



Ten-year follow up of patients with first-episode schizophrenia spectrum disorder from an early intervention service: Predictors of clinical remission and functional recovery

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ABSTRACT

The long-term recovery rate of patients with schizophrenia-spectrum disorders has been persistently low despite the implementation of early intervention (EI) services internationally. It is, therefore, important to identify the modifiable factors during the early stage of the illness that predict long-term remission and recovery. The aim of this study is to explore the predictive value of the early stage clinical factors on the clinical remission and functional recovery at 10-year follow-up of patients with schizophrenia-spectrum disorders who received a 2-year EI service. Patients who received the EI service throughout the region of Hong Kong between 1st July 2001 and 30th June 2002 and with a diagnosis of schizophrenia-spectrum disorder were identified from the centralized hospital database (Clinical Management system, CMS). Semi-structured clinical interview was conducted at 10-year follow-up with a successful interview rate of 74.3% (n = 107). Clinical data was systematically retrieved each month for the first three years from the CMS and written clinical records using a standardized data entry form based on operationalized definitions. Results found shorter duration of untreated psychosis (DUP) predicted long-term clinical remission; higher educational level and shorter period of unemployment during the initial three years of the illness predicted functional recovery. Higher educational level, longer period of employment and planned medication discontinuation during the initial three years predicted complete recovery. The current study demonstrates the long-term impact of DUP and suggests improvement of employment during the early stage of illness could be a potential target for further improvement of the service.

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1. Introduction

The optimal goal for management of patients with schizophrenia is the attainment of recovery. Overall recovery can be conceptualized as achieving both symptomatic remission and functional recovery over a period of time (Lieberman and Kopelowicz, 2005). The goal of the early intervention services developed internationally is to improve the long-term outcomes of patients with psychosis. Many studies have reported the short-term benefit of the early intervention service in improving symptom control and functional recovery (Chen et al., 2011; Craig et al., 2004; Kane et al., 2016; Petersen et al., 2005). However, long-term follow-up studies failed to show positive impact of the EI service on symptomatic remission and functional recovery (Chan et al., 2015; Secher et al., 2015). The recovery rate at 10-year follow-up of patients received the EI service was found to be about 14% (Austin et al., 2013). This is similar to the results of a meta-analysis which suggested that

the median long-term rate of recovery for patients with schizophrenia is only 13.5% (mean: 16.4%, interquartile range: 8.1% to 20.0%) and has not improved over time (Jääskeläinen et al., 2013). This highlights the importance of identifying early treatment stage factors, particularly modifiable ones, that predict long-term recovery, in order to facilitate further service development.

Many studies have consistently reported that poor premorbid functioning (Albert et al., 2011; Bobes et al., 2009; Petersen et al., 2008), greater symptoms at early stage (Chang et al., 2012; Verma et al., 2012; Wunderink et al., 2009) and longer duration of untreated psychosis (DUP) (Perkins et al., 2005) are associated with poor short-term recovery. Long DUP was also found to be a consistent predictor of poor long-term outcomes (Penttilä et al., 2014; Tang et al., 2014). However, studies on other predictors of long-term outcomes are relatively few. Premorbid functional deficit and early negative symptoms were reported to be predictors for poor long-term outcomes in earlier studies (Fenton and McGlashan, 1991; Jarbin et al., 2003; Möller et al., 2002; Robinson et al., 2004). Recent studies further suggested that lower severity of negative symptoms predicts better rate of recovery at 10-year follow-up (Austin et al., 2013). Low level of positive symptoms at

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early stage of diagnosis predicts clinical remission at 10-year follow-up (Ten Velden Hegelstad et al., 2013). Over a 10-year period, Friis et al. (2016) reported that short DUP and early remission of the first episode are significant predictors of good outcomes.

These studies primarily examined looked at either clinical remission or functional recovery; few explored both in the same study sample. However, factors contributing to the clinical and functional outcomes are likely to be different. A study suggested that premorbid functioning was more related to the functional outcome and DUP was more related to the symptomatic outcome at 10-year follow-up (White et al., 2009). Furthermore, most recent studies focused on a broad spectrum psychosis diagnosis. Yet, patients with schizophrenia-spectrum diagnosis have consistently been found to have poorer prognosis than patients with affective psychosis diagnosis (Bowtell et al., 2017; Chang et al., 2016). Predictive factors for long-term outcomes may be different. Use of minimum effective dose of antipsychotic medication is the standard recommendation for the management of patients in the EI service (Bertolote and McGorry, 2005). Most guidelines have also recommended maintenance of antipsychotic medication at minimum effective dose for a duration of one to two years (Taylor and Kapur, 2011). Early medication discontinuation is likely to be common among patients receiving EI service. However, its impact on the long-term outcome is still not clear (Bowtell et al., 2017).

As such, the aims of the current study is to explore the predictive value of early illness stage clinical and treatment related factors at early stage of the illness on recovery at 10 years among patients with schizophrenia-spectrum disorders received 2-year EI service. Both clinical remission and functional recovery will be studied to identify differential predictive factors. Apart from early clinical and functional characteristics, effects of early decision of medication discontinuation will also be studied. Results of this study could provide information for further development of the early intervention service to improve the long-term outcomes of the subgroups of patients who have poor outcomes.

2. Methods

2.1. Settings

The early intervention (EI) service, Early Assessment Service for Young People with Psychosis (EASY) program, was implemented as a region-wide service in 2001 in Hong Kong. It provides a 2-year case management phase-specific service for patients aged 15–25 years with first episode psychosis (Tang et al., 2010). The pace of transition from the EI service to the general adult service in the third year depends on the clinical needs of the individual patients.

2.2. Sample

Consecutive patients who received the EI service in the whole region of Hong Kong between 1st July 2001 and 30th June 2002 and with a diagnosis of schizophrenia-spectrum disorder were identified from the centralized hospital database (Clinical Management system, CMS). Patients with comorbid organic brain conditions, drug-induced psychosis, learning disabilities or had more than one month of prior psychiatric treatment before presentation were excluded. There were 148 patients identified. All identified patients were approached for a face-to-face interview at 10-year of their entry to the service. Those who were still engaged with the public mental health service 10 years after they entered the EASY service were interviewed at the outpatient or inpatient units. Interviews of patients who were not receiving any service from the public mental health system were arranged in the community. Informed consent was obtained from all patients. The current study was part of a larger study comparing long-term outcomes of early intervention and standard care services (Chan et al., 2015). The study was approved

by the institutional review board and ethics committees of all seven research sites in Hong Kong.

2.3. Assessments and clinical information of first three years

Semi-structured interviews were carried out by experienced researchers. Demographic information including age, gender, education level, employment status were obtained. Symptoms were assessed using Positive and Negative Syndrome Scale for schizophrenia (PANSS) (Kay et al., 1987). Functioning was assessed using Social and Occupational Functioning Assessment Scale (SOFAS) (APA and APA Task Force on DSM-IV, 2000) and Strauss and Carpenter Scale (SCS) (Strauss and Carpenter, 1972).

All clinical information of patients during the initial three years was obtained from the CMS and written clinical records by trained researchers. The baseline data obtained including diagnosis, age of onset, mode of onset, duration of untreated psychosis (DUP), and positive and negative symptoms at onset. Clinical symptoms were measured with the Clinical Global Impressions - Schizophrenia (CGI-SCH) scale (Haro et al., 2003). DUP was defined as the period (in days) between the first appearance of psychotic symptoms and the prescription of antipsychotic medication by a psychiatrist. Mode of onset was categorized into two modes, acute (development of an episode within one month) and gradual (development of an episode more than one month). The baseline diagnosis was determined by the clinician on the basis of the ICD-10 criteria using all available clinical information. Data were systematically retrieved each month for the first three years using a standardized data entry form based on operationalized definitions. This covered the two-year EI service and the transitional year after the EI service facilitating the gradual transfer of patients to the general psychiatric service. Clinical information during the first three years included the number of hospitalizations, number of relapses, medication adherence, employment condition, clinical symptoms measured with CGI-SCH, and mean Defined Daily Dose (DDD) (Nosè et al., 2008) of antipsychotic medication. Adherence to medication for each patient was given a score of 1 to 3 for each month and an average of three years was generated with 1 being good adherence and 3 being poor adherence. Decision on planned discontinuation of antipsychotic medication during the initial three years was also documented. Relapse was operationally defined as a change in the CGI-SCH scores from 1 to 3 or from 4–6 to 5–7, followed by hospitalization or adjustment of antipsychotic medication (Haro et al., 2011). Months of fulltime open employment, unemployment (including in the rehabilitation settings) over the three years were calculated. An average of CGI-SCH positive and negative symptoms over the three years was calculated using CGI-SCH score of each month. These were used to indicate general clinical conditions over the three years.

Longitudinal diagnosis was determined using all available information, both clinical interview and medical records based on DSM-IV Axis I disorder (SCID-I; First, 1997) criteria. Clinical remission was defined operationally as patients with PANSS items P1, P2, P3, N1, N4, N6, G3, G5, G9 scored ≤ 3 at 10-year follow up and CGI positive and CGI negative ≤ 3 for 6 months before the assessment (Andreasen et al., 2005). Functional recovery was defined as all SCS items scored ≥ 2 and SOFAS total score ≥ 61 (Strauss et al., 2010). Complete recovery was defined as achieving both symptomatic remission and functional recovery.

2.4. Statistical analysis

All statistical analyses were conducted using SPSS version 24. Basic demographics, baseline clinical characteristics and clinical characteristics over the initial three years of treatment were used in the univariate analysis of predictors of clinical remission, functional recovery and complete recovery status using logistic regression. Odds ratio and 95% confidence intervals (CI) were reported. The Kolmogorov–Smirnov test was used to test for the normality of the variables. Because of skewness

of the DUP data, log-transformed DUP was used for analysis. The strategy of the Last-Observation-Carried-Forward was used to manage missing information in the clinical record review of the initial three years. Only variables that were found to be significant in the univariate analysis were included in the multivariate analysis to identify the prediction model of clinical remission, functional recovery and complete recovery at ten-year follow up. Forward stepwise logistic regression analysis was employed in the current study to identify the significant variables and best fit model.

The data quality during the data collection period was monitored through fortnightly consensus meetings among the clinicians and researchers. An experienced clinician and two researchers completed medical record reviews of 12 patients with the data collection form used in the current study. Intraclass correlation coefficient (ICC) test was used to test for validity of CGI-SCH positive and CGI-SCH negative scores. The validity test results (CGI-S positive: ICC = 0.89; CGI-S negative: ICC = 0.77) suggested that the ratings of researchers were comparable to the ratings of the clinician. The inter-rater reliability of the researchers was also assessed for PANSS and SOFAS obtained from 10 patients. Results (PANSS: ICC = 0.88; SOFAS: ICC = 0.97) indicated the concordance between researchers was satisfactory.

3. Results

The successful follow up rate of the current study was 74.3% (N = 110). Seven patients were deceased, 17 refused and 14 patients could not be traced. There were no significant differences on the demographic and baseline clinical variables between the interviewed and not interviewed patients (Table 1 of Supplementary results). After the longitudinal diagnosis review, three patients were excluded from the analysis as they did not have a schizophrenia-spectrum diagnosis (one had substance induced psychosis and two patients had affective psychosis). The schizophrenia-spectrum disorder includes schizophrenia, schizoaffective disorder, brief psychotic disorder and psychosis not otherwise specified. The total number of interviewed sample was 107.

3.1. Clinical remission

Fifty-two patients (48.6%) achieved clinical remission at 10-year assessment. Compared with non-remitted patients, remitted patients had

significantly shorter DUP. Significantly more remitted patients had an acute-onset illness (Table 1). Binary logistic regression was conducted with both as independent variables and only log DUP was found to be significant (Table 4). The model with log DUP was significant ($\chi^2 = 6.66$, $df = 1$, $p = 0.01$) in explaining variance of clinical remission between 6.6% and 8.9%.

3.2. Functional recovery

Forty patients (37.4%) achieved functional recovery at 10-year assessment. Patients with functional recovery had significantly more years of education, less negative symptoms at baseline, less negative symptoms on average and fewer months of unemployment over the initial three years in the service (Table 2). Binary logistic regression found only years of education and months of unemployment during the initial three years were significant (Table 4). The model with these two factors was significant ($\chi^2 = 10.91$, $df = 2$, $p = 0.004$) in explaining 9.8% to 13.3% of variance of functional recovery.

3.3. Complete recovery

Twenty-seven patients (25%) achieved complete recovery at 10-year assessment. Patients with planned medication discontinuation, more years of education and more months of full time employment during the initial three years were more likely to achieve complete recovery (Table 3). Binary logistic regression found the model with these three factors was significant ($\chi^2 = 16.55$, $df = 3$, $p = 0.001$) in explaining the 15.3% to 22.2% of variance of complete recovery. All three factors were significant in the model (Table 4).

4. Discussion

4.1. Summary of findings

The current study found that about half of the patients with schizophrenia-spectrum disorders who had received 2-year EI service achieved clinical remission at 10-year follow up. However, only 37.4% achieved functional recovery and 25% achieved complete recovery. The rate of clinical remission is similar to the results of previous studies of patients from the EI service followed at 10 years (Austin et al., 2013;

Table 1

Logistic regression analysis of demographic and early clinical characteristics relating to clinical remission at 10 year follow up.

	Clinical remission		OR	95% CI	P
	Yes	No			
Demographics					
Age of onset (S.D.)	21.25 (3.19)	20.62 (2.94)	1.07	0.94–1.22	0.32
Years of education (S.D.)	11.02 (2.22)	10.47 (2.32)	1.12	0.93–1.34	0.23
Gender (male, n, %)	25, 48.1	26, 57.8	1.48	0.66–3.30	0.34
Baseline clinical characteristics					
LogDUP (S.D.)	1.67 (0.75)	2.06 (0.69)	0.48	0.27–0.86	0.01
Mode of onset (acute) (n, %)	23, 44.2	11, 24.4	2.45	1.02–5.87	0.04
Baseline positive symptoms (CGI pos) (S.D.)	4.15 (0.98)	3.98 (0.89)	1.23	0.80–1.89	0.36
Baseline negative symptoms (CGI neg) (S.D.)	2.62 (1.34)	2.91 (1.49)	0.86	0.64–1.15	0.30
Clinical characteristics of initial 3 year					
Mean CGI pos (S.D.)	1.60 (0.53)	1.63 (0.56)	0.88	0.42–1.86	0.75
Mean CGI neg (S.D.)	1.37 (0.42)	1.43 (0.41)	0.70	0.27–1.84	0.47
Number of hospitalization (S.D.)	0.96 (0.95)	1 (1.28)	0.97	0.68–1.39	0.86
Number of relapse (S.D.)	0.63 (0.93)	0.73 (0.99)	0.90	0.59–1.37	0.61
Planned medication discontinuation, yes (n, %)	14 (26.9)	5 (11.1)	0.34	0.11–1.03	0.06
Medication compliance (S.D.)	1.17 (0.27)	1.16 (0.30)	1.87	0.34–10.65	0.48
Mean DDD (S.D.)	0.57 (0.45)	0.57 (0.35)	0.98	0.36–2.64	0.96
Months of full time employment (S.D.)	15.13 (12.41)	11.93 (11.48)	1.02	0.99–1.06	0.19
Months of unemployment (S.D.)	9.13 (9.33)	12.42 (9.50)	0.99	0.95–1.03	0.56

CI: confidence interval; S.D.: standard deviation; P: p-value; DUP: duration of untreated psychosis; CGI_pos: clinical global impression on positive symptoms; CGI_neg: clinical global impression on negative symptoms; DDD: Defined Daily Dose.

Months of unemployment including period of unemployment and rehabilitation.

Table 2
Logistic regression analysis of demographic and early clinical characteristics relating to functional recovery at 10 year follow up.

	Functional recovery		OR	95% CI	P
	Yes	No			
Demographics					
Age of onset (S.D.)	21.30 (3.42)	20.65 (2.90)	1.07	0.94–1.22	0.30
Years of education (S.D.)	11.50 (2.14)	10.48 (2.26)	1.23	1.02–1.48	0.03
Gender (male, n, %)	18, 45	36, 54.5	1.47	0.67–3.23	0.34
Baseline clinical characteristics					
LogDUP (S.D.)	1.89 (0.67)	1.88 (0.78)	1.01	0.59–1.71	0.98
Mode of onset (acute) (n, %)	15, 37.5	20, 30.3	1.38	0.60–3.16	0.45
Baseline positive symptoms (CGI pos) (S.D.)	4.13 (0.79)	4.09 (0.99)	1.04	0.68–1.60	0.85
Baseline negative symptoms (CGI neg) (S.D.)	2.28 (1.32)	2.88 (1.41)	0.72	0.54–0.98	0.03
Clinical characteristics of initial 3 year					
Mean CGI pos (S.D.)	1.74 (0.78)	1.58 (0.52)	1.50	0.80–2.83	0.21
Mean CGI neg (S.D.)	1.28 (0.40)	1.47 (0.52)	0.31	0.10–0.94	0.04
Number of hospitalization (S.D.)	0.88 (0.91)	0.98 (1.20)	0.91	0.63–1.31	0.62
Number of relapse (S.D.)	0.60 (0.81)	0.79 (1.10)	0.82	0.54–1.24	0.35
Planned medication discontinuation, yes (n, %)	11 (27.5)	9 (13.6)	0.42	0.16–1.12	0.08
Medication compliance (S.D.)	1.21 (0.35)	1.16 (0.28)	1.58	0.44–5.66	0.48
Mean DDD (S.D.)	0.54 (0.40)	0.56 (0.39)	0.90	0.33–2.47	0.84
Months of full time employment (S.D.)	16.88 (13.57)	12.14 (10.97)	1.03	1.00–1.07	0.05
Months of unemployment (S.D.)	9.75 (10.39)	15.17 (10.87)	0.95	0.92–0.99	0.02

CI: confidence interval; S.D.: standard deviation; P: p-value; DUP: duration of untreated psychosis; CGI_pos: clinical global impression on positive symptoms; CGI_neg: clinical global impression on negative symptoms; DDD: Defined Daily Dose.
Months of unemployment including period of unemployment and rehabilitation.

Ten Velden Hegelstad et al., 2013). However, the rate of complete recovery of the current study is slightly higher than the median (13.5%) and mean (16.4%) of the recovery rate found in a meta-analysis (Jääskeläinen et al., 2013). One of the possible explanations would be the use of different definitions of recovery. In the meta-analysis, patients were considered to be recovered only when their recovery status lasted for two years. However, the current study only required patients to have six months duration of recovery using a recent definition (Andreasen et al., 2005). Shorter DUP was found to predict clinical remission in the current study. On the other hand, higher level of education, lower level of negative symptoms and less months of unemployment at early stage of the illness predicted functional recovery. However, only years of education and months of unemployment were found significant in the final model. Patients with higher

educational level, more months of full time employment and planned medication discontinuation during early stage of the illness were more likely to achieve complete recovery at 10 years.

4.2. DUP and clinical remission

Shorter DUP was found to predict clinical remission but not functional recovery nor complete recovery. This echoed results of previous studies. In a meta-analysis of DUP as predictor of long-term outcomes of patients with schizophrenia, longer DUP was found to predict long-term symptomatic outcome but was not associated with employment, quality of life or hospitalization (Penttilä et al., 2014). However, DUP could only explain a small variance of clinical remission at 10-year follow up in the current study. This suggests that the effect of DUP on

Table 3
Logistic regression analysis of demographic and early clinical characteristics relating to complete recovery at 10 year follow up.

	Complete recovery		OR	95% CI	P
	Yes	No			
Demographics					
Age of onset (S.D.)	21.96 (3.31)	20.62 (2.87)	1.17	1.00–1.37	0.05
Years of education (S.D.)	11.67 (2.08)	10.47 (2.29)	1.27	1.03–1.55	0.02
Gender (male, n, %)	13 (48.1)	41 (56.2)	1.38	0.57–3.34	0.48
Baseline clinical characteristics					
LogDUP (S.D.)	1.78 (0.69)	1.92 (0.77)	0.78	0.43–1.40	0.41
Mode of onset (acute) (n, %)	12 (44.1)	22 (30.1)	1.86	0.75–4.60	0.18
Baseline positive symptoms (CGI pos) (S.D.)	4.11 (0.80)	4.08 (1.00)	1.03	0.75–1.65	0.89
Baseline negative symptoms (CGI neg) (S.D.)	2.48 (1.34)	2.81 (1.42)	0.84	0.61–1.17	0.30
Clinical characteristics of initial 3 year					
Mean CGI pos (S.D.)	1.63 (0.55)	1.60 (0.53)	1.12	0.49–2.54	0.89
Mean CGI neg (S.D.)	1.31 (0.44)	1.44 (0.42)	0.42	0.12–1.44	0.30
No. of hospitalization (S.D.)	0.81 (0.92)	1.05 (1.18)	0.81	0.53–1.25	0.79
No. of relapse (S.D.)	0.52 (0.70)	0.78 (1.08)	0.74	0.45–1.23	0.25
Planned med discontinuation, yes (n, %)	9 (33.3)	10 (13.7)	0.32	0.11–0.90	0.03
Medication compliance (S.D.)	1.18 (0.33)	1.17 (0.27)	1.16	0.26–5.18	0.85
Mean DDD (S.D.)	0.53 (0.41)	0.58 (0.40)	0.70	0.22–2.24	0.55
Months of full time employment (S.D.)	18.44 (14.23)	12.11 (10.83)	1.04	1.01–1.08	0.02
Months of unemployment (S.D.)	10.70 (11.30)	14.85 (10.62)	0.96	0.92–1.01	0.09

CI: confidence interval; S.D.: standard deviation; P: p-value; DUP: duration of untreated psychosis; CGI_pos: clinical global impression on positive symptoms; CGI_neg: clinical global impression on negative symptoms; DDD: Defined Daily Dose.
Months of unemployment including period of unemployment and rehabilitation.

Table 4

Binary logistic regression analysis of clinical remission, functional recovery and complete recovery at ten-year follow up.

	B	S.E.	OR, exp (B)	95% CI	p-Value
Clinical remission					
Log DUP	−0.74	0.30	0.48	0.27–0.86	0.01
Functional recovery					
Years of education	0.20	0.95	1.22	1.01–1.47	0.04
Months of unemployment	−0.05	0.02	0.95	0.92–0.99	0.02
Complete recovery					
Years of education	0.25	0.11	1.28	1.02–1.60	0.03
Months of full time employment	0.05	0.02	1.05	1.01–1.09	0.02
Planned medication discontinuation	−1.58	0.60	0.21	0.06–0.67	0.01

B: beta coefficient; S.E.: standardized error; OR: odds ratio; CI: confidence interval; DUP: duration of untreated psychosis.

long-term clinical remission is small and other factors should be considered. In a study looking at relationship of early clinical outcomes and clinical remission at 10-year follow up, [Ten Velden Hegelstad et al. \(2013\)](#) found that the effect of DUP disappear when adding duration of psychosis in the first year of treatment. This suggests that the initial response to treatment is likely to be an important factor but the current study did not measure that. Despite the small effect of DUP, results of the current study highlight the importance of DUP reduction as one of the key components of the EI service. Specific strategies to reduce DUP have been explored in different studies ([Connor et al., 2016](#); [Lloyd-Evans et al., 2015](#); [Melle et al., 2004](#); [Padilla et al., 2015](#); [Schiffman et al., 2015](#); [Srihari et al., 2014](#)). However, studies have not shown an overwhelming success in reducing DUP through the implementation of specialized early intervention programs in many countries or regions, particularly among the younger populations ([Chan et al., 2016](#)). Further exploration and implementation of effective strategies is needed.

4.3. Predictors of functional recovery

Years of education was found to be a predictor of functional and complete recovery in the current study. It may reflect premorbid functioning which has also been suggested as a key predictor of long-term functional outcomes ([White et al., 2009](#)). However, this may not be a modifiable factor after the onset of the illness. Previous studies have persistently suggested that more severe negative symptoms at early stage predicted poor long-term functional recovery or general recovery ([Álvarez-Jiménez et al., 2012](#); [Austin et al., 2013](#); [Lambert et al., 2010](#); [White et al., 2009](#)). Our study suggested the same, which further highlighted the importance of identifying and improving negative symptoms early in the treatment. However, only years of education and months of unemployment were significant in the final model but not negative symptoms. One of the reasons may be the relationship between negative symptoms and functioning ([Chang et al., 2011](#); [Rammou et al., 2017](#)). The importance of early unemployment in predicting poor long-term outcomes supports the effort to implement specific services in the EI intervention programs to improve employment apart from improving the negative symptoms ([Craig et al., 2014](#); [Hegelstad et al., 2017](#); [Killackey, 2015](#)). On the other hand, the model with these two variables only explained a small variance of functional recovery. This suggests that other factors may also be involved. Younger age of onset has been suggested to be related to poorer long-term outcomes ([Friis et al., 2016](#)), however, it was not found in the current study. The age limit of the early intervention service may be one of the possible explanations. Previous studies also found females had better recovery rate ([Álvarez-Jiménez et al., 2012](#); [Robinson et al., 2004](#)), but it was not found in the current study. One of the possible explanations may be the high proportion of male patients in the previous studies. There was over 70% male patients in one of the studies ([Álvarez-Jiménez et al., 2012](#)), yet only half of the current study population was

male. Local epidemiological study has also suggested that the prevalence rate of psychotic illness between male and female were similar ([Chang et al., 2017](#)).

4.4. Planned discontinuation of antipsychotic medication

The current study found that patients who had planned antipsychotic medication discontinuation early in the treatment were more likely to achieve complete recovery at 10-year follow-up. Current study reflected a naturalistic profile of the antipsychotic treatment in the EI service. Patients who had planned antipsychotic medication discontinuation were more likely to have better engagement with the service and better early recovery. Therefore, this result suggests that those who recover well early are more likely to achieve recovery in long term. Furthermore, the results should be appreciated with the limitations that only small number of patients had planned discontinuation of antipsychotic medications (N = 19). Despite randomized control trials showing early antipsychotic medication discontinuation increased the short-term relapse rate ([Chen et al., 2010](#)), results of current study suggest that planned medication discontinuation in a group of patients selected by clinician in a natural clinical setting may be beneficial in long-term recovery. Though there are some studies looking at the long-term effects of early medical discontinuation in patients with schizophrenia, results have been inconsistent ([Bowtell et al., 2017](#)). The heterogeneity of patient outcomes indicates that only some patients may benefit from early medication discontinuation. However, little is known about the patient characteristics to differentiate these groups. Further study should be designed by taking into the consideration of the heterogeneity of the clinical sample. Clinical guidelines should be established by taking into the consideration of the difference of patient characteristics.

4.5. Limitations

Results of the current study should be interpreted with the consideration of its limitations. Despite the satisfactory follow up rate and representative of the sample, the study has small sample size and may be under powered to detect some predictive factors. Though there are were no significant differences at baseline characteristics between the interviewed and non-interviewed group, sampling bias may still be possible because of the attrition. Furthermore, the follow-up rate of those who were still engaged with the service was likely to be higher than those who did not. It is possible that patients with good functioning were more difficult to be contacted. This may negatively bias the results. As the DUP in the current study was measured retrospectively using clinical record, which might have limited the accuracy of the measurement of DUP and possibly the estimate of its effect size. The quality of the clinical data over the initial three years relied on the quality of the clinical records. However, the reliability of the data collection was ensured in the current study. Results of the current study may not be generalized to patients with other psychosis diagnosis and age groups. The study was exploratory in nature. Without correction of multiple testing, results of the current study should be considered as a basis for the development of future confirmatory studies.

4.6. Conclusions

Despite the limitations stated, the current study highlighted the presence of differential factors contributing to the clinical and functional recovery. Long DUP, more negative symptoms and unemployment during the early stage of the illness were found to be modifiable factors for long-term clinical remission and functional recovery. These could be potential targets for further service development of the early intervention programs. Considering the likely beneficial effect of the early planned discontinuation of medication, further studies and clearer guidelines on early medication discontinuation are needed.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2018.08.022>.

Conflict of interest

The authors declare no conflicts of interest.

Contributors

Dr. Sherry Kit Wa Chan was the principle investigator of the funded project and was responsible for design the study, conducting the statistical analysis and preparing the manuscript. Dr. Wing Chung Chang and Dr. Edwin Ho Ming Lee were responsible for patient recruitment and interpretation of the results. Dr. Christy Lai Ming Hui and Prof Eric Yu Hai Chen were responsible for interpretation of the results. All authors approved the final manuscript.

Role of the funding source

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References

- Albert, N., Bertelsen, M., Thorup, A., Petersen, L., Jeppesen, P., Le Quack, P., Krarup, G., Jørgensen, P., Nordentoft, M., 2011. Predictors of recovery from psychosis analyses of clinical and social factors associated with recovery among patients with first-episode psychosis after 5 years. *Schizophr. Res.* 125, 257–266.
- Álvarez-Jiménez, M., Gleeson, J.F., Henry, L.P., Harrigan, S.M., Harris, M.G., Killackey, E., Bendall, S., Amminger, G.P., Yung, A.R., Herrman, H., Jackson, H.J., McGorry, P.D., 2012. Road to full recovery: longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. *Psychol. Med.* 42, 595–606.
- Andreasen, N.C., Carpenter Jr., W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am. J. Psychiatry* 162, 441–449.
- APA & APA Task Force on DSM-IV, 2000. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. American Psychiatric Association, Washington, DC.
- Austin, S.F., Mors, O., Secher, R.G., Hjorthøj, C.R., Albert, N., Bertelsen, M., Jensen, H., Jeppesen, P., Petersen, L., Randers, L., Thorup, A., Nordentoft, M., 2013. Predictors of recovery in first episode psychosis: the OPUS cohort at 10 year follow-up. *Schizophr. Res.* 150, 163–168.
- Bertolote, J., McGorry, P., 2005. Early intervention and recovery for young people with early psychosis: consensus statement. *Br. J. Psychiatry Suppl.* 48, s116–s119.
- Bobes, J., Ciudad, A., Alvarez, E., San, L., Polavieja, P., Gilaberte, I., 2009. Recovery from schizophrenia: results from a 1-year follow-up observational study of patients in symptomatic remission. *Schizophr. Res.* 115, 58–66.
- Bowtell, M., Ratheesh, A., McGorry, P., Killackey, E., O'Donoghue, B., 2017. Clinical and demographic predictors of continuing remission or relapse following discontinuation of antipsychotic medication after a first episode of psychosis. A systematic review. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2017.11.010>.
- Chan, S.K.W., So, H.C., Hui, C.L.M., Chang, W.C., Lee, E.H.M., Chung, D.W.S., Tso, S., Hung, S.F., Yip, K.C., Dunn, E., Chen, E.Y.H., 2015. 10-Year outcome study of an early intervention program for psychosis compared with standard care service. *Psychol. Med.* 45, 1181–1193.
- Chan, S.K.W., Chau, E.H.S., Hui, C.L.M., Chang, W.C., Lee, E.H.M., Chen, E.Y.H., 2016. Long term effect of early intervention service on duration of untreated psychosis in youth and adult population in Hong Kong. *Early Interv. Psychiatry* <https://doi.org/10.1111/eip.12313>.
- Chang, W.C., Hui, C.L.M., Tang, J.Y.M., Wong, G.H.Y., Lam, M.M.L., Chan, S.K.W., Chen, E.Y.H., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. *Schizophr. Res.* 133, 22–28.
- Chang, W.C., Tang, J.Y., Hui, C.L., Lam, M.M., Chan, S.K., Wong, G.H., Chiu, C.P., Chen, E.Y., 2012. Prediction of remission and recovery in young people presenting with first-episode psychosis in Hong Kong: a 3-year follow-up study. *Aust. N. Z. J. Psychiatry* 46, 100–108.
- Chang, W.C., Lau, E.S.K., Chiu, S.S., Hui, C.L.M., Chan, S.K.W., Lee, E.H.M., Chen, E.Y.H., 2016. Three-year clinical and functional outcome comparison between first-episode mania with psychotic features and first-episode schizophrenia. *J. Affect. Disord.* 200, 1–5.
- Chang, W.C., Wong, C.S.M., Chen, E.Y.H., Lam, L.C.W., Chan, W.C., Ng, R.M.K., Hung, S.F., Cheung, E.F.C., Sham, P.C., Chiu, H.F.K., Lam, M., Lee, E.H.M., Chiang, T.P., Chan, L.K., Lau, G.K.W., Lee, A.T.C., Leung, G.T.Y., Leung, J.S.Y., Lau, J.T.F., van Os, J., Lewis, G., Bebbington, P., 2017. Lifetime prevalence and correlates of schizophrenia-spectrum, affective, and other non-affective psychotic disorders in the Chinese adult population. *Schizophr. Bull.* 21 (43(6)), 1280–1290.
- Chen, E.Y.H., Hui, C.L.M., Lam, M.M.L., Chiu, C.P.Y., Law, C.W., Chung, D.W.S., Tso, S., Pang, E.P.F., Chan, K.T., Wong, Y.C., Mo, F.Y.M., Chan, K.P.M., Yao, T.J., Hung, S.F., Honer, W.G., 2010. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 341, c4024.
- Chen, E.Y.H., Tang, J.Y.M., Hui, C.L.M., Chiu, C.P.Y., Lam, M.M.L., Law, C.W., Yew, C.W.S., Wong, G.H.Y., Chung, D.W.S., Tso, S., et al., 2011. Three-year outcome of phase-specific early intervention for first-episode psychosis: a cohort study in Hong Kong. *Early Interv. Psychiatry* 5, 315–323.
- Connor, C., Birchwood, M., Freemantle, N., Palmer, C., Channa, S., Barker, C., Patterson, P., Singh, S., 2016. Don't turn your back on the symptoms of psychosis: the results of a proof-of-principle, quasi-experimental intervention to reduce duration of untreated psychosis. *BMC Psychiatry* 16, 127.
- Craig, T.K.J., Garety, P., Power, P., Rahaman, N., Colbert, S., Fornells-Ambrojo, M., Dunn, G., 2004. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ* 329, 1067.
- Craig, T., Shepherd, G., Rinaldi, M., Smith, J., Carr, S., Preston, F., Singh, S., 2014. Vocational rehabilitation in early psychosis: cluster randomised trial. *Br. J. Psychiatry* 205, 145–150.
- Fenton, W.S., McGlashan, T.H., 1991. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Arch. Gen. Psychiatry* 48, 978–986.
- Friis, S., Melle, I., Johannessen, J.O., Rössberg, J.I., Barder, H.E., Evensen, J.H., Haahr, U., Ten Velden Hegelstad, W., Joa, I., Langeveld, J., Larsen, T.K., Opjordsmoen, S., Rund, B.R., Simonsen, E., Vaglum, P.W., McGlashan, T.H., 2016. Early predictors of ten-year course in first-episode psychosis. *Psychiatr. Serv.* 67, 438–443.
- Haro, J.M., Kamath, S.A., Ochoa, S., Novick, D., Rele, K., Fargas, A., Rodríguez, M.J., Rele, R., Orta, J., Kharbeng, A., Araya, S., Gervin, M., Alonso, J., Mavreas, V., Lavrentzou, E., Lontos, N., Gregor, K., Jones, P.B., on behalf of the SOHO Study Group, 2003. The Clinical Global Impression-Schizophrenia Scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatr. Scand.* 107, 16–23.
- Haro, J.M., Novick, D., Bertsch, J., Karagianis, J., Dossenbach, M., Jones, P.B., 2011. Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study. *Br. J. Psychiatry* 199, 194–201.
- Hegelstad, W.T.V., Bronnick, K.S., Barder, H.E., Evensen, J.H., Haahr, U., Joa, I., Johannessen, J.O., Langeveld, J., Larsen, T.K., Melle, I., Opjordsmoen, S., Rund, B.R., Rossberg, J.I., Simonsen, E., Vaglum, P.W., McGlashan, T.H., Friis, S., 2017. Preventing poor vocational functioning in psychosis through early intervention. *Psychiatr. Serv.* 68, 100–103.
- Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J.J., Saha, S., Isohanni, M., Veijola, J., Miettunen, J., 2013. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr. Bull.* 39, 1296–1306.
- Jarbin, H., Ott, Y., Von Knorring, A.-L., 2003. Adult outcome of social function in adolescent-onset schizophrenia and affective psychosis. *J. Am. Acad. Child Adolesc. Psychiatry* 42, 176–183.
- Kane, J.M., Robinson, D.G., Schooler, N.R., Mueser, K.T., Penn, D.L., Rosenheck, R.A., Addington, J., Brunette, M.F., Correll, C.U., Estroff, S.E., Marcy, P., Robinson, J., Meyer-Kalos, P.S., Gattlieb, J.D., Glynn, S.M., Lynde, D.W., Pipes, R., Kurian, B.T., Miller, A.L., Azrin, S.T., Goldstein, A.B., Severe, J.B., Lin, H., Sint, K.J., John, M., Heinssen, R.K., 2016. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am. J. Psychiatry* 173, 362–372.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.
- Killackey, E., 2015. Resignation not accepted: employment, education and training in early intervention, past, present and future. *Early Interv. Psychiatry* 9, 429–432.
- Lambert, M., Karow, A., Leucht, S., Schimmelmann, B.G., Naber, D., 2010. Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. *Dialogues Clin. Neurosci.* 12, 393–407.
- Liberman, R.P., Kopelowicz, A., 2005. Recovery from schizophrenia: a concept in search of research. *Psychiatr. Serv.* 56, 735–742.
- Lloyd-Evans, B., Sweeney, A., Hinton, M., Morant, N., Pilling, S., Leibowitz, J., Killaspy, H., Tanskanen, S., Totman, J., Armstrong, J., Johnson, S., 2015. Evaluation of a community awareness programme to reduce delays in referrals to early intervention services and enhance early detection of psychosis. *BMC Psychiatry* 15, 98.
- Melle, I., Larsen, T.K., Haahr, U., Friis, S., Johannessen, J.O., Opjordsmoen, S., Simonsen, E., Rund, B.R., Vaglum, P., McGlashan, T., 2004. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Arch. Gen. Psychiatry* 61, 143–150.
- Möller, H.-J., Bottlender, R., Gross, A., Hoff, P., Wittmann, J., Wegner, U., Strauss, A., 2002. The Kraepelinian dichotomy: preliminary results of a 15-year follow-up study on functional psychoses: focus on negative symptoms. *Schizophr. Res.* 56, 87–94.
- Nosé, M., Tansella, M., Thornicroft, G., Schene, A., Becker, T., Veronese, A., Leese, M., Koeter, M., Angermeyer, M., Barbui, C., 2008. Is the Defined Daily Dose system a reliable tool for standardizing antipsychotic dosages? *Int. Clin. Psychopharmacol.* 23, 287–290.
- Padilla, E., Molina, J., Kamis, D., Calvo, M., Stratton, L., Streljevic, S., Aleman, G.G., Guerrero, G., Bourdieu, M., Conesa, H.A., Escobar, J.I., de Erausquin, G.A., 2015. The efficacy of targeted health agents education to reduce the duration of untreated psychosis in a rural population. *Schizophr. Res.* 161, 184–187.
- Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., Miettunen, J., 2014. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br. J. Psychiatry* 205, 88–94.
- Perkins, D.O., Gu, H., Boteva, K., Lieberman, J.A., 2005. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am. J. Psychiatry* 162, 1785–1804.
- Petersen, L., Jeppesen, P., Thorup, A., Abel, M.-B., Øhlenschlaeger, J., Christensen, T.Ø., Krarup, G., Jørgensen, P., Nordentoft, M., 2005. A randomised multicentre trial of

- integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ* 331, 602.
- Petersen, L., Thorup, A., Øqhlenschlaeger, J., Christensen, T.Ø., Jeppesen, P., Krarup, G., Jørgensen, P., Mortensen, E.L., Nordentoft, M., 2008. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. *Can. J. Psychiatr.* 53, 660–670.
- Rammou, A., Fisher, H.L., Johnson, S., Major, B., Rahaman, N., Chamberlain-Kent, N., Stone, J.M., 2017. Negative symptoms in first-episode psychosis: clinical correlates and 1-year follow-up outcomes in London Early Intervention Services. *Early Interv. Psychiatry* <https://doi.org/10.1111/eip.12502>.
- Robinson, D.G., Woerner, M.G., McMeniman, M., Mendelowitz, A., Bilder, R.M., 2004. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am. J. Psychiatry* 161, 473–479.
- Schiffman, J., Stephan, S.H., Hong, L.E., Reeves, G., 2015. School-based approaches to reducing the duration of untreated psychosis. *Child Adolesc. Psychiatr. Clin. N. Am.* 24, 335–351.
- Secher, R.G., Hjorthøj, C.R., Austin, S.F., Thorup, A., Jeppesen, P., Mors, O., Nordentoft, M., 2015. Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. *Schizophr. Bull.* 41, 617–626.
- Srihari, V.H., Tek, C., Pollard, J., Zimmet, S., Keat, J., Cahill, J.D., Kucukgoncu, S., Walsh, B.C., Li, F., Gueorguieva, R., Levine, N., Mesholam-Gately, R.I., Friedman-Yakoobian, M., Seidman, L.J., Keshavan, M.S., McGlashan, T.H., Woods, S.W., 2014. Reducing the duration of untreated psychosis and its impact in the U.S.: the STEP-ED study. *BMC Psychiatry* 14, 335.
- Strauss, J.S., Carpenter Jr., W.T., 1972. The prediction of outcome in schizophrenia. I. Characteristics of outcome. *Arch. Gen. Psychiatry* 27, 739–746.
- Strauss, G.P., Harrow, M., Grossman, L.S., Rosen, C., 2010. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. *Schizophr. Bull.* 36, 788–799.
- Tang, J.Y.M., Wong, G.H.Y., Hui, C.L.M., Lam, M.M.L., Chiu, C.P.Y., Chan, S.K.W., Chung, D.W.S., Tso, S., Chan, K.P.M., Yip, K.C., Hung, S.F., Chen, E.Y.H., 2010. Early intervention for psychosis in Hong Kong—the EASY programme. *Early Interv. Psychiatry* 4, 214–219.
- Tang, J.Y.-M., Chang, W.-C., Hui, C.L.-M., Wong, G.H.-Y., Chan, S.K.-W., Lee, E.H.-M., Yeung, W.-S., Wong, C.-K., Tang, W.-N., Chan, W.-F., Pang, E.P.-F., Tso, S., Ng, R.M.-K., Hung, S.-F., Dunn, E.L.-W., Sham, P.-C., Chen, E.Y.-H., 2014. Prospective relationship between duration of untreated psychosis and 13-year clinical outcome: a first-episode psychosis study. *Schizophr. Res.* 153, 1–8.
- Taylor, D.P.P., Kapur, S., 2011. *Prescribing Guidelines in Psychiatry*. 11th ed. Wiley-Blackwell.
- Ten Velden Hegelstad, W., Haahr, U., Larsen, T.K., Auestad, B., Barder, H., Evensen, J., Joa, I., Johannessen, J.O., Langeveld, J., Melle, I., Opjordsmoen, S., Rossberg, J.I., Rund, B.R., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S., 2013. Early detection, early symptom progression and symptomatic remission after ten years in a first episode of psychosis study. *Schizophr. Res.* 143, 337–343.
- Verma, S., Subramaniam, M., Abdin, E., Poon, L.Y., Chong, S.A., 2012. Symptomatic and functional remission in patients with first-episode psychosis. *Acta Psychiatr. Scand.* 126, 282–289.
- White, C., Stirling, J., Hopkins, R., Morris, J., Montague, L., Tantam, D., Lewis, S., 2009. Predictors of 10-year outcome of first-episode psychosis. *Psychol. Med.* 39, 1447–1456.
- Wunderink, L., Sytema, S., Nienhuis, F.J., Wiersma, D., 2009. Clinical recovery in first-episode psychosis. *Schizophr. Bull.* 35, 362–369.