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ORIGINAL RESEARCH ARTICLE

Problem Gambling Associated with Aripiprazole: A Nested Case-Control Study in a First-Episode Psychosis Program

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Abstract

Background Aripiprazole has been linked to cases of problem gambling (PBG), but evidence supporting this association remains preliminary. Additionally, data specific to PBG in individuals with first-episode psychosis (FEP) receiving aripiprazole are limited to a few case reports, even though aripiprazole is widely used among this population that might be especially vulnerable to PBG.
Methods To examine this association, a nested case-control study was conducted in a cohort of 219 patients followed at a FEP program located in the Quebec City, Quebec, Canada, metropolitan area. Fourteen cases meeting the PBG criteria according to the Problem Gambling Severity Index were identified and matched for gender and index date to 56 control subjects.
Results In the univariable conditional logistic regression analysis, the use of aripiprazole was associated with an increased risk of PBG (odds ratio [OR] 15.2; 95% confidence interval [CI] 2.1–670.5). Cases were more likely to have a prior gambling history (either recreational or problematic) than controls at admittance in the program; they were also more frequently in a relationship and employed. After adjustment for age, relationship status, employment and Cluster B personality disorders, the use of aripiprazole remained associated with an increased risk of PBG (OR 8.6 [95% CI 1.5–227.2]).
Conclusions Findings from this study suggest that FEP patients with a gambling history, problematic or not, may be at increased risk of developing PBG when receiving aripiprazole. They also highlight the importance of systematically screening for PBG all individuals with psychotic disorders, as this comorbidity hinders recovery. While the results also add credence to a causal association between aripiprazole and PBG, further prospective studies are needed to address some of the limitations of this present study.

Key Points

Aripiprazole use in young adults with first-episode psychosis is associated with an increased risk of problem gambling (PBG).

The risk of PBG seems to be higher in individuals with a previous history of gambling, either recreational or problematic, who are in a relationship and employed.

Further research is needed to better characterize which patients are the most at risk of PBG, but in the meantime systematic screening and monitoring of this adverse event should be emphasized.

1 Introduction

Case reports of problem gambling (PBG) and impulse control disorders emerging in individuals treated with aripiprazole have led Health Canada (2015) and the United States Food and Drug Administration (FDA) (2016) to issue safety warnings. It has been speculated that aripiprazole's partial agonist activity at D3 dopamine receptors could explain its potential association with PBG [1], given that such events have been documented with full dopamine agonists used in Parkinson's disease (e.g. ropinirole and pramipexole) [2–6].

Two pharmacovigilance studies have addressed this issue by comparing the proportion of all serious adverse event reports associated with aripiprazole that involved PBG with the same proportion for all other drugs, using the proportional reporting ratio (PRR). The first study, using the FDA Adverse Event Reporting System, yielded a PRR of 8.6 for the association between aripiprazole and impulse-control disorders, including PBG [7], and the second, using the European pharmacovigilance database, obtained a PRR of

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15.3 for the association between aripiprazole and PBG [8]. However, these studies had limitations that prevent drawing firm conclusions. First, as only a small proportion of adverse events are reported in pharmacovigilance databases, they are prone to reporting biases. Second, as estimates of PRRs are obtained from the total number of adverse events reported for a given drug, they heavily depend on the drug's overall side-effects profile. Third, pharmacovigilance databases do not contain sufficient information on potential confounders to allow controlling for their effects and to assess causality.

To our knowledge, only a single study using a case-control design has examined the association between aripiprazole and PBG. In their study, Etminan and colleagues identified 355 PBG cases and matched them with 3550 controls within an American health claims database including over 6,000,000 subjects [9]. Among this sample, five cases and 11 controls had filled at least one prescription of aripiprazole, yielding a rate ratio of 5.2 (95% confidence interval [CI] 1.8–15.4) compared with 7.6 (95% CI 2.8–21.1) for the use of either ropinirole or pramipexole [9]. Again, this study suffered from an important underreporting of PBG, as the estimated prevalence of PBG in their complete population was 0.006%, much below the 1.0% estimated prevalence in the USA population [10]. Also, this study did not provide results specifically for schizophrenia spectrum disorders (SZSPD) subjects, a population that needs to be separately studied as it presents a dopamine dysfunction that may influence the possible behavioral adverse events of dopamine agonists [11, 12].

Specific evidence for an association between aripiprazole and PBG in SZSPD is limited to case reports. A recent review including 16 reports of PBG cases occurring in SZSPD patients treated with aripiprazole concluded that the link of causality could not be adequately assessed in most of the cases given the lack of documentation [13], a conclusion shared with a previous review [1]. This paucity of research is concerning, given that aripiprazole is frequently prescribed in this population, which might be up to four times more likely to suffer from PBG than the general population [14–16]. Among SZSPD patients, young adults with first-episode psychosis (FEP) may be particularly vulnerable to PBG, as known risk factors for PBG are more frequent in this population, such as younger age, male gender, comorbid substance use disorders (SUDs) and Cluster B personality disorders [17–20].

To address these limitations, we conducted a chart review study using a nested case-control design to evaluate the association between aripiprazole use and PBG in patients attending a FEP program, taking into account known PBG risk factors. The current study is, to our knowledge, the first that used a design other than case reports or database analyses to examine the relationship between aripiprazole use and PBG in SZSPD.

2 Methods

2.1 Study Design and Population

This nested case-control study was conducted in the entire cohort of 219 outpatients followed between November 1, 2015, and February 1, 2018 in the only FEP program in the Quebec City, Quebec, Canada, metropolitan area (approximately 750,000 inhabitants). This clinic provides a 3-year intensive multidisciplinary follow-up for approximately 50 new patients annually.

Inclusion criteria into this program were aged 18–30 years, having a SZSPD diagnosis (i.e. schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder, unspecified psychosis, schizoaffective disorder or drug-induced psychosis) and previous exposure to antipsychotic treatment for $\leq$ 6 months. Exclusion criteria were moderate or severe mental retardation, psychotic mood-disorder and psychosis due to a general medical condition.

2.2 Source of Data

The main sources of data were the patients' medical files, which include exhaustive information gathered through an intensive interdisciplinary follow-up with a psychiatrist, social worker and psychiatric nurse as well as a psychologist, occupational therapist and pharmacist, if needed. The typical frequency of meeting with any of the clinical staff varied from once a week to once a month. Patients' relatives were also regularly contacted during treatment in the context of ongoing family intervention and provided collateral information that was included in the patients' medical files.

2.3 Subjects

2.3.1 Cases

PBG was defined according to the Problem Gambling Severity Index (PGSI) threshold for PBG (see *Measures* below) [21]. This outcome was preferred over the DSM-5 diagnosis of gambling disorder [22], since individuals meeting the PGSI threshold for PBG without meeting the DSM-5 criteria nevertheless suffer from clinically meaningful consequences [23]. Cases were included notwithstanding whether or not they had a PBG history prior to entrance in the program. None had active PBG at admission in the program, as systematically documented at admission by both the clinical psychiatrist and the psychiatric nurse. Six cases were previously described in a case series [24].

Cases were identified through a two-step procedure. First, any mention of PBG was sought through a thorough review of the medical files of all 219 patients by two clinical

psychiatry pharmacists (OC and SC). The PGSI was rated whenever there was any mention of gambling. Second, the clinical staff involved with all subjects were individually met and questioned for any information on PBG that could have been missed during the files review; this process did not yield additional cases. The case's index date was defined as the first mention of gambling activities in the medical file, as available data did not allow an accurate retrospective assessment of the date of PBG onset.

2.3.2 Controls

All patients for whom no PBG was identified at any point during their follow-up were eligible as potential controls. Each PBG case was paired to four controls in order to maximize statistical efficiency while taking into account available resources. Controls were matched for gender, as being male is a well-replicated risk factor for PBG [16, 18], and had to be in active treatment at the cases' index date. When more than four controls were available for a case, random selection was applied. No control could be paired with two specific cases.

2.4 Measures

The PGSI is a questionnaire comprising nine items rated using a Likert scale, resulting in a final score ranging from 0 to 27 with corresponding severity levels of non-problem gambling (score of 0), low-risk gambling (score of 1–4), moderate-risk gambling (score of 5–7) and PBG (score of 8+) [21, 25]. Although not validated in the SZSPD population, the PGSI is one of the most widely used PBG screening instruments in various population settings and it has been used in two previous studies to measure PBG in samples of SZSPD patients [14, 16, 26, 27].

Demographic and clinical data retrieved from the medical files at the date closest to the cases' index date included lifetime history of criminality, community treatment order and psychiatric hospitalization, severity of psychopathology (as rated by the Clinical Global Impression scale—Severity [CGI-S]) [28] and main and comorbid DSM-5 diagnoses (including SUDs) established by the treating psychiatrist. Past and current medication were cross-retrieved from the patients' medical files and the clinic's electronic prescription tool. Current exposure to aripiprazole was defined as receiving either the oral or long-acting injectable formulations on the index date and for at least the previous 7 days.

2.5 Statistical Analysis

Subjects' demographic and clinical characteristics as well as aripiprazole treatment-related factors are presented using descriptive statistics. A multivariable conditional logistic regression model was constructed using the procedure suggested by Hosmer, Lemeshow and Sturdivant [29]. First, univariable models were adjusted for factors known to influence risk of PBG based on epidemiological studies (i.e. Cluster B personality disorders, SUD, age) [18]. Second, factors that were statistically associated with PBG risk at the 0.10 confidence level were further considered in the multivariable model. Finally, because of the risk of overfitting at this level, a backwards selection at the 0.05 confidence level was performed in the multivariable model. Conditional odds ratios (ORs) are presented with 95% CIs. Descriptive analyses were performed with SPSS® version 25 (IBM Analytics, Armonk, NY, USA) while the conditional logistic regression was adjusted using SAS® version 9.4 (SAS Institute Inc, Cary, NC, USA).

2.6 Ethics

Study protocol was reviewed and approved by the institution's ethics board and access to patients' medical files was granted by the professional services' director. No signed consent was requested, as data collection did not require contact with patients. All research data were anonymized.

3 Results

3.1 Descriptive Characteristics

Among the 219 patients treated in the clinic during the study period, 14 PBG cases (6.4%) were identified, among whom half had a prior history of gambling at admission. These 14 cases were paired with 56 controls through the procedure described above, for a final sample of 70 patients.

Main demographic and clinical characteristics are presented in Table 1. The average age of the sample was 24.5 (± 3.4) years, 92.9% were men, 75.7% were Caucasians and they had been followed at the clinic for an average of 499 (± 409) days at the index date. Mean overlap between cases' and controls' follow-up periods was 63% and all controls were in active follow-up at the cases' index date.

Regarding potential confounders, there was a strong and statistically significant association between PBG and being in a relationship, being employed and having a prior gambling history, either recreational or problematic. There were no differences between groups for education level, criminality, community treatment order and CGI-S ratings. To examine the possibility of an indication bias (i.e. aripiprazole users differing from aripiprazole non-users), we compared these two groups on the variables listed in Supplementary Table 1 (see Electronic Supplementary Material [ESM]), which revealed that aripiprazole users were more likely to present a lifetime alcohol use disorder.

3.2 Problem Gambling and Aripiprazole

Twelve out of the 14 PBG cases (85.7%) and 19 out of the 56 controls (33.9%) were currently treated with aripiprazole, resulting in an OR of 15.2 (95% CI 2.1–670.5; $p = 0.001$) (Table 2). After adjusting for age, relationship status, employment and Cluster B personality disorders, current use of aripiprazole remained associated with an increased risk of PBG (OR 8.6; 95% CI 1.5–227.2; $p = 0.012$). The same trend was maintained when considering other definitions of aripiprazole exposure, such as lifetime use (i.e. having ever received at least one dose of aripiprazole) (OR 4.7; 95% CI 1.0–37.3; $p = 0.052$). To examine if matching on gender introduced bias, a sensitivity analysis was performed excluding female subjects and results were not substantially changed (adjusted OR 9.4; 95% CI 1.3–279.6).

Lifetime alcohol use disorder and prior gambling history, two potentially important confounding factors, could not be included in the multivariable analyses of the association between aripiprazole and PBG because of quasi-complete separation of cases, introducing instability in the multivariable model estimates. In a sensitivity analysis, lifetime alcohol use disorder was added to a conditional logistic regression with current aripiprazole use as an independent variable. The association between current aripiprazole use and PBG remained significant and similar to the previous multivariable model (OR 13.6; 95% CI 1.7–110; $p = 0.015$). A similar sensitivity analysis for prior gambling history was impossible because none of the controls with a prior gambling history were currently using aripiprazole and PBG cases who had no such antecedent were currently receiving aripiprazole (Table 3), reinforcing the separation of cases and controls. Nevertheless, the association between current aripiprazole use and PBG was found to be statistically significant when considering only patients without a prior gambling history (Fisher's exact test, $p = 0.002$).

There were no significant differences between PBG cases and controls for factors related to aripiprazole treatment (i.e. pharmaceutical formulation, mean doses and treatment duration; Supplementary Table 2, see ESM) nor for other factors pertaining to the pharmacological treatment (e.g. concomitant medication; Supplementary Table 3, see ESM).

Table 1 Characteristics of problem gambling (PBG) cases and control subjects

Variables	Cases ($n = 14$)	Controls ($n = 56$)	OR (95% CI)	p value
Male gender, *n* (%)	13 (92.9)	52 (92.9)	1.0 (1.0–1.0)	1.000
Age, mean ± SD, years	26.1 ± 2.9	24.1 ± 3.5	1.2 (1.0–1.5)	0.059
Follow-up duration, mean ± SD, days[a]	532 ± 506	491 ± 385	1.0 (1.0–1.0)	0.738
Caucasian, *n* (%)	11 (78.6)	42 (75.0)	1.2 (0.3–4.6)	0.793
In a relationship, *n* (%)	5 (35.7)	4 (7.1)	14.5 (1.6–129.6)	0.016
Living independently, *n* (%)	7 (50.0)	19 (34.5)[b]	1.8 (0.6–5.7)	0.331
Education level, mean ± SD, years	11.2 ± 2.4	10.8 ± 2.4[b]	1.1 (0.8–1.4)	0.604
Employment, *n* (%)	12 (85.7)	27 (48.2)	5.2 (1.1–23.9)	0.033
Criminal offence (lifetime)[c], *n* (%)	2 (14.3)	7 (12.5)	1.2 (0.2–6.2)	0.860
Community treatment order (lifetime)[c], *n* (%)	2 (14.3)	10 (17.9)	0.7 (0.1–4.2)	0.739
Psychiatric hospitalization (lifetime)[c], *n* (%)	6 (42.9)	32 (57.1)	0.6 (0.2–1.8)	0.349
Current CGI-S score, mean ± SD	3.1 ± 1.3	2.8 ± 1.2	1.2 (0.8–1.9)	0.405
Cluster B personality disorder, *n* (%)	5 (35.7)	16 (28.6)	1.4 (0.4–5.2)	0.587
Prior gambling history[d], *n* (%)	7 (50.0)	4 (7.1)	22.4 (2.7–186.1)	0.004
Tobacco use (lifetime)[c], *n* (%)	10 (71.4)	34 (63.0)[e]	1.5 (0.4–5.4)	0.564
Alcohol use disorder (lifetime)[c], *n* (%)	8 (57.1)	19 (33.9)	2.8 (0.8–10.2)	0.114
Cannabis use disorder (lifetime)[c], *n* (%)	9 (64.3)	39 (69.6)	0.8 (0.2–2.7)	0.694
Amphetamine use disorder (lifetime)[c], *n* (%)	7 (50.0)	21 (37.5)	1.7 (0.5–5.7)	0.384

CGI-S Clinical Global Impressions—Severity, *CI* confidence interval, *OR* odds ratio, *SD* standard deviation

[a]Duration of the follow-up at the clinic up to the index date

[b]Missing data for $n = 1$

[c]*Lifetime* indicates that the variable was positive either prior to the patient being admitted in the clinic or at some point during follow-up

[d]*Prior* indicates that the variable was positive prior to the patient being admitted in the clinic

[e]Missing data for $n = 2$

Table 2 Crude and adjusted odds ratios (ORs) for use of aripiprazole and risk of problem gambling

Aripiprazole use	Total ($n = 70$) n (%)	Cases ($n = 14$) n (%)	Controls ($n = 56$) n (%)	Crude OR		Adjusted OR[a]	
				OR (95% CI)	p value	OR (95% CI)	p value
No current use	39 (55.7)	2 (14.3)	37 (66.1)	1.0 (reference)		1.0 (reference)	
Current use[b]	31 (44.3)	12 (85.7)	19 (33.9)	15.2 (2.1–670.5)	0.001	8.6 (1.5–227.2)	0.012
Lifetime use[c]	36 (51.4)	12 (85.7)	24 (42.9)	6.3 (1.3–59.2)	0.013	4.7 (1.0–37.3)	0.052

[a]Adjusted for age, relationship status, employment and Cluster B personality disorders

[b]Patients receiving aripiprazole, either the oral or long-acting injectable (LAI) formulations, on the index date and for at least the previous 7 days

[c]Patients who were currently receiving aripiprazole at the index date or had ever received at least one dose of aripiprazole, either the oral or LAI formulations

4 Discussion

4.1 Summary of Main Results

In this first nested case-control study conducted in a clinical setting, as opposed to pharmacovigilance databases, a strong and significant association was found between aripiprazole use and PBG (OR 15.2) that persisted after controlling for known PBG risk factors. Additional post-hoc analyses suggested that neither a confounding effect of a prior history of PBG nor of a lifetime comorbid alcohol use disorder could account for the association between PBG and aripiprazole.

4.2 Methodological Limitations

These findings must be interpreted in light of the following limitations. First, due to the modest sample size, the CI for the size of the association between aripiprazole and PBG is large, so the strength of the association reported herein must be interpreted cautiously.

Second, PBG identification was done retrospectively and not blind to treatment. Hence, some observation bias may have resulted from the fact that aripiprazole has been suspected of causing PBG since Health Canada and the FDA issued warnings in 2015–2016. Furthermore, it was not based on a systematic longitudinal screening, but rather on clinicians' observation. These aspects are mitigated by the fact that multiple sources of clinical information were gathered in the context of an intensive follow-up in a FEP program, with frequent, well documented, different health care providers' contact with patients and family members. Consequently, PBG sensitivity detection was optimized and the likelihood of a selective PBG non-detection bias in aripiprazole non-exposed patients was reduced. Furthermore, the exhaustiveness of overall PBG detection, herein 6.4%, is comparable to, or even greater than, those reported in previous studies, reflecting good PBG recognition, leaving little room for possible selective detection bias [14, 16]. Also, the case identification procedure was completed prior to collection of demographic and clinical variables (including medication), preventing a rater's observation bias. While such limitations are inherent to the purely naturalistic design of the study, this latter factor allowed the inclusion of the full cohort of patients, thereby preventing a non-participation bias that could have occurred otherwise.

Third, observational studies, such as the present one, are prone to confounding. For instance, there might be an indication bias, where patients prescribed aripiprazole would systematically differ from those prescribed other antipsychotics regarding risk factors for PBG. Subjects on aripiprazole differed from those not on aripiprazole only for a more frequent lifetime comorbid diagnosis of alcohol use disorder; as reported above, the association between aripiprazole exposure and PBG persisted after including this potential confounding factor in a bivariable analysis. Regarding other

Table 3 Problem gambling and current aripiprazole use among subgroups of patients based on prior gambling history

Aripiprazole use	With prior gambling history		p value[a]	Without prior gambling history		p value[a]
	Cases ($n = 7$) n (%)	Controls ($n = 4$) n (%)		Cases ($n = 7$) n (%)	Controls ($n = 52$) n (%)	
No current use	2 (28.6)	4 (100.0)	0.061	0 (0.0)	33 (63.5)	0.002
Current use[b]	5 (71.4)	0 (0.0)		7 (100.0)	19 (36.5)	

[a]Fisher's exact test

[b]Patients receiving aripiprazole, either the oral or long-acting injectable formulations, on the index date and for at least the previous 7 days

potential confounding factors, the association between aripiprazole and PBG persisted while taking them into account in the multivariable analyses. While we cannot rule out some residual confounding that may occur in small samples even when using multivariable regression, these additional multivariable analyses suggest that such confounding is unlikely to account for the observed association between aripiprazole and PBG.

Fourth, whereas the included patients are at least representative of the FEP population, the results obtained cannot be generalized to other populations in which aripiprazole is used (e.g. bipolar I and major depressive disorders), given the differences in clinical and neurobiological profiles, particularly with regards to dopamine dysfunction [11, 12]. The present findings also cannot be readily extrapolated to non-FEP patients with SZSPD, as longer illness duration and cumulative exposure to dopamine receptor antagonists could lead to distinct biological and behavioral responses to partial agonists, such as aripiprazole.

4.3 Comparison with Previous Literature

Evidence of an association between aripiprazole and PBG is sparse, and data for people with SZSPD only consist of case reports [13, 24], which limits the comparability of the results herein obtained. Therefore, the strength of the relationship between aripiprazole and PBG, estimated in this study with an adjusted OR of 8.6, neither confirms nor contradicts the RR of 5.2 found by Etminan and colleagues, notably due to the important differences across studies regarding the methodology used as well as the type of populations studied [9]. Added together though, these two findings add credence to a genuine causal association between aripiprazole use and PBG occurrence. Finally, although factors related to aripiprazole treatment, such as dose, duration of exposure and pharmaceutical formulation, have been hypothesized to modulate the risk of PBG emergence [1, 8, 13, 30], no such association was found in this study.

The 6.4% prevalence of PBG in the present FEP population was markedly greater than the estimated prevalence of 0.4% in the Quebec general population [31]. This finding is consistent with previous studies conducted with samples of patients with SZSPD that have reported the prevalence of PBG to be around four times higher than that of the general population [14–16]. Interestingly, two of these studies measured PBG using the PGSI and found prevalence of PBG to be quite similar to the one obtained herein, ranging from 4.7 to 5.8% [14, 16]. Hence, as patients included in these previous studies were on average above 35 years old, the present study is the first to generalize such results to the younger FEP population. This finding further reinforces that patients with SZSPD are more prone to develop PBG, which could possibly result from not only the presence of multiple known risk factors for PBG in this population, such as personality disorders and SUDs [18], but also from a genetic predisposition partially shared by SZSPD and PBG, as recently proposed [32].

Interestingly, every patient who was receiving aripiprazole and had a history of gambling, whether it was recreational or problematic, developed a full-blown PBG, although this finding is supported only by a limited number of cases (see Table 3). In a review of published PBG cases associated with the use of aripiprazole in SZSPD, it was noted that half of them had a PBG history prior to aripiprazole exposure [13]. Hence, FEP patients with a gambling history, problematic or not, may be particularly at risk of developing PBG when prescribed aripiprazole. As for Cluster B personality disorders, such a comorbidity had been found to be highly prevalent in patients with PBG [33], but no statistically significant difference was found in the present study. Also, while an association between PBG and comorbid SUDs has been observed in the general and SZPSD populations [14, 16, 18], the relatively small sample size of this study combined with the high incidence of comorbid SUDs among FEP patients did not allow the assessment of such an association.

5 Conclusions

Taking into account the methodological considerations discussed above, the present results add to the evidence that PBG is a frequent comorbidity in SZSPD and call for the implementation of a systematic monitoring approach. Even though these results provide support to a causal association between aripiprazole and PBG, further prospective studies replicating these findings in larger samples are still needed before calling for a fundamental reconsideration of aripiprazole use in SZSPD. Such studies are needed to better identify the profile of at-risk patients for developing PBG and eventually delineate new prevention and treatment approaches adapted to this vulnerable population.

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Declarations

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Availability of data and material All data generated or analysed during this study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions Olivier Corbeil and Stéphanie Corbeil conceptualized the research question and study design, collected the data, interpreted the results and wrote the first draft of the manuscript. Pierre-Hugues Carmichael conducted the analyses and interpreted the results. Michel Dorval, Isabelle Giroux and Christian Jacques conceptualized the research question and study design. Marie-France Demers and Marc-André Roy interpreted the results and supervised the project. All authors critically revised the manuscript and approved the final manuscript that was submitted.

Ethics approval Study protocol was reviewed and approved by the institution's ethics board and access to patients' medical files was granted by the professional services' director. No signed consent was requested, as data collection did not require contact with patients. All research data were anonymized.

Consent to participate Not applicable.

Consent for publication Not applicable.

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