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Clinical outcomes and diagnostic stability in first-episode other specified schizophrenia spectrum and other psychotic disorder: evidence for a distinct clinical entity

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Abstract

Research on the clinical outcomes and diagnostic stability of first-episode other specified schizophrenia spectrum and other psychotic disorder (FE-OSSO) remains very limited. This study was conducted to identify baseline demographic and clinical features and cognitive function, as well as 2-year outcomes of patients with FE-OSSO compared with those with first-episode schizophrenia (FE-SZ). The study subjects were 100 patients with FE-OSSO and age- and sex-matched 110 patients with FE-SZ. Four OSSO subtypes were classified according to the clinical manual. We compared clinical variables, cognitive function, and 2-year outcomes (treatment response, remission/recovery, compliance, drop out, relapse) between the two groups. In addition, diagnostic stability was ascertained over the 2-year follow-up. Patients with FE-OSSO had lower symptom severity, lower medication doses, greater rumination and higher cognitive functioning than those with FE-SZ. They also exhibited lower proportion of good compliance and higher rates of partial remission at the 1-year and/or 2-year follow-up compared with those with FE-SZ. Diagnostic stability was substantially high, 91.1%, during the 2-year follow-up. These findings indicate that OSSO has unique clinical features and high diagnostic stability, suggesting that it should be treated as a distinct clinical entity. The next phase of early intervention should focus on preventing the progression from OSSO to more severe illness, SZ, by identifying which OSSO cases are at highest risk of conversion to SZ.

Introduction

Psychotic disorder not otherwise specified (PNOS) in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV has been changed to other specified schizophrenia spectrum and other psychotic disorder (OSSO) and unspecified schizophrenia spectrum and other psychotic disorder (USSO) in DSM-5[1]. To date, there has been a dearth of research on PNOS because it was often used as a temporary diagnosis when inadequate or contradictory information is present. However, with the introduction of DSM-5, cases with insufficient information (e.g., in emergency room situations) are classified as USSO, and growing interest in OSSO is therefore expected. Examples of OSSOs in DSM-5 include persistent auditory hallucinations (AHs), delusions overlapping with significant mood episodes, Attenuated Psychosis Syndrome (APS), and delusional symptoms in a partner of someone with delusional disorder.

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Table 1 Comparison of baseline demographic and clinical characteristics between patients with FE-OSSO and FE-SZ.

Variables	*N*	FE-OSSO	*N*	FE-SZ	*p*-value
Age (years)	100	28.98 ± 9.9	110	29.11 ± 9.48	0.923
Sex	100		110		0.968
Male		43 (43/100)		42.7 (47/110)	
Female		57 (57/100)		57.3 (63/110)	
Education (years)	100	13.98 ± 2.84	110	14.24 ± 2.37	0.481
DUP (months)	100	6.28 ± 8.95	110	4.71 ± 7.22	0.165
DI (months)	100	10.57 ± 10.86	110	9.57 ± 9.71	0.487
Medication					
CPZ equivalent (mg/day)	93	182.38 ± 160.61	107	305.42 ± 236.02	<0.001
Antipsychotic drug naïve		2.15 (2/93)		1.87 (2/107)	
Antipsychotic drug free		5.38 (5/93)		0.93 (1/107)	
Subtype of OSSO	100				
Pure delusion		41 (41/100)			
Delusion with attenuated AH		40 (40/100)			
Pure AH		5 (5/100)			
AH with attenuated delusion		9 (9/100)			
Not classified		5 (5/100)			
PANSS					
Positive symptoms	100	14.62 ± 5.02	110	19.6 ± 7.61	<0.001
Negative symptoms	100	11.56 ± 4.06	110	16.4 ± 7.05	<0.001
General psychopathology	100	28.47 ± 7.07	110	36.88 ± 12.24	<0.001
Total score	100	54.65 ± 13.35	110	72.88 ± 23.13	<0.001
CDSS	99	5.56 ± 4.23	109	6.02 ± 4.75	0.458
SOFAS	100	59.19 ± 11.03	110	55.36 ± 13.94	0.028
BCSS					
Positive-self	95	9.85 ± 5.91	105	10.56 ± 5.32	0.376
Negative-self	95	8.38 ± 5.93	105	8.22 ± 6.19	0.852
Positive-others	95	8.02 ± 5.59	105	9.67 ± 5.37	0.035
Negative-others	95	8.12 ± 7.23	105	6.89 ± 6.09	0.197
BS					
Total score	86	17.58 ± 8.39	105	14.71 ± 9.41	0.025
Emotional	86	10.03 ± 4.92	105	8.37 ± 5.34	0.027
Cognitive	86	7.55 ± 4.05	105	7.04 ± 4.21	0.397
ETI-SR					
General trauma	93	1.90 ± 1.61	104	1.84 ± 2.04	0.798
Physical punishment	93	1.90 ± 1.61	104	1.96 ± 1.77	0.809
Emotional abuse	93	2.01 ± 1.56	104	1.83 ± 1.82	0.447
Sexual event	93	0.55 ± 1.10	104	0.66 ± 1.33	0.507
Total score	93	6.37 ± 4.01	104	6.29 ± 5.57	0.911

All variables are expressed as mean ± SD or % (n/N).

AH Auditory Hallucination, *BCSS* Brief Core Schema Scales, *BS* Brooding scale, *CDSS* Calgary Depression Scale for Schizophrenia, *CPZ equivalent* Chlorpromazine Equivalent Dose, *DI* Duration of Illness, *DUP* Duration of Untreated Psychosis, *ETISR* Early Trauma Inventory Self Report, *FE-OSSO* First-Episode Other Specified Schizophrenia Spectrum and Other Psychotic Disorders, *FE-SZ* First-Episode Schizophrenia, *PANSS* Positive and Negative Syndrome Scale, *SOFAS* Social and Occupational Functioning Assessment Scale.

APS is considered separately in the section on conditions for future study, whereas the clinical utility of delusional symptoms in a partner of someone with delusional disorder is questionable. This led us to refine the former two examples into four clinical subtypes, i.e., pure delusion, delusion with attenuated AHs, pure AHs, and AHs with

Table 2 Comparison of baseline cognitive function between patients with FE-OSSO and FE-SZ.

Variables	*N*	FE-OSSO	*N*	FE-SZ	*p*-value
Verbal learning test					
A6	92	10.15 ± 3.06	93	8.85 ± 3.92	0.013
Delayed recall	92	9.59 ± 3.43	93	8.43 ± 3.74	0.030
Total recall	92	47.22 ± 11.12	93	43.58 ± 12.25	0.036
Digit span test					
Forward correct response	88	13.34 ± 3.57	93	12.03 ± 3.86	0.019
Forward maximum number of digits	88	7.15 ± 1.13	93	6.65 ± 1.34	0.007
Backward correct response	88	10.85 ± 3.52	93	9.24 ± 3.66	0.003
Backward maximum number of digits	88	5.48 ± 1.29	93	4.78 ± 1.43	<0.001
Auditory CPT					
Correct response	92	121.10 ± 15.09	93	106.75 ± 23.93	<0.001
Commission error	92	10.04 ± 9.86	93	15.95 ± 13.02	<0.001
Wisconsin card sorting test					
Categories completed	92	5.00 ± 1.86	91	4.10 ± 2.18	0.003
Perseverative error	91	12.96 ± 9.68	91	16.82 ± 13.04	0.024
Word fluency test					
Animals	92	16.3 ± 4.62	94	14.16 ± 4.29	0.001
Stationery items	92	14.75 ± 4.52	94	12.85 ± 5.44	0.010
ㄱ	92	9.73 ± 4.63	94	8.45 ± 4.63	0.061
ㅅ	92	11.68 ± 5.02	94	10.07 ± 4.82	0.027
ㅇ	92	9.89 ± 4.38	94	9.30 ± 4.42	0.359
DSST	82	58.05 ± 14.36	91	50.38 ± 16.32	0.001

All variables are expressed as mean ± SD.

ACPT auditory continuous performance test, *DSST* Digit symbol substitution test, *FE-OSSO* First-Episode Other Specified Schizophrenia Spectrum and Other Psychotic Disorders, *FE-SZ* First-Episode Schizophrenia.

attenuated delusion, based on our previous study[2]. To facilitate more accurate subtyping of OSSO, we developed a clinical manual for the assessment of OSSO (Supplementary file). With these more refined subtypes, we hope to stimulate more transformative research on the importance of studying OSSO and on the prioritization of treatment objectives for patients with OSSO.

Until now, few studies have investigated the clinical outcomes of OSSO or PNOS. Several studies reported that subjects with PNOS had low Positive and Negative Syndrome Scale (PANSS) scores, high Global Assessment of Functioning Scale (GAF) scores[3] and better 6-month remission rates[4]. In contrast, Kendler and Walsh reported that the outcome of PNOS was considerably worse and similar to that seen in patients with schizophrenia (SZ)[5]. Neurocognitive profiles in PNOS were not found to be significantly different from those in SZ[6]. Our group previously reported, using a partially overlapping sample from the same cohort, that patients with PNOS showed less severe symptoms at baseline, better treatment responses at 2 months, and higher remission rates at 12 months compared to SZ[7]. Recently, a Norwegian group observed more favorable long-term outcomes in PNOS than in schizophrenia spectrum disorders (SSD)[8]. Overall, the existing literature suggests mixed findings regarding clinical severity, and systematic long-term follow-up studies remain limited.

In terms of diagnostic stability, one meta-analysis reported that 36% of patients with PNOS retained their initial diagnosis after an average of 4.5 years of follow-up[9]. More specifically, the diagnostic congruence for PNOS was 44% at the 1-year follow-up[10] and 25–51.5% at the 2-year follow-up[11–13]. In previous analyses of our cohort, we reported higher diagnostic stability rates of 53.7% for PNOS, in which only 11.1% of cases were classified as having inadequate information, and 84% for the first two OSSO subtypes at the 1-year follow-up, respectively[2,7]. These findings suggest that although the diagnostic stability of PNOS is generally low, diagnostic accuracy can be

Table 3 Comparison of clinical outcomes between patients with FE-OSSO and FE-SZ at 2-month, 1-year and 2-year.

	2-month		*p*-value	1-year		*p*-value	2-year		*p*-value
	FE-OSSO	FE-SZ		FE-OSSO	FE-SZ		FE-OSSO	FE-SZ	
Treatment response at 2-month									
Yes	77.89(74/95)	70.83 (68/96)	0.264						
Compliance									
Good	89.36(84/94)	91.67 (88/96)	0.790	76.81 (53/69)	88.57 (62/70)	0.045	82.14 (46/56)	93.65 (59/63)	0.042
Fair	6.38 (6/94)	4.17 (4/96)		17.39 (12/69)	4.29 (3/70)		8.93 (5/56)	0.00 (0/63)	
Poor	4.26 (4/94)	4.17 (4/96)		5.80 (4/69)	7.14 (5/70)		8.93 (5/56)	6.35 (4/63)	
Not assessed	0	0		18	3		22	2	
Drop out	16.00 (16/100)	12.73 (14/110)	0.498	33.00 (33/100)	40.00 (44/110)	0.293	42.00 (42/100)	52.73 (58/110)	0.120
Relapse	0.00 (0/100)	1.04 (1/96)	0.306	6.90 (6/87)	10.96 (8/73)	0.365	21.80 (17/78)	20.00 (13/65)	0.793
Remission and Recovery									
Partial remission (6-month)				50.57 (44/87)	31.50 (23/73)	0.015			
Full remission (6-month)				37.93 (33/87)	42.47 (31/73)	0.560			
Non-remission (6-month)				11.49 (10/87)	26.03 (19/73)	0.010			
Partial remission (6-month) and Partial functioning (6-month)				42.53 (37/87)	28.77 (21/73)	0.071			
Full remission (6-month) and Full functioning (6-month)				27.59 (24/87)	30.14 (22/73)	0.723			
Partial remission (6-month)							41.03 (32/78)	30.77 (20/65)	0.199
Full remission (6-month)							39.74 (31/78)	53.85 (35/65)	0.092
Non-remission (6-month)							19.23 (15/78)	15.38 (10/65)	0.54
Partial recovery (1 year)							34.62 (27/78)	32.31 (21/65)	0.780
Full recovery (1 year)							28.21 (22/78)	30.77 (20/65)	0.737
Conversion	1 (1/100)			4.60 (4/87)			8.97 (7/78)		
Conversion of Subtype of OSSO									
Pure delusion	0 (0/41)			0 (0/37)			6.45 (2/31)		
Delusion with attenuated AH	2.50 (1/40)†			8.57 (3/35)			11.76 (4/34)		
Pure AH	0 (0/5)			0 (0/4)			0 (0/4)		
AH with attenuated delusion	0 (0/9)			12.50 (1/8)			12.50 (1/8)		
Not classified	0 (0/5)			0 (0/3)			0 (0/1)		

All variables expressed as % (number of event/number of individuals followed up at each time point except the drop-out and relapse); Drop out reported as % (number of individuals who were not followed up at each time point/number of individuals at baseline) and relapse reported as % (number of event/number of individuals followed up at each time point plus those who dropped out after relapse).

FE-OSSO First-Episode Other Specified Schizophrenia Spectrum and Other Psychotic Disorders, *FE-SZ* First-Episode Schizophrenia.

†Changed to bipolar disorder.

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Table 4 Baseline demographic and clinical predictors for conversion in patients with FE-OSSO.

Variables	*N*	*p*-value	HR (95% CI)
Age (years)	100	0.126	0.88 (0.75–1.04)
Sex	100		
Male	43	1 (reference)	
Female	57	0.802	1.21 (0.27–5.44)
Education (years)	100	0.263	0.90 (0.75–1.08)
DUP (months)	100	0.365	0.94 (0.82–1.07)
DI (months)	100	0.132	0.89 (0.77–1.03)
CPZ equivalent (mg/day)	93	0.667	1.00 (1.00–1.00)
Subtype of OSSO			
Pure delusion		1 (reference)	
Delusion with attenuated AH	95	0.385	2.13 (0.39–11.70)
Pure AH	95	0.998	0.00 (0.00–Inf)
AH with attenuated delusion	95	0.553	2.07 (0.19–22.91)
PANSS			
Positive symptoms	100	0.006	1.20 (1.05–1.37)
Negative symptoms	100	0.913	1.01 (0.84–1.22)
General psychopathology	100	0.069	1.09 (0.99–1.20)
Total score	100	0.034	1.05 (1.00–1.11)
CDSS	99	0.650	0.96 (0.79–-1.16)
SOFAS	100	0.241	0.96 (0.89–1.03)
BCSS			
Positive-self	95	0.024	1.14 (1.02–1.27)
Negative-self	95	0.172	0.90 (0.77–1.05)
Positive-others	95	0.864	1.01 (0.89–1.15)
Negative-others	95	0.619	1.03 (0.93–1.13)
BS			
Total score	86	0.320	0.94 (0.83–1.06)
Emotional	86	0.505	0.93 (0.75–1.15)
Cognitive	86	0.215	0.84 (0.64–1.11)
ETI-SR			
General trauma	93	0.538	1.14 (0.75–1.73)
Physical punishment	93	0.039	1.68 (1.03–2.75)
Emotional abuse	93	0.416	1.23 (0.75–2.01)
Sexual event	93	0.349	0.47 (0.10–2.28)
Total score	93	0.245	1.12 (0.93–1.34)

AH Auditory Hallucination, *BCSS* Brief Core Schema Scales, *BS* Brooding scale, *CDSS* Calgary Depression Scale for Schizophrenia, *CI* Confidence Interval, *CPZ* equivalent Chlorpromazine Equivalent, *DI* Duration of Illness, *DUP* Duration of Untreated Psychosis, *ETI-SR* Early Trauma Inventory Self Report, *HR* Hazard Ratio, *PANSS* Positive and Negative Syndrome Scale, *SOFAS* Social and Occupational Functioning Assessment Scale, *FE-OSSO* First-Episode Other Specified Schizophrenia Spectrum and Other Psychotic Disorders.

substantially improved by selecting more homogenous and well-characterized cases either by excluding individuals with insufficient information or by applying refined OSSO subtypes.

The present study was conducted to compare clinical features, cognitive function, and 2-year outcomes between patients with first-episode OSSO (FE-OSSO) and age- and sex-matched patients with FE-SZ. Importantly, the diagnostic stability of FE-OSSO and its conversion rate to other diagnoses were examined. In addition, baseline predictors of diagnostic conversion over the 2-year follow-up were assessed.

Results

Baseline sociodemographic and clinical characteristics and cognitive functioning

At baseline, patients with FE-OSSO showed significantly lower CPZ-equivalent doses compared with patients with FE-SZ ($p < 0.001$). The FE-OSSO group showed significantly lower PANSS positive, negative, general psychopathology, and total scores (all $p < 0.001$), and higher SOFAS score ($p = 0.028$) than the FE-SZ group. The FE-OSSO group demonstrated a significantly lower BCSS Positive-others score than the FE-SZ group ($p = 0.035$). In contrast, the FE-OSSO group showed significantly higher BS total and emotional brooding scores ($p = 0.025$ and $p = 0.027$). No significant group differences were found in the CDSS or ETI-SR scores (Table 1). The FE-OSSO group demonstrated significantly better baseline performance than the FE-SZ group across most neuropsychological measures, including verbal learning test, digit span test, Auditory CPT, WCST, word fluency test and DSST (all $p < 0.05$) (Table 2). Comparisons of demographic and clinical characteristics and cognitive functioning between patients with FE-OSSO who dropped out vs. those followed up over 2 years is shown in Supplementary Tables 1 and 2. Those who dropped out had more negative symptoms.

Follow-up outcomes and conversion rates

Treatment response at the 2-month follow-up as well as dropout and relapse rates at 2-month, 1-year and 2-year were comparable between patients with FE-OSSO and FE-SZ (all $p > 0.05$). Relapse rates calculated by treating drop-out cases as relapses are shown in Supplementary Table 3. In contrast, medication compliance differed significantly during the follow-ups, with the FE-OSSO group showing a lower proportion of good compliance than the FE-SZ group at 1-year ($p = 0.045$) and 2-year ($p = 0.042$). However, there were no significant between-group differences when compliance was dichotomized as either good versus fair/poor or good/fair versus poor (data not shown).

The FE-OSSO group demonstrated a significantly higher rate of partial remission (6-month) at 1-year compared with the FE-SZ group ($p = 0.017$). The results for relapse, remission and recovery were unchanged after excluding phone-assessed cases ($n = 11$) from the FE-OSSO group (Supplementary Table 4). Conversion rates in the FE-OSSO increased over time, from 1.00% (1/100) at 2-month, to 4.60% at 1-year and 8.97% at 2-year. Interestingly, conversions were mainly observed in the subtypes of AH with attenuated delusion and delusion with attenuated AH (Table 3).

Predictors of conversion in patients with FE-OSSO

Significant predictors were a higher baseline PANSS positive score (HR = 1.20, 95% CI 1.05–1.37, $p = 0.006$), PANSS total score (HR = 1.05, 95% CI 1.00–1.11, $p = 0.034$), higher BCSS Positive-self score (HR = 1.14, 95% CI 1.02–1.27, $p = 0.024$) and physical punishment (HR = 1.68, 95% CI 1.03–2.75, $p = 0.039$) (Table 4). No significant cognitive predictors were identified (Supplementary Table 5).

Discussion

To date, only a few studies have investigated the clinical outcomes of FE-OSSO or FE-PNOS, partly because these diagnoses have been considered temporary. By excluding individuals with insufficient information and classifying OSSO into four distinct subtypes, we sought to achieve a more consistent and accurate characterization of clinical outcomes in FE-OSSO. Overall, patients with FE-OSSO showed not only milder symptomatology and higher cognitive functioning at baseline, as well as better remission at the 1-year follow-up compared with those with FE-SZ, but also substantially higher diagnostic stability over the 2-year follow-up.

As for clinical features, we observed lower symptom severity and lower CPZ equivalent dose in patients with FE-OSSO compared to those with FE-SZ. The former finding is consistent with reports from European studies[3,6,8] as well as with our previous studies[2,7]. The observation of lower CPZ equivalent dose replicates the finding of Li et al.[7], whereas this aspect was not examined in the three European studies. Interestingly, patients with FE-OSSO exhibited higher emotional and total scores on the BS than those with FE-SZ, reflecting greater rumination in the former group. Rumination is a repetitive and negatively valenced thinking style[14]. It has been reported to be associated with positive[15,16] and negative[17] symptoms as well as suicidality[18,19] in patients with psychosis. This finding stresses the need for routine assessment of the presence and severity of rumination at the initial evaluation of patients with suspected FE-OSSO, as well as consideration of interventions to alleviate rumination.

With respect to cognitive functioning, patients with FE-OSSO showed consistently higher performance across all cognitive domains compared to FE-SZ patients. This finding is in contrast with two previous studies[6,7] which reported no significant differences between the two groups. However, given that in those studies, the mean values of cognitive domains in PNOS were lower than those in SZ and that the PNOS sample sizes were small ($n = 29$ or $n = 35$), the null findings may reflect limited statistical power and a type II error. Although we did not directly compare cognitive functioning between patient groups and HC, given the cumulative evidence of cognitive impairment in psychosis, our findings suggest that OSSO may represent an intermediate state along the continuum of the psychosis spectrum.

Regarding clinical outcomes, both groups showed higher rates (71~78%) of treatment response at 2-month follow-up. This finding is not surprising given that antipsychotic drug treatment is very effective in first-episode psychosis (FEP)[20]. Despite generally good compliance in both groups, patients with FE-OSSO showed a significantly lower proportion of good compliance at the 1-year and 2-year follow-ups than those with FE-SZ. This finding replicates our previous study[7]. Relapse rates did not differ between the two groups (6.9% and 10.96% at the 1-year and 21.8% and 20.0% at the 2-year) and were lower than those reported in other studies of FEP[21,22]. However, when a conservative approach was applied, which treats drop-out as relapse, the relapse rates at 1 year and 2 years increased to 19.0% and 35.11% for FE-OSSO and to 38.10% and 48.51% for FE-SZ, respectively. Importantly, patients with FE-OSSO exhibited a higher rate of partial remission at the 1-year compared with patients with FE-SZ. Previous studies have also reported higher rates of full remission at 6 months[4] and at 12-month[7], better global outcomes at a mean of 16 years after onset[5], and higher rates of remission and clinical recovery after 7 to 10 years of follow-up[8] in PNOS compared to SZ. The better clinical outcome of FE-OSSO observed in the present study may be associated with less severe baseline psychopathology. Overall, despite a higher rate of partial remission at the 1-year follow-up, patients with FE-OSSO showed a relatively lower proportion of good compliance and similarly high drop-out and relapse rates compared with those with FE-SZ. These findings underscore the need for targeted psychosocial interventions to address the low proportion of good compliance and high drop-out in FE-OSSO. In addition, the relatively high rate of partial remission in FE-OSSO may be viewed not only as evidence of a more favorable outcome than FE-SZ, but also as an indication of incomplete recovery and a potential missed opportunity for achieving full remission. In routine clinical settings, patients with OSSO are generally not distinguished from those with other schizophrenia-spectrum psychoses and may therefore receive similar treatment approaches. Given the heterogeneity of treatment outcomes in FEP, a "one-size-fits-all" approach may not adequately address the distinct clinical characteristics and treatment needs of different patient subgroups[23]. More individualized and measurement-based treatment strategies[24] may potentially facilitate progression from partial to full remission in patients with OSSO. However, whether treatment strategies specifically tailored to OSSO can improve full remission rates requires further investigation.

The diagnostic stability of FE-OSSO in the present study is 91.1% at the 2-year follow-up. This finding is in sharp contrast to that reported in a meta-analysis, which found a stability rate of 36% at a mean follow-up of 4.5 years[9]. However, our previous study also reported a diagnostic stability of 78.4% at the 1-year follow-up[7]. A possible explanation for this high diagnostic stability in our two studies is that the proportion of patients with inadequate information was minimal (11.1%) in the study by Li et al. (2022) and that such cases were excluded in the present study. It is of note that in Widing et al. (2020), 56% of PNOS cases fell into categories with contradictory definitions or were associated with inadequate information[3]. In addition, it may be related to the fact that all 11 individuals who were evaluated via telephone were clinically stable and did not convert.

Most converted cases in the present study were diagnosed with SZ, consistent with previous studies[10,13]. Interestingly, conversion rates were highest among patients with AH accompanied by attenuated delusion. Similarly, our previous study found higher conversion rates in patients with persistent AHs and those with inadequate information[7]. In line with these findings, Widing et al. (2023) also reported that most cases converting from PNOS to SSD originated from the cases with contradictory or inadequate information (5/7, 71.4%)[8]. These findings stress the importance of specifying subgroups in research on OSSO. Lastly, predictors of diagnostic conversion found to be significant were higher PANSS positive symptom and total scores, higher positive-self score on the BCSS and higher physical punishment score on the ETI-SR. Except for the higher positive-self score, the other two factors are clinically understandable. In particular, the association with childhood trauma underscores the importance of addressing this issue in order to prevent conversion, given that childhood trauma is closely associated with an increased risk of psychosis or SZ[25–27]. However, given the small number of events and the consequently limited statistical power, cautious interpretation is warranted.

The findings of the present study should be interpreted in light of several limitations. First, telephone evaluations were conducted only for some patients with FE-OSSO. However, after excluding individuals who were assessed by telephone, the clinical outcomes did not change. Second, Inter-rater reliability was not formally assessed across sites or between on-site assessors. This limitation may be particularly relevant to OSSO subtype classification, which was performed retrospectively using the recently developed clinical manual. Third, given the small to modest number of conversion events, larger studies are needed to identify robust predictors and high-risk subtypes of conversion in FE-OSSO. The greatest strength of this study is that this is the first prospective naturalistic observational study investigating a broad range of clinical features, including symptoms, cognition and outcomes in patients with FE-OSSO, distinguished from USSO and further classified into four distinct subtypes. In the clinical staging model proposed by McGorry et al. (2006), FEP falls under stage 2 with no detailed diagnostic features listed[28]. Based on our findings regarding clinical features and outcomes, we propose that stage 2 can be further divided into stages 2a and 2b corresponding to FE-OSSO and FE-SZ, respectively.

In conclusion, patients with FE-OSSO were found to have lower symptom severity, greater rumination, lower compliance and higher rates of partial remission compared with those with FE-SZ. In addition, greater diagnostic stability was observed over the two-year follow-up. Together, these findings indicate that OSSO should be considered a distinct clinical entity. Moreover, while early intervention efforts have traditionally focused on preventing the transition from clinical high risk for psychosis to overt psychosis, the next phase of early intervention should target prevention of progression from OSSO to SZ.

Methods

Participants

The participants enrolled in the current study were selected from participants of the multicentre, longitudinal Korean Early Psychosis Study (KEPS), for which the inclusion and exclusion criteria can be found in our previous study[29]. In short, the exclusion criteria consist of patients with a substance- or medication-induced psychotic disorder, psychotic disorder due to another medical condition, mental intellectual disability disorder, and severe neurological disorders such as epilepsy, stroke, dementia, or Parkinson's disease.

At the time of analysis in 2025, we identified 100 patients with FE-OSSO who had been followed for 2 years after enrollment. To compare outcomes between OSSO and SZ, age- and sex-matched patients with FE-SZ who had also completed 2 years of follow-up were randomly selected from the total cohort of 556 patients with psychosis. Individuals with a duration of illness (DI) less than 2 years were considered to have FE illness. Two experienced psychiatrists at each institute classified OSSO subtypes using a clinical manual developed for OSSO assessment (Supplementary file). All participants provided written informed consent in accordance with a protocol approved by the Ethics Committee of the Jeonbuk National University Hospital (approval number CUH 2014-11-002).

Assessments

Sociodemographic and clinical data

Sociodemographic data were obtained at baseline. For clinical data, duration of untreated psychosis (DUP); DI; PANSS[30], Clinical Global Impression scales (CGI)[31], Social and Occupational Functioning Assessment Scale (SOFAS)[32], and Calgary Depression Scale for Schizophrenia (CDSS)[33,34]; were evaluated. Several self-rating scales, such as the Brooding Scale (BS)[35], Brief Core Schema Scales (BCSS)[36]; and Early Trauma Inventory Self Report-Short Form (ETISR-SF)[37], were surveyed. We calculated chlorpromazine (CPZ) dose equivalents based on defined daily doses[38].

Cognitive functioning

Computerized neurocognitive tests (CNT, MaxMedica, Inc., Seoul, Korea) were administered to each subject at baseline. The cognitive domains of attention, verbal memory, executive functioning, language and psychomotor speed were evaluated using digit span assessment and auditory continuous performance test (A-CPT), a verbal learning test, the Wisconsin Card Sorting Test (WCST), a word-fluency test, and digit symbol substitution test (DSST), respectively.

Outcome measures

The treatment response at the 2-month follow-up was defined based on a CGI-Severity (CGI-S) score ≤3 or a decrease of ≥2 if the baseline score was ≥4, a CGI-Improvement (CGI-I) score of 1 or 2, a decrease of ≥30% in the total PANSS score or four positive items (P1, P2, P3 and P6) on the PANSS with a ≥30% decrease in score compared to baseline. Patients were considered to have achieved symptomatic partial remission at 1-year follow-up if they maintained a score of 3 on at least eight PANSS items for more than 6 months: P1, P2, P3, N1, N4, N6, G5 and G9[39]. Full remission was defined as scores ≤2 on the eight PANSS items[40]. Partial and full functioning were defined as SOFAS scores ≥ 61 and 71 for more than 6 months, respectively. The criteria for partial or full recovery at the 2-year follow-up were as follows: eight PANSS item scores of 3 or ≤2 and SOFAS scores ≥61 or 71, respectively, with these conditions persisting for ≥ 1 year[29,41]. For patients with FE-OSSO, conversion to any other diagnosis during the 2-year follow-up was also evaluated.

Medication compliance was clinically assessed based on patient and caregiver reports regarding the proportion of prescribed medication taken during the interval between two consecutive visits and was categorized as good (≥80%), fair (50–79%), or poor (≤49%). Drop-out was defined as missing two consecutive outpatient clinic visits. However, patients were included in the study again if they returned to the clinic. Relapse was defined as an exacerbation of symptoms after symptomatic remission. Symptom exacerbation included psychiatric hospitalization, a CGI-S score ≥4 with an increase of ≥2, a CGI-I score ≥6 (much worse), a score of ≥4 for a psychosis item (P1, P2, P3 or P6) with an increase of ≥2, a ≥25% increase in the total PANSS score or a ≥10-point increase if the baseline score was ≤40, deliberate self-injury, clinically serious suicidal or homicidal ideation, or a suicide attempt or violent behaviour resulting in significant injury to another person or property[41]. The denominator for the relapse rate was defined as the sum of individuals followed up at each assessment time point and those who dropped out after relapse.

To ensure inter-rater reliability for the PANSS, SOFAS, remission and relapse evaluation between sites, psychiatrists with more than 2 years of experience in this field participated in the rating process, and several workshops were held during the recruitment period. Eleven individuals with FE-OSSO who dropped out before the 2-year follow-up were further evaluated via telephone interviews. The timing of the telephone assessments for the 11 participants varied from 27 to 113 months after baseline. However, clinical status and diagnosis were retrospectively assessed with reference specifically to the 2-year follow-up point to ensure consistency in the timing of the diagnostic stability assessment.

Statistical analysis

The demographic and clinical variables at baseline were compared between the two patient groups using independent *t*-tests and chi-square tests as appropriate. Given the small number of converters among patients with FE-OSSO, only univariable Cox regression was performed to examine predictors of conversion. Patients who dropped out or did not convert by the 2-year follow-up were censored. All statistical analyses were performed using R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria) in RStudio (version 2026.1.0.392; Posit Software, Boston, MA, USA) and p-values < 0.05 were considered to indicate statistical significance.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Enrolled patients provided written informed consent. The examination was made in accordance with the approved principles.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41537-026-00804-4.

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Author contributions Y.-C.C. conceptualized the study. Y.-C.C., A.S., W.S.K. and S.O. performed the study and acquired data. A.S. and N.S. conducted statistical analyses. Y.-C.C. and L.L. analyzed and interpreted the data. L.L. drafted the manuscript. Y.-C.C. critically revised the manuscript. All authors critically reviewed the manuscript and provided important intellectual input. Y.-C.C. received the grant. All authors approved the final manuscript.

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Data availability In accordance with the "DFG Guidelines on the Handling of Research Data", we will make all data available upon request. The data set will be archived for at least 5 years after publication.

Competing interests The authors declare no competing interests.

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