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# Prediction of psychosis in prodrome: development and validation of a simple, personalized risk calculator

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## Abstract

**Background.** This study aim to derive and validate a simple and well-performing risk calculator (RC) for predicting psychosis in individual patients at clinical high risk (CHR).

**Methods.** From the ongoing ShangHai-At-Risk-for-Psychosis (SHARP) program, 417 CHR cases were identified based on the Structured Interview for Prodromal Symptoms (SIPS), of whom 349 had at least 1-year follow-up assessment. Of these 349 cases, 83 converted to psychosis. Logistic regression was used to build a multivariate model to predict conversion. The area under the receiver operating characteristic (ROC) curve (AUC) was used to test the effectiveness of the SIPS-RC. Second, an independent sample of 100 CHR subjects was recruited based on an identical baseline and follow-up procedures to validate the performance of the SIPS-RC.

**Results.** Four predictors (each based on a subset of SIPS-based items) were used to construct the SIPS-RC: (1) functional decline; (2) positive symptoms (unusual thoughts, suspiciousness); (3) negative symptoms (social anhedonia, expression of emotion, ideational richness); and (4) general symptoms (dysphoric mood). The SIPS-RC showed moderate discrimination of subsequent transition to psychosis with an AUC of 0.744 ($p < 0.001$). A risk estimate of 25% or higher had around 75% accuracy for predicting psychosis. The personalized risk generated by the SIPS-RC provided a solid estimate of conversion outcomes in the independent validation sample, with an AUC of 0.804 [95% confidence interval (CI) 0.662–0.951].

**Conclusion.** The SIPS-RC, which is simple and easy to use, can perform in the same manner as the NAPLS-2 RC in the Chinese clinical population. Such a tool may be used by clinicians to counsel appropriately their patients about clinical monitor *v.* potential treatment options.

## Original Article

*Dr Larry J. Seidman passed away on 7 September 2017. Dr Robert W. McCarley passed away on 27 May 2017. Both were founders and core members of the SHARP (ShangHai At Risk for Psychosis) project.

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Schizophrenia (SZ) is a severe mental disorder that can cause chronic disability, affecting about 1% of the world population (Kahn *et al*., 2015). Psychosis is especially traumatic for affected individuals and their families because the peak onset, especially in SZ, occurs between 15 and 30 years of age, interrupting social and work development just at the time of transition into adulthood. China has the largest population in the world at 1.3 billion, of which about 30% are 15–45 years of age. The average life-time prevalence rate of SZ in China is about 0.8% (Zhang *et al*., 1998; Phillips *et al*., 2009), which makes China the country with the most SZ patients (12 million). Poor understanding of the early signs of psychosis and the stigma attached to mental illness are related to delays in seeking treatment and to poor treatment outcome. There is thus an obvious need and urgency for prevention and early intervention for SZ in China.

As with other chronic serious diseases, prevention in medicine is focusing increasingly on individualization and precision in psychosis, of which SZ constitutes the majority of cases. Although many studies of subjects with clinical high risk (CHR) for psychosis have been conducted over the last decade, contributing to the possibility of predicting psychosis (Cannon *et al*., 2008; Fusar-Poli *et al*., 2012, 2013), only about 20% of CHR-identified cases have been found to convert to psychosis within a 2-year period (Fusar-Poli *et al*., 2013). More importantly, CHR cases and their families are interested in individual risk estimates and functional outcomes (Zhang *et al*., 2018*b*). Clinicians in particular recognize the importance of discerning accurately how much 'real' risk is faced by those CHRs, because this information may



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affect treatment and monitoring strategies. Extensive research suggests that there are differences in baseline clinical characteristics, such as greater severity of thought disorder symptoms (DeVylder *et al.*, 2014; Perkins *et al.*, 2015), functional decline (Thompson *et al.*, 2011; Li *et al.*, 2017), and deficits in neurocognition (Seidman *et al.*, 2010, 2016) and social cognition (Zhang *et al.*, 2016, 2018*a*), between CHR individuals who converted to psychosis and those who did not. Existing literature concerning these predictors offers the hope of developing multivariable models (Michel *et al.*, 2014; Cornblatt *et al.*, 2015) with a wide set of clinical factors to improve the power of prediction.

Within this context, an individualized risk calculator (RC) was developed in the second phase of the North American Prodrome Longitudinal Study (NAPLS-2) (Cannon *et al.*, 2016). This RC is an open-access online tool for predicting CHR individual likelihood of conversion to psychosis. Based on the database of 596 CHR subjects with up to 2 years of follow-up, a model-predicted risk of 0.2 or higher reached a specificity of 72.1% and a sensitivity of 66.7%. At the same time, an independent CHR sample ($n$ = 210) from the Early Detection, Intervention, and Prevention of Psychosis Program (EDIPPP) was applied to assess the predictive ability of the NAPLS-2 psychosis RC (Carrion *et al.*, 2016). This external sample validated the RCs accuracy, with a sensitivity and specificity of 58.3% and 72.6%, respectively. The accuracy of the RC was highly dependent on valid and accurate data, which were derived from the Structured Interview for Prodromal Syndromes (SIPS), MATRICS Consensus Cognitive Battery (MCCB), Global Functioning: Social Scale, Childhood Trauma and Abuse Scale, and Research Interview Life Events Scale. However, the RCs reliance on excessively subjective assessments may reduce its replicability, especially when applied to cases outside of North America, such as Asia.

Although most CHR cases were identified through SIPS (Miller *et al.*, 2002, 2003), which has been adopted by several countries and programs as the gold standard tool of CHR identification, much useful information in SIPS was not used efficiently in predicting conversion. For example, rated scales for negative, disorganized, and general symptoms in SIPS were only used as additional descriptive information to estimate the severity of prodromal symptoms. Nonetheless, they neither contributed to the CHR diagnosis nor predicted the conversion to psychosis. The objective of this study is to develop a simple, SIPS-based, individualized RC (SIPS-RC) that could be used by the clinical help-seeking population to determine their risk of conversion to full psychosis; it also aims to help clinicians decide whether extremely close attention to such real CHR cases is warranted or more positive intervention strategies to prevent future psychosis should be adopted. To maximize the accessibility and ease of use of the SIPS-RC developed in this study, it is designed to only use information that is commonly known to an identified CHR individual and preferably not to require any complex calculations. Subsequently, we assessed the performance of the SIPS-RC by evaluating its predictive accuracy when applied to an external validation sample.

## Methods

### Sample

The Research Ethics Committee at the Shanghai Mental Health Center (SMHC) approved the study in 2011, 2013 and 2015. The 417 participants with CHR included in this study were recruited based on a two-stage (self-report screen and face-to-face interview) method. All the participants gave written informed consent at the recruitment stage of the study. Those younger than 18 years were signed up for the study by their parents, who provided consent, and the youth provided assent. In the first stage, the CHR status was screened by the Prodromal Questionnaire-Brief Version (PQ-B) (Loewy *et al.*, 2011), which is a 21-item self-report measure derived from the 92-item Prodromal Questionnaire (Loewy *et al.*, 2005). Positive screening was defined as a total score of 3 or higher on the PQ-B, a PQ-B distress score of 6 or higher, and/or one or more first-degree relatives with affective or non-affective psychosis. In the second stage, which followed screening, CHR status was confirmed by a face-to-face interview using SIPS (Miller *et al.*, 2003). This CHR cohort was taken from the outpatient department of SMHC, which is China's largest outpatient medication–management and psychotherapy providing mental health clinic. The ShangHai At Risk for Psychosis (SHARP) program was conducted with CHR subjects enrolled in an early identification program for psychosis, implemented at one site, namely, the SMHC in China (Zhang *et al.*, 2014, 2017).

The sample approached were those who sought an initial appointment at SMHC consecutively. Participants had to fulfill at least one of the prodromal syndrome criteria: (1) brief intermittent psychotic syndrome (BIPS), (2) attenuated positive symptom syndrome (APSS), or (3) genetic risk and deterioration syndrome (GRDS). Exclusion criteria were: age under 14 years or above 45 years; an IQ of below 70 (the Wechsler Abbreviated Scale of Intelligence test was applied for general intellectual ability assessment); a present or past psychotic episode; a past usage of antipsychotics; a present severe somatic disease (e.g. pneumonia, cancer, or heart failure), mental retardation, or dementia; a present or a history of psychoactive drug (e.g. methamphetamine, etc.) abuse.

At baseline, 417 CHR participants were recruited as the development sample, of whom 355 met the criteria for APSS; 24 for GRDS; 28 for both APSS and GRDS; and 14 for BIPS. Table 1 presents their baseline demographic and clinical characteristics. At follow-up, CHR subjects were re-assessed every 6 months by face-to-face interview or telephone using SIPS/SOPS. Of the total 417 CHR participants, 349 completed at least a year of follow-up (until 30 August 2017; the longest follow-up case was 6 1/2 years), during which 83 converted to psychosis and 68 were lost. A total of 191 CHR participants were re-assessed through face-to-face interviews and the rest by telephone. Of those who were lost to follow-up, 29 could not be contacted, and 39 refused any further contact within the first year. The average follow-up period in this sample was 42.4 ± 20.4 months [25% percentile = 26, median = 37, 75% percentile = 57, range (18–78) months].

The validation sample was made up of 100 CHR subjects ascertained from 2015 to 2016, following the same inclusion and exclusion criteria, CHR and conversion criteria and procedures. Of the initial 100 CHR subjects, 91 (91.0%) had at least a 1-year follow-up assessment. Of those, 10 (11.0%) transitioned to psychosis over 1 year of follow-up.

### CHR criteria

The SIPS (Miller *et al.*, 2003) was used to determine whether subjects met the criteria for putatively prodromal syndrome (CHR status) or the Presence of a Psychotic Syndrome (POPS) (McGlashan *et al.*, 2010). The SIPS consists of 19 items that assess

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**Table 1.** Baseline demographic and clinical variables, comparison between converters and non-converters, and between those who completed follow-up assessments and those who were lost

| Variables | Total sample | Followed ($n = 349$) | | Lost | Converters *v.* non-converters | | Followed *v.* lost | |
|---|---|---|---|---|---|---|---|---|
| | | Converters | Non-converters | | $t/Z/\chi^2$ [a] | $p$ | $t/Z/\chi^2$ [a] | $p$ |
| Cases [*n* (%)] | 417 | 83 (19.9) | 266 (63.8) | 68 (16.3) | – | – | – | – |
| Age (years) [mean (S.D.)] | 20.9 (6.4) | 20.4 (5.6) | 20.6 (6.3) | 22.8 (7.2) | $t = 0.329$ | 0.743 | $t = 2.373$ | 0.020 |
| Male [*n* (%)] | 200 (48.0) | 47 (56.6) | 119 (44.7) | 34 (50.0) | $\chi^2 = 3.586$ | 0.058 | $\chi^2 = 0.135$ | 0.713 |
| Education (years) [mean (S.D.)] | 11.4 (3.0) | 11.1 (2.8) | 11.3 (3.1) | 11.8 (7.2) | $t = 0.604$ | 0.547 | $t = 1.413$ | 0.158 |
| Structured Interview of Prodrome Syndromes (SIPS/SOPS) | | | | | | | | |
| Family history[b] [*n* (%)] | 45 (10.8) | 7 (8.4) | 25 (9.4) | 13 (19.1) | $\chi^2 = 0.071$ | 0.790 | $\chi^2 = 5.851$ | 0.016 |
| Schizotypal personality disorder [*n* (%)] | 20 (4.8) | 4 (4.8) | 13 (4.9) | 3 (4.4) | $\chi^2 = 0.001$ | 0.980 | $\chi^2 = 0.026$ | 0.871 |
| Highest GAF in past year [mean (S.D.)] | 78.6 (4.7) | 79.1 (3.4) | 78.1 (5.2) | 79.7 (4.2) | $Z = 1.168$ | 0.243 | $Z = 1.623$ | 0.105 |
| Current GAF [mean (S.D.)] | 55.2 (7.8) | 53.3 (6.0) | 55.1 (7.9) | 57.7 (8.7) | $Z = 2.423$ | **0.015** | $Z = 2.638$ | 0.008 |
| Drop GAF[c] [mean (S.D.)] | 23.4 (7.8) | 25.8 (6.4) | 23.0 (7.8) | 22.1 (8.7) | $Z = 3.521$ | **<0.001** | $Z = 1.224$ | 0.221 |
| Positive symptoms [median, mean (S.D.)] | | | | | | | | |
| P1 – Unusual thought content | 4, 2.8 (1.9) | 4, 3.3 (1.8) | 4, 2.8 (1.9) | 3, 2.4 (1.9) | $Z = 1.774$ | **0.076** | $Z = 2.070$ | 0.038 |
| P2 – Suspiciousness | 4, 3.1 (1.9) | 4, 3.6 (1.7) | 4, 3.1 (1.9) | 3, 2.6 (1.8) | $Z = 2.205$ | **0.027** | $Z = 2.684$ | 0.007 |
| P3 – Grandiose ideas | 0, 0.2 (0.6) | 0, 0.2 (0.7) | 0, 0.2 (0.7) | 0, 0.1 (0.3) | $Z = 0.094$ | 0.925 | $Z = 1.367$ | 0.172 |
| P4 – Perceptual abnormalities | 3, 2.5 (2.1) | 3, 2.6 (2.2) | 3, 2.5 (2.1) | 2, 2.1 (2.2) | $Z = 0.402$ | 0.688 | $Z = 1.641$ | 0.101 |
| P5 – Disorganized communication | 0, 0.5 (1.0) | 0, 0.7 (1.3) | 0, 0.4 (0.9) | 0, 0.5 (1.0) | $Z = 2.612$ | **0.009** | $Z = 0.501$ | 0.617 |
| Negative symptoms [median, mean (S.D.)] | | | | | | | | |
| N1 – Social anhedonia | 3, 2.6 (1.3) | 3, 3.1 (1.3) | 3, 2.5 (1.3) | 2, 2.4 (1.3) | $Z = 3.484$ | **<0.001** | $Z = 1.797$ | 0.072 |
| N2 – Avolition | 3, 2.5 (1.3) | 3, 2.7 (1.2) | 3, 2.5 (1.3) | 2, 2.3 (1.2) | $Z = 1.100$ | 0.271 | $Z = 1.373$ | 0.170 |
| N3 – Expression of Emotion | 1, 1.4 (1.4) | 2, 1.8 (1.5) | 1, 1.3 (1.4) | 1, 1.2 (1.4) | $Z = 2.633$ | **0.008** | $Z = 1.097$ | 0.273 |
| N4 – Experience of emotions and self | 1, 1.4 (1.4) | 1, 1.6 (1.4) | 1, 1.4 (1.4) | 1, 1.1 (1.2) | $Z = 1.532$ | 0.126 | $Z = 1.685$ | 0.092 |
| N5 – Ideational richness | 0, 0.5 (1.0) | 1, 0.9 (1.1) | 0, 0.4 (0.9) | 0, 0.5 (0.9) | $Z = 4.560$ | **<0.001** | $Z = 0.658$ | 0.510 |
| N6 – Occupational functioning | 3, 3.4 (1.6) | 3, 3.7 (1.6) | 3, 3.3 (1.5) | 3, 3.1 (1.7) | $Z = 1.873$ | **0.061** | $Z = 1.264$ | 0.206 |
| Disorganization symptoms [median, mean (S.D.)] | | | | | | | | |
| D1 – Odd behavior of appearance | 0, 0.7 (1.1) | 1, 0.8 (1.0) | 0, 0.7 (1.2) | 0, 0.7 (1.2) | $Z = 1.895$ | **0.058** | $Z = 1.087$ | 0.277 |
| D2 – Bizarre thinking | 2, 2.0 (1.9) | 2, 2.4 (1.9) | 2, 2.0 (1.9) | 1, 1.7 (1.8) | $Z = 1.768$ | **0.077** | $Z = 1.851$ | 0.064 |
| D3 – Trouble with focus and attention | 2, 2.4 (1.1) | 2, 2.4 (1.1) | 2, 2.4 (1.0) | 2, 2.3 (1.1) | $Z = 0.452$ | 0.651 | $Z = 1.571$ | 0.116 |
| D4 – Impairment in personal hygiene | 0, 0.5 (0.8) | 0, 0.6 (0.8) | 0, 0.4 (0.7) | 0, 0.5 (0.9) | $Z = 2.695$ | **0.007** | $Z = 0.712$ | 0.477 |
| General symptoms [median, mean (S.D.)] | | | | | | | | |
| G1 – Sleep disturbance | 3, 2.4 (1.3) | 2, 2.2 (1.3) | 3, 2.4 (1.3) | 3, 2.6 (1.4) | $Z = 1.244$ | 0.213 | $Z = 1.472$ | 0.141 |
| G2 – Dysphoric mood | 3, 3.1 (1.4) | 3, 2.8 (1.3) | 3, 3.2 (1.4) | 3, 3.0 (1.4) | $Z = 2.574$ | **0.010** | $Z = 0.759$ | 0.448 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| G3 – Motor disturbances | 0, 0.2 (0.6) | 0, 0.3 (0.8) | 0, 0.2 (0.6) | 0, 0.1 (0.4) | $Z = 0.256$ | 0.798 | $Z = 1.143$ | 0.253 |
| G4 – Impaired tolerance to normal stress | 3, 3.2 (1.4) | 3, 3.2 (1.5) | 4, 3.3 (1.4) | 3, 2.9 (1.4) | $Z = 0.858$ | 0.391 | $Z = 2.237$ | 0.025 |

*p* in bold is significant at the 0.05 level.
[a]$t/Z/\chi^2$: *t* for independent *t* test, *Z* for Mann–Whitney *U* test (nonparametric test), $\chi^2$ for $\kappa$ test.
[b]Family history: having at least one first-degree relative with psychosis.
[c]Drop GAF: GAF score baseline from highest in the past year.

four symptom domains: positive symptoms (scales P1–P5: P1 – unusual thought content, P2 – suspiciousness, P3 – grandiosity, P4 – perceptual abnormalities, and P5 – disorganized communication), negative symptoms (scales N1–N6: N1 – social anhedonia, N2– avolition, N3 – expression of emotion, N4 – experience of emotions and self, N5 – ideational richness, and N6 – occupational functioning), disorganized symptoms (scales D1–D4: D1 – odd behavior of appearance, D2 – bizarre thinking, D3 – trouble with focus and attention, and D4 – impairment in personal hygiene), and general symptoms (scales G1–G4: G1 – sleep disturbance, G2 – dysphoric mood, G3 – motor disturbances, and G4 – impaired tolerance to normal stress).

Two types of severity scale are employed to evaluate these listed symptoms. Positive symptoms in SIPS are rated on a 0–6 scale, with 6 indicating 'severe and psychotic' and 3–5, a prodromal range symptom. Patients diagnosed with one or more psychosis high risk syndromes require further evaluation with the SOPS scales regarding their negative, disorganized, and other symptoms. This kind of additional information, which is not eligible for the diagnosis of psychosis high risk syndromes, is valuable in quantifying the evaluation, describing the diversity, and detecting the severity of psychosis high risk syndromes. In SIPS, the ratings of negative, disorganized, and general symptoms range from 0 (no symptom) to 6 (extremely severe) points.

CHR criteria include three syndromes. First, BIPS is indicated by the recent onset of positive symptoms rated at a 6 level and occurring at least a few minutes a day at least once a month but not at a sufficient frequency or duration to meet the criteria of POPS. Second, APSS criteria are met by at least one P symptom rated between 3 and 5, present at least once a week on average in the last month, and either new within the past year or rated at least one point higher (indication of a worsening case) than the year prior. Third, GRDS is indicated by functional deterioration [30% drop in Global Assessment of Functioning (GAF) score within 12 months] in the context of schizotypal personality disorder or at least one first-degree relative with psychosis.

As reported in previous studies (Zhang *et al.*, 2014), the Chinese version (Zheng *et al.*, 2012) of SIPS/SOPS, which was developed by the SHARP team, also demonstrated good inter-rater reliability (the Intraclass Correlations Coefficient $r = 0.96$, $p < 0.01$ on the SIPS total score) and validity (26.4%, converted to psychosis in the succeeding 2 years) in a Chinese clinical population. Expressed as the $\kappa$ value, the agreement rate between the four psychiatrists was 0.81–0.95. The inter-rater reliability (ICC) for the SIPS/SOPS positive symptoms ranged from 0.86 (P5) to 0.98 (P4) among the four raters. The Cronbach's $\alpha$ for all SOPS items was 0.71, and the total SOPS score was correlated significantly with the Chinese PANSS total score ($r = 0.63$, $p < 0.01$). The first author was certified on the SIPS at Yale University-sponsored SIPS/SOPS trainings, along with Drs Woodberry and Seidman, who have extensive experience with the SIPS/SOPS in the North American NAPLS and other CHR research projects.

### Conversion criteria

The outcome in this study was conversion to psychosis. Conversion was determined using the criteria of POPS (McGlashan *et al.*, 2010) from SIPS. Conversion was defined based on the presence of a 6-level positive symptom (the rating '6' refers to severe and psychotic, i.e. conviction of psychotic experiences) that is either dangerous, disorganized, or occurring at least an hour a day on average

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**Table 2.** Predictor variable combinations, individual predictive accuracy, and reduction as binary variable

| Four dimensions | Variables selected | Predictive accuracy AUC (95% CI) | *p* | Cut-off methods transform to binary variable |
|---|---|---|---|---|
| Functional decline ($F-f$) | Drop GAF | 0.628 (0.563–0.693) | <0.001 | ($F-f=0$) < 25<br>($F-f=1$) ⩾ 25 |
| Severity of positive symptoms ($F-p$) | P1 + P2 + P5 | 0.614 (0.549–0.679) | 0.002 | ($F-p=0$) ⩽ 3<br>($F-p=1$) > 3 |
| Severity of negative symptoms (F – $n$) | N1 + N3 + N5 | 0.643 (0.575–0.711) | <0.001 | ($F-n=0$) < 6<br>($F-n=1$) ⩾ 6 |
| Severity of disorganization symptoms ($F-d$) | D1 + D2 + D4 | 0.590 (0.523–0.657) | 0.013 | ($F-d=0$) < 3<br>($F-d=1$) ⩾ 3 |
| Severity of general symptoms ($F-g$) | G2 | 0.591 (0.521–0.661) | 0.012 | ($F-g=0$) < 3<br>($F-g=1$) ⩾ 3 |

GAF, Global Assessment of Functioning; AUC, the area under the curve from the receiver operating characteristic curve; CI, 95% confidence interval.

four days a week for at least longer than 16 h. Among the 83 converters, 74 subjects were diagnosed with SZ; 7 subjects, with bipolar disorder with psychotic symptoms; and 1 subject, with obsessive-compulsive disorder (OCD) with psychotic symptoms. One subject died through suicide under psychotic symptoms. Among the converters, 59 subjects were hospitalized either at SMHC or in local psychiatric units.

### *Data analysis*

The SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The data were assessed by Levene's test analyses for normality. Four steps were undertaken to build a multivariate proportional hazards model to predict the likelihood of conversion to psychosis based on each participant's SIPS variables. The first step was the selection of indicators based on SIPS variables with significance or a trend toward significance ($p < 0.1$), followed by a determination of the differences of indicators between the converter and non-converter groups. SIPS variables were described and compared between groups using the nonparametric Mann–Whitney *U* test for non-normally distributed continuous data. Second, to avoid overfitting the model, the indicators were integrated based on SIPS structured domains. The integrated indicators were entirely derived from SIPS, which may be administered easily and widely in general clinical settings that provide services for the high-risk population. Third, the predictive values of the integrated indicators were tested according to the area under the receiver operating characteristic (ROC) curve (AUC). Those indicators with non-normal distribution characteristics were modified into two classified variables (0, 1). The ROC curve for each indicator was applied to find the optimal cut-off point for predicting psychosis. The cut-off scores were used to reduce these complicated rank indicators into simple binary variables. Third, the binary variables were used in a logistic regression model to predict the likelihood of conversion to psychosis. The odds ratios (OR) and 95% confidence intervals (CI) of indicators in the model were estimated for the risk of conversion to psychosis. Fourth, variables from each CHR case were entered into the regression model (SIPS-RC), to construct a new variable of individual risk ratio. The ROC methodology was used to assess the discriminative power of the probabilities. Consequently, a map of the probability of conversion to psychosis was made, comprising all the combinations of indicators in the SIPS-RC. The corresponding risk for conversion of psychosis for each specific CHR case can then be figured out quite conveniently. Finally, the SIPS-RC was then used to generate risk estimates for each case in the validation sample. The validation analysis was carried out by the AUC. The diagnostic accuracy (sensitivity, specificity) was examined across different levels of the SIPS-RC predicted risk.

## Results

### *Calculator development*

Baseline subject demographic and clinical characteristics are summarized in Table 1. There were no significant differences between those who converted and did not convert on any of the demographic and genetic risk (family history and schizotypal personality disorder) variables. According to the Mann–Whitney *U* (nonparametric statistics) test, nine SIPS variables reached significances, and four had a trend toward significance. Significant differences found in this study were that individuals with older age, family history, higher baseline GAF scores, and lower P1, P2, and G4 scores were more likely to be lost during the follow-up than those who completed the follow-up.

To meet the aim of developing a simple practical tool for psychosis conversion prediction, the researchers' selection of indicators included SIPS variables for which the differences were almost statistically significant ($p < 0.1$) between converters and non-converters (see Table 1). Those variables were then integrated into five dimensions based on the SIPS structures (GAF drop and four domains). For greater ease of administration, indicators with non-normal distribution characteristics were transformed by the ROC method to establish two classified variables (0, 1). The AUC listed in Table 2 was used to test the effectiveness of discrimination of conversion by individual variable.

As shown in Table 3, a binary regression model was used to evaluate the effect of five key predictor variables selected in Table 2 on prediction of conversion. The overall model achieved a classification accuracy rate of 76.2%. In terms of individual variables, except for severity of disorganization symptoms ($F-d$), the variables in the model showed good discrimination. Among the four variables, functional decline ($F-f=1$), high scores on positive ($F-p=1$) and negative symptoms ($F-n=1$), and low score on G2 ($F-g=0$) were significant predictors of conversion to psychosis.

Table 3 presents the values of risk probabilities generated by the regression model for each case and then used in the ROC

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**Table 3.** Logistic regression for predicting the conversion to psychosis

| Predictor variable | $\beta$ | S.E. | OR | 95% CI | Wald statistic | $p$ Value |
|---|---|---|---|---|---|---|
| Functional decline ($F-f$) | −2.065 | 0.540 | 0.127 | 0.044–0.365 | 14.649 | <0.001 |
| Severity of positive symptoms ($F-p$) | −1.973 | 0.745 | 0.139 | 0.032–0.599 | 7.011 | 0.008 |
| Severity of negative symptoms ($F-n$) | −0.493 | 0.223 | 0.611 | 0.394–0.945 | 4.899 | 0.027 |
| Severity of disorganization symptoms ($F-$ d) | Excluded from the model | | | | | |
| Severity of general symptoms ($F-g$) | 0.418 | 0.251 | 1.519 | 0.929–2.485 | 4.027 | 0.045 |

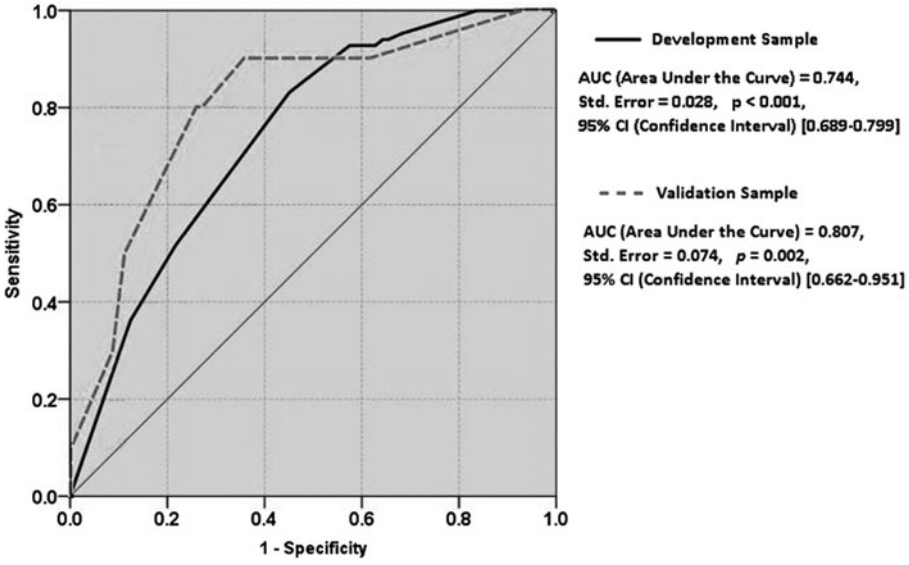


**Fig. 1.** ROC curve for the development and validation model.

analysis. The overall model for predicting conversion was significant with the overall classification accuracy of 68.9–79.9% (see Fig. 1). Demanding a sensitivity of 83.1% under moderate specificity (54.9%) for the prediction of psychosis, the risk probability (generated from regression) cut-off value was ≧25.

The map of calculated risk based on the four variables [functional decline ($F-f$), severity of positive symptoms ($F-p$), severity of negative symptoms ($F-n$), and severity of general symptoms ($F-g$)] from the SIPS evaluation was developed to assist health-care professionals, thereby increasing the predictive power for psychosis. In Fig. 2, the paths simply estimate using 'yes' or 'no' the four dimensions selected through the regression model above. For example, in the case of a CHR individual identified by SIPS, with a baseline GAF score of 54, a highest GAF score of 79 in the previous year, and with the following ratings: P1 = 4, P2 = 4, P5 = 0, N1 = 1, N3 = 1, N5 = 0, G2 = 2, the values of four dimensions would be $F-f=1$, $F-p=1$, $F-n=0$, and $F-g=0$, yielding a psychosis risk estimate of 30.7% (see Fig. 2). CHR cases with a psychosis risk estimate higher than the cutoff value of 25% would have around 75% accuracy in predicting psychosis.

### *Calculator validation*

The CHR subjects in the validation and development samples were compared with demographic and clinical variables (online Supplementary Data 1). In comparison with the development sample, the validation sample had a younger mean age of 18.9 years (S.D. = 5.6), roughly equal sex ratio (female 56.0%), and the most common CHR subtype [Attenuated Positive Symptoms (APS); 99.0%], and the most common positive symptoms of this sample were unusual thought content (P1, 77.0%), followed by suspiciousness (P2, 75.0%), and abnormal perception (P4, 61.0%). However, rates of family history of psychosis were much lower in the validation sample than in the development sample (3.0% and 10.8%, respectively). The validation sample showed significantly less functional decline and significantly more severe symptoms in unusual thought content and suspiciousness.

The SIPS-RC was then used to provide probability estimates of conversion to psychosis for each individual in this sample. Figure 1 shows that when conversion to psychosis is the principal endpoint, the ROC analysis resulted in an AUC of 0.804 (95% CI 0.662–0.951) for the probability risk estimates. The 25% SIPS-RC predicted risk provided a sensitivity of 50% and a specificity of 89%, and a SIPS-RC predicted risk of 15% provides a better balance between sensitivity and specificity levels at 80% and 74% with the external validation sample. The sensitivity and specificity values for these thresholds were at acceptable levels for clinical application.

## Discussion

Psychiatrists and psychologists have become more focused on the exact risk for psychosis rather than a 'category' with a low rate of conversion to psychosis. Therefore, assessing a patient's unique predicting risk is necessary, so that experts can counsel their patients appropriately about clinical monitoring *v.* potential treatment options, especially the use of antipsychotics. Consequently,

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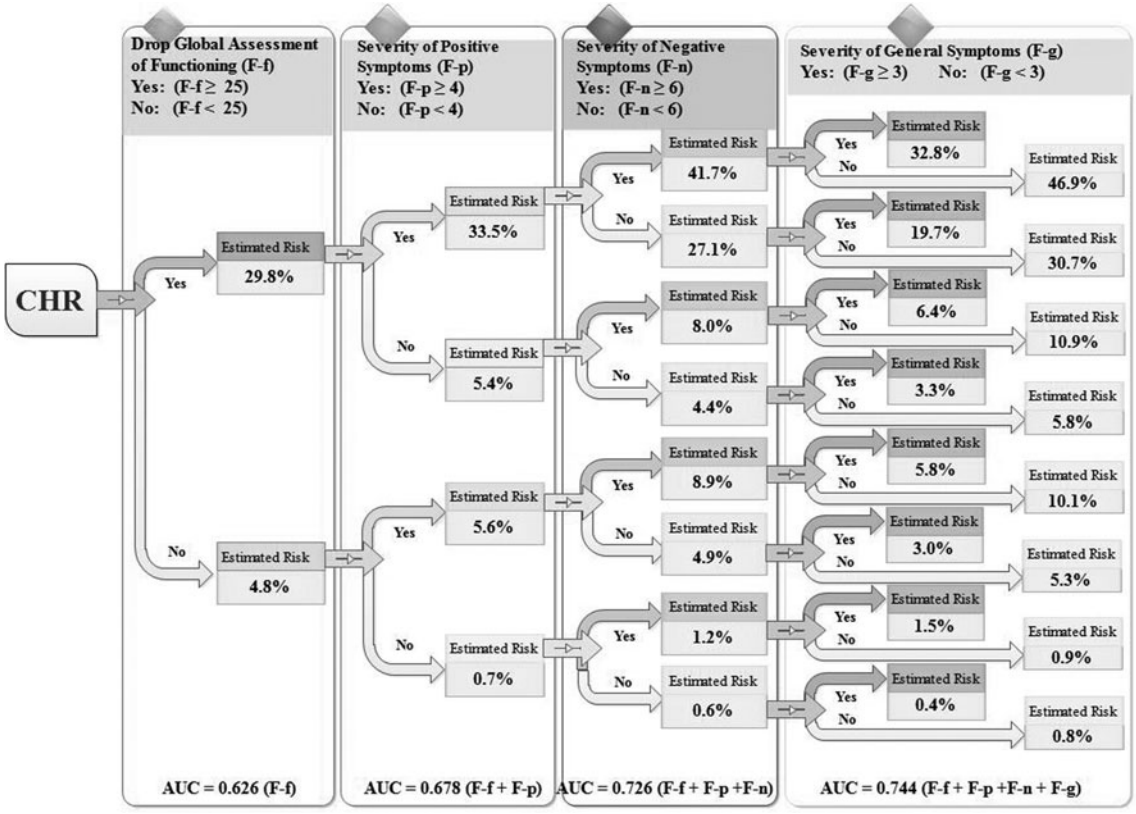


**Fig. 2.** The path map of calculated risk for individuals with CHR of psychosis. Clinical high risk (CHR); discrimination performance (ability of the model to correctly distinguish between converters and non-converters) was assessed by the AUC; Drop GAF: (the highest GAF score in the past year from the baseline) minus (GAF score at baseline); functional decline ($F-f$, 1 = Drop GAF $\geqslant$ 25), severity of positive symptoms ($F-p$, 1 = P1 + P2 + P5 $\geqslant$ 4), severity of negative symptoms ($F-n$, 1 = N1 + N3 + N6 $\geqslant$ 6), and severity of general symptoms ($F-g$, 1 = G2 $\geqslant$ 3).

a clinical prediction tool capable of estimating a patient-specific risk for conversion to psychosis after the conduct of a formal SIPS evaluation would be of great value in guiding patients' and clinicians' decision-making in the clinical setting. In line with this, the current study developed a practical and simple tool for the individualized prediction of psychosis using only variables from the SIPS, which is available in most CHR studies. To the best of the researchers' knowledge, this is the simplest RC around the world, and the first attempt to develop an Asian population-based psychosis prediction model. The current study demonstrated that its proposed SIPS-RC exhibits moderate performance for the prediction of psychosis; however, it is clearly inferior to the CHR status itself, which only predicts less than 30% of the cases that would convert to psychosis.

This SIPS-RC was developed to provide estimated risks using a defined set of SIPS variables. This tool can be used as a screening process in counseling and making decisions prior to considering antipsychotics treatment, particularly in research-based clinical settings. With an emphasis on the principal of 'maximizing intervention effects and minimizing damage effects' in early intervention of psychosis, the RC offers unique opportunities to these CHR individuals to improve overall care. Moreover, the accuracy of the SIPS-RC reported in this study (AUC = 0.74) is comparable with the results of previous studies developing and evaluating the performance of the NAPLS-2 calculator (0.71 and 0.79, respectively) (Cannon *et al.*, 2016; Carrion *et al.*, 2016). However, the current RB-C has the obvious advantages of its high homogeneity (SIPS has been widely used all over the world), speed (it saves more than half the time), simplicity (only four dichotomous variables are included in the RC), and convenient (a patient-specific risk for conversion to psychosis can be found from the path map in Fig. 2).

There are several reasons the SIPS-based simple RC can perform in the same manner as the NAPLS-2 model, which integrated five measurements. First, the baseline severity levels of unusual thought content (P1), suspiciousness (P2), and global function decline are highly important predictors in both samples. In addition, SIPS scores are also at the core of the NAPLS-2 model. Evidence has been increasing that baseline disordered thought symptoms (Cannon *et al.*, 2008; Fusar-Poli *et al.*, 2013) and functional deterioration (Cornblatt *et al.*, 2007; Zhang *et al.*, 2017) are key risk factors for predicting the onset of psychosis in those with a CHR syndrome. Second, in addition to these two major components (positive thought symptoms and functional decline), the RC developed in this study included negative symptoms in SIPS as a predictor variable, but without the neurocognitive variables of verbal learning and memory, and speed of processing in the NAPLS-2 model. However, the negative symptoms can be impacted by cognitive deficits, while cognitive decline generally is complicated by the deterioration of negative symptoms. Numerous studies (Ventura *et al.*, 2009; Rabany *et al.*, 2011) have revealed a highly positive correlation between negative symptoms and cognitive test performances. Third, as mentioned by Cannon *et al.* (2016) in their NAPLS-2 calculator research, other variables, such as stressful life events and traumas, that had been excluded from this study's model, have a negligible

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impact on their own or in combination with other variables in the NAPLS-2 prediction model. As for the family history of psychosis, the lower proportion of family-history-positive cases in the SHARP sample could also account for the lower predictive power. There is also the possibility that information on psychosis history may be easily overlooked or unreported (Milne *et al.*, 2009) in the SHARP sample due to the lack of psychiatric resources available to the older generation and the stigma attached to diagnostic labels (Roy *et al.*, 1996).

Interestingly, the current study found that CHRs with lower severity ratings on dysphoric mood (G2) in SIPS general symptoms had a significantly higher transition risk than CHRs with higher severity ratings. This finding is inconsistent with many previous studies (Fusar-Poli *et al.*, 2014; Kline *et al.*, 2018), which found that baseline mood disturbance is associated with impaired global functioning and poor prognosis but had no effect on risk of transition to full psychosis. However, previous studies had not included other variables, such as dysphoric mood, as a protective factor for predicting psychosis. This is not entirely unexpected given that mood disturbances are not essential to the onset of psychosis. CHR cases with a high level of dysphoric mood may be caused by the high level of anxiety and fear toward the recent onset of attenuated psychotic symptoms, suggesting that a better insight into these abnormal experiences. Nevertheless, the G2 dysphoric mood item selected from SIPS only illustrates certain partial information on emotional instability and irritability, leading to difficulties in reflecting the complete features of mood status or mood disorders.

The strengths of this study include its longitudinal design and its status as a pioneer in developing and validating the first individualized psychosis RC based on the Chinese clinical population, which comprises one fifth of the world's population. In this study, a relatively large sample was followed up on a medium- and long-term basis (1–6 years), with a relatively low lost follow-up rate. However, several limitations of this study must be considered. First, although our independent sample showed that the SIPS-RC performed quite well in psychosis prediction, it must be tested and replicated using other external datasets, especially in samples from different countries. Moreover, the limited number of CHRs in the validation sample ($n = 91$) especially for converters ($n = 10$), the shorter follow-up (1 year), and poor match of the severity levels of clinical symptoms with the development sample might reduce the statistical power on the validity of SIPS-RC. Second, although the SIPS-RC developed in this study does not include biological variables, due to our aim of simplicity and validity for a wide range of cases, future studies must include biomarkers in the RC to improve the performance of psychosis prediction. Third, the SIPS-RC was designed only to predict conversion to psychosis, and does not cover the CHR-identified individuals who did not convert to psychosis but have poor functional outcomes in the real world. van Os and Guloksuz (2017) argued that the full range of person-specific psychopathology must be considered for CHR youth, rather than linking CHR/ultra-high risk (UHR) and conversion to a transdiagnostic dimension of psychosis. Finally, as the SIPS scores are at the core of the model, the SIPS-RC must only be used in settings in which clinicians have had rigorous SIPS training, limiting its implementation to the non-clinic-based populations. However, the clinical use of the SIPS-RC will depend in part on its sensitivity and specificity, how clinicians think about its utility and accuracy, the language that clinicians use to explain scores, and the motivation and ability on the part of the patient and family to use this information. Future studies should test how patients, families, or treatment providers use or indeed desire such information.

## Conclusion

The data reported in this study confirm that the developed SIPS-RC is well-performing, widely compatible, and easily applicable to almost all SIPS-identified CHR cases, as well as to clinical services and research. The SIPS-RC appears to have the potential to determine the probability that a CHR individual will develop psychosis, and it may provide a foundation for individualized early intervention in the CHR population.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718002738.

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**Conflict of interest.** None.

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