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1. Identification of Biomarkers for early prediction of thymic or psychotic trajectories following First-Episode Psychosis

Introduction

Psychosis, a symptom complex, appears in disorders like schizophrenia, bipolar disorder, and major depression, significantly impacting the quality of life. The DSM-5 classifies psychotic disorders by delusions, hallucinations, disorganized thinking, abnormal motor behavior, and negative symptoms, but this framework does not capture the varied clinical trajectories of these disorders. First Episode Psychosis (FEP) lacks a universal definition. It is typically diagnosed upon initial psychosis without prior history, excluding substance-induced causes, though some cases involve delays in care and diagnosis during relapses. The main challenge for clinicians is differentiating between psychosis related to mood disorders (unipolar or bipolar) and non-affective psychosis, such as schizophrenia spectrum disorders. This diagnostic instability complicates treatment, as mood disorders require thymoregulatory treatment and non-affective psychoses need atypical antipsychotics.[1] Prognostic studies show that over half of FEP patients do not reach remission. A key factor is the Duration of Untreated Psychosis (DUP), with shorter DUP linked to better outcomes.[2] Biomarker development is crucial for early prediction of FEP progression, supporting more accurate diagnoses, classification of phenotypes, and personalized treatment strategies to predict efficacy and minimize side effects.[1] So, this review aimed to identify and prioritize biomarkers from existing literature for investigation, with a focus on their potential use in the early prediction of progression from FEP to mood or psychotic disorders.

Methods

In this systematic review, the literature review was conducted across four databases—PubMed, Scopus, PsycINFO, and Web of Science—as per PRISMA guidelines. Search terms related to FEP and biomarkers were used. Included studies involved biological sampling from FEP cohorts, assessing one or more biomarkers to differentiate progression to affective or non-affective psychosis. The risk of bias for each study was evaluated using the QUADAS-2 tool. Data extracted included biostatistical measures (e.g., sensitivity, specificity, Receiver Operating Characteristic (ROC) analyses) and statistically significant findings on biomarkers that may differentiate subgroups or have prognostic value regarding disease progression in FEP samples.

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Results

Eight studies were included in the final analysis. Several biomarkers demonstrated promising discriminatory potential for predicting post-FEP evolution, including interleukins IL-6, IL-12p40, and IL-1β, as well as mRNA expression levels of the DICER-1 and AKT-1 genes. Broad-spectrum approaches in other studies also identified potential leads for additional biomarkers. One study examined plasma cytokine levels in 75 FEP patients, with affective trajectory assessed at a 12-month follow-up. Most participants were receiving pharmacological treatment at the time of biological sampling, which occurred within the first year of symptom onset (Table 1).

Study	**Study sample**	**Biomarkers studied**	**Result**	**Biomarkers significance**
Cytokine alterations in first-episode schizophrenia and bipolar disorder: Relationships to brain structure and symptoms.[3]	HC (n = 53); First-episode schizophrenia patients (SZ, n = 69); First-episode bipolar patients with psychotic features (BD, n = 16).	IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IFN-γ, and TNF-α	No significant differences between BD and SZ groups. The trend of higher IL-10 levels among the BD group. The trend of higher IL-2, IL-1β, IL-6, and IFNγ among the schizophrenia group.	IL-10 is an anti-inflammatory cytokine. IL-2, IL-6, IL-1β are pro-inflammatory cytokines.

Table 1: Plasma circulating cytokines levels

Discussion

Emerging biomarkers, including mRNA expression of AKT1 and DICER1 genes, and levels of IL-6, IL-12p40, and IL-1β, show potential for predicting post-FEP trajectories.[1] Hughes et al. found significantly lower levels of IL-12p40, IL-1β, IL-6, TNF-α, and MIP-1β in non-affective FEP patients after LPS stimulation. ROC analysis revealed strong predictive value for IL-6 (AUC = 0.9571), IL-12p40 (AUC = 0.9154), and IL-1β (AUC = 0.8000), suggesting these inflammatory markers could help differentiate progression to affective or non-affective psychosis.[4]

Conclusion

The current study underscores the importance of replicating research focused on the predictive value of various biological markers in FEP. Two key leads emerged from the analysis: genetic markers, specifically mRNA expression of the AKT1 and DICER1 genes, and inflammatory markers, including IL-6, IL-12p40, and IL-1β, which show potential in predicting thymic trajectory following a first psychotic episode. Furthermore, it is crucial to standardize methodologies across studies and prioritize the development of predictive models incorporating multiple biomarkers to strengthen their statistical significance and clinical applicability.

Standardizing methodologies and integrating multiple biomarkers into predictive models will enhance their clinical relevance and accuracy, ultimately improving early intervention strategies for first-episode psychosis.

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2. Impact of behavioral health clinic on patient care outcomes

Introduction

Fragmentation in mental health services, such as inadequate primary care and outpatient follow-up, significantly impacts patient care.[1] Behavioral health crises, marked by severe distress due to mental health or substance use disorders, often require emergency intervention. Notably, one in eight emergency department (ED) visits is for a behavioral health crisis, which can be effectively managed in community-based behavioral health crisis care services.[2] To address these barriers, an innovative community-based behavioral health clinic (BHC) was established as the first facility in the state to offer both urgent care and facility-based crisis services. Funded by multiple sources, including government, private insurers, and a contracted health system, the clinic provides critical services such as individual therapy, crisis stabilization, partial hospitalization, substance abuse intensive outpatient services, specialized group therapy, medication management (including long-acting injectable antipsychotic (LAI) administration), and a peer living room.[1] This study assessed the impact of the BHC on length of stay (LOS), psychiatric rehospitalization rates, and all-cause ED visits. In addition, it analyzed how various patient characteristics interact with these primary outcomes.

Methods

This retrospective cohort study was conducted within a community-based health system where the medical records of adult patients who experienced psychiatric hospitalization both before and following the establishment of the behavioral health clinic (BHC) were reviewed. Data collected included patient demographics (age, gender, race, ethnicity), health insurance status, psychiatric diagnoses, medication history, and behavioral health encounters within one-year post-discharge from the index psychiatric hospitalization. Primary outcomes were analyzed using Chi-Square and Mann-Whitney U tests, while secondary outcomes were evaluated through Poisson and logistic regression models. The study was deemed exempt from review by both the health system and university institutional review boards.

Results

A total of 1,069 patients met the inclusion criteria, with 501 in the pre-BHC cohort and 568 in the post-BHC cohort. Following the establishment of the BHC, the mean length of stay (LOS) significantly increased by 1.26 days. Additionally, there was a statistically significant reduction in rehospitalization rates at 30 days (-10.3%) and 1 year (-28.2%), as well as a decrease in emergency

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department (ED) visit rates at 30 days (-8.3%) and 1 year (-13.5%) (Table 1). A diagnosis of schizophrenia and the prescription of LAI were associated with a significant increase in LOS, while being uninsured was linked to a significant decrease in LOS. Male gender and a diagnosis of schizophrenia were associated with a significant increase in ED visits, whereas identification as White or Caucasian, being uninsured or having private insurance, and receiving a prescription for an LAI were associated with a significant decrease in ED visits.

Outcome	2019 (*N* = 501)	2022 (*N* = 568)
Index psychiatric hospitalization mean LOS	5.26 days	6.52 days
30-day mean number of ED visits	2.13	1.83
1-year mean number of ED visits	5.53	4.76
30-day rehospitalization rate	21.4%	11.1%
1-year rehospitalization rate	81.4%	53.2%
30-day ED visit rate	34.5%	26.2%
1-year ED visit rate	81.8%	68.3%

LOS = length of stay, ED = emergency department, [a] Wilcoxon Rank Sum test, [b] Chi-Square test with df = 1

Table 1. Patient outcomes before and after the creation of BHC

Discussion

The study's subgroup analysis revealed that, in comparison to White or Caucasian patients, Black or African American patients saw significantly greater ED visits over the year after their index psychiatric hospitalization.[1] This result is in line with data from the U.S. Department of Health and Human Services, which showed that between 2018 and 2020, non-Hispanic Black individuals had greater rates of ED visits for mental health issues than non-Hispanic White adults.[3] Furthermore, this cohort's higher ED visits were associated with male gender and diagnoses of substance use disorder (SUD) or schizophrenia. These findings align with a Canadian study that discovered comparable patterns in mentally ill people.[4]

Conclusion

The current study concluded that the community-based BHC effectively decreases psychiatric hospitalizations and ED visits by offering accessible outpatient crisis management services. Identifying key patient characteristics that influence these outcomes can help optimize care and prevent unnecessary inpatient admissions.

The community-based Behavioral Health Clinic (BHC) reduces psychiatric hospitalizations and ED visits by providing accessible outpatient crisis services.

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3. Prevalence of Depression and Anxiety Among Individuals with Chronic Pain

Introduction

Chronic pain (CP), defined as pain persisting for over three months, is a prevalent and debilitating condition affecting approximately 21% of adults.[1] While various medical and psychological interventions provide limited pain relief, CP frequently coexists with depression and anxiety, further complicating patients' health outcomes. Notably, CP, alongside depression and anxiety, both major risk factors for suicidal ideation and attempts, is recognized by the World Health Organization (WHO) as a significant contributor to suicide risk.[2] Depression and anxiety are leading causes of disability worldwide, negatively impacting quality of life and life expectancy. Population-based studies estimate that 20% to 40% of adults with CP experience these mental health conditions; however, prevalence rates vary widely across studies and pain conditions. Despite their high burden, treatment options remain scarce, and individuals with comorbid mental health conditions are often excluded from chronic pain clinics and clinical trials.[1] A comprehensive systematic review and meta-analysis are essential to accurately assess the global prevalence of depression and anxiety among adults with CP. So, this study assessed the prevalence rates and identified factors that influence variability, ultimately guiding public health strategies and informing treatment development to improve outcomes for individuals with CP.

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Methods

In this systematic review and meta-analysis, a literature search of MEDLINE, Embase, PsycINFO, and the Cochrane Library identified 31,159 records, with 5,177 full-text articles screened and included studies reported the prevalence of depression or anxiety using validated assessment tools among adults with chronic pain (excluding chronic headache disorders). Following the PRISMA guidelines, data extraction was conducted via Covidence. Two independent reviewers performed screening, full-text review, data extraction, and risk-of-bias assessment. Random-effects meta-analyses were used to pool prevalence estimates, assess moderators, and compare prevalence rates between chronic pain and control groups. Identified moderators included pain condition, recruitment setting, continent, age, sex distribution, and pain duration.

Results

A systematic review of 376 studies from 50 countries included 347,468 individuals with chronic pain (mean age: 51.3 ± 9.5 years; 70.0% female). The prevalence of clinical symptoms of depression and anxiety was 39.3% (95% CI, 37.3%-41.1%; I^2 = 98.9%) and 40.2% (95% CI, 38.0%-42.4%;I^2 = 99.0%), respectively, with variation across pain conditions and the highest rates observed among younger individuals (Figure 1). Diagnostically, 36.7% (95% CI, 29.0%-45.1%) met criteria for major depressive disorder, while 16.7% (95% CI, 11.8%-23.2%) had generalized anxiety disorder. Depression and anxiety were more prevalent among women, younger individuals, and those with nociplastic pain. Additionally, assessment type was significantly associated with the prevalence of depression symptoms, anxiety symptoms, generalized anxiety disorder, and panic disorder.

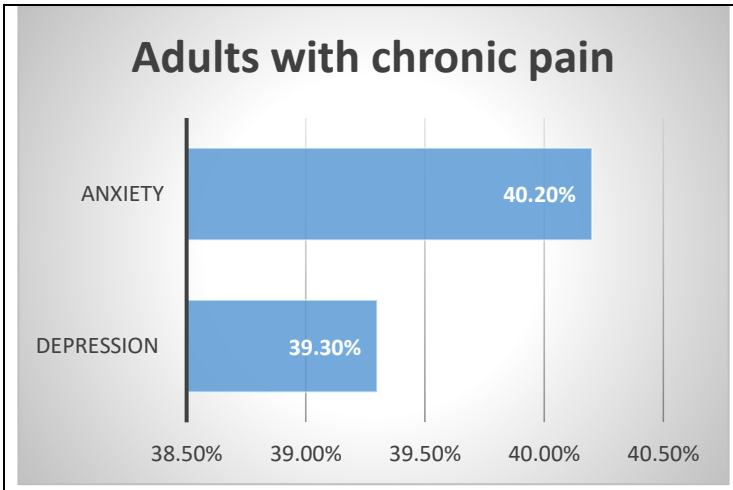

Figure 1: Prevalence of Clinical Symptoms of depression and anxiety

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Discussion

This study found high rates of depression (39.3%) and anxiety (40.2%) among adults with chronic pain, with prevalence highest in younger individuals, women, and those with nociplastic pain.[1] Similarly, Dudeney et al. reported increased anxiety (34.6%) and depression (12.2%) among youth with chronic pain, with symptoms exceeding clinical thresholds in 23.9% and 23.5%, respectively.[3] Both studies highlight the significant mental health burden of chronic pain, emphasizing the need for targeted interventions, particularly for younger individuals and high-risk groups.

Conclusion

This meta-analysis found that 40% of adults with chronic pain experience clinically significant depression and anxiety, with higher prevalence in women, younger individuals, and those with nociplastic pain. These findings highlight the need for routine screening, equitable access to care, and innovative treatments.

Adults who were younger, female, and with nociplastic pain were more likely to have co-occurring chronic pain and depression or anxiety.

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4. Case Report on Psychosis in a Middle-Aged Man with Primary Hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is commonly associated with symptoms such as urolithiasis, osteopenia, osteoporosis, abdominal cramping, peptic ulceration, and psychiatric manifestations including depression, anxiety, cognitive dysfunction, insomnia, confusion, and behavioral changes. While mild hypercalcemia (<12 mg/dL) may cause subtle symptoms like cognitive changes or anxiety, more severe hypercalcemia can lead to altered mental status or psychosis.[1] Mild hypercalcemia is often asymptomatic but increasingly detected through routine calcium screening. Notably, psychiatric symptoms can occur even in mild cases, and these do not always correlate with calcium levels. Older patients tend to develop more frequent and severe psychiatric manifestations compared to younger individuals.[2] This case report describes a middle-aged patient with mild hypercalcemic PHPT, whose psychotic symptoms resolved following parathyroidectomy. This highlights the importance of considering PHPT in the differential diagnosis of psychosis, regardless of age, and suggests that surgical intervention should be considered if psychosis persists despite medical treatment.

Case presentation

A 48-year-old male with no prior history of physical or mental health issues, substance use, or familial psychiatric conditions was admitted for psychiatric evaluation following the onset of paranoia about a suspicious vehicle in his neighborhood, which he believed was associated with a reported crime. Initial evaluations suggested paranoid schizophrenia. On admission, he presented with agitation and persistent fears for his family's safety, without hallucinations. He remained alert and oriented, with no physical symptoms. Treatment with Aripiprazole 6 mg/day was initiated. Laboratory findings revealed mild hypercalcemia (serum calcium 11.5 mg/dL; normal range 9.2–10.6 mg/dL) and slightly low phosphate levels (serum phosphate 2.9 mg/dL; normal range 3.0–4.9 mg/dL). Liver, kidney, and thyroid functions were within normal limits, but elevated parathyroid hormone (PTH)-intact levels of 106 pg/mL (normal range 11.0–67.0 pg/mL) indicated hyperparathyroidism (Table 1).

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Despite treatment with 80 U/day of Elcatonin via intramuscular injection for one week, hypercalcemia persisted. During the 8-day hospitalization, his condition fluctuated, and he developed disorientation, agitation, and delirium, necessitating transfer to a tertiary care center for further evaluation. At the tertiary facility, laboratory tests confirmed persistent hypercalcemia and elevated PTH levels. Hypercalcemia was not attributed to other factors. Diagnostic imaging, including a 99mTc-methoxyisobutylisonitrile scintigraphy and contrast-enhanced CT, identified an abnormality in the left inferior parathyroid gland, confirming a diagnosis of PHPT. No abnormalities were observed in the thyroid or pituitary glands. His bone mineral density was 0.882 g/cm² at lumbar vertebrae 2–4, with a T-score of −1.2, indicating osteopenia and prompting surgical consideration.

Laboratory results	Value	Normal range
Albumin (g/dL)	3.8	3.7–4.7
Total serum calcium (mg/dL)	11.1	9.2–10.6
Phosphorus (mg/dL)	3.3	3.0–4.9
PTH-intact (pg/mL)	106	11.0–67.0
1,25 dihydroxy vitamin D_3 (pg/mL)	41.9	
PTHrP (pmol/L)	< 1.0	0–1.1

Abbreviation: PTHrP, parathyroid hormone-related protein.

Table 1: Patient's Laboratory Results Upon Hospital Admission

Treatment with alendronate (5 mg/day) reduced serum calcium levels to 10.5 mg/dL, resulting in an improvement in his disorientation and altered mental state. Although calcium levels remained within normal range, PTH levels remained elevated (104 pg/mL), and paranoid delusions persisted over the subsequent 4 weeks. A left inferior parathyroidectomy was performed, revealing a parathyroid adenoma. Postoperative recovery included normalization of serum calcium (9.3 mg/dL) and PTH (14.3 pg/mL). The patient's delusions resolved within 10 days, and his aripiprazole dosage was reduced to 3 mg/day, eventually being discontinued after 3 years without recurrence of psychiatric symptoms. His aggressive behavior, attributed to PHPT-induced psychosis, was not prosecuted, and the patient has been symptom-free for more than a decade.

Discussion

PHPT should be considered in the differential diagnosis of acute changes in mental state, particularly in older adults. This is crucial because PHPT is treatable, and addressing the underlying condition can resolve psychiatric symptoms, potentially avoiding long-term antipsychotic use and its associated risks.[3] The relationship between hyperparathyroidism, hypercalcemia, and neuropsychiatric symptoms, including psychosis, is complex. While the exact pathophysiology remains unclear,

recognizing this association is vital for timely diagnosis and management. Early identification and appropriate endocrine intervention can significantly improve patient outcomes.[1]

Conclusion

This case underscores the importance of considering PHPT in patients of all ages presenting with psychosis, even in the presence of mild hypercalcemia. When medical management proves ineffective, surgical intervention should be considered as a viable treatment option for PHPT.

Mild serum calcium elevations can cause significant psychiatric disturbances, emphasizing the need for a thorough endocrine evaluation in new-onset psychosis.

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