Baseline PANSS Symptoms Predict Relapse Risk in Placebo-Treated Patients

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5
placebo-controlled relapse-prevention trials

557
placebo-randomized participants

HR 1.06 p = .05
per 1-point higher baseline PANSS Positive score

HR 0.94 p = .01
per 1-point higher baseline PANSS Negative score

METHODOLOGICAL ISSUE ADDRESSED

Identifying baseline symptom criteria that predict relapse is important for both schizophrenia trial design and clinical practice.

Depending on a trial's objective, enrollment criteria should either:

- select patients at **sufficient relapse risk** to detect a relapse-prevention effect, or
- select **lower-risk patients** in negative symptom or cognition studies.

Clarifying which baseline symptoms predict time to relapse could refine eligibility criteria and improve trial efficiency.

INTRODUCTION

We aimed to determine whether baseline **psychopathology**, measured on entry into double-blind treatment, predicts **survival time to relapse** among patients randomized to **placebo** in antipsychotic relapse-prevention studies.

We examined the independent associations of positive, negative, and general psychopathology symptoms with relapse risk.

METHODS

Data source
Individual-patient data on placebo-randomized participants from **five placebo-controlled relapse-prevention studies** with a double-blind phase of at least **6 months**, obtained through **Vivli** and **YODA**.

Sample
Placebo-randomized participants, **n = 557**.

Outcome
Survival time to relapse. Relapse was defined as a **12-point increase on PANSS total score** as per Siafis et al., 2024.

Statistical analysis
Cox proportional-hazards regression. Predictors were PANSS Positive, Negative, and General Psychopathology subscale scores, age, and sex.

RESULTS

- Higher baseline **positive** symptoms were associated with **increased** relapse risk (HR = 1.06, p = .05).
- Higher baseline **negative** symptoms were associated with **decreased** relapse risk (HR = 0.94, p = .01).
- Age and sex were retained as covariates.

Baseline predictor	HR	p
PANSS Positive	1.06	.05
PANSS Negative	0.94	.01

Table 1. Cox proportional-hazards model: baseline PANSS subscale scores and time to relapse. Hazard ratios are per 1-point higher baseline score. Age and sex were retained as covariates.

Hazard ratio per 1-point higher baseline score (95% CI)

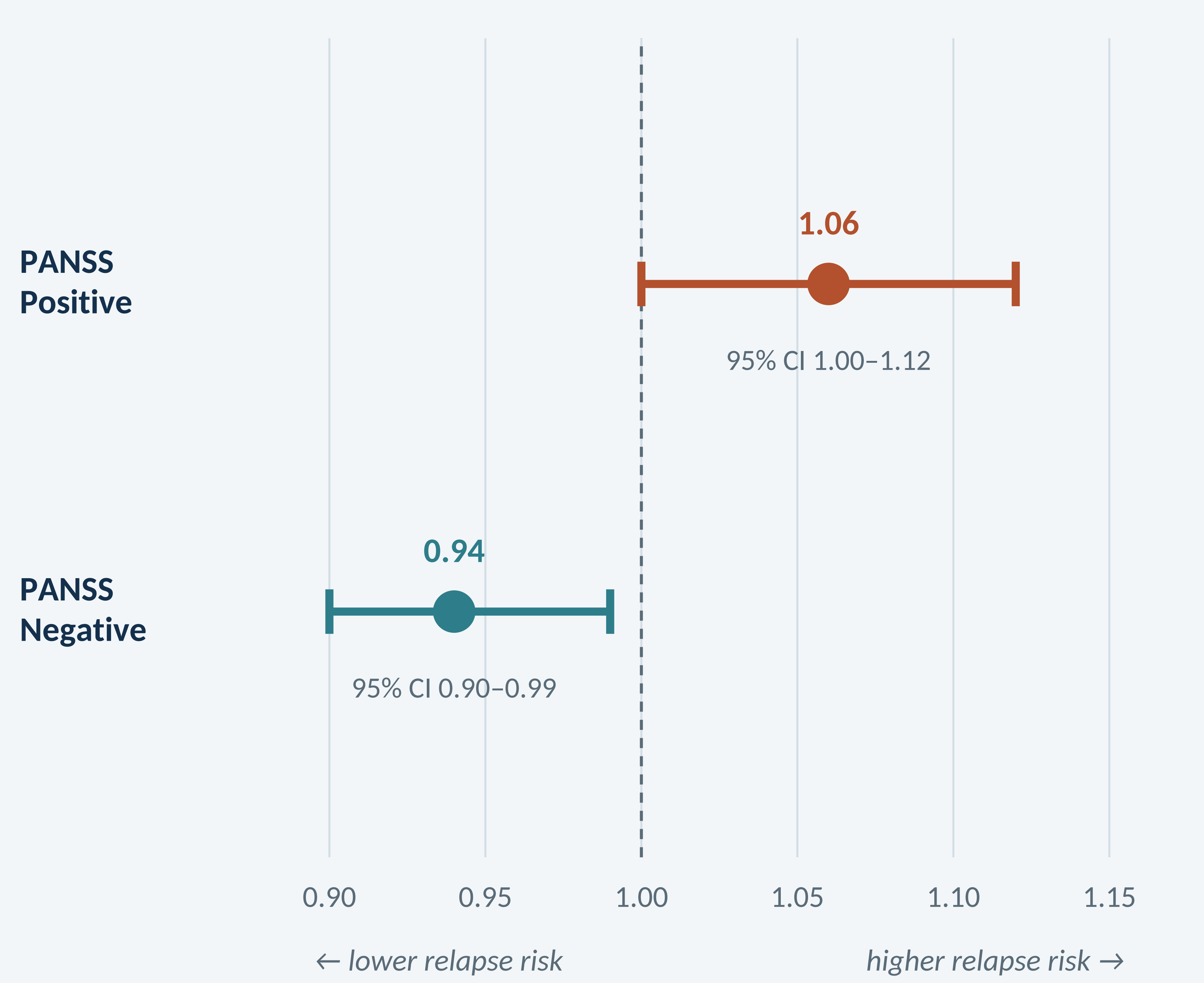

PANSS Positive
1.06
95% CI 1.00–1.12
PANSS Negative
0.94
95% CI 0.90–0.99
0.90
0.95
1.00
1.05
1.10
1.15
← lower relapse risk
higher relapse risk →

Figure 1. Hazard ratios with 95% confidence intervals. Points to the right of 1.0 indicate higher relapse risk; points to the left indicate lower relapse risk. Confidence intervals are derived from the reported hazard ratios and p-values.

MODEL-IMPLIED EFFECT SIZE

Model-implied hazard ratio by score difference

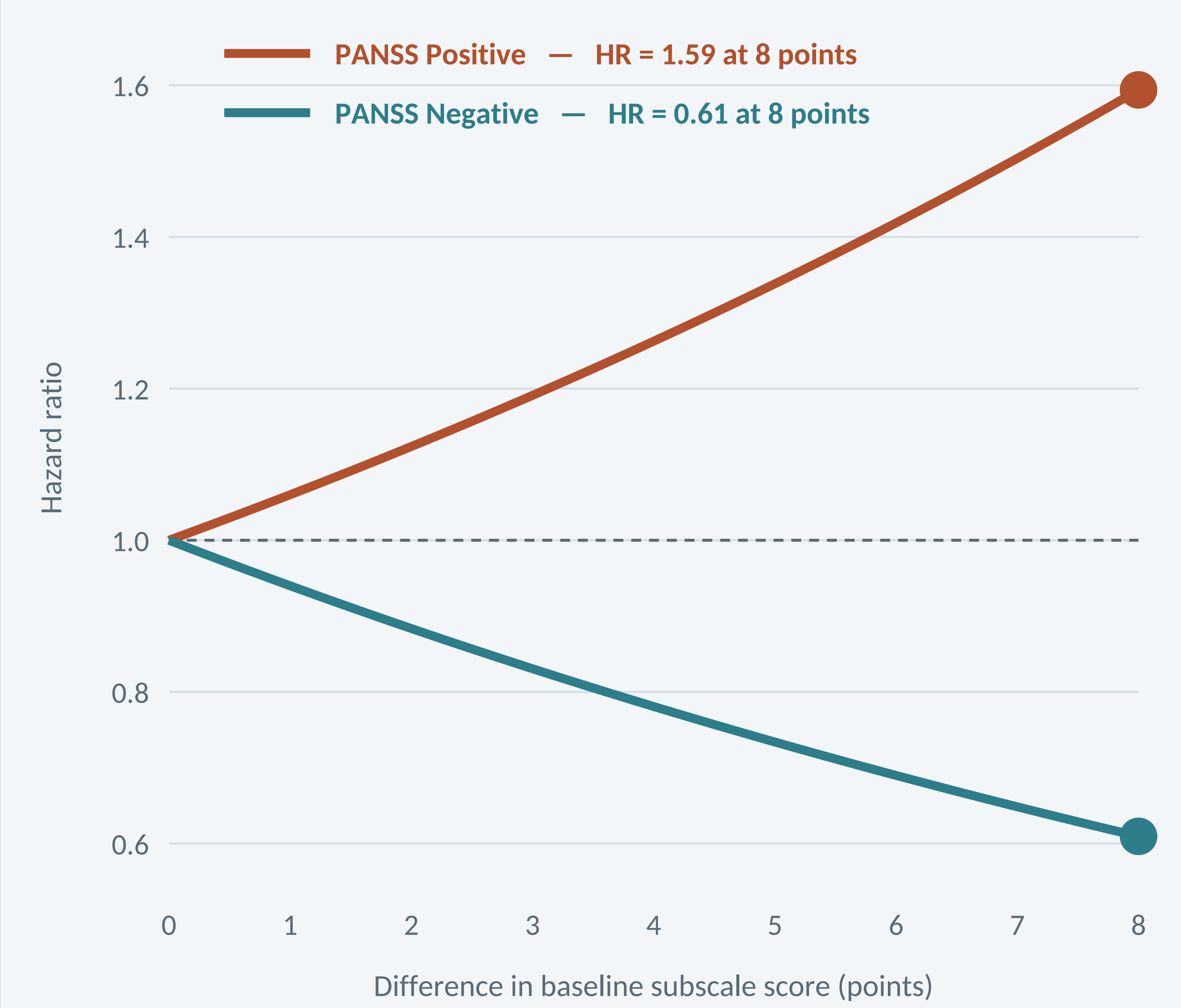

PANSS Positive — HR = 1.59 at 8 points
PANSS Negative — HR = 0.61 at 8 points
Hazard ratio
1.6
1.4
1.2
1.0
0.8
0.6
0
1
2
3
4
5
6
7
8
Difference in baseline subscale score (points)

Figure 2. Hazard ratios implied by the model in Table 1 for between-patient differences of 1–8 points on a baseline subscale, holding other covariates constant.

CONSIDERATIONS FOR TRIAL DESIGN

Relapse-prevention trials
Selecting patients with **higher baseline positive** and **lower baseline negative** symptoms may yield a sample at greater relapse risk, which is needed to detect a relapse-prevention effect.

Negative symptom or cognition trials
The opposite baseline profile may identify a **lower-risk sample**, in which relapse is a competing event rather than the outcome of interest.

These directions are hypothesis-generating and require prospective testing before they are used as eligibility criteria.

CONCLUSIONS

- Among placebo-treated patients, baseline symptom profiles predicted relapse risk in **opposing directions**: positive symptoms increased risk, whereas negative symptoms appeared protective.
- Baseline PANSS Positive and Negative subscale scores may help refine **eligibility and enrichment criteria** in clinical trials and improve trial efficiency.
- **Prospective validation is warranted.**

LIMITATIONS

- Post-hoc analysis of pooled data from previously completed trials that differed in design, duration, and relapse ascertainment.
- Relapse was operationalized by a single PANSS-based criterion (a 12-point increase on the total score).
- Analyses were restricted to the placebo-randomized subsample; findings may not generalize to actively treated patients.
- Associations are observational within randomized arms and are not causal.

ACKNOWLEDGMENTS AND DATA SOURCE

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REFERENCE

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Disclosures

One or more authors report potential conflicts which are described in the program