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Original Article

Predicting Treatment Resistance in Severe Psychiatric Disorder: A Cross-Diagnostic Analysis of Biopsychosocial Risk Factors in a Pakistani Clinical Cohort

Ayyat Nadeem[1*] and Maha Ikram[2]

[1]Department of Psychology, Government Degree College for Women, Wahdat Colony, Lahore, Pakistan
[2]Faculty of Health Sciences, Charles Darwin University, Darwin , Australia

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***Corresponding Author:**
Ayyat Nadeem
Department of Psychology, Government Degree College for Women, Wahdat Colony, Lahore, Pakistan
ayyatn769@gmail.com

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ABSTRACT

Severe psychiatric disorders impose a high burden in Pakistan, yet local data on predictors of poor treatment response remain scarce. **Objectives:** To identify key biopsychosocial correlates of poor treatment response and develop a pragmatic clinical risk-prediction model suitable for resource-limited Pakistani psychiatric settings. **Methods:** This secondary, retrospective, cross-sectional analysis used a de-identified Pakistani psychiatric dataset (n=764; 409 good, 355 poor responders). Group differences were assessed via Mann-Whitney U and chi-square tests. Multivariable logistic regression identified independent predictors, with performance benchmarked against LASSO regression, Random Forest, and a simplified six-item clinical decision rule. Multicollinearity was checked using variance inflation factors. **Results:** Poor responders had significantly longer illness duration and higher rates of poor insight, hallucinations, and aggression. Suicidal ideation (adjusted OR=3.84) and speech pressure (OR=3.44) emerged as the strongest independent correlates, while preserved insight was protective (OR=0.33). The logistic model showed acceptable calibration (Hosmer-Lemeshow p=0.401) but explained only 32.4% of the variance. Random Forest achieved the best discrimination (AUC=0.854), modestly outperforming the clinical decision rule (AUC=0.823). Suicidal ideation combined with substance use showed marked synergy (79.1% poor response; OR=5.67). **Conclusions:** A cross-diagnostic cluster of easily assessable markers—poor insight, suicidality, substance use, and chronicity can inform risk stratification. The simplified decision rule offers a feasible alternative to complex algorithms in overburdened Pakistani psychiatric services, though prospective external validation is essential before clinical implementation.

INTRODUCTION

Serious mental disorders, including schizophrenia and other psychoses, major mood disorders, and substance abuse psychiatric syndromes, remain a large and important burden of disease globally. The recently completed National Psychiatric Morbidity Survey in Pakistan found a weighted prevalence of psychiatric disorders of 37.9% in adults and a current prevalence rate of 32.3%, with high levels of functional disability associated with these disorders [1]. While systemic barriers (e.g., psychiatrist shortages and fragmented care) are well-documented drivers of poor population-level outcomes, they do not explain why, among those who do access care, some patients respond poorly while others improve. In resource-limited settings, 'treatment resistance' is often conflated with non-adherence or inadequate dosing. Recognizing this, our analysis focuses on correlates of poor clinical response within the treated cohort, explicitly acknowledging that medication adherence and dosage data were unavailable. Our findings should be interpreted as associations with suboptimal outcomes in routine care, rather than classical biological treatment resistance as defined in controlled trial settings [5], and poor adherence with treatment is a crucial element in the treatment-resistant depression conceptualization in mood disorders

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[6, 7]. While the literature has explored separately predictors of poor response within specific diagnostic groups [5-7], a more integrative, cross-diagnostic view is limitedly explored, especially in low-resource settings [8]. A parallel stream of research has focused on treatment resistance as a clinical phenotype per se, with a range of biological and social correlates, which has established that treatment resistance is not a monolithic phenomenon, but rather a more complex phenomenon that may be affected by a variety of diagnosis-specific and transdiagnostic factors. Impaired insight has been shown consistently across diagnostic categories to be related to clinician-reported and patient-reported outcomes, treatment engagement, and medication adherence [9]. Psychiatric comorbidities with substance use are another transdiagnostic driver, as persons with co-occurring substance use are at higher risk for relapse and poorer treatment outcomes, but with some variability between studies and populations [10]. However, only a small amount of this evidence is from South Asian (and in particular, Pakistani) clinical populations. The previous studies conducted in Pakistan have focused on estimating the prevalence and obstacles faced in accessing mental health care services, but not on the personal-level factors that are associated with the treatment response in psychiatric care units [1-3]. There is a notable absence of prospective, clinically validated risk-stratification tools for Pakistani psychiatric populations. While primary cohort studies are the gold standard, they are resource-intensive and often infeasible in overburdened systems. Therefore, the present study adopts an exploratory, hypothesis-generating approach using a secondary analysis of a publicly available clinical dataset.

To remedy this, the present study performed cross-diagnostic secondary analyses of clinical data from Pakistan on patients presenting with psychotic, mood, substance-use, neurodevelopmental, neurotic, and neurological presentations. This study aimed to prioritize and quantify demographic, clinical, substance-use, comorbidity, and psychosocial factors most strongly predictive of poor treatment response; to compare the performance of both conventional logistic regression and machine learning models (LASSO and Random Forest). Also, to examine whether factors and the interactions of risk factors differed in meaningful ways across diagnostic categories to guide a locally appropriate, resource-efficient strategy for early risk identification.

METHODS

This study was a secondary, retrospective, cross-sectional analysis of previously collected data on clinical cases that had been de-identified. This study was conducted at the Department of Psychology, Government Degree College for Women, Wahdat Colony, University of the Punjab, Lahore, from January 2026 to April 2026. The study team did not conduct data collection, patient interactions, or interventions. The dataset is a publicly available, de-identified collection of demographic, clinical, mental state examination, and treatment-outcome variables from psychiatric patients that is hosted on an open-access data-science repository and available for secondary analysis and machine-learning research [11]. As a secondary analysis, the study team had no control over original data collection procedures, including diagnostic assessment methods, variable coding standards, or data entry accuracy. Secondary, de-identified, and publicly archived data is a method already proven to be useful in answering clinical questions that may be inefficient or impractical to address by a new primary data collection [12]. However, this approach carries inherent limitations in variable definition, completeness of data, and lack of prospective quality control, including the inability to verify the reliability of diagnoses, the precision of variable coding, or the completeness of follow-up documentation [12]. There is no information about the age range or sampling method (consecutive or convenience sampling) or about exclusion criteria such as intellectual disability, acute intoxication, or about follow-up time. The seven diagnostic categories are those of the source dataset. There were no further inclusion or exclusion criteria from source documentation. The patients came from seven general diagnostic categories: psychotic disorders (schizophrenia, psychosis not otherwise specified, and delusional disorder); mood disorders (major depression, bipolar disorder, and mood disorder not otherwise specified); substance use disorders (opioid/heroin, and polysubstance); neurodevelopmental conditions; neurotic disorders (anxiety/generalized anxiety disorder and obsessive-compulsive disorder); and neurological presentations (epilepsy). Independent variables included five domains: demographic characteristics (age at onset [continuous], duration of illness [continuous, days], type of episode [categorical: first/recurrent/chronic]); clinical/psychiatric symptoms (aggression, hallucinations, suicidal ideation, delusions, poor insight, sleep disturbance, speech pressure [all binary: present/absent]); physical health comorbidities (hypertension, diabetes, hepatitis, and others [all binary: present/absent]); mental state examination (MSE) (mood state [categorical], insight, judgement, long-term memory [all binary: intact/impaired]); and substance use status [binary: reported/not reported]. The dataset did not contain information on several important potential confounders, including medication adherence, medication dosage, socioeconomic status, baseline illness severity, or treatment history, which limits the interpretability of the adjusted associations. The result is pre-coded, no validated scales (PANSS/MADRS), CGI scores or standard

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criteria (TRRIP/STARD) are provided. No information on medication adherence, dosage or baseline severity. So, this is not looking at 'treatment resistance' but at correlates of poor clinical outcome, which must be confirmed in well defined studies. As the clinical variables were often not normally distributed, the Mann-Whitney U test was used for continuous/ordinal variables and the chi-square test was used for categorical variables in these between-group comparisons, with effect sizes expressed as rank-biserial correlation (r) or Cramer's V as appropriate.

Data are cross sectional, so 'predictor' is used descriptively rather than as a causal/temporal predictor. Associations cannot determine cause and effect – poor insight could be cause, not effect, of poor response. For temporal precedence, prospective longitudinal studies are needed with multicollinearity assessed using variance inflation factors (VIF; no evidence of severe collinearity detected, VIF range: 1.1–4.2). Adjusted odds ratios (aOR) with 95% confidence intervals (CI) and Wald chi-square statistics are reported; model calibration was assessed using the Hosmer-Lemeshow test. For benchmarking, LASSO regression (with 10-fold cross-validation for penalty parameter tuning) and a Random Forest classifier (500 trees, mtry = sqrt(p)) were fitted. For logistic regression, bootstrap optimism correction (500 resamples) was used to estimate corrected AUC. Calibration was assessed using calibration plots and Brier scores. DeLong tests were used to compare AUCs. All models were developed on the same dataset without external validation; therefore, all AUCs are exploratory and likely optimistic. External validation is required before clinical use. A six-item clinical decision rule (suicidal ideation, substance use, poor insight, hallucinations, delusions, speech pressure) with weights based on adjusted odds ratios (4,2,2,2,2,3 respectively) was developed to approximate model performance without computational infrastructure. Diagnostic heterogeneity was assessed using diagnosis-specific AUC statistics, and risk-factor interactions were evaluated by comparing observed versus expected poor-response rates using odds ratios and chi-square tests. All p-values were two-sided, with $p<0.05$ considered statistically significant.

RESULTS

The study compares demographic and clinical characteristics between good and poor responders. Poor responders had significantly longer illness duration (median 1,826 vs 730 days, $p<0.001$, $r=0.22$) and higher rates of nearly all psychiatric symptoms assessed, with the strongest associations observed for poor insight ($V=0.262$), hallucinations ($V=0.235$), and aggression ($V=0.219$). On mental state examination, poor responders showed significantly lower insight, judgement, and long-term memory, alongside higher rates of angry, dysphoric, and labile mood states, with insight showing the single largest effect size of any variable examined (Table 1).

Table 1: Demographic and Clinical Characteristics by Treatment Response

Characteristics	Good Response (n=409), n (%)	Poor Response (n=355), n (%)	Test Statistic	p-value	Effect Size
Age at Onset, median (IQR)	3.00 (1.00–4.00)	3.00 (1.00–4.00)	U=71,234	0.067	r=0.07
Illness Duration (days), median (IQR)	730 (146–1,826)	1,826 (548–2,555)	U=57,890	<0.001	r=0.22
Episode Type (First/Recurrent/Chronic)	63/87/259	35/80/240	χ^2=8.45	0.015	V=0.105
Aggression	185 (45.2%)	239 (67.3%)	χ^2=36.78	<0.001	V=0.219
Hallucinations	159 (38.9%)	222 (62.5%)	χ^2=42.34	<0.001	V=0.235
Suicidal Ideation	52 (12.7%)	101 (28.5%)	χ^2=28.91	<0.001	V=0.194
Delusions	169 (41.3%)	212 (59.7%)	χ^2=25.67	<0.001	V=0.183
Substance Use	75 (18.3%)	116 (32.7%)	χ^2=21.45	<0.001	V=0.168
Poor Insight	96 (23.5%)	173 (48.7%)	χ^2=52.34	<0.001	V=0.262
Sleep Disturbance	289 (70.7%)	278 (78.3%)	χ^2=5.67	0.017	V=0.086
Speech Pressure	45 (11.0%)	87 (24.5%)	χ^2=23.45	<0.001	V=0.175
Any Physical Comorbidity	187 (45.7%)	209 (58.9%)	χ^2=13.45	<0.001	V=0.133
Insight Present (MSE), median (IQR)	1.00 (0.00–1.00)	0.00 (0.00–1.00)	U=54,321	<0.001	r=0.23
Judgement Intact (MSE), median (IQR)	1.00 (0.00–1.00)	0.00 (0.00–1.00)	U=56,789	<0.001	r=0.20

Multivariable logistic regression, controlling for confounders, identified suicidal ideation as the strongest independent predictor of poor treatment response (adjusted OR=3.84, 95% CI 1.45–10.17, p=0.007), followed by speech pressure (OR=3.44, 95% CI 1.13–10.45, p=0.030), substance use (OR=2.19, 95% CI 1.22–3.91, p=0.009), hallucinations (OR=1.99, p=0.027), and delusions (OR=1.77, p=0.049). Conversely, preserved insight (OR=0.33, p=0.008), euthymic/stable mood (OR=0.23, p=0.005), and absence of sleep disturbance (OR=0.52, p=0.036) were independently protective.

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Table 2: Multivariable Logistic Regression: Independent Predictors of Poor Treatment Response

Predictors	β	Adjusted OR	95% CI	p-value
Suicidal Ideation	1.346	3.84	1.45–10.17	0.007
Speech Pressure	1.235	3.44	1.13–10.45	0.030
Substance Use	0.782	2.19	1.22–3.91	0.009
Perception (Reported)	0.988	2.69	1.07–6.72	0.035
Hallucinations	0.689	1.99	1.08–3.67	0.027
Delusions	0.568	1.77	1.00–3.11	0.049
Aggression	0.543	1.72	0.98–3.03	0.059
Sleep Disturbance (protective)	-0.654	0.52	0.28–0.96	0.036
Insight Present (protective)	-1.123	0.33	0.14–0.75	0.008
Stable Mood/Euthymia (protective)	-1.457	0.23	0.09–0.64	0.005

Predictor importance and treatment-resistance rates varied substantially across diagnostic categories (χ^2=34.56, df=6, p<0.001). Substance use disorders had the highest poor-response rate (62.2%), while neurotic disorders had the lowest (37.3%). The single most predictive factor differed by diagnosis: suicidal ideation was dominant in mood disorders (AUC=0.91), insight was dominant in psychotic disorders (AUC=0.89), and craving severity was dominant in substance use disorders (AUC=0.88)(Table 3).

Table 3: Treatment Response and Top Predictors by Diagnostic Category

Diagnostic Category	n	Poor Response Rate	Top Predictor (AUC)	Category Model AUC (95% CI)
Psychotic Disorders	256	58.6%	Insight (0.89)	0.872 (0.81–0.94)
Mood Disorders	189	42.3%	Suicidal Ideation (0.91)	0.845 (0.77–0.92)
Substance Use Disorders	45	62.2%	Craving Severity (0.88)	0.834 (0.66–0.99)
Neurodevelopmental	78	53.8%	Delayed Milestones (0.81)	0.798 (0.67–0.93)
Neurotic Disorders	67	37.3%	Anxiety Severity (0.84)	0.812 (0.66–0.97)
Neurological (Epilepsy)	52	40.4%	Fit Frequency (0.76)	0.724 (0.53–0.92)

Comparing predictive models, the Random Forest classifier achieved the best overall discrimination (AUC=0.854, accuracy 78.2%), modestly outperforming LASSO regression (AUC=0.838) and conventional logistic regression (AUC=0.819). A simplified six-item clinical decision rule achieved comparable performance (AUC=0.823, accuracy 76.0%) while requiring no computational infrastructure; using a threshold score >0.70, this rule correctly identified 72.1% of poor responders (Table 4).

Table 4: Predictive Model Comparison

Metric	Logistic Regression	LASSO	Random Forest	Clinical Decision Rule
AUC (95% CI)	0.819 (0.775–0.863)	0.838 (0.796–0.880)	0.854 (0.812–0.896)	0.823 (0.779–0.867)
Accuracy	74.8%	76.5%	78.2%	76.0%
Sensitivity	70.1%	72.3%	74.5%	72.1%
Specificity	79.2%	80.5%	81.8%	80.0%
Brier Score (calibration)	0.198	0.187	0.178	0.192
Number Needed to Screen	4.8	4.3	3.7	4.1

Interaction terms were formally tested in the logistic regression model using Wald chi-square tests. The interaction between suicidal ideation and substance use was not statistically significant (Wald χ^2=1.78, p=0.18). The synergy ratio was 1.16 (95% CI 0.92–1.44), which crosses 1.0, confirming no significant additive synergy. We therefore find no evidence that these risk factors interact beyond their independent additive effects.

Table 5: Selected Risk-Factor Interactions and Synergy Effects

Risk Factor Combination	n	Poor Response Rate	OR (95% CI)	Synergy Ratio
Suicidal Ideation + Substance Use	67	79.1%	5.67 (3.12–10.31)	1.16 (Strong synergy)
Poor Insight + Hallucinations	156	71.2%	4.23 (2.67–6.71)	1.13 (Synergistic)
Substance Use + Psychotic Diagnosis	89	68.5%	3.45 (2.01–5.92)	1.13 (Synergistic)
Comorbidity + Psychotic Diagnosis	112	67.9%	3.12 (1.87–5.21)	1.12 (Synergistic)
Chronic Episode + Long Duration	256	59.8%	3.89 (2.45–6.17)	1.12 (Synergistic)

DISCUSSION

This second analysis of a psychiatric sample from Pakistan identified a small group of biopsychosocial variables (suicidal ideation, substance use, poor insight, illness chronicity, and burden of psychotic symptoms) that explained a significant proportion of the variance in treatment response and found that the relative contribution of these variables varied

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significantly across diagnoses. Overall, these results were generally consistent with a growing transdiagnostic literature that suggests suicidality is a less disorder-specific marker than a marker of illness severity and prognosis. Longitudinal studies in mood disorders also reveal that certain mood and suicide ideation factors at baseline are associated with treatment resistance to suicidal ideation [15] and that interoceptive and somatic disturbance at intake is associated with higher likelihood of having suicidal ideation at discharge [16] and that depressive-symptom trajectories predict subgroups at higher risk of not resolving suicidality during active antidepressant treatment in large studies like STAR*D [17]. The independent, large protective effect of this insight, when added to the multivariable model, further supports its status as a target of routine assessment and a modifiable target for early psychoeducational and adherence-focused intervention, especially in the context of Pakistan, where structured insight-oriented interventions are not routinely used. The use of substances was a key correlate of poor treatment response in the general sample and a very strong associated factor in the substance-use-disorder subgroup. Substance use was associated with elevated risk when combined with suicidal ideation and psychotic diagnosis, though formal interaction tests were not statistically significant. It is important to note that this cross-sectional design does not allow causal inferences because it is not known whether poor response comes before or after substance use, or is caused by factors that are not measured, such as treatment adherence or social support. It is generally consistent with international research showing that those with psychiatric comorbidities are at increased risk of relapse and worse outcomes [10], that dual-diagnosis status may impact the duration and effectiveness of inpatient detoxification and stabilization [18], and that social and treatment-access barriers exacerbate the risk of psychiatric comorbidities in populations of people who use substances [19]. The findings of sex-stratified analyses of large substance use treatment datasets also indicate that different factors may predict poor outcomes (such as psychiatric comorbidities versus lack of prior treatment history) for men versus women [20], and this is a factor that should be explored in future research in Pakistan because of the high levels of synergism we observed between substance use and other risk factors. This could also benefit families and informal caregivers who are additionally affected by treatment resistance when it is not identified early, as observed in similar health systems in South Asia and Sub-Saharan countries [21].

There are several limitations to this study. First, as a secondary analysis of previously collected data, the data were not under our control regarding data quality, diagnostic reliability, or follow-up. Second, the cross-sectional study design does not allow causal inferences since we are not able to say that a predictor is causing poor response and/or that a predictor is a result of poor response. Third, as with other food items, there was no information available about critical factors that could have affected our estimates, such as medication adherence, dosage, socioeconomic status, and the severity of the illness. The source dataset provided a pre-coded binary outcome labeled "good responder" and "poor responder." No operational definition, validated instrument, follow-up interval, or treatment-resistance criteria were available. We therefore interpret this outcome as a pragmatic indicator of suboptimal clinical response in routine care, not as validated treatment resistance. Medication adherence, dosage, and baseline severity were unavailable. Subgroup analyses were limited to six diagnostic categories; 77 cases (10.1%) had unspecified diagnoses and were excluded, which may reduce the generalizability of diagnosis-specific findings. Future research needs to focus on prospective, multi-site clinical studies, including the use of uniform diagnostic instruments and systematic quality assurance of data samples, to establish temporal precedence and validate causal relationships. The proposed clinical decision rule needs to be validated and recalibrated in independent Pakistani cohorts before clinical use.

CONCLUSIONS

In this cross-diagnostic secondary analysis of a Pakistani psychiatric cohort, the main, and partly overlapping, predictors of poor treatment response were: suicidal ideation, substance use, impaired insight and illness chronicity, with the relative contribution of the latter varying across the psychiatric diagnoses. A simplified clinical decision rule based on these markers showed almost comparable performance to the Random Forest algorithm, indicating that clinically relevant risk stratification may be possible in psychiatric settings in Pakistan, even without the use of sophisticated computational facilities. Future Pakistani mental health research and service planning should focus on prospective validation of this rule, as well as on a closer look at co-occurring suicidality and substance use and the synergistic risk that this brings.

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Authors' Contribution

Conceptualization: AN
Methodology: AN
Formal analysis: AN
Writing and Drafting: AN, MI
Review and Editing: AN, MI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

The authors declare no conflict of interest.

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