Drug and Alcohol Dependence 237 (2022) 109507

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Identifying key risk factors for premature discontinuation of opioid use disorder treatment in the United States: A predictive modeling study

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ARTICLE INFO

Keywords:
Treatment for opioid use disorder
Treatment attrition
Machine learning
Opioid
Buprenorphine
Methadone

ABSTRACT

Background: Treatment for opioid use disorder (OUD), particularly medication for OUD, is highly effective; however, retention in OUD treatment is a significant challenge. We aimed to identify key risk factors for premature exit from OUD treatment.

Methods: We analyzed 2,381,902 cross-sectional treatment episodes for individuals in the U.S., discharged between Jan/1/2015 and Dec/31/2019. We developed classification models (Random Forest, Classification and Regression Trees (CART), Bagged CART, and Boosted CART), and analyzed 31 potential risk factors for premature treatment exit, including treatment characteristics, substance use history, socioeconomic status, and demographic characteristics. We stratified our analysis based on length of stay in treatment and service setting. Models were compared using cross-validation and the receiver operating characteristic area under the curve (ROC-AUC).

Results: Random Forest outperformed other methods (ROC-AUC: 74%). The most influential risk factors included characteristics of service setting, geographic region, primary source of payment, and referral source. Race, ethnicity, and sex had far weaker predictive impacts. When stratified by treatment setting and length of stay, employment status and delay (days waited) to enter treatment were among the most influential factors. Their importance increased as treatment duration decreased. Notably, importance of referral source increased as the treatment duration increased. Finally, age and age of first use were important factors for lengths of stay of 2–7 days and in detox treatment settings.

Conclusions: The key factors of OUD treatment attrition identified in this analysis should be more closely explored (e.g., in causal studies) to inform targeted policies and interventions to improve models of care.

1. Introduction

Opioid-related deaths have risen dramatically since the 1990s, with over 90,000 deaths in the United States in 2020 alone (Ahmad et al., 2021). With an estimated 1.6 million people suffering from opioid use disorder (OUD), millions more lives are impacted beyond victims of fatal

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https://doi.org/10.1016/j.drugalcdep.2022.109507
Received 10 December 2021; Received in revised form 22 April 2022; Accepted 18 May 2022
Available online 21 May 2022
0376-8716/

overdoses (SAMHSA, 2020).

Treatment for OUD, particularly medication for OUD (MOUD), is highly effective (Wakeman et al., 2020). Treatment success depends on adherence and retention in care (Timko et al., 2016). Research indicates that while there is variation by treatment type (e.g., MOUD or psychosocial treatment), OUD treatment of all kinds suffers from high rates of premature exit. For instance, studies published between 2001 and 2019 reported that almost half of individuals in treatment are not retained at 12 months, with further attrition for longer timeframes (O'Connor et al., 2020). Globally, studies citing treatment discontinuity are common (Basu et al., 2017; Berghofer et al., 2002). Better retention in treatment requires an improved understanding of the characteristics and needs of target populations, and to date, the literature offers limited and conflicting evidence.

Two systematic reviews (Brorson et al., 2013; Lappan et al., 2020) summarized several hundred studies, showing that literature on predictors of treatment retention, adherence, or discontinuation shared small sample sizes (e.g., median N = 144 among studies included in the 2013 review), and limited scope and generalizability (e.g., faith-based treatment, or male populations only). Also, the reviewed studies considered few covariates, and those were primarily demographics (e.g., education, sex (Longabaugh et al., 2009; Sayre et al., 2002; Vendetti et al., 2002)). Furthermore, where there was overlap in factors included across studies, the results were often conflicting. For example, 64 of the 122 studies included in the 2013 review examined the role of sex. Only 10 reported a statistically significant relationship, with five reporting male sex as a predictor of treatment discontinuation and five reporting female sex as a predictor of discontinuation. Less than 10% of studies investigated the relationship between retention and treatment-specific factors such as the method, setting, and duration (Brorson et al., 2013). In Lappan et al. (2020), a similar focus on demographic factors, such as age, sex, and education was evident. For example, 146 of the 151 studies examined the role of age, with studies generally concluding that age was not a significant predictor of premature treatment exit. The only participant characteristics associated with discontinuation were race, income, daily cigarettes smoked, and heroin and cocaine use. Since the publication of these systematic reviews, a 2021 study specific to retention in MOUD found that methamphetamine use, younger age, and homelessness were risk factors for treatment discontinuation (Krawczyk et al., 2021). Another recent study found that the length of stay in a treatment facility, the state and geographical region of treatment, and patients' age and employment status had strong associations with treatment discontinuation (Gautam and Singh, 2020).

Despite the substantial body of literature on the opioid overdose crisis, the importance of treatment, and concerns about treatment retention (NASEM, 2019), a large-scale, multi-year analysis of both demographic *and* contextual factors contributing to premature treatment exit has not been conducted. To address this gap, we conducted a machine learning analysis based on millions of treatment episodes with a large holistic set of predictors that cover individual-level and system-level factors. This is in contrast with prior studies on much narrower sets of predictors. Our objective was to determine which factors best predict treatment attrition, and critically, how those factors vary across different lengths of stay in treatment and treatment settings. Illuminating specific factors from this rich national data source can help pinpoint factors that should be more closely explored to inform targeted interventions.

2. Methods

2.1. Study population

The cohort consisted of all OUD treatment episodes included in the Treatment Episode Data Set-Discharges (TEDS-D) (SAMHSA, 2015)—a national data system that contains records of individuals ages 12 and older derived from substance use disorder treatment facilities. Because TEDS is admission-based, records represent treatment episodes, rather than unique individuals (SAMHSA, 2019). The national system includes facilities that receive any federal funding; varying by state, this can also include facilities such as private doctors' offices. Cross-sectional data from 2015 until the most recent available year, 2019, were combined. If a state did not report sufficient data in a year, the Substance Abuse and Mental Health Services Administration excluded the state from the TEDS system (Table S1). Years prior to 2015 were excluded because they collected fewer variables. Included were episodes where individuals reported use of heroin or other opioids. In addition, similar to prior research (Askari et al., 2020), any treatment episode that was ended due to a transfer to another program or facility was excluded—reasons for transfer are not reported in TEDS-D. No other inclusion or exclusion criteria were used.

We followed best practice observational study reporting guidelines (von Elm et al., 2007). Complete datasets, code, and results are available on GitHub (https://github.com/castaff/TEDS_Treatment_Attrition) for review and reproducibility (Beam and Kohane, 2018). The analysis was not pre-registered, and the results should be considered exploratory.

2.2. Factors and factor creation

To predict treatment discontinuation, we included 23 raw factors from TEDS-D that were collected at admission in addition to length of stay in treatment, the only covariate collected at discharge. Included risk factors were demographics, frequency of substance use, routes of substance administration, self-reported substances used, treatment history, source of referral, and planned treatment type (i.e., whether MOUD was planned in the patient's treatment). Health insurance and the primary source of payment variables had overlaps, so we only included the primary source of payment which provided more information.

By combining and recoding existing factors, we also created several additional variables. The first reflects minimum reported age at which the individual began using substances (Jordan and Andersen, 2017). The second presents the maximum frequency of nonmedical opioid use. A third variable was created indicating any current heroin use, and the fourth indicated any injection drug use (Uusküla et al., 2015). Finally, four binary factors were created indicating whether individuals had used substances falling into the broad categories of stimulants, hallucinogens, sedatives, or tranquilizers.

In total, 31 factors were included. A table of excluded variables and the reasons for exclusion can be found in Table S2, along with a description of variable recoding.

2.3. Outcome

We dichotomized the reason for discharge to "dropped out of treatment" vs. all other reasons for treatment discharge (i.e., treatment completion, termination by the facility, incarceration, and death). Transfers to another treatment program or facility were not included in our outcome variable. "Dropped out of treatment" included clients who exited treatment for unknown reasons as well as those who left against professional advice or were lost to follow-up and discharged administratively. The outcome was non-missing for all treatment episodes.

2.4. Machine learning analysis

We conducted a classification analysis, using several tree-based approaches. First, we evaluated Classification and Regression Trees (CART). To avoid over-fitting, the CART models were grown and pruned according to cost-complexity pruning. With CART, what is made up for in interpretability is lost in accuracy, since there can be large differences between trees based on changes in the data sampled for model training (Breiman et al., 1984). Subsequently, we tested bootstrap aggregated trees. Bagged CART can potentially improve model variance and accuracy if each individual tree has low bias and weakly correlated predictions (Breiman, 1996). Afterward, we assessed the performance of the random forest. Differentiating it from bagged trees, random forest fits each tree in a subset of the predictors to reduce the correlation among them (Breiman, 2001). Lastly, we considered tree-based gradient boosting (i.e., boosted CART). The boosting algorithm creates an ensemble of weak learners to produce final predictions by sequentially growing trees using the information from previous trees (Chen and Guestrin, 2016).

We compared the performance of the four modeling approaches using 10-fold cross-validation on complete records only. Missing values in factors with more than 20% missingness were replaced by an unknown level. The remaining records with missing values in at least one factor were excluded. The data were divided into a training and a testing set, using a 75% and 25% split. We performed 10-fold cross-validation on the 75% training set. To evaluate the performance of each approach, we used the receiver operating characteristic area under the curve (ROC-AUC). This metric is one of the most common measures in classification models for evaluating the trade-off between sensitivity (i.e., true-positive rate) and specificity (i.e., one minus the false-positive rate) (Kuhn and Johnson, 2013). Based on the highest ROC-AUC, we selected the best-performing approach in the cross-validation analysis. The best-performing approach was fit on the complete training set, and its performance assessed on the testing set with complete records only.

We evaluated the performance of the machine learning models in complete records to avoid unnecessary uncertainty in the input data. However, since there was no evidence indicating that the data were not missing at random, we aimed to evaluate the performance of the best-performing approach on imputed data. Before applying the approach, we imputed any missing data using a random forest-based imputation method (Stekhoven and Bühlmann, 2012). This imputation method creates a random forest model to predict the missing values for each factor using the remaining variables in the data. The imputation process is repeated sequentially until the difference between the previous and new imputed data increases in its continuous and categorical parts. These data were also divided into a training and a testing set, using a 75% and 25% split. Missing data were imputed on the training set and the testing set independently to avoid data leakage (Stekhoven and Bühlmann, 2012).

We then trained the best-performing approach on the imputed training set and evaluated its performance on the imputed testing set. Additionally, models were fit based upon imputed data stratified by year, lengths of stay in treatment, and treatment settings. Model performance was assessed with ROC and precision-recall (P.R.) AUC as well as accuracy.

Permutation variable importance, which computes the decrease in model performance when the order of data in a predictor is randomly changed (i.e., shuffled), was reported. In addition, partial dependence plots were created for the top ten influential variables. These plots depict the marginal effect a variable has on the predicted outcome of a given machine learning model (Friedman, 2001). All analyses were performed using R statistical programming language version 3.3, using the tidymodels, rpart, baguette, ranger, xgboost, vip, broom, pdp and missForest packages. Data preprocessing was conducted with dplyr.

2.5. Patient and public involvement

Because the study involved retrospective analysis of data, patients and members of the public were not directly involved in the study

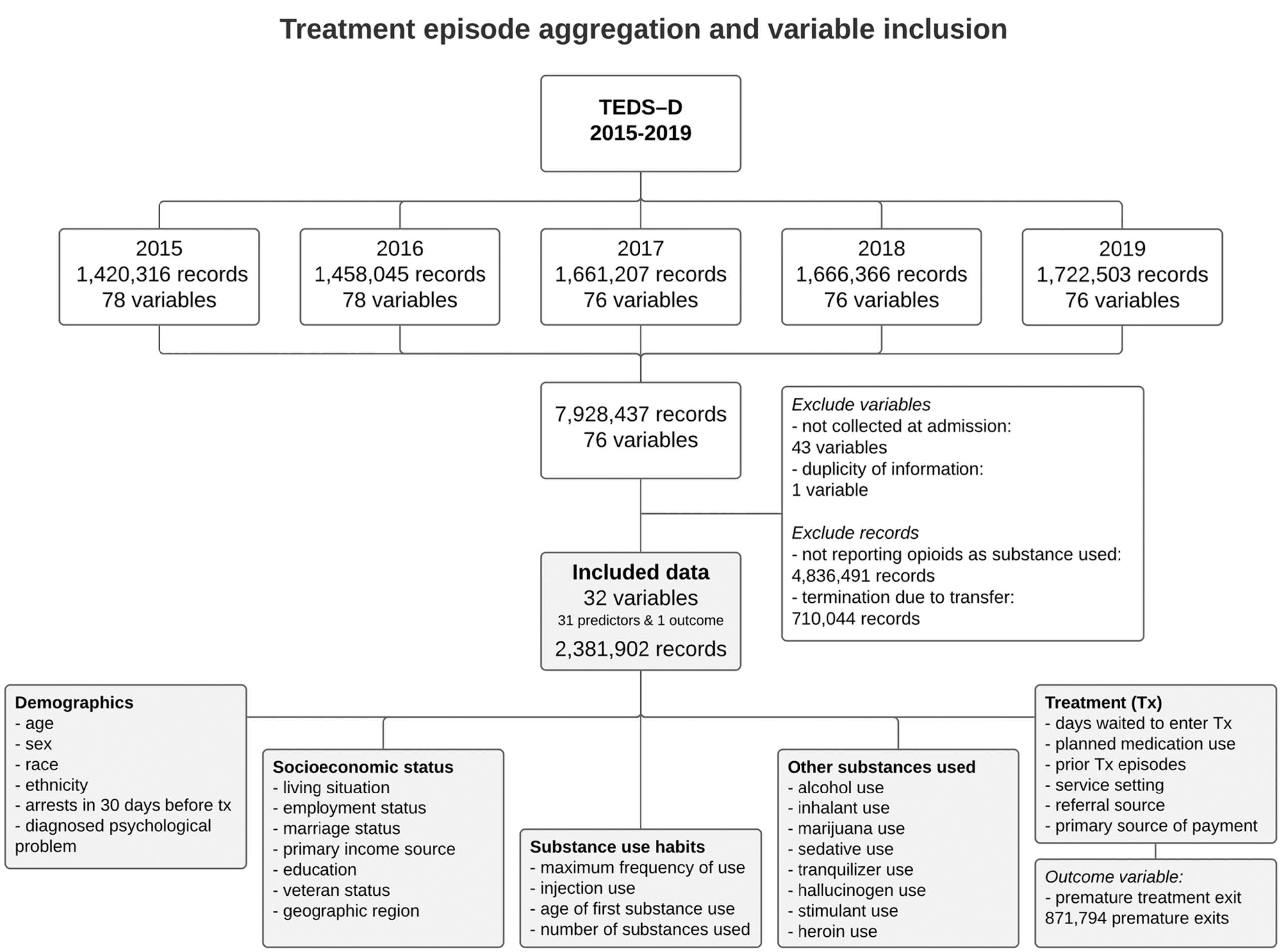

Fig. 1. Episode and variable inclusion and exclusion.

design. This study was deemed exempt by the institutional review board at the University of North Carolina at Chapel Hill.

3. Results

Fig. 1 presents an overview of the study data. After excluding variables not collected at treatment admission, episodes without reported opioid use, and terminations due to transfers, 2381,902 episodes were included in the analysis. Most variables had missing values on less than 10% of the records, with primary source of payment for treatment, days waited before entering treatment, primary source of income, and marriage status missing more than 20% of values. A complete summary of missingness can be found in Table S3.

3.1. Descriptive results

The vast majority (75%) of opioid-related treatment episodes were among white individuals. Of all opioid-related episodes, stimulants were the most often co-occurring substance reported (38%), followed by alcohol (22.1%), and cannabis (21.0%). Overall, a total of 871,794 (36.6%) opioid-related treatment episodes resulted in treatment discontinuation.

Table S4 presents a full listing of the characteristics of individual treatment episodes, stratified by premature treatment exit status. The most represented age group among all episodes was 25–34 years, which accounted for 43% of the episodes resulting in premature exit. Among episodes in which individuals discontinued treatment, 35% had planned to use MOUD at baseline, as compared to 22% of those who did not exit treatment prematurely. Also, among episodes in which individuals discontinued treatment, 58% self-referred to treatment, as compared to 50% who did not discontinue treatment.

3.2. Machine learning results

Using the complete data set, we used 1100,838 treatment episodes for training and 366,945 for testing (see Fig. S1). Comparing the four classification methods, the random forest classifier performed the best, achieving a mean ROC-AUC of 74% with a standard deviation of 0.001, across the 10-fold cross-validation. Fig. S2 presents the comparison of the ROC-AUCs for the four modeling approaches. On the unseen-by-the-model testing set, the random forest achieved an accuracy of 69%, an ROC-AUC of 73%, and a PR AUC of 79%. When the random forest approach was fit on the imputed training set (n = 1786,426) and evaluated in the imputed testing set (n = 595,476), it attained an accuracy of 69%, with an ROC-AUC of 71%, and a PR AUC of 79%. Of greater relevance to treatment decisions is the relative importance of included factors in predicting premature treatment exit.

The full ranking of important factors can be seen in Fig. 2. The most influential predictor was service setting (i.e., rehab, ambulatory, or detox). Its exclusion from the model decreased accuracy by more than

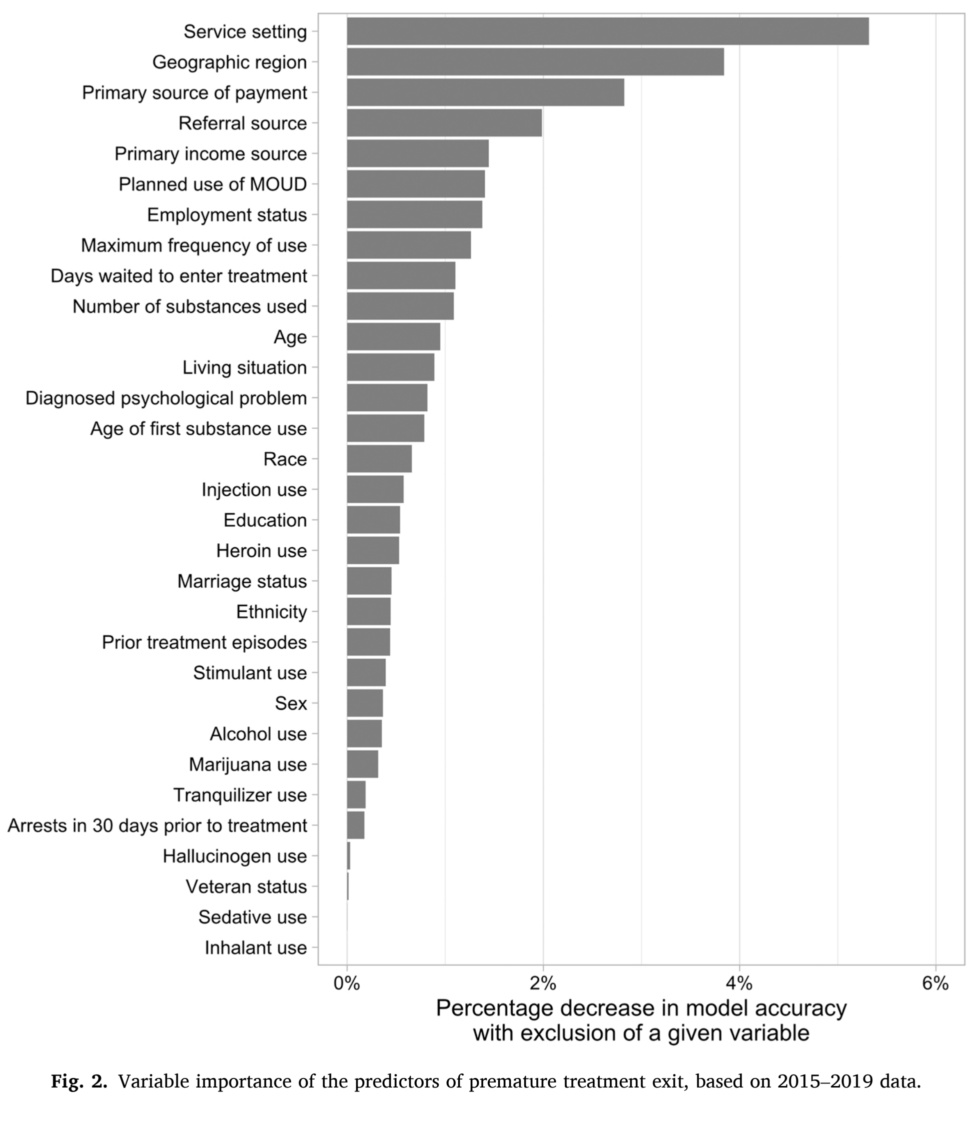

Fig. 2. Variable importance of the predictors of premature treatment exit, based on 2015–2019 data.

5%. In addition to service setting, geographic region (i.e., Census region), primary source of payment for treatment, and referral source each produced an accuracy decrease of about 2% or higher. Interestingly, reported heroin use, injection use, race, and ethnicity were low on the list of importance. Variable importance remained largely unchanged when the model was fit on individual years (see Fig. S3).

Fig. 3 shows the marginal impact of different levels of each of the 10 most important variables on treatment dropout with partial dependence plots—northeast geographic region, other government payment as the source of payment, criminal justice treatment referral, no planned use of MOUD, and no use in the past month were associated with the largest decreases in treatment retention.

In Fig. 4, we present the top 10 most influential factors stratified by length of stay (LOS) in treatment, ranging from one day to more than a year—see Table S5 for number of episodes per category. The results show that geographic region consistently remained as one of the top two factors in any LOS. Similarly, service setting remained among the top factors, except when the LOS is more than a year. Importantly, primary source of payment consistently remained as one of the top factors in all LOS categories. Employment status and days waited to enter treatment move down in the relative order of importance as the LOS increases. Another observation is that referral source moves up in the rank of importance as the LOS increases. A similar pattern is also observed for planned use of MOUD, except that it is not among the top 10 factors for the LOS of 2–7 days. Another factor that is not in the top 10 list of 2–7 LOS category is the maximum frequency of nonmedical opioid use. Interestingly, these two factors are replaced with age and age of first use. No age-related factor is observed in the other LOS categories. Finally, race and ethnicity show up only for a LOS of over one year; however, these variables have a marginally small effect.

Fig. 5 represents the top 10 most influential factors based on various treatment settings (i.e., ambulatory, detox, and rehab). The results show that geographic region and primary source of payment consistently remain as one of the two top factors in any treatment setting. Four other factors also appear in the top-10 list of any treatment setting: referral source, employment status, primary income source, and days waited to enter treatment. Age and age of first substance use appear in the detox category—age also appears in the rehab category, however as the 10th factor with a relatively small importance level. Additionally, maximum frequency of nonmedical opioid use appears in ambulatory and rehab settings; diagnosed psychological problem appears in ambulatory and detox settings; and living situation appears in detox and rehab settings. Finally, planned MOUD appears only in the ambulatory setting.

4. Discussion

We used a series of machine learning models to predict premature OUD treatment exit using treatment episode data from TEDS-D. With 31 predictors spanning demographics, substance use habits, and treatment information, we developed a series of models to help clarify factors most influential in determining whether an individual will exit treatment prior to completion. Notably, we found that system-level factors, including treatment service setting, geographical region, primary source of payment, and treatment referral source, were the strongest predictors of treatment discontinuation, as opposed to individual-level factors. Some prior research has stressed the importance of providing system-level support to promote treatment retention (e.g., reducing initial clinic requirements, financial and transportation supports) (Cochran et al., 2019; Cottrill et al., 2019; Mackey et al., 2020; Madras et al., 2020). However, this remains an understudied area. This study highlights additional key targets to examine for potential system-level intervention (e.g., related to service setting dynamics, payment sources and related payment barriers and facilitators, referral roles and supports).

While we found that service setting was the most important predictor of attrition, only 3% of papers reviewed by Brorson et al. (2013) did so. Service setting options captured in TEDS-D include detox, short- and long-term inpatient care, and different forms of ambulatory care, each with differing implications for transportation, finances, and other factors. Though longer-term and/or ambulatory care-based treatment modalities offer more chances to lose patients in the process of care, we found that patients are less likely to prematurely exit these. Certain treatments, such as MOUD (i.e., methadone, buprenorphine, or naltrexone), have consistently been shown to lead to better outcomes (Wakeman et al., 2020). Furthermore, research indicates that if a patient undergoes detox, it is most effective when coupled with residential care or MOUD (Walley et al., 2020). Further work on effective care models that support patient decisions, while encouraging evidence-based options (including coupling of treatment services and settings), is needed.

Another notable feature is geographic region. Fig. 3 highlights a meaningful difference in attrition across regions, where the likelihood of premature exit was highest in the Northeast, followed by the South and U.S. territories. Research indicates that this heterogeneity may exist due to infrastructural factors related to treatment access, social factors like stigma, and socioeconomic factors such as likelihood of working a manual labor job (Abraham et al., 2018; Langabeer et al., 2019). A lot of this heterogeneity remains causally unexplained and should be subject to more investigation (Rigg et al., 2018).

While socioeconomic status and income are occasionally tested (Brorson et al., 2013), our model is the first to include the primary source of payment for treatment. We find it to be the third most influential factor, with highest rates of premature treatment exit in individuals paying with other government payments and Medicaid. This connection bears further research. It is possible that programs accepting public payers differ from those accepting commercial insurance, or there could be ties to socioeconomic status and potential multicollinearity with social determinants of health or employment status. However, simply knowing risk of treatment attrition is high among Medicaid enrollees provides an intervention opportunity. Additionally, research indicates that Medicaid beneficiaries have a high prevalence of comorbidities and barriers to health care, including affordable and accessible transportation, which may contribute to this attrition (Akinyemiju et al., 2016). More recently, state Medicaid programs have attempted to remove insurance-based barriers (e.g., prior authorizations) to MOUD initiation (Cohen, 2022). Additionally, a few states have developed innovative OUD-related health homes, which coordinate patients' medical and behavioral health needs and services and work to address social determinants of health affecting patient care (Clemans-Cope et al., 2017). Additional work to disseminate such models of whole-person care remains a clear need.

Referral source was also an important predictive factor, with referral from criminal legal settings associated with increased probability of premature treatment exit. Research indicates that 15% of deaths following release from prison are related to opioids and decreased tolerance thereof, and up to 65% of the U.S. prison population may have an active substance use disorder (Binswanger et al., 2013). The Substance Abuse and Mental Health Services Administration and others have increased resources to support access to MOUD in prisons and post-release. However, additional types of support are needed. It is also apparent that coerced treatment, i.e., treatment mandated by the courts, may not be an effective strategy (Parhar et al., 2008).

Notably, age and age of first use had a relatively low impact on model predictive accuracy. Although age of first substance use has not been investigated in this context, there is evidence of its ties to development of OUD (Jordan and Andersen, 2017) and eventual admission to treatment (Strashny, 2013). Most studies assess the impact of age on treatment exit, and just 36% of the studies investigating age found a significant relationship. Of these, 88% linked younger age to increased risk of premature treatment exit (Brorson et al., 2013; Lappan et al., 2020). Additional research on how substance use trajectories influence treatment initiation and retention trends is needed, as well as how types of treatment retention support may differ across the life span.

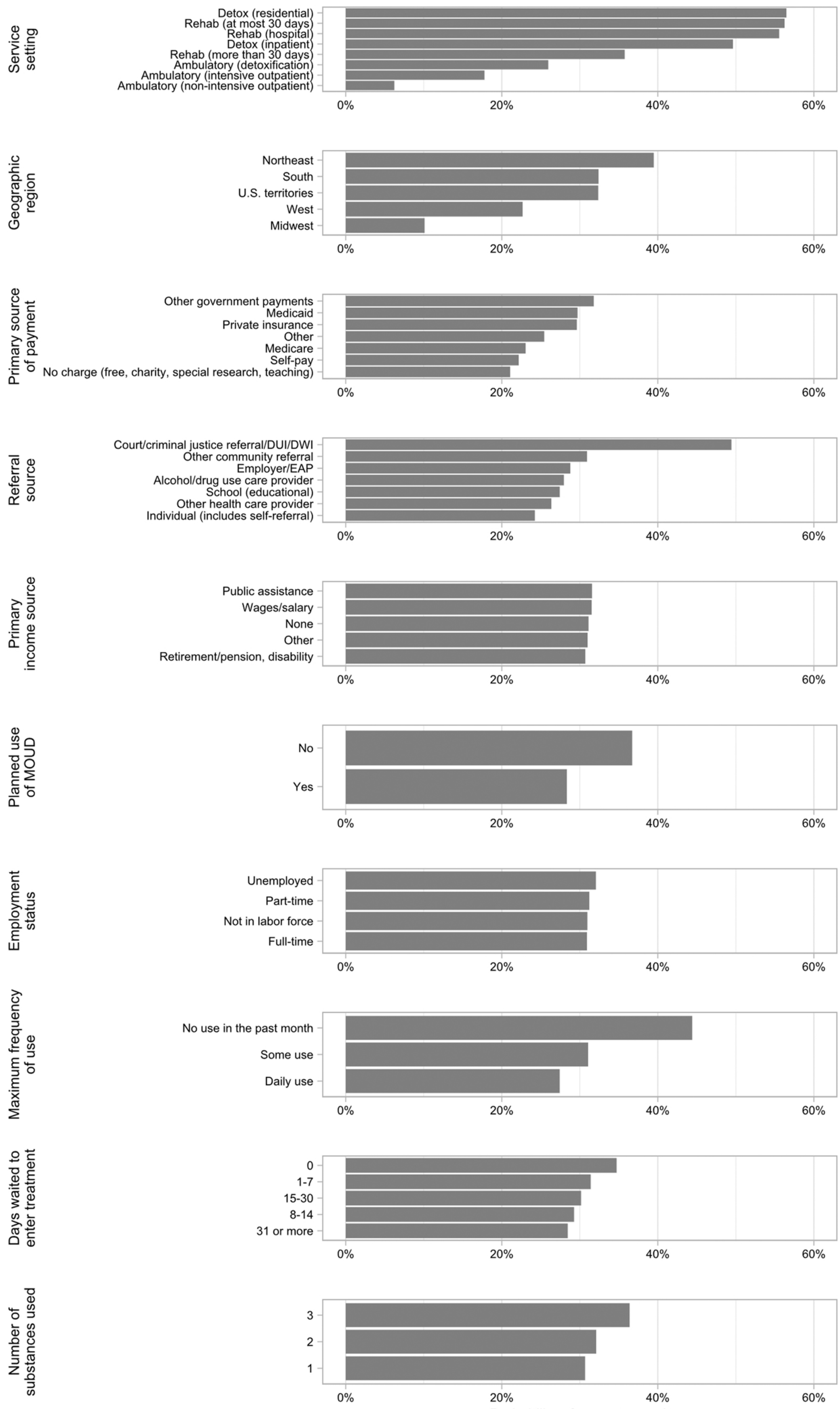

Fig. 3. Partial dependence plots of most influential variables, based on 2015–2019 data.

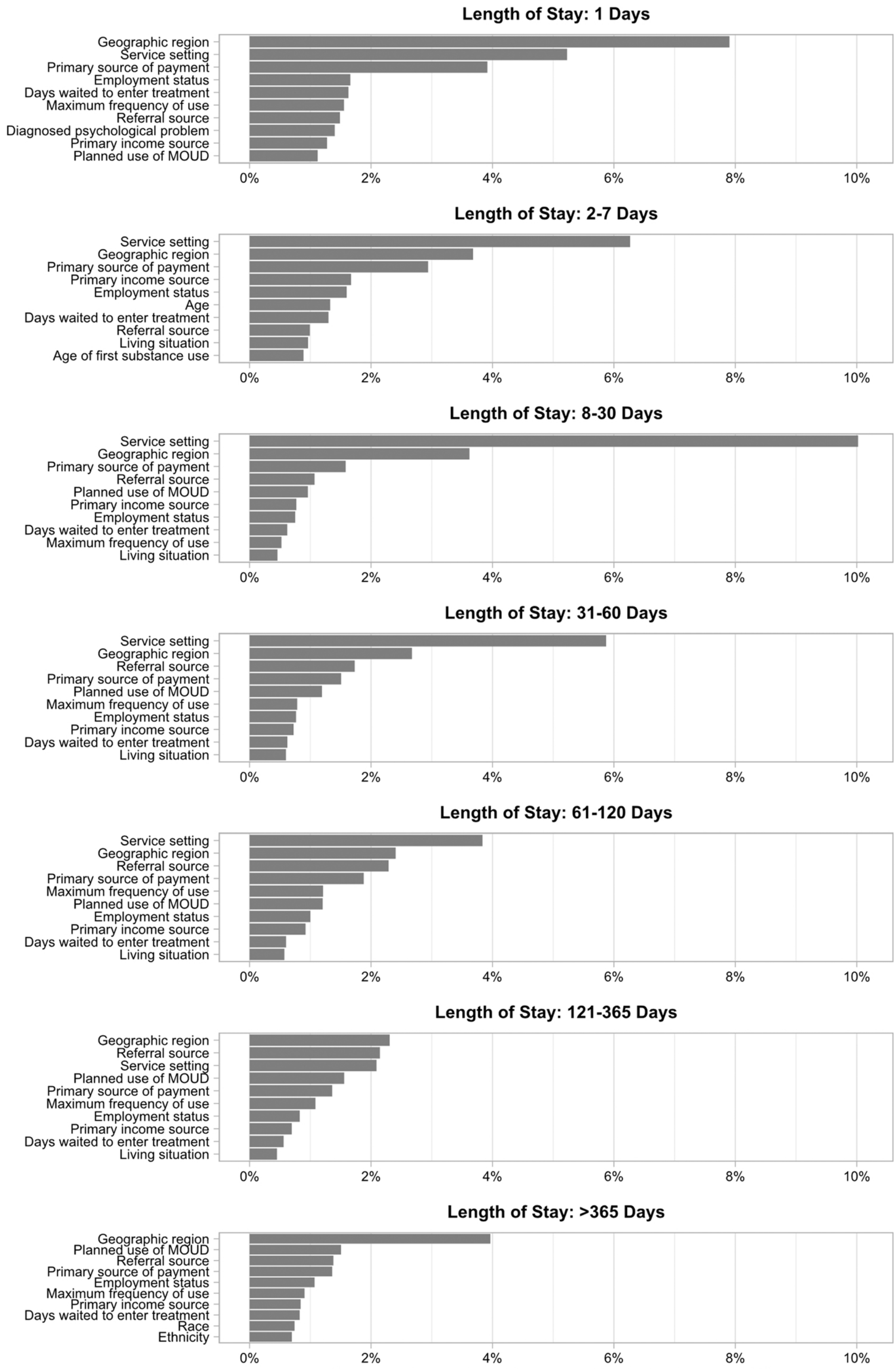

Fig. 4. Most influential variables based on different lengths of stay in treatment, based on 2015–2019 data.

In contrast with the many small cohort and retrospective studies on premature treatment discontinuation, this analysis utilized records from millions of substance use treatment episodes. We leveraged these data to study predictors of treatment discontinuation, taking advantage of a rich set of covariates and the 2381,902 treatment episodes. This provided a larger sample size and the ability to explore a wider range of risk factors than any other study on the subject. Also differentiating this study, we utilized a supervised machine learning approach. This method offers a distinct benefit over previous analyses by considering possible interactions and multicollinearity among factors. Finally, random forest models are helpful in assessing nonlinearities, which are challenging to parse out with classic regression-based models.

This study is subject to several limitations. First, TEDS-D is an observational dataset that relies on submissions from individual states. Depending on the year, some states do not submit data and are not included (Table S1). Nonresponse may be associated with higher rates of treatment discontinuation due to less treatment funding or substance use support, which may lead to underestimates of treatment

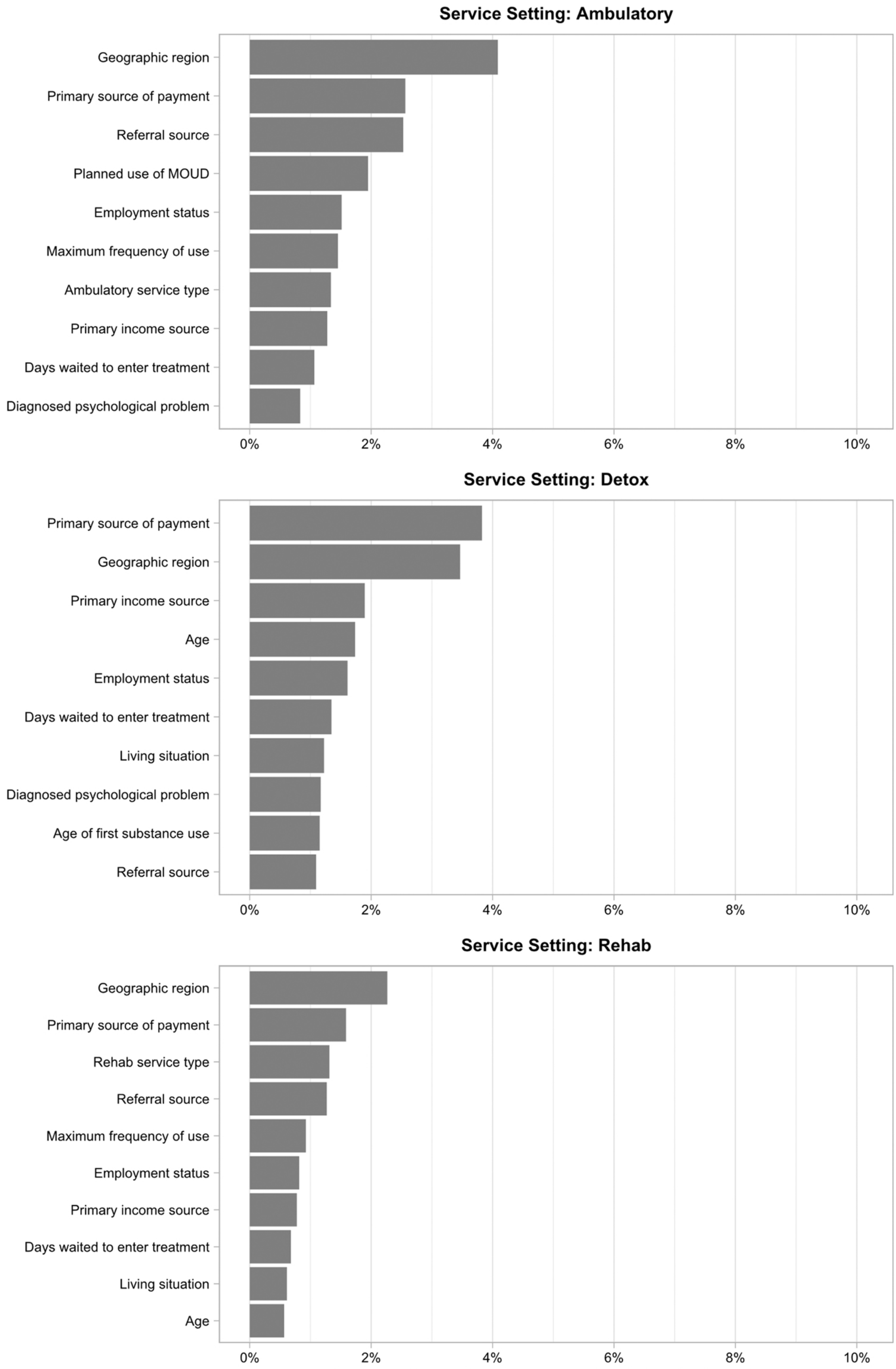

Fig. 5. Most influential variables based on different treatment service settings, based on 2015–2019 data.

discontinuation rates. Second, TEDS-D has a minimum set of data elements that states are required to report, including demographic and substance use factors. Factors outside of this minimum requirement can be missing. These missing data were imputed using a random forest, and though the efficacy of this method has been described in detail (Kokla et al., 2019; Pantanowitz and Marwala, 2008), imputation is not a perfect solution. We report our results on complete records (without imputation) in Fig. S4, and the findings are generally similar to those with imputation. Third, some of the variables collected rely on patient self-report and are therefore, subject to recall and social desirability biases (e.g., history of substances used). Still, intake procedures are conducted with confidentiality via trained treatment staff to receive assessments that are as accurate as possible to inform treatment recommendations.

Another critical limitation of TEDS-D is that it represents treatment episodes, not individuals. Therefore, our findings should not be used to estimate an individual’s risk of treatment discontinuation. As more states uniquely identify individuals and bundle treatment episodes

(SAMHSA, 2015), it may be possible to estimate the difference between modeling treatment episodes and individuals in the future. Understanding this difference is outside the scope of our work and merits follow-up dedicated to addressing it specifically.

TEDS-D also only includes facilities that are licensed or certified by states. Because of differences in individual state policies, some states include private doctors' offices and other private clinics, and some do not. While it is the most complete survey of treatment facilities, TEDS-D is an undercount, both because of non-reporting and excluded private facilities. Additionally, there could be bias based on the attributes of individuals that exit state-sponsored facilities vs. those that might exit private doctors' offices.

Reasons for treatment discharge that were not considered to be premature treatment discontinuation initiated by the patient included completion, termination by the facility, and transfer to another facility or treatment program; a future analysis could consider any premature exit, whether initiated by patient or facility, as a failure. Additionally, future analyses should examine predictors of discontinuation by specific type of treatment received. While we included analyses stratified by treatment service setting, future analyses examining predictors of discontinuation for specific types of treatment is warranted. Relatedly, there is considerable variation in response to OUD treatment. Because of this, there is a great need to identify patients who may not respond well or are more likely to exit treatment prematurely, and thus, may require specific types of treatment, new or innovative treatment models, or specific intensive treatment supports. Although we identified key predictors of premature treatment exit, we cannot conclude that these are causal relationships. Still, these serve as important areas for future research to further explore specific causal mechanisms. Understanding the dynamics surrounding these key factors holds important clinical relevance for future treatment decisions and models of care.

In summary, we demonstrated that a predictive modeling approach for premature OUD treatment exit can be constructed using a dataset of U.S. adults receiving treatment for OUD at state-affiliated treatment facilities. Our results are a step towards addressing the varying likelihoods of treatment attrition across patients and modalities of treatment. The combination of effective treatment interventions with data on an individual's risk level can help channel resources toward targeted mechanisms of attrition for specific patients.

Funding

CS, WJM, and MSJ were supported in part by the U.S. Food and Drug Administration (grants U01FD006868 and U01FD007064).

Role of Funding Source

This article reflects the views of the authors and should not be construed to represent the views or policies of the U.S. Food and Drug Administration or the Department of Health and Human Services.

CRediT authorship contribution statement

Celia Stafford and Wesley J. Marrero performed data collection and machine learning analyses. Wesley J. Marrero and Mohammad S. Jalali provided critical review of the analysis. Celia Stafford, Wesley J. Marrero, and Mohammad S. Jalali created the visualizations. All authors performed the interpretation of the results and revised the manuscript for important intellectual content. Celia Stafford and Wesley J. Marrero contributed equally. Mohammad S. Jalali supervised the project. All authors approved the final version of the article.

Conflict of Interest

The authors declare no competing interests.

Data Availability

Datasets, code, and results are available in the online supplementary document and on GitHub (https://github.com/castaff/TEDS_Treatment_Attrition).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109507.

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