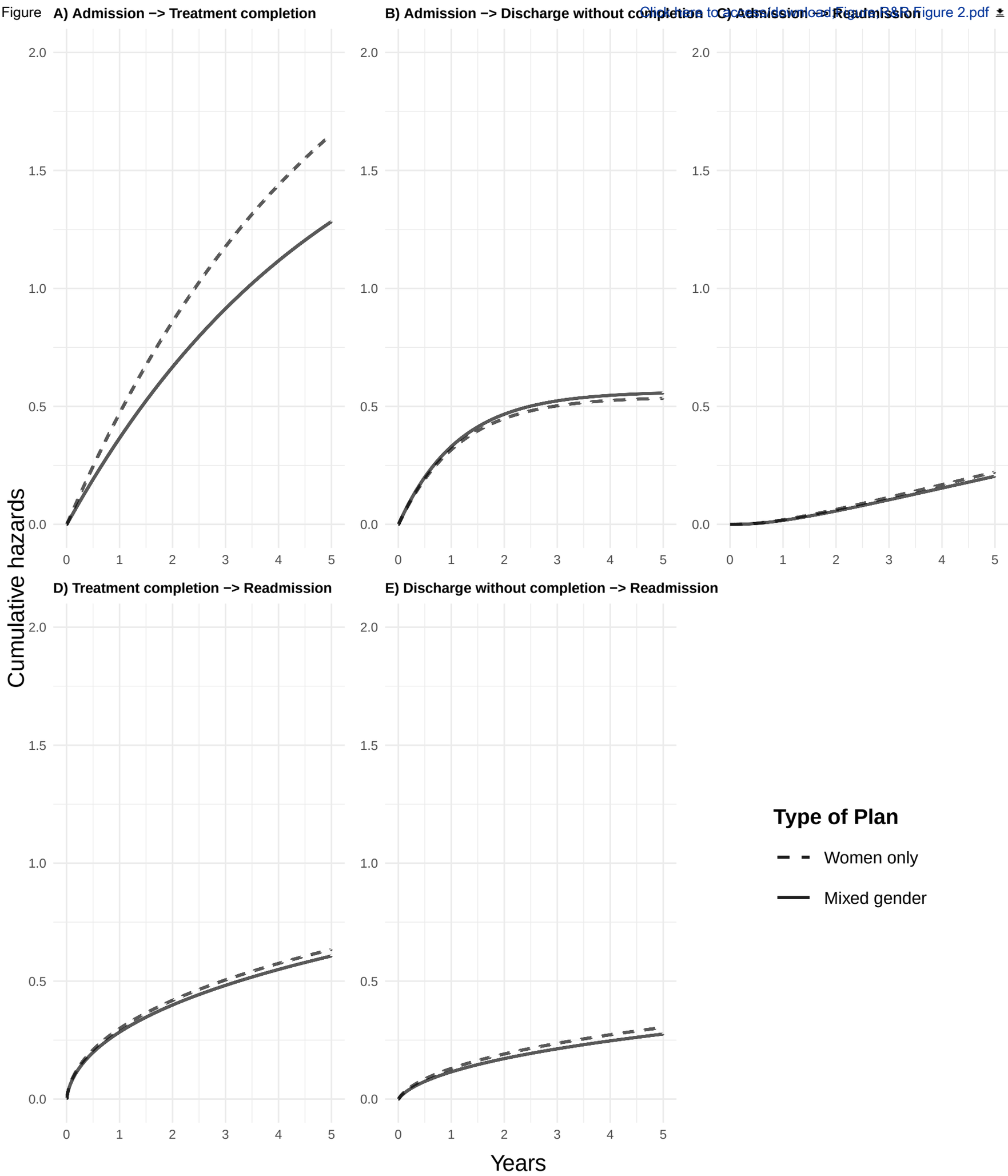
Figure 2. Cumulative hazards of transitioning across different states among women in women-only vs. mixed-gender treatment programs

Note. Dashed line: Women-only program. Solid line: Mixed-gender program. Both lines represent hazards for average covariate values, which are woman aged 30-39, who completed high school or less, reported alcohol as the primary substance at admission, had a daily consumption frequency, moderate biopsychosocial status (i.e., multidimensional clinical appraisal of SUD severity made by the professional team), stayed temporarily with a relative, had co-occurring SUD (i.e., diagnosis of abuse of dependence of one additional substance), had more than one child, and were in a residential treatment modality.

Figure



Figure



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