

Risk factors for re-attempt and suicide within 6 months after an attempt in the French ALGOS cohort: A survival tree analysis

Alice Demesmaeker^{1*}, Emmanuel Chazard², Guillaume Vaiva^{1,3}, Ali Amad¹

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INTRODUCTION: Understanding the cumulative effect of several risk factors involved in suicidal behavior is crucial for the development of effective prevention plans. The objective of this study is to provide clinicians with a simple predictive model of the risk of suicide attempts (SAs) and suicide within 6 months after SA.

METHOD: A prospective observational cohort of 972 subjects was used to perform a survival tree analysis with all socio-demographic and clinical variables available at inclusion. Then, the results of the decision tree were used to define a simple predictive algorithm for clinicians.

RESULTS: The results of survival tree analysis highlighted three subgroups of patients with an increased risk of SA or death by suicide within 6 months after SA: patients with alcohol use disorder and a previous SA with acute alcohol use (risk ratio (RR) 2.92 [2.08; 4.10]), patients with anxiety disorders (RR 0.98 [0.69; 1.39]), or patients with a history of more than 2 SAs in the past 3 years (RR 2.11 [1.25; 3.54]). The good prognosis group comprised all other patients.

CONCLUSION: By using a data-driven method, we identified four clinical factors interacting together to reduce or increase the risk of recidivism. These combinations of risk factors allow for a better evaluation of a subject's suicide risk in clinical practice.

Key Words: *Suicide; Suicide attempt; Risk factor; Alcohol use disorder*

INTRODUCTION

With approximately 800,000 deaths by suicide throughout the world every year, including 10,000 in France, preventing suicide is a major public health issue [1]. In 2013, the World Health Assembly adopted the first-ever Mental Health Action Plan of the World Health Organization (WHO) [2]. This plan aims to reduce the rates of suicide by 10% from 2020. Nonetheless, worldwide suicide rates have been declining over recent decades except in the United States [3]. For example, the standardized mortality rate in France has decreased from 16.86 per 100,000 inhabitants in 2011 to 13.21 per 100,000 inhabitants in 2016 according to the national French death register "CépiDc" [4].

The understanding of risk factors involved in suicidal behavior is crucial for the development of effective prevention plans. Interestingly, one of the most robust risk factors for death by suicide corresponds to a history of previous suicide attempts (SAs) [5–7], as a substantial number of patients who attempt suicide ultimately die by suicide. According to a recent systematic review and meta-analysis, the pooled estimated incidence rate of subsequent fatal self-harm after an index attempt was relatively high at 1 year (1.6%) and even higher at 10 years (4.2%) [8]. Moreover, a recent exhaustive study of two national French registers including 45 million inhabitants highlighted that 1 year after SA, 2.6% of the subjects had died, 34.4% of them by suicide [9]. According to this study, the period of greatest risk of death by suicide corresponds to the first six months after SA. In addition, if a previous SA is a risk factor for subsequent suicide, SA is also a strong predictor for suicide re-attempt. For instance, after 1 year, nonfatal repetition rates are approximately 15% [10]. Similar results were found in France, with a recurrence of SA estimated at 12% within the first year after nonfatal self-harm, with the vast majority of recurrence of SA occurring within the first 6 months (75%) [9].

Beyond the risk related to a previous SA, several other factors seem to be involved in death by suicide in patients with a history of self-harm. In a cohort study defined from Danish registers, it has been shown that individuals who use a violent SA method (e.g., jumping from a high place or

in front of traffic) form a high-risk group for suicide [7]. Another Danish cohort study highlighted that age over 35 years, as well as hanging, strangling or suffocation as the method of the index attempt or receiving psychiatric hospitalization for this attempt, were also risk factors for future suicide [11]. Finally, the exploration of Swedish registers demonstrated that suffering from severe mental illness such as bipolar or psychotic disorder and a previous attempt by hanging were the most important risk factors for subsequent suicide [12].

To summarize, repetition of SA, the use of a violent method for a previous SA and a severe mental illness are the main factors involved in death by suicide according to different national registers. Moreover, the first six months after SA seem to be a particularly high-risk period for re-attempt and subsequent suicide.

Interestingly, it has been suggested that a subject's suicide risk was not limited to one event but would rather correspond to the interplay of different factors occurring throughout life from pre-birth (e.g., low birth weight and genetic predisposition) to adulthood (socioeconomic factors, severe mental illness, substance abuse) [1]. In the same way, it has recently been indicated that the lifetime cumulative effect of several risk factors should be considered instead of individual risk factors for suicide being examined [3].

While the current scientific literature can determine the extent to which an individual or environmental factor increases the risk of SA or death by suicide through the use of conventional statistical methods, the published results encounter many drawbacks. The methods employed rarely produce simple tools that can be used by clinicians and hardly explore the interactions between variables [3]. Interestingly, flexible data-mining methods derived from computer science, such as survival trees, have been developed to detect interactions among variables that best explain a time-dependent variable of interest by means of recursive partitioning [13]. The objective of this study is to provide clinicians with a simple predictive model of the risk of SA and suicide within 6 months after SA.

¹Inserm, University Lille, CHU Lille, U1172 - LilNCog - Lille Neuroscience & Cognition, France; ²Department of Public Health, University Lille, CHU Lille, ULR 2694, CERIM, F-59000 Lille, France; ³Centre National de Ressources et de Résilience (CN2R), F-59000 Lille, France

*Correspondence to: Dr. Alice Demesmaeker, Hospital Fontan, CHU de Lille, F-59037, Lille Cedex, France, Tel: + 33 3 20 44 42 15; e-mail alice.demesmaeker@chru-lille.fr

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RESEARCH METHODOLOGY

Study design

A prospective observational cohort of 972 subjects from the ALGOS study was used for the analysis. The ALGOS study is a multi-centric, prospective, single-blind randomized and controlled clinical trial with two parallel groups. Participants in the intervention group received a brief contact intervention for 6 months [14], and control participants did not receive any intervention. Both groups were used in the present study. This study was conducted in 23 French emergency services. Patients included were men and women of legal age who survived a SA in the 7 days prior to inclusion, regardless of the method used for the SA. Patients who had no suicidal intent, were homeless, were under guardianship, or were multi-repeaters (more than 4 SAs in the last 3 years) were excluded from the study.

This study has received authorization from AFFSAPS (number NCT01123174) and has been approved by the Committee for the Protection of Persons in the North-West Region (CPP North-West decision 09/63).

Data collection

At inclusion, data on sociodemographic characteristics (age, gender, family and work status), number of previous SAs and method of SA (drug overdose, acute alcohol use), as well as responses to a questionnaire based on Beck's intentionality scale, were collected for all subjects. This questionnaire explored the circumstances related to the SA (expression of suicidal ideations, suicidal project, testamentary precautions, suicide note), predisposing factors (family history of mental illness, chronic pain, chronic medical condition, social isolation) and precipitating factors (self-medication, poor adherence to treatment, negative life events). All participants were also assessed by using screening question(s) from the MINI (Mini International Neuropsychiatric Interview) corresponding to the main criteria for major depressive disorder, anxiety disorder (generalized anxiety disorder or panic disorder), alcohol use disorder (AUD) and eating disorder [15].

At 6 months, the number of suicidal recurrences and the date of the first recurrence were evaluated for all participants through a standardized telephone interview.

STATISTICAL ANALYSIS

Descriptive analyses

Descriptive statistics were calculated for the variables of interest. Continuous variables are presented as the means and standard deviations

TABLE 1
Baseline characteristics of participants.

Characteristics	All Patients N = 972 N (%)
Intervention group	
ALGOS	480 (49.4)
Control	492 (50.6)
Age (mean ± SD: 38 ± 13.3)	
18–35 y	226 (23.3)
36–55 y	558 (57.4)
> 55 y	188 (19.3)
Women	618 (63.6)
Men	354 (36.4)
Living alone	515 (53.1)

(SDs). Asymmetric distributions are reported with the median and the first and third quartiles (Q1-Q3). The 95% confidence intervals (95% CIs) were calculated using the central limit theorem. Discrete variables are expressed as frequencies and percentages.

Automated risk prediction

To explain the risk of suicide re-attempt within 6 months after an index SA, we performed a survival tree with all the variables available at inclusion (age, gender, family and work status, randomization group, number of previous SAs, suicidal method used for the index SA, acute alcohol use during index SA) and clinical data. Survival trees are predictive data mining and decision support tools allowing us to obtain homogeneous classes of individuals with regard to the time-dependent variable of interest, based on recursive partitioning, by handling interactions between covariates [13]. Then, survival curves estimated by the Kaplan-Meier method were drawn corresponding to the leaves of the tree. Tree performance was assessed through a ROC curve and area-under-the-curve (AUC) estimation.

Predictive algorithm for clinicians

Finally, the results of the decision tree were used to define a simple predictive algorithm for clinicians. Kaplan-Meier curves were also drawn, and the AUC was computed. The hazard ratio and its 95% CI were computed using a Cox model.

Only complete cases were analyzed. Tests were 2-sided, and p-values were considered significant under 0.05. The Rpart package from R software version 3.6.1 was used for the analysis [16].

RESULTS

A total of 972 participants were included (cf. Table 1 and Supplementary Figure 1). Regarding the number of previous SAs, more than half of the patients were first-time attempters (53.3%). In addition, a high proportion of patients suffered from major depressive disorder and anxiety disorder (42.6% and 47.2%, respectively) at inclusion.

For 880 participants (90.5%), the complete status at 6 months was known. Of these patients, 117 (13.3%) had repeated SAs, and 11 (1.1%) completed suicide. Ninety-two patients (9.5%) were lost to follow-up at 6 months (47 women and 45 men). Fifty-two (56.5%) of them were between 26 and 50 years old, and 53 (57.6%) were first attempters.

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Employed	619 (63.9)
First-attempters	518 (53.3)
Lifetime diagnosis (per MINI)	
Major depressive disorder	412 (42.6)
GAD or Panic disorder	455 (47.2)
Alcohol use disorder	166 (17.2)
Eating disorder	47 (4.9)
Method of SA	
SA by medication overdose	912 (94)
SA with AAU	417 (43.7)
Circumstances related to the SA	
Expression of suicidal ideations	334 (34.7)
Suicidal project	141 (14.6)
Testamentary precautions	18 (1.9)
Suicide note	125 (12.9)
Predisposing factors	
Family history of mental illness	320 (35.7)
Chronic pain	139 (14.4)
Chronic medical condition	195 (20.1)
Social isolation	197 (20.4)
Precipitating factors	
Self-medication	189 (19.8)
Poor adherence to treatment	172 (18.1)
Negative life events in the last 6 months	616 (64.4)
SA= suicide attempt	
GAD= generalized anxiety disorder	
AAU= acute alcohol use	

Supplementary Figure 1) CONSORT Study flow chart.

Automated risk prediction

Of the 878 (90.3%) patients, complete cases (i.e., the root node of the tree) that were used for the analysis, 115 (13.1%) had repeated SAs (Figure 1). The CART (Classification and regression trees) algorithm highlighted five leaves (i.e., defining subgroups), among which three present an increased risk of SA or suicide.

The first subgroup (leaf N°1), (Figure 1) was composed of 361 individuals without AUD, with less than 2 previous SAs in the past 3 years and without anxiety disorder. Twenty-three of these participants repeated SA in the six months. The relative event rate (RER) compared to the root was 0.49, and the risk ratio (RR with 95% CI) was 0.36 [0.23; 0.55].

The next subgroup (leaf N°2, Figure 1) was composed of 325 individuals without AUD, with a history of 1 or 2 previous SAs in the past 3 years and anxiety disorder. Forty-two of those 325 subjects repeated SA in the 6 months. Suffering from an anxiety disorder (generalized anxiety or panic disorder) non-significantly increases the risk of SA and suicide for these patients, with an RER of 1 and an RR of 0.98 [0.69; 1.39].

In the third leaf (leaf N°3, (Figure 1) composed of 46 individuals without AUD and with a history of more than 2 SAs in the past 3 years, 12 individuals repeated SA. Furthermore, recurrence of SA was associated with an increased risk of SA re-attempt and suicide, the RER was equal to 2, and the RR was 2.11 [1.25; 3.54].

The fourth subgroup (leaf N°4, (Figure 1) was composed of 19 individuals with AUD and without acute alcohol use during their last SA. None of them repeated SA. Therefore, the RER was 0.28, and the RR was close to 0.

Finally, the last subgroup (leaf Nr 5 in (Figure 1) was composed of individuals with AUD and acute alcohol use (AAU). Among those 127 patients, 38 (29.9%) repeated SA or died by suicide. The RER was 2.2 in regard to the root, and the RR was 2.92 [2.08; 4.10].

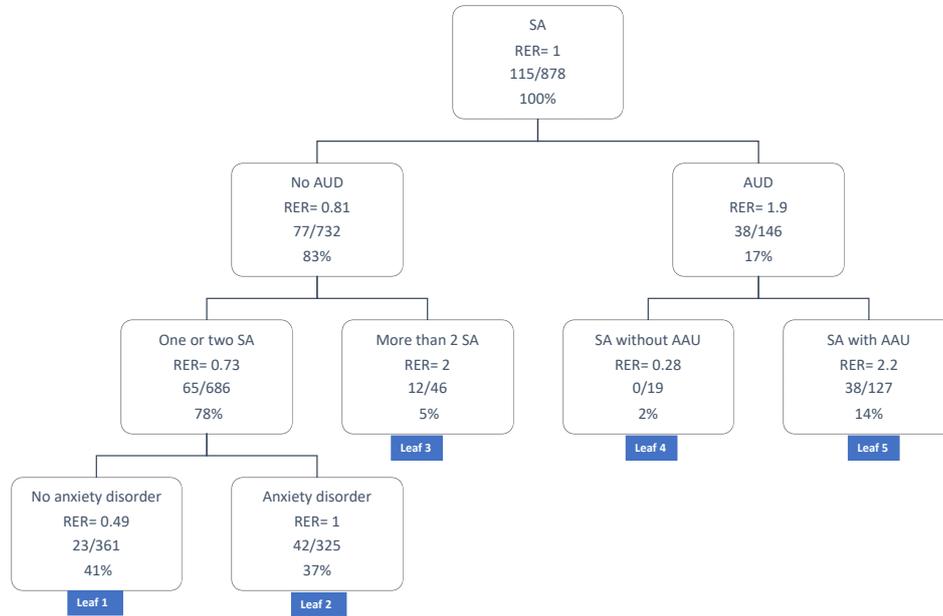
The survival curves of each terminal leaf representing the time before the first recurrence of SA within 6 months, estimated by the Kaplan-Meier method, are rendered in Figure 2.

Predictive algorithm for clinicians

Based on the previous results, to provide clinicians with a simple predictive algorithm, we separated the patients into two groups of good or poor prognosis. The poor prognosis group is composed of participants with acute alcohol use during their last SA, with anxiety disorder, or with a history of

more than 2 SAs in the past 3 years. The good prognosis group comprised all other patients. The survival curves with the confidence interval corresponding to the good and bad prognosis groups are rendered in Figure 3. The poor prognosis group appears to be a risk factor for SA re-attempt, with HR=1.78 [1.42; 2.24] (p<0.01). This predictive algorithm obtains an

AUC of 0.63. The corresponding ROC curve is available in Supplementary Figure 2. It renders a specificity of 0.47 [0.42; 0.50], a sensitivity of 0.8 [0.73; 0.87], a positive predictive value of 0.19 [0.15; 0.22], and a negative predictive value of 0.94 [0.92; 0.96].



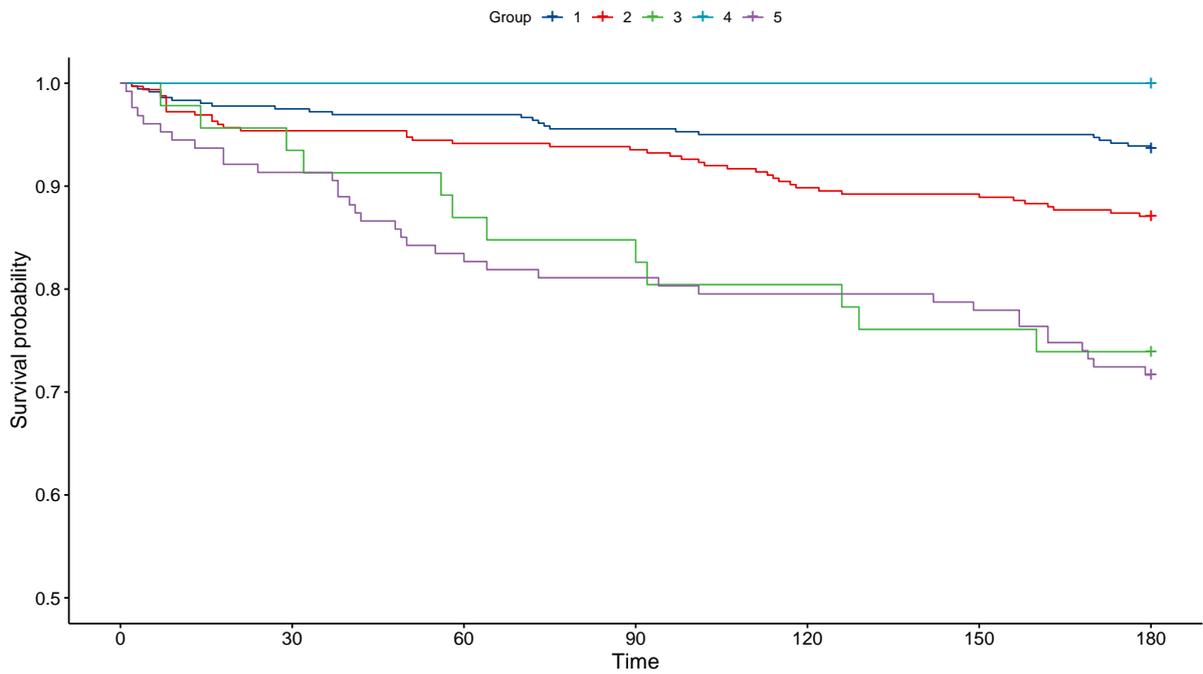
SA= suicide attempt

RER= relative event rate compared to the root (proportion of events in the node on the proportion of events in the root)

AUD= substance use disorder

AAU= acute alcohol use

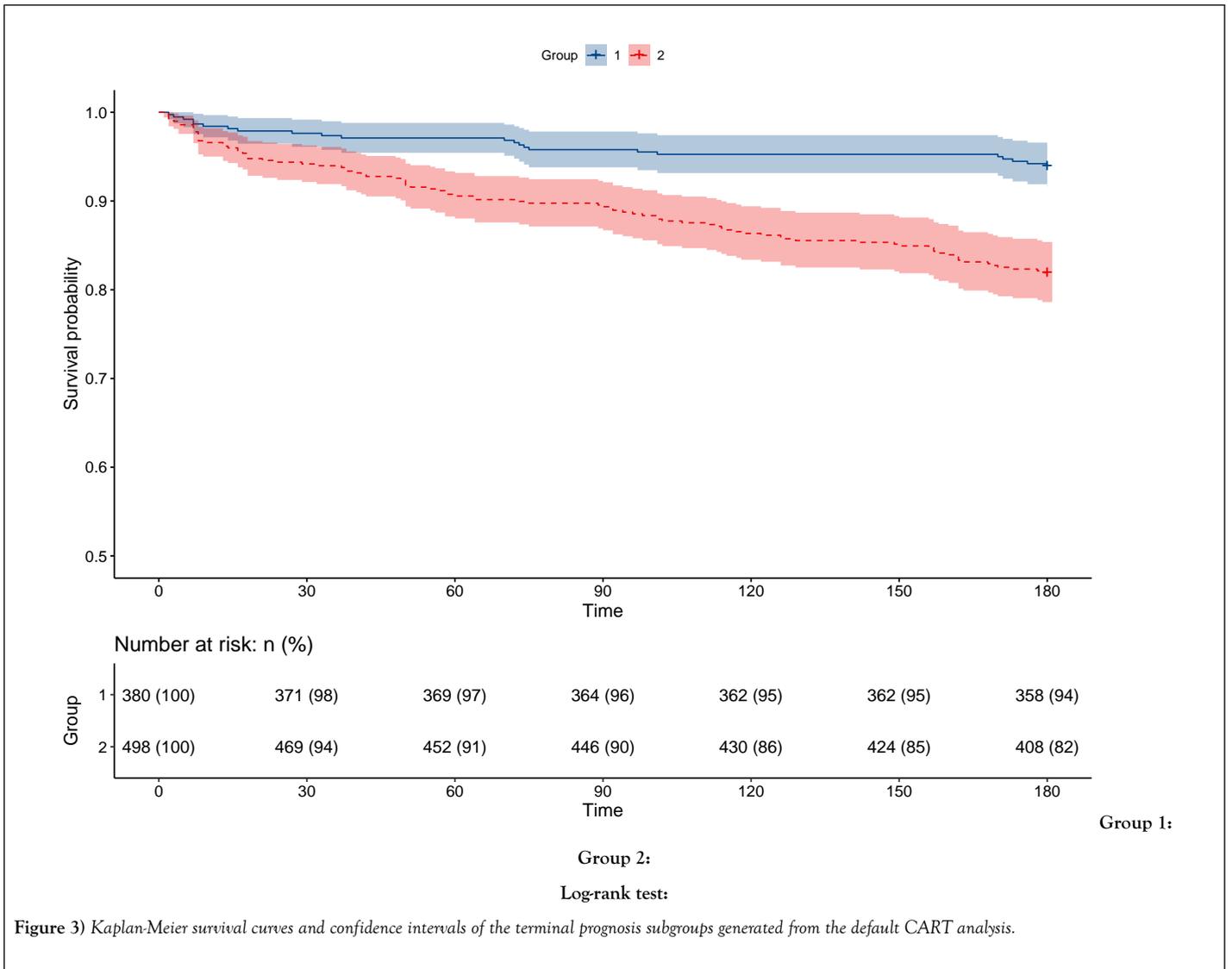
Figure 1) Survival tree for suicide re-attempt and suicide at 6 months after SA.

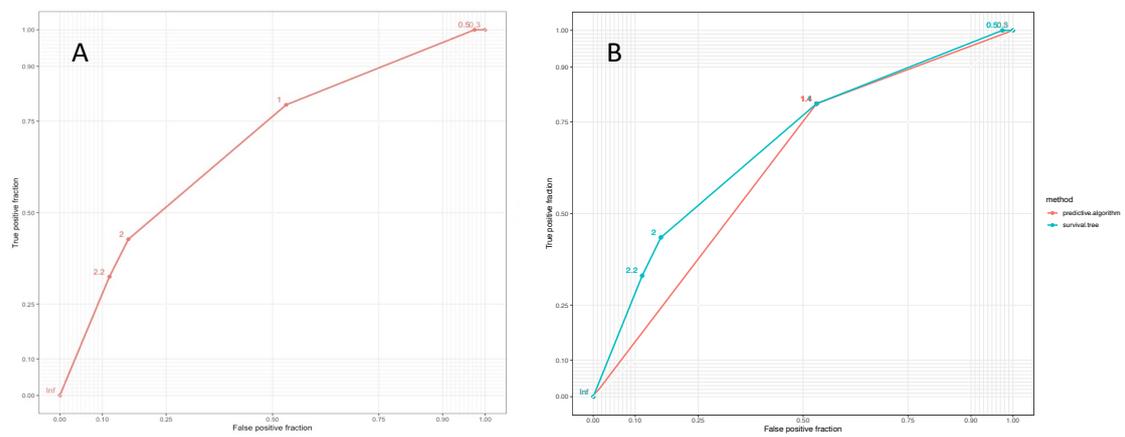


		Number at risk: n (%)						
Group		0	30	60	90	120	150	180
1		361 (100)	352 (98)	350 (97)	345 (96)	343 (95)	343 (95)	339 (94)
2		325 (100)	310 (95)	306 (94)	304 (94)	292 (90)	290 (89)	283 (87)
3		46 (100)	43 (93)	40 (87)	39 (85)	37 (80)	35 (76)	34 (74)
4		19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)
5		127 (100)	116 (91)	106 (83)	103 (81)	101 (80)	99 (78)	91 (72)

- Group 1:** Subjects with one or two previous SAs and no anxiety disorder
- Group 2:** Subjects with one or two previous SAs and an anxiety disorder
- Group 3:** Subjects with more than two previous SAs
- Group 4:** Subjects with AUD and a previous SA without acute alcohol use
- Group 5:** Subjects with AUD and a previous SA with acute alcohol use

Figure 2) Kaplan-Meier survival curves of the 5 terminal subgroups generated from the default CART analysis.





Tree and predictive algorithm performance were assessed through an ROC curve and area under the curve estimated at 0.7 and 0.6, respectively. **Supplementary Figure 2) ROC curve of the survival tree (A) and predictive algorithm (B).**

DISCUSSION

Through this study, a very simple algorithm of SA re-attempts or suicide was proposed. This algorithm was based on four simple clinical factors and still had good predictive power. Indeed, two groups of good or poor prognosis of suicide re-attempt were identified according to the sociodemographic or clinical elements collected after their previous SA. The poor prognosis group is composed of participants suffering from AUD with AAU during their last SA, those with anxiety disorders such as generalized anxiety or panic disorder, or those with a history of more than 2 SAs in the past 3 years. This predictive algorithm can be easily used by clinicians assessing patients who have attempted suicide to provide the most appropriate medical care.

The results of our survival tree analysis highlighted three subgroups of patients with an increased risk of SA or death by suicide within 6 months after SA. The first subgroup was composed of patients with an alcohol use disorder and a previous SA with acute alcohol use. Moreover, subjects with AUD for which previous SA was associated with an AAU had an even greater risk of suicide re-attempt (RER= 2.2), while those without AAU had a lower risk (RER= 0.28). Thus, AAU during the last SA appears to be a determining factor in the future prognosis. The second subgroup corresponds to patients with a history of more than 2 previous SAs in the past 3 years. Finally, the last subgroup is composed of patients with generalized anxiety or panic disorder, without AUD and with less than 2 previous SAs in the past 3 years. Therefore, the increased risk of SA or death by suicide is best explained by one of these conditions: AUD associated with acute alcohol use during the last SA, an anxiety disorder, and the recurrence of SA.

Interestingly, we used a survival tree to explore the possible interaction between a great number of sociodemographic or clinical variables. Although

this method is rarely used in medical research, it allows us to identify the most relevant factors in a dataset without establishing a specific hypothesis and to study the association of different factors regarding a time variable of interest (i.e., the risk of suicide/re-attempt after SA). In contrast, traditional methods to analyze survival data are based on the Cox proportional hazard regression model to test a specific link between the covariates and the response. In this type of model, any interaction between variables must be specified beforehand.

Very few studies have focused on the association among risk factors using data-driven methods. Among decision trees, a regression tree was used in a study aiming to build a dynamic clinical decision-support system (CDSS) for suicide prevention in 2802 suicide attempters [17]. Compared to our results, the authors identified impulsivity aspects and some interactions of factors that pose a particular risk of recidivism, such as eating disorders for women or a history of familial suicidal behavior and employment status for men. Another decision tree based on the CHAID algorithm (chi-square automatic interaction detection) of 2,754 middle and high schools also found different explanatory factors, such as the severity of depression, which seems to be the strongest variable predicting SA interacting with greater delinquency and lower family intimacy to increase the risk of SA [18]. In addition, a classification tree developed to predict a high risk of SA in 6,686 Chinese high school students indicated interactions among depression, anxiety, social support, gender, self-esteem, family cohesion and adaptability as predictors of high suicide attempt risk (e.g., female adolescents with low social support and low depression scores were at high risk of SA) [19]. Therefore, anxiety seems to be the only risk factor found in both of our studies. Finally, among 218 patients discharged from psychiatric hospitalization after an SA, a recursive partitioning classification tree highlighted that previous SA characteristics (such as definite plans or extensive preparation) posed a high risk of re-attempt [20]. In fact, studies

investigating the interactions of factors to assess suicidal risk are rare. However, these emerging methods based on computer science have shown particularly good results to evaluate high-risk groups for suicide in a study comparing different statistical or computer-based methods [21].

Studies that have used more conventional methods (such as logistic regressions or Cox models) and that focus on few risk factors that are hypothesis-driven have often shown that certain factors are powerful in predicting suicide. According to our results, having an AUD or anxiety disorder (generalized anxiety or panic disorder) appears to be a determining factor in the prognosis after SA. Regarding psychiatric disorders, a meta-analysis obtained similar results with an increased risk of suicide in patients with opioid use or women with alcohol use disorder [22]. In contrast, a more recent study found the highest rates of suicide in subjects with substance use disorder but also the lowest rates in those with anxiety disorders [23].

Our findings also indicate an interaction between AUD and a previous SA with acute alcohol use, thus increasing the risk for these patients. Nevertheless, a recent review on risk factors for SA and suicide in patients with substance use disorder did not show any interaction with acute alcohol use during last SA but did show an association with environmental factors (marital and interpersonal relationship disruption, occupational and financial stressors, recent heavy substance use) as well as a history of previous SA [24]. Similar results were found in the Australian Treatment Outcome Study among subjects suffering from heroin dependence, with high odds ratios for sociodemographic factors (female gender, younger age, less education) and acute substance use (polydrug use, benzodiazepine use and recent heroin overdose) [25].

Alcohol use disorder is a well-known risk factor for suicidal behavior [26]. Regarding AUD, a Korean study confirmed an increased risk of SA with a logistic regression for students who used alcohol daily (odds ratio (OR) = 8.00) [27]. Moreover, in a recent study using logistic regression, an increased risk of SA was associated alcohol-related deaths following self-harm in addition to unemployment, sickness or disabled status, among other factors; interestingly, SA was also associated with alcohol use during previous self-harm [28]. Conversely, our study also found a significant reduction in the risk of recurrence in patients suffering from AUD who had not consumed alcohol during their previous suicidal act. It could be suggested that a reduction or cessation of alcohol consumption or the medical management of the alcohol use disorder may decrease the risk of suicide behavior.

Additionally, statistical methods such as multivariate Cox regression models used to predict the risk of recidivism have also shown an increased risk in patients who have made at least one attempt in their lifetime [29]. Nevertheless, our method suggested an increased risk of re-attempt for patients with more than 2 SAs in the past 3 years, thus indicating the need to pay more attention to these patients.

STRENGTHS

One of the strengths of our study is that among the large number of variables studied, a small number of factors are ultimately involved in suicide re-attempts and suicide and are brought to light by the CART method. The terminal nodes are clinically pertinent and based on simple combinations of medical risk factors. Moreover, the survival curve estimated by the Kaplan-Meier method corresponding to each terminal node showed very different prognoses depending on the subgroup to which they belonged. Another strength is the simple and intuitive nature of the CART algorithm, which allows for easy reading and captures much of the relevant covariate structure of the data.

LIMITATIONS

One of the limits of this study is the relatively high number of patients lost to follow-up at 6 months (9.5%). Nonetheless, the ALGOS study was composed of a sufficient number of patients, and most of the patients lost to follow-up were younger than 60 years old and were first attempters and thus were at lower risk for SA and death by suicide. In addition, baseline assessment investigated only four psychiatric disorders from the MINI. However, focusing on these common disorders appears to be convenient in

clinical practice, especially during a first psychiatric interview in an emergency room setting. Finally, alcohol use disorder is common in France and may affect a large proportion of the subjects in our study. This could be a limit to the extrapolation of our results to other parts of the world.

CONCLUSION

In this study, we suggested that the medical history and the method used for the previous SA were the most important risk factors for suicidal behavior. Indeed, by using a data-driven method, we found that alcohol use disorder and acute alcohol consumption during the last SA were associated with an increase in the risk of recidivism, such as anxiety disorder and recurrence of SA. The absence of these factors allowed for a decrease in this risk, and then the interaction of these various factors contributes to reducing or increasing the risk of recidivism. To better understand the risk factors associated with suicide, we need to consider what happens with combinations of risk factors rather than examining them one by one or by using classical methods such as logistic regression. Suicide prevention should therefore also take place at several levels with better management of psychiatric disorders and increased secondary prevention of suicidal patients, with a focus on those with an alcohol use disorder.

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CONFLICT OF INTEREST

None declared.

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