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# Double Prevention in Outpatient Forensic Care; Early Psychotic Experiences and Its Relationship with Aggression and Antisocial Personality Disorder

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### **Abstract**

Although there is evidence for the effectiveness of early interventions among Ultra-high risk (UHR) for psychosis, detection and intervention in forensic patients is lacking. This study aimed to establish the prevalence of UHR among this population and its relationship with aggression. Because there are indications that the relationship between prodromal symptoms and aggression might be particularly strong in antisocial personality disorder (ASPD), we specifically looked at the relationships within this group. Data were collected by using the Prodromal Questionnaire (PQ-16) and the Aggression Questionnaire (AQ), the semi-structured interview CAARMS and file study. Participants with ASPD (N = 30) and without this disorder (N = 44) were compared. Within this forensic setting, the prevalence of ultra-high risk for psychosis was significantly higher compared to regular mental health care. We found a significant relationship between prodromal psychotic symptoms and aggressive feelings (anger and hostility). In patients with ASPD, we also found a significant relation between prodromal psychotic symptoms and physical violence. This implies that patients in the prodromal phase have a higher risk to behave aggressively.

## **Keywords**

Early Detection, Aggression, Prodromal, Ultra-High Risk, Psychotic Symptoms, Antisocial Personality Disorder, Prevention

## 1. Introduction

In forensic mental healthcare, aggression is a major problem (Dickens et al., 2013), especially among patients with antisocial personality disorder (ASPD) (Whiting et al., 2021). Various factors, like impulsivity, trauma, substance abuse and social circumstances, have been found to be related to aggressive behavior in patients diagnosed with ASPD (Azevedo et al., 2020; De Wit-De Visser et al., 2023; Wojciechowski, 2020). A factor that has received relatively little attention in this population is screening on a routine basis for susceptibility for an "at risk mental state" to psychosis, although there appear to be relations between early-onset psychosis, ASPD and forensic history (Huber et al., 2016). In psychiatry, there is a lot of experience in how to screen psychosis susceptibility on a routine basis in a standardized way, with the possibility of early intervention, in order to limit serious suffering. These procedures could possibly also be applied in forensic psychiatry in order to reduce aggressive behavior.

Psychotic episodes are related to severe psychopathology and worse social functioning. Therefore, psychotic disorders are a serious mental health problem (McGlashan, 1999; Rossler et al., 2005). A patient's transition to psychosis is associated with a reduced quality of life and increased suffering. Therefore, the prognosis for people with a psychotic vulnerability is not favorable, despite the innovations in pharmaceutical and psychosocial treatment (van der Gaag et al., 2019). Especially the duration of untreated psychosis (DUP) was associated with poor outcome and was designated as a prognostic risk factor (McGlashan, 1999; van der Gaag et al., 2019). Therefore, early detection of psychotic vulnerability provides an opportunity to prevent further symptomatology.

Prior to developing a first psychotic episode, most patients seek for help in mental healthcare for other psychiatric symptoms like depression, anxiety and sleeping problems. During the year before a first psychotic episode, 60% of patients were diagnosed with another psychiatric classification (Simon et al., 2018). These previous consults provide clinical opportunities to screen for psychotic symptoms. A meta-analysis (Fusar-Poli et al., 2012) showed that screening for the risk of psychotic symptoms is effective. The detected group of individuals at risk of developing psychotic symptoms is described as individuals with an "at risk mental state" (ARMS) or "clinical high risk" (CHR). Recent meta-analyses found that individuals with high risk have a likelihood of 25% - 35% to develop a psychotic episode (Salazar de Pablo et al., 2021; Ising et al., 2016). The risk of developing psychosis continued to increase after 2 years, cumulating to 25% at 3 years and reaching 35% at 10 years. These individuals do not yet meet the criteria for a psychotic episode; ARMS is thus a heterogeneous risk profile and not a disorder (Van der Gaag, 2019).

Besides screening for the risk of developing a psychosis, 10% of the screened patients in specialised mental health care, between 18 and 35 years, already meet the criteria of a psychotic episode (Ising et al., 2012). Thus, screening can also detect unrecognized psychosis and allows shortening of DUP, which is associated with a better prognosis (Valmaggia et al., 2015; van der Gaag et al., 2019).

Rietdijk and colleagues (2010) published the Dutch Early Detection Intervention Evaluation (EDIE-NL) study. When ultra-high risk is detected, an add on cognitive behavioural therapy for psychotic symptoms (CBT-P) is offered which aims to reduce the distress associated with psychotic symptoms and improve functioning. Several studies have demonstrated that CBT-P can result in improved functioning by a decrease of positive symptoms and improvement in negative symptoms (Wykes et al., 2008; Burns et al., 2014; van der Gaag et al., 2019). In Netherlands, various mental health care institutions have implemented early detection programs. During the past decade, studies have shown that such an approach is effective as the risk of transition to a psychotic episode conform DSM criteria (APA, 2013) decreases, even after a four-year follow-up period (Ising et al., 2016, Salazar de Pablo et al., 2021).

So far, most studies were administered in a general mental healthcare population. However, psychotic symptoms like frequent paranoia, hostility and distrust are also observed in the forensic in- and outpatient setting (Coid et al., 2016, Joubert & Zaumseil, 2020). In a study of young prisoners in the UK (Evans et al., 2017), some of these prisoners showed psychotic symptoms and 4.4% of them met the criteria for "ultra-high risk". Dalteg and colleagues (2014) found an association between high rates of conduct disorder problems and ADHD in childhood and psychosis in adulthood. Systematic research on early detection of psychotic symptoms, especially in outpatient forensic mental healthcare settings, is limited. This is problematic because several studies revealed a relationship between psychotic symptoms, violent behavior and acts of crime (Coid et al., 2016; Fazel et al., 2009; van Dongen et al., 2015).

Moreover, in forensic outpatient settings, patients are often referred because of (imminent) aggressive or abusive behavior. In a study on prevalence of violent behavior among ultra-high risk patients, Brucato et al. (2019) found that the presence of violent ideation and violent behavior at baseline significantly predicted aggressiveness as well as psychosis during follow-up, independently of over forty clinical and demographic variables. They also found that the risk of violence increases towards conversion to a psychotic episode and then peaks around time of conversion. There's also some literature suggesting that a history of delinquent behaviors may increase the likelihood of violence in psychotic illness (Winsper et al., 2013; Brucato et al., 2019). Coid and colleagues (2016) showed that when ultrahigh risk symptoms are present in combination with a comorbid antisocial personality disorder, it is even more likely that violence occurs. Physical violence is associated with various negative outcomes for patients and staff (Joubert & Zaumseil, 2020). In a meta-analysis a strong association was found between Psychotic Like Experiences (PLE) (thus, UHR) and violent incidents (Coid et al., 2016). This relation was not significant when individuals actually met the criteria for "psychosis". This suggests that when people who have a risk for psychotic symptoms, are in the prodromal phase, have a higher likelihood of engaging in violent incidents than people with a psychotic disorder. Having suspicious thoughts turned out to be the strongest predictor. This demonstrates the importance of detecting ultrahigh risk in people with suspicious, violent and antisocial behavior. However, early detection of psychotic complaints in the context of violence is not a standard practice in forensic mental health care and has not been conducted so far.

Given the limited knowledge of the occurrence and coherence between specific forensic related disorders and psychotic symptoms in outpatient forensic healthcare, the objective of this study was to gain insight in the prevalence of psychotic symptoms in outpatient forensic care, and their relationship with aggressive behaviour, in order to optimize treatment. A better understanding of the relationship between psychosis and violence may help reduce the presence of violence within this population, prevent patients from being stigmatized due to an act of violence arising from their mental disorder, and even save lives. Therefore, the present study will focus on the prevalence of ultra-high risk among patients in a forensic psychiatric setting. Because there are indications that the relationship between prodromal symptoms and aggression might be particularly strong in ASPD (Coid et al., 2016; Huber et al., 2016), we specifically looked at the relationships within this group, and the relation of these psychotic symptoms with aggression and antisocial personality disorder.

## 2. Methods and Measurements

## 2.1. Participants

Participants (N = 76) were recruited in a forensic psychiatric outpatient setting (FPP) in the Netherlands. In this setting, individuals were treated with psychiatric diagnoses related to aggression, rule breaking and/or antisocial behaviour (forensic psychiatric problems) and/or a juridical disposition. Patients whom were diagnosed with a psychotic disorder or whom received treatment for psychotic symptoms prior to the current study were excluded from the sample. See **Table 1** for characteristics of the sample.

**Table 1.** Characteristics and scores and Standard deviations (SD) on the Aggression Questionnaire (AQ) and the Prodromal Questionnaire (PQ-16) of forensic patients with and without Anti-social personality Disorder (ASPD).

	No ASPD $(n = 46)$	ASPD $(n = 30)$	Total (n = 76)
Age in years (SD) range	40.2 (12.3) 20 - 62	39.8 (10.6) 22 - 58	3 40.0 (11.6) 20 - 62
Gender (M/F)	38/8 (83/17%)	27/3 (90/10%)	65/11 (86/14%)
Education level			
Low	10 (23%)	12 (46%)	22 (31%)
Medium	27 (61%)	13 (50%)	40 (57%)
High	7 (16%)	1 (4%)	8 (11%)
AQ-Physical aggression (SD)*	2.99 (.83)	3.40 (.92)	3.15 (.88)
AQ Verbal aggression (SD)*	2.93 (.77)	3.63 (1.89)	3.20 (1.35)
AQ Anger (SD)*	2.97 (.69)	3.35 (.91)	3.12 (.80)
AQ Hostility (SD)	3.26 (1.04)	3.38 (.998)	3.30 (1.02)
PQ (SD)	4.90 (3.48)	5.75 (3.70)	5.24 (3.57)
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Note: \*:p < .05.

We compared a group of patients with anti-social personality disorder diagnosis (ASPD) (N=30) with a group without the ASPD diagnosis (N=46). The antisocial personality disorder was diagnosed at the FPP during intake or treatment prior to selection for this study, using the Structured Clinical Interview for DSM-5 (SCID-5-PD). The SCID-5-PD is a semi-structured diagnostic interview guide which is used to determine the presence of personality disorders (First et al., 2015). It is administered by a mental healthcare professional who is familiar with the DSM-5 classification and diagnostic criteria. All diagnostic symptoms are coded as "present", "subthreshold", or "absent".

## 2.2. Procedures

Data was collected by standardized routine outcome measurements; Prodromal Questionnaire-16 (PQ-16) and Aggression Questionnaire (AQ), semi-structured interviews CAARMS (Comprehensive Assessment of At Risk Mental States) and file study.

During intake, patients completed the PQ-16 and the AQ. For those who scored above the cut off score of six on the PQ-16, a face-to-face interview was conducted, using the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005).

To determine the psychotic symptoms, the PQ-16 was administered. The PQ-16 is a shortened version of the original 92 item Prodromal Questionnaire (PQ-92). It enables the detection of ultra-high risk (UHR) patients in adult mental health services. The PQ-16 contains nine hallucination-like items, five delusion-like items and two negative symptom items. The reliability of the questionnaires in our data was calculated. In this sample we have a Cronbach's alpha of .81 on the Prodromal Questionnaire (PQ-16). A score between .7 and .8 is suggested to be reliable.

The Comprehensive Assessment of At Risk Mental State (CAARMS) is a semistructured interview, developed to identify individuals at risk for psychosis (Raballo et al., 2011). During the interview, several positive symptoms of psychosis (disorganised speech, unusual thought content, perceptual abnormalities and non-bizarre ideas) are surveyed and assessed in terms of frequency, associated distress and occurrence (with or without the use of illicit substances). The stepped approach using the PQ-16 plus the CAARMS assessment has been successfully validated (Loewy et al., 2011; Rietdijk et al., 2012). In adults, the PQ-16 uses a cutoff score of six or more. The PQ combined with CAARMS, predicts UHR/Psychosis diagnosis with high sensitivity (87%) and specificity (87%).

The Aggression Questionnaire (AQ) was used to elicit detailed information about aggressive thoughts, feelings and behaviour. This 29 items questionnaire is scored on a 5-point Likert scale and contains four subscales: Physical aggression, Verbal aggression, Anger and Hostility. The psychometric properties of this instrument have been established (Meesters et al., 1996). In this sample we have a Cronbach's alpha of .81 on the AQ. The Aggression Questionnaire has four

subscales, each of them differing in reliability. Reliability of physical aggression was .76, verbal aggression .16, anger .75 and hostility .70. Inspection of the reliability of verbal aggression showed that item 22 diminished the reliability. Cronbach alpha without item 22 showed a reliability of .63. The results of our analysis however did not change essentially whether the 4 or 5 verbal aggression items were used. Therefore, we reported the full verbal aggression scale in our results.

## 2.3. Data Analysis

Statistical analyses were conducted using the program Statistical Package for Social Science (SPSS), version 27. In order to gain insight into the prevalence of ultra-high risk among patients in forensic psychiatric settings, descriptive statistics were used; numbers and proportions (percentages) for categorical variables, and means, medians and ranges for continuous variables.

T-tests were performed to get insight in the differences in the relation of prodromal symptoms and aggression, between patients with an antisocial personality disorder (ASPD) and patients without this diagnosis.

## 2.4. Ethical Aspects

Approval of the study was given by the Ethical Committee of the Participating Institution. The data were gathered and analyzed anonymously by separating the informed consent declaration from the questionnaires to guarantee that the answers on the questionnaires would have no consequences for the participants. The researchers declared that they had no conflicts of interest regarding this study.

#### 3. Results

Characteristics and scores of forensic patients with and without an ASPD diagnosis in this sample are presented in **Table 1**.

In order to analyze whether aggression and prodromal symptoms differed for patients with or without a ASPD diagnosis, we performed an independent t-test with Group (ASPD/No-ASPD) as independent variable and the subscales of the AQ and the PQ-16 as dependent variables. Analyses revealed that the scores in the two groups differed from each other regarding Physical aggression, (t = 2.03, p < .05), Verbal aggression (t = 2.27, p < .05), and Anger (t = 2.03, p < .05), but did not differ from each other on Age, (t = 1.14, p > .89) and Hostility, (t = .50, p > .61). Chi-square analyses revealed that ASPD and No-ASPD did not differ from each other on gender, (chi-square = .81, p > .37). and education level, (chi-square oi = .53, p > .07). To rule out the possible effects of gender, age and education level, these demographic variables were used as covariates in subsequent analyses.

In order to get insight into the relations between the variables, correlations were calculated between the scores on the Aggression Questionnaire (AQ) and the Prodromal Questionnaire (PQ-16). To investigate whether these relations were different for patients with an ASPD diagnosis, we also calculated the correlations for the two groups separately. Results are presented in **Table 2**.

**Table 2.** Correlations between the scores on the Aggression Questionnaire (AQ) and the Prodromal Questionnaire (PQ-16) for the total population and the no ASPD and ASPD groups separately.

	AQ-Physical	AQ Verbal	AO Angor	AQ Hostility
	aggression	aggression	AQ Anger	
AQ Verbal aggression				
total	.24*			
no ASPD/ASPD	.30*/.16 #			
AQ Anger total no ASPD/ASPD	.71** .62**/.77**	.24* .64**/.00 #		
AQ Hostility total no ASPD/ASPD	.51** .44**/.62**	.14 .46**/04#	.62** .56**/.72**	
PQ total no ASPD/ASPD	.40** .25/.57**#	.11 .41**/09 #	.51** .37*/.64**	.55** .43**/.74**#

Note: \*: p < .05, correlations for no ASPD and ASPD are significantly different at p < .05; \*\*: p < .001, correlations for no ASPD and ASPD are significantly different at p < .001; #: significant difference between ASPD and No ASPD.

The correlation between the PQ-16 and physical aggression differed significantly between the two groups; there was a significant correlation for the ASPD group and not for the Non-ASPD group. The correlations between verbal aggression and the other AQ scales and the PQ-16 were also significantly different between the two groups; For the Non-ASPD group, correlations were significant, for the ASPD group they were not. When the correlations were significant in both groups, we tested the significance of the difference between the two correlations by converting the correlation coefficients into standardized z scores and calculating the z score for the difference. The correlations between hostility and the PQ-16 were both significant but also significantly different (z = -2.0, p < .05). There were no significant differences between the groups for the other correlations.

In order to investigate whether there was a difference between patients with and without ultra-high risk and psychotic patients, we performed an ANOVA with psychotic symptoms (no UHR, UHR, psychotic) as independent variable and the Aggression Questionnaire (AQ) and the Prodromal Questionnaire (PQ-16) as dependent variable. The results are presented in **Table 3**.

In our research population within the group ages 15 - 35 (this is conformed international consensus), 21.2 percent of patients met the criteria for ultra-high risk for developing psychotic symptoms. This is much higher than the percentage found in regular mental health care, where prevalence is 4% (Rietdijk & van der Gaag, 2014).

It turned out that in our sample, 9.1% already had enough psychotic symptoms for diagnosing a psychotic disorder. The groups differed significantly from each other in Hostility (F(2, 69) = 7.00, p < .01), and the PQ (F(2, 69) = 7.76, p < .01). Regarding hostility, a Bonferroni post hoc test revealed that the UHR and No UHR differed significantly from the psychotic group (p < .01 and p < .05 respectively) and

differed significantly from each other (p = .05).

**Table 3.** Characteristics and scores on the Aggression Questionnaire (AQ) and the Prodromal Questionnaire (PQ-16) of forensic patients with and without ultra-high risk (UHR) on psychosis and actual psychosis.

	No UHR (n = 48)	UHR (n = 15)	Psychotic (n = 7)
Age in years (SD) range	40.9 (12.1) 20 - 62	36.9 (10.7) 21 - 53	40.1 (8.4) 32 - 55
Gender (M/F)	41/7 (85/15%)	13/2 (87/13%)	6/1 (86/14%)
Education level			
Low	10 (23%)	5 (33%)	2 (33%)
Medium	26 (61%)	9 (60%)	4 (67%)
High	7 (16%)	1 (7%)	0 (0%)
ASPD/No ASPD	17/31 (35/65%)	10/5 (67/33%)	4/3 (57/43%)
AQ-Physical aggression (SD)	3.16 (.90)	3.27 (.76)	2.49 (.95)
AQ Verbal aggression (SD)	3.33 (1.57)	3.17 (.83)	2.31 (.90)
AQ Anger (SD)	3.06 (.82)	3.32 (.51)	2.67 (.92)
AQ Hostility** (SD)	3.22 (1.04)	3.91 (.58)	2.23 (.97)
PQ** (SD)	4.18 (3.27)	7.93 (2.76)	5.29 (5.21)

Note \*:p < .05, \*\*: p < .01.

In order to investigate which factor predicted physical aggression, we performed a stepwise hierarchical regression entering the demographic variables in the first step, the PQ-16 in the second step and ASPD in the third step. The R-change in the second step was significant, ( $\Delta R^2 = .34$ , p < .001, standardized B = .50, p < .001). The R-change in the third step was not significant.

## 4. Discussion

The aim of this study was to investigate whether the prevalence of psychotic symptoms in a forensic setting is comparable to prevalence in regular mental health care and if there is a relationship between psychotic symptoms and aggression. We found a five-fold greater prevalence (21.2%) of patients who met the current criteria of ultra-high risk, compared to 4% in regular mental health care (Rietdijk et al., 2012).

One in every five patients experienced such a level of prodromal symptoms that they were, conform the adopted criteria, at high risk of developing a psychosis. Whether symptoms as hostility and threat must be viewed as actual pathology, early prodromal symptoms, or maybe actual threats because of social context, criminal neighbourhood, engaging in threatening situations and/or criminal acts, is not yet clear. We've established that the number of prodromal symptoms in this setting is considerably higher than in regular mental health care, which is in line with suggestions in literature that a history of delinquent behaviours may increase the likelihood of violence in psychotic illness (Winsper et al., 2013; Brucato et al.,

2019). Further investigation of the validity of these symptoms is needed to explore this at-risk group within the forensic setting. In order to understand why people engage in aggressive behaviour, offer them better treatment and learn to prevent aggressive incidents, we explored the relationship between early psychotic symptoms and aggression.

We found that prodromal symptoms in the forensic population were related to physical aggression, and even stronger in patients with an ASPD diagnosis. This is in line with literature which states that prodromal symptoms like paranoia, hostility and distrust are threatening experiences and can cause hypervigilance, stress and trigger aggressive behaviour and acts of crime (Brucato et al., 2018; Fazel et al., 2009). Our findings that individuals with an at-risk mental state in combination with an ASPD diagnosis, reported more aggression than forensic patients without this diagnosis may not seem surprising, since aggression is one of the symptoms of ASPD (APA, 2013). But because our study did not only reveal higher levels of aggression compared to forensic patients without an ASPD diagnosis, but also revealed a stronger relation between prodromal symptoms and physical aggression, our findings suggest that screening on at risk mental state may be even more relevant in patients with ASPD regarding risk assessment for violent behaviour.

Our study also indicated that having an at risk mental state increased the risk of anger and hostility. This is in line with Coid et al. (2016) who found that especially the prodromal phase of psychotic complaints gave an increased risk of aggression, and that when someone is actually psychotic, this leads to a decrease in aggression. As in the study of Coid et al. (2016), the participants in our study scored lower on the various scales of the AQ after actually experiencing a psychotic condition. In particular, the score on the hostility scale was significantly lower in people with a psychotic disorder. However, the number of people with a psychotic disorder was too small to draw firm conclusions.

A significant difference was found regarding the experience of hostility, verbal and physical aggression between people with prodromal complaints who meet the criteria for an antisocial personality disorder and people who do not. In people without ASPD, no significant relationship between increase in prodromal symptoms and physical aggression was found. The relationship between hostility and prodromal complaints is significantly stronger in people with ASPD. In their meta-analysis, Coid et al. (2016) also found no significant difference for gender, substance abuse, or any other comorbidity with violence. We can conclude that people with ASPD and increasing psychotic complaints, have an increased risk of physical incidents of aggression. This information can be valuable for preventive screenings to prevent violent crimes. This is important in the light of research that shows that the reluctance of many clinicians to provide treatment to ASPD patients is fuelled by the feeling of being out of control in the therapeutic alliance with ASPD patients (van Dam et al., 2022). Knowledge about the specific mechanisms underlying aggressive behaviour may also increase feelings of competence

in clinicians and subsequently the willingness to provide treatment to patients with ASPD (Aerts et al., 2023; van Dam et al., 2022).

It seems that a substantial amount of people who are being referred to the forensic outpatient clinic, have prodromal psychotic symptoms, while little attention is paid to the detection thereof. To date, a control program such as aggression replacement training (ART) or emotion regulation is often offered for aggression (Currie et al., 2012). Based on this study, we can recommend to screen on prodromal psychotic symptoms and to offer specific treatment. Knowledge of psychotic symptoms is recommended in professionals who work with this group of patients, because it can be one of the factors that lead people to acts of violence (Van Dongen et al., 2015). Furthermore, in all offending patients with psychotic symptoms, different treatment strategies can be indicated, focusing on personality or other comorbid disorders, but on psychotic symptoms for all (Van Dongen et al., 2015).

This study has some limitations. The screening method used in this study, was developed for regular mental health care. Further research is needed to determine whether screening for at risk mental state in the forensic outpatient care is effective with the existing resources or whether the prodromal symptoms in this target group may be more validly measured in another way. Another limitation is the lack of information with regard to the severeness of psychopathology. For the ASPD sample, a personality disorder was diagnosed. For the other part of our sample, we did not distinguish between participants with personality disorders or other developmental and/or psychological disorders. The nature and severity of the pathology might affect the outcome.

#### 5. Conclusion

Given the limited knowledge of the occurrence and coherence between specific forensic related disorders and psychotic symptoms in outpatient forensic healthcare, the objective of this study was to gain insight into the prevalence of psychotic symptoms in the forensic setting and their relationship with aggressive behaviour. This objective was chosen in order to improve quality of treatment and better understanding of the origin of aggressive escalations. The results of this study indicate the importance of screening for psychotic symptoms in forensic patients, as there are higher rates of people with an at-risk mental state in forensic health care than in general population. Early detection therefore seems a necessity in the prevention of transgressive behaviour and can be seen as a risk-reducing tool. Unfortunately, so far, in outpatient forensic mental healthcare, there is relatively little attention for the detection of psychotic symptoms, which may lead to under-treatment of severe psychopathology.

Additionally, we found that prodromal psychotic symptoms have a strong relationship with aggressive behaviour in people with an ASPD diagnosis. Within this group, higher rates of physical aggression, anger and hostility were found. Even though the vast majority of patients did not show a consistent pattern of aggressive

behaviour, detecting psychotic symptoms in an early phase within this population can prevent patients' suffering as well as suffering of people around them.

Thus, screening for at risk mental state in the forensic population can prevent possible psychotic episodes and with that reduced quality of life and increased suffering, prevent aggressive escalations and help to provide the most appropriate treatment.

## **Conflicts of Interest**

The authors declare no conflicts of interest regarding the publication of this paper.

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