

The association between comorbid psychiatric diagnoses and hospitalization-related factors among individuals with schizophrenia

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ABSTRACT

Background: Though schizophrenia is associated with substantial psychiatric comorbidity, data pertaining to multiple comorbid psychiatric disorders among individuals with schizophrenia is missing. Furthermore, despite abundant research indicating that the course of schizophrenia is characterized by relapses, often leading to psychiatric emergency room visits and consequent hospitalizations, data regarding the association between different comorbid psychiatric diagnoses among schizophrenia patients, and these hospitalization-related factors is lacking. The aim of this study was to describe the number and types of comorbid psychiatric diagnoses of inpatients diagnosed with schizophrenia, and to explore whether these are associated with hospitalization-related factors. **Methods:** Registry data from the years 1997–2017 was analyzed from a large psychiatric hospital database. We compared the annual mean number of psychiatric emergency room visits and hospitalizations, as well as mean length of hospitalizations, among individuals with schizophrenia and no additional psychiatric diagnosis, to those with one or more comorbid psychiatric diagnoses. Furthermore, we compared these hospitalization-related based on the different types of the comorbid diagnoses.

Results: Among inpatient individuals with schizophrenia, the greater the number of comorbid psychiatric diagnoses, the higher the increase in number of emergency room visits and hospitalizations, as well as in the mean length of hospitalizations. Furthermore, all comorbid psychiatric disorders explored were found to be associated with an increase in the mentioned hospital-related factors. Such diagnoses include substance use disorders, bipolar, personality and depressive disorders, which were the most common disorders associated with schizophrenia.

Conclusions: Comorbid psychiatric disorders among inpatients with schizophrenia are associated with greater utilization of hospital-related services. These comorbid disorders should be addressed in the assessment and treatment of patients suffering from schizophrenia.

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1. Introduction

Mental disorders consist of a heterogeneous group of problems, defined by different symptoms, usually related to abnormality of thought, emotion, behavior and relationships [1]. Examples of major mental disorders include schizophrenia, bipolar disorder and depression. Mental disorders are highly prevalent worldwide, have been associated with substantial disability and present a leading cause of global burden of disease [2,3]. Schizophrenia is a highly disabling disorder, leading to impairment in cognitive, social and occupational functioning,

and posing a health and economic burden on patients, their families and society [4,5]. The estimated lifetime prevalence of the disease is 0.3%–1% [2,6]. Psychiatric comorbidity (i.e., the presence of two or more concurrent psychiatric disorders) has a wide effect on diagnosis, treatment and prognosis of psychiatric disorders [7]. Schizophrenia is associated with substantial psychiatric comorbidity [8–11]; it has been suggested about 50% of schizophrenia patients suffer from an additional psychiatric disorder [10–12]. The most common comorbid psychiatric disorders among these patients include depression, substance use disorders, obsessive-compulsive disorder and anxiety disorders [6,9–11]. All major psychiatric disorders among individuals with schizophrenia have been linked with poorer mental health, more severe psychopathology, lower quality of life, worse prognosis, and are seen as a contributor to the high rate of morbidity and mortality among these patients [9–11].

Despite findings regarding the detrimental effects of comorbid psychiatric disorders among schizophrenia patients, the majority of studies focus on one specific comorbidity [11], without taking into account complexities associated with several concurrent comorbidities. Numerous

Abbreviations: SUDs, substance use disorders; OCD, obsessive-compulsive disorder; LOS, length of stay; ICD-10, International Classification of Diseases Tenth revision; ER, emergency room; ANOVA, Analysis of Variance; ANCOVA, Analysis of Covariance; IRB, Institutional Review Board.

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studies have explored the comorbidity between schizophrenia and substance use disorders (SUDs) [9,13,14], depression [9,11], panic disorders [9,15] and obsessive-compulsive disorder (OCD) [11,15]. To a lesser extent, comorbid manic episodes [13], personality disorders [13] and mental retardation [16] have been explored.

The course of schizophrenia is usually chronic, and characterized by relapses of psychotic symptoms [2,17], which may lead to psychiatric hospitalizations. The relapses are associated with deteriorating function, refractoriness to future treatment and an increase in the overall costs of hospitalizations [2,18–21]. Several predictors for rehospitalizations among schizophrenia patients have been identified. These included nonadherence with antipsychotic treatment [22–25], illness severity [26–28], longer duration of illness [29] and number of previous hospitalizations [28,30]. Comorbidities with SUDs [24] well as depressive symptoms [9] have also been linked with relapse or rehospitalizations among these individuals. Data linking additional comorbid diagnoses with rehospitalizations is scarce, as is data regarding the number of comorbid psychiatric diagnoses and this outcome among schizophrenia patients.

Predictors of the length of stay (LOS) during hospitalizations among psychiatric patients have also been explored in numerous studies. Several factors have been found to be associated with longer LOS, such as homelessness [31], unemployment [32] and larger hospital size [33]. Diagnostic correlates of LOS include a diagnosis of a psychotic disorder [34], mood disorders and SUDs [35]. Despite this, little has been published regarding determinants of LOS specifically among individuals with schizophrenia. While available research indicates that wide community-based services [36], female gender [37] and treatment with long-acting antipsychotics were associated with shorter LOS, the role of psychiatric comorbidities as a potential determinant has gained little attention.

While it has been shown that schizophrenia patients present high utilizers of psychiatric emergency services [38–40], aside from SUDs [38,41], little is known regarding the correlation between various comorbid psychiatric diagnoses and the pattern of emergency room visits among schizophrenia patients.

The aim of this study was to explore: a) the number and types of comorbid psychiatric diagnoses among psychiatric inpatients suffering from schizophrenia; b) the association between comorbid psychiatric diagnoses and the number and length of hospitalizations among individuals with schizophrenia and c) the association between comorbid psychiatric diagnoses and emergency room visits among individuals with schizophrenia.

2. Methods

2.1. Study population

The Israeli mental health services consist of outpatient clinics, rehabilitation services and psychiatric hospitalization services. The psychiatric hospitalization system is comprised of 14 psychiatric hospitals and 12 psychiatric departments in general hospitals. The hospitalization services are provided as inpatient care or day hospitalization [42]. All psychiatric services in Israel, both inpatient and outpatient, are provided through the public health services and covered by one of the four Health Maintenance Organizations (HMOs) in Israel.

In this study, registry data was analyzed from a large psychiatric hospital database. Lev-Hasharon is government psychiatric hospital in the center of Israel, serving a catchment area of 500,000 residents. The hospital has a 260-bed capacity with 4 acute inpatient units and 4 chronic units, each housing approximately 35 patients. We analyzed data from records of inpatients hospitalized between June 1997–June 2017. The records were drawn from the central hospital database, which includes basic registry data regarding each hospitalization for every patient, since 1997 (the year the computer-based database was developed). For each patient, the personal data was analyzed

from their first to latest full hospitalization within the 20-year span (i.e., ongoing hospitalizations were not included).

We included patients aged 18–65 who were assigned a diagnosis of schizophrenia (ICD-10 code F20, including subtypes) or schizoaffective disorder (F25, including subtypes) at discharge any time during the 20-year span (designated in our study as “schizophrenia”). The following additional major psychiatric diagnoses were included, and allocated to diagnostic groups as follows: organic, including symptomatic, mental disorders (ICD-10 codes F00–F09; “organic disorders”); mental and behavioral disorders due to psychoactive substance use (F10–F19; “substance use disorders”); manic episode and bipolar affective disorder (F31–F32; “bipolar disorders”); depressive episode and recurrent depressive disorder (F33–F34; “depressive disorders”); phobic and other anxiety disorders (F40–F41; “anxiety disorders”); obsessive-compulsive disorder (F42); post-traumatic stress disorder (F43.1); eating disorders (F50); specific, mixed and other personality disorders (F60–F61, “personality disorders”); habit and impulse disorders (F63); mental retardation (F70–F79); pervasive developmental disorders (F84); hyperkinetic disorders (F90) and mental disorder, not otherwise specified (F99).

All diagnoses were made by senior staff psychiatrists, based on International Classification of Disease tenth edition (ICD-10) criteria.

2.2. Variables

The following sociodemographic data was extracted from patient's records: gender, age, marital status, country of birth and employment status. All sociodemographic data was derived from the first hospitalization of the patient within the 20-year range explored. Hospitalization-related factors (total and annual mean) included: number of hospitalizations, number of hospitalization days and number of psychiatric emergency room (ER) visits. This was done for each subject by dividing the total number of hospitalizations, number of hospitalization days and number of psychiatric ER visits by the number of years from first to last full hospitalization during study period (e.g., for a patient with 5 hospitalization from 2000 to 2010, the total hospitalizations for this patient is 5, and the mean annual number of hospitalizations is 0.5 (= 5 / 10).

It has been shown that among high utilizers of psychiatric emergency services, frequent visits usually end with discharge [43]. In order to explore emergency service utilization among the studied subjects, we analyzed their patterns of discharge from the ER, by dividing them categorically into two groups, that were assumed to represent lower and higher utilizers of psychiatric emergency services: 1. Number of ER visits never followed by discharge (i.e. every ER visit followed by hospitalization, representing justified visits from lower utilizing subjects), and 2. ER visits followed by either hospitalization or discharge (the option of discharge led to the inclusion of the higher utilizing subjects). Each subject was allocated to one of the two groups, and the pattern of ER utilization was further explored by describing the two groups' distribution among the number of comorbid diagnoses.

2.3. Study design

First, we compared hospitalization-related factors based on the number of comorbid diagnoses (in addition to schizophrenia) subjects had: schizophrenia and no comorbid diagnosis, schizophrenia + 1 comorbid diagnosis, schizophrenia + 2 comorbid diagnoses, schizophrenia + 3 or more comorbid diagnoses. Second, we compared hospitalization-related factors based on the type of comorbid diagnoses (e.g., schizophrenia + depression, schizophrenia + anxiety disorders, etc.), comparing each group with those who were diagnosed with schizophrenia only. The comorbid diagnoses included were: organic disorders, SUDs, bipolar disorders, depressive disorders, OCD, personality disorders and mental retardation. These categories were based on paired comorbid psychiatric diagnoses and not exclusive, which may have resulted in overlap between the subjects in the different groups (i.e., individuals

with schizophrenia, depression and an anxiety disorder were included both in the “schizophrenia + depression” category as well as in the “schizophrenia + anxiety disorder” category. In all cases, individuals with schizophrenia and no comorbid diagnosis served as the reference group. Categories with 30 or less patients were excluded, as a minimum of 30 subjects is an acceptable minimal group size used in parametric tests [44,45].

2.4. Statistical analysis

Descriptive statistics were used to describe the sociodemographic variables, and a Chi square test or one-way Analysis of Variance (ANOVA) were performed to compare the data between groups of patients according to the number of comorbid psychiatric diagnoses. Sociodemographic data that was found to differ significantly between the groups was controlled for using an Analysis of Covariance (ANCOVA) or logistic regression. A one-way ANOVA was performed to compare annual means (number of hospitalizations, number of hospitalization days and psychiatric ER visits) between the groups according to their number of comorbid diagnoses. Multiple *t*-tests were conducted to compare the same annual means between groups with a principal comorbid diagnosis to the group of patients with no comorbid diagnosis. In cases in which variables were not normally distributed, a natural log transformation was applied, and statistical analyses were performed on the transformed data. In these cases, we reported median values. When the assumption of homogeneity of variance (according to Levene's test) was violated, we used the Welch-F-ratio, an appropriate *p* value was reported, and a post-hoc analysis was done using the Games-Howell method. Due to multiple *t*-tests performed in the last part of the study (comparison of hospitalization-related factors based on type of comorbid diagnoses), a Bonferroni correction was conducted, resulting in a new *p*-value of <0.007 ($0.05/7 = 0.007$). Since a *p*-value < 0.001 is more common in scientific papers and is also more conservative, we chose this to be the *p*-value applied. We then uniformly applied this same *p*-value to the rest of the analyses in the study. All analyses were performed using SPSS version 23 for windows.

2.5. Ethics

The study was approved by the local Institutional Review Board (IRB).

3. Results

3.1. Sociodemographic characteristics

The sample included a total of 3637 schizophrenia patients, which comprised 49.2% of the initial population drawn from the registry data ($n = 7387$). The distribution of sociodemographic characteristics according to number of comorbid diagnoses are shown in Table 1. The

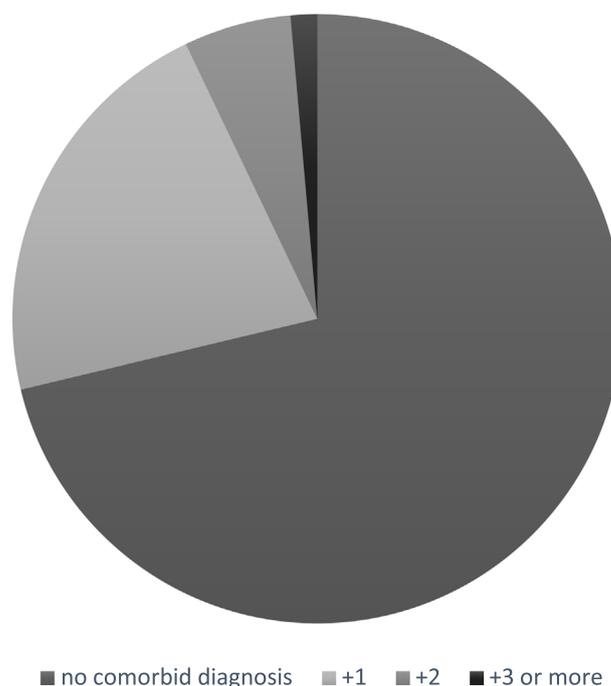


Fig. 1. Frequency of patients according to number of comorbid psychiatric diagnoses beyond schizophrenia. +1, one comorbid diagnosis beyond schizophrenia; +2, two comorbid diagnoses; +3 or more, three comorbid diagnoses or more.

majority of patients were male (66.6%), and the mean age at the first hospitalization was 36.52 years ($SD = 12.59$). The mean age of first hospitalization for patients diagnosed with schizophrenia was significantly older than those with one or more comorbid diagnosis. Most patients were divorced or widowed (86.6%), born in Israel (63.8%), and unemployed (79.3%) at the time of first hospitalization.

3.2. Number and type of diagnoses

Fig. 1 shows the frequency of comorbid diagnoses among individuals in the study. Among all subjects, 71.3% of the patients had schizophrenia without any comorbid diagnosis, 21.6% had one comorbid diagnosis, 5.7% had two comorbid diagnoses, and 1.4% had three or more comorbid diagnoses. Of the patients with one additional diagnosis, the most prevalent diagnoses were SUDs (49.4%) followed by bipolar disorder (17.5%). Of the patients with two additional diagnoses, the most prevalent diagnosis combination was SUDs and personality disorders (31.4%), and of the patients with three or more additional diagnoses, the most prevalent diagnosis combination was SUDs, bipolar and personality disorders (19.6%).

Table 1
Sociodemographic characteristics according to number of diagnoses beyond schizophrenia.

	NCD ^a	+1	+2	+3 or more	Chi square/ANOVA	<i>p</i> value
Age at first hospitalization (Mean, SD)	37.59 (12.65)	34.34 (12.18)	32.61 (11.55)	31.73 (11.54)	ANOVA	<0.001
Sex, n (%)					Chi square	0.002
	Male	1684 (65)	555 (70.5)	153 (73.9)		
	Female	908 (35)	232 (29.5)	54 (26.1)		
Marital status, n (%)					Chi square	0.375
	Married	221 (10.5)	54 (9.3)	18 (10.7)		
	Divorced/widowed	1820 (86.3)	506 (87.4)	147 (87.5)		
	Single	64 (3.0)	19 (3.3)	3 (1.8)		
Country of birth, n (%)					Chi square	0.143
	Israel	1625 (62.7)	520 (66.1)	142 (68.6)		
	Other	967 (37.3)	267 (33.9)	65 (31.4)		
Employment status, n (%)					Chi square	0.729
	Working or studying	546 (21.1)	160 (20.4)	38 (18.4)		
	Unemployed or retired	2040 (78.9)	636 (79.6)	169 (81.6)		

+1, one comorbid diagnosis beyond schizophrenia; +2, two comorbid diagnoses; +3 or more, three comorbid diagnoses or more. ANOVA, Analysis of Variance; SD, standard deviation.

^a NCD = no comorbid diagnosis.

3.3. Comparison of hospitalization-related factors based on number of comorbid diagnoses

The greater the number of comorbid diagnoses, the greater the mean annual number of hospitalizations was (Fig. 2a), the longer the average

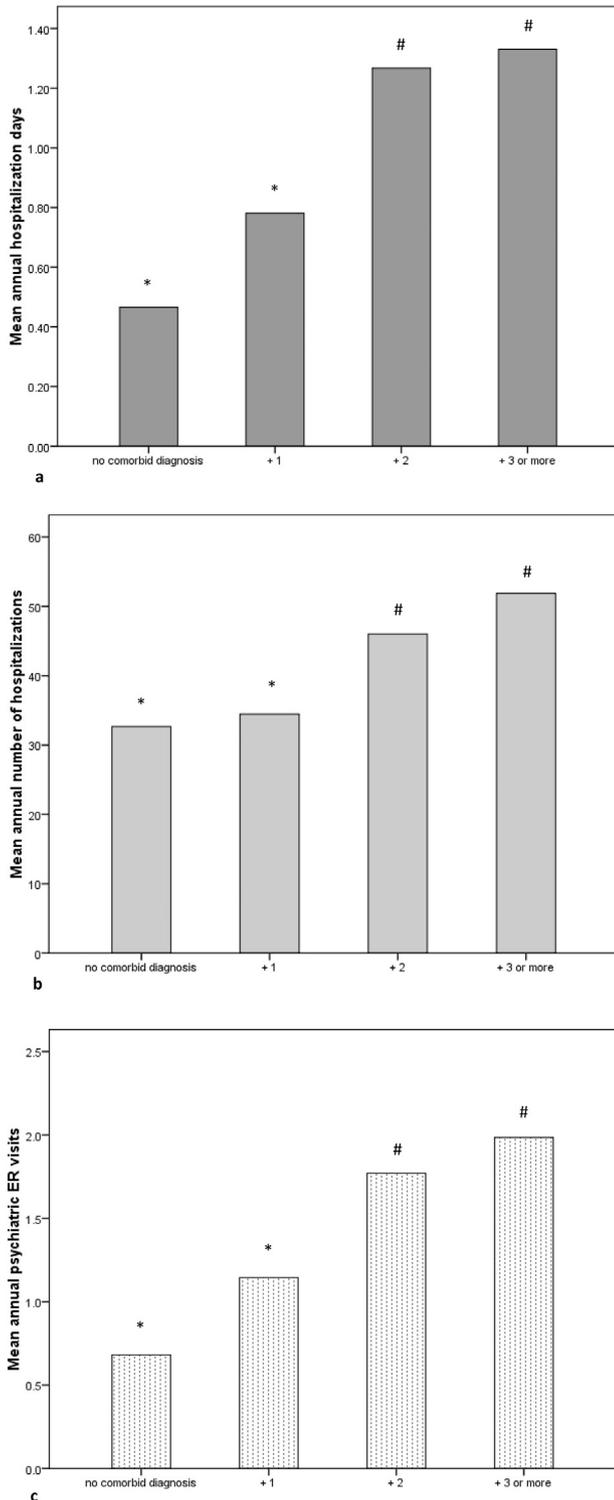


Fig. 2. Comparison of hospitalization-related factors based on number of comorbid diagnoses: mean annual number of hospitalizations (a), mean annual length of hospitalizations (in days) (b) and mean annual number of psychiatric emergency room visits (c). +1, one comorbid diagnosis beyond schizophrenia; +2, two comorbid diagnoses; +3 or more, three comorbid diagnoses or more. Abbreviations: ER, Emergency room. * = Significant difference from all other groups ($p < 0.001$). # = Significant difference from “no comorbid diagnosis” and “+1”.

length of the hospitalizations (Fig. 2b) and the greater the mean annual number of psychiatric ER visits (Fig. 2c) ($p < 0.001$ for all comparisons). Results remained significant after controlling for age and gender. The median number of hospitalizations per year for patients with schizophrenia and no comorbid diagnosis was 0.22 (CI 95% 0.21–0.23), while that of patients with one, two or three or more diagnoses were 0.49 (CI 95% 0.44–0.54), 0.71 (CI 95% 0.65–0.84) and 1.11 (CI 95% 0.85–1.53), respectively. The median length of hospitalizations (in days) per year for patients with schizophrenia and no comorbid diagnosis was 10.97 (CI 95%: 10.08–11.89), while that of patients with one, two or three or more diagnoses were 18.06 (CI 95% 16.05–19.78), 30.67 (CI 95% 24.28–37.0) and 42.32 (CI 95% 33.93–59.89), respectively. The median number of psychiatric ER visits per year for patients with schizophrenia and no comorbid diagnosis was 0.31 (CI 95%: 0.30–0.33), while that of patients with one, two or three or more diagnoses were 0.70 (CI 95%: 0.64–0.79), 1.06 (CI 95%: 0.92–1.31) and 1.79 (CI 95%: 1.45–2.08), respectively.

In addition, the greater the number of comorbid diagnoses, the greater percent of patients who visited the ER and may have been discharged thereafter (as opposed to being hospitalized after every visit) (Fig. 3). No comorbid diagnosis: 51.9%, one additional diagnosis: 64.2%, two additional diagnoses: 77.3%, three or more additional diagnoses: 90.2%. The relation between these variables was significant, $\chi^2 (3, N = 3637) = 100.87, p < 0.001$, and remained significant after controlling for age and gender.

3.4. Comparison of hospitalization-related factors based on type of comorbid diagnoses

Seven groups of principal comorbid diagnoses were identified: SUDs (15.1%), bipolar disorders (6%), personality disorders (4%), depressive disorders (3.5%), organic disorders (2.8%), mental retardation (2.6%), and OCD (1.7%). All diagnoses beyond schizophrenia were associated with significant increase in the mean annual number of hospitalizations (Fig. 4a), length of hospitalizations (Fig. 4b) and number of psychiatric ER visits (Fig. 4c), when compared to patients with schizophrenia and no comorbid diagnosis.

4. Discussion

We explored the association between comorbid psychiatric diagnoses among individuals with schizophrenia and hospitalization-related factors. All comorbid psychiatric disorders explored were found to be associated with an increase in the mean number and length of psychiatric hospitalizations as well as with the mean number of psychiatric emergency room visits. In addition, we found that the greater the number of comorbid diagnoses, the higher this increase among all hospitalization-related factors explored.

Psychiatric comorbidities among psychiatric patients are a highly prevalent phenomenon, associated with higher level of disease severity [46]. Despite this, data regarding the specific correlation between comorbidities among major diagnoses and hospitalization measures are scant. Among patients with major depression, it was found that anxiety disorders, PTSD and alcohol abuse were associated with a greater risk for hospitalization, and that the greater the number of comorbidities, the greater the risk for hospitalization [47]. Bipolar disorder is highly comorbid with other psychiatric disorders [46,48], yet other than SUDs, which were correlated with more hospitalizations among bipolar patients [49], the clear association to hospitalization factors has not been outlined.

We found that almost one third of schizophrenia patients had at least one additional psychiatric diagnosis. Psychiatric comorbidity among schizophrenia has been shown to be a prevalent phenomenon [9,10,12,13] that may be partially responsible for the clinical heterogeneity of the disease [50]. A number of studies have shown that about 50% percent of schizophrenia patients suffer from an additional diagnosis

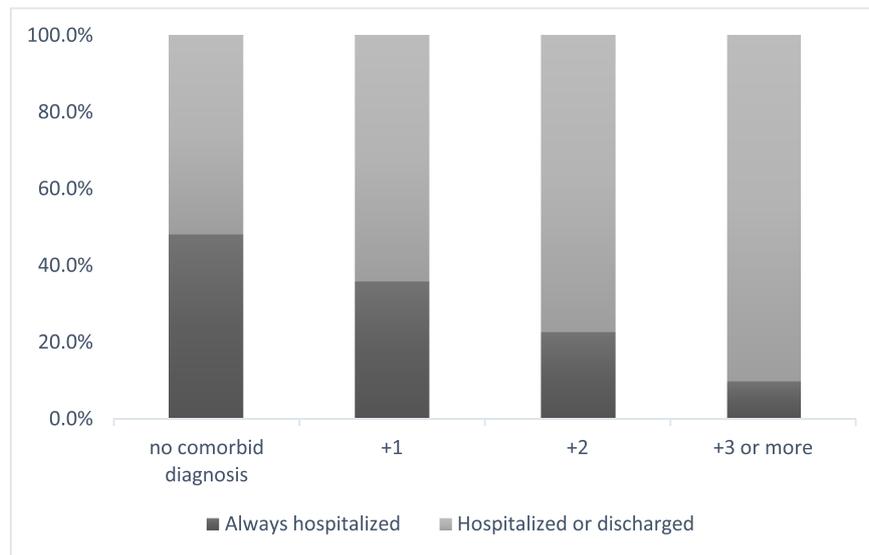


Fig. 3. Consequences of psychiatric emergency room visit according to number of diagnoses. +1, one comorbid diagnosis beyond schizophrenia; +2, two comorbid diagnoses; +3 or more, three comorbid diagnoses or more.

[10–12]. To our knowledge, studies exploring multiple comorbidities among schizophrenia patients are lacking, yet a prevalence of 13.5%–29% was described for schizophrenia and two other additional diagnoses [8,12]. The prevalence of comorbid psychiatric disorders in our study were lower than the abovementioned studies. One plausible explanation for this discrepancy may be associated with the use of registry-based data; perhaps there has been under-diagnosis of additional psychiatric comorbidities among schizophrenia patients, by the clinicians who allocated the diagnoses. Another possible reason may be the generally lower rates of depression and anxiety disorders (including OCD) in Israel [51–53], as well as lower rates of alcohol and some drug use disorders [51,54–56], while the prevalence of schizophrenia in Israel is comparable to that in other high-income countries [51,57,58].

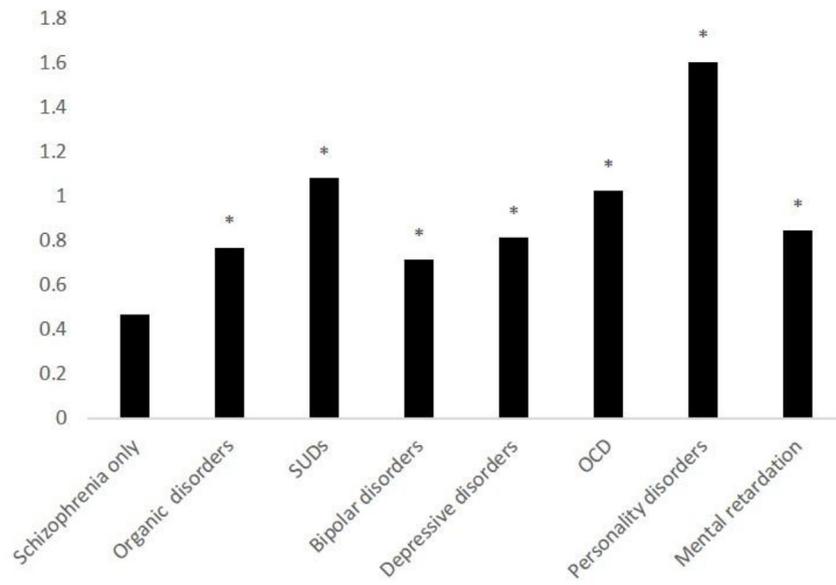
A noteworthy finding in our study is the earlier age of hospitalization among patients with comorbid diagnoses, in contrast to patients with schizophrenia only. Several previous studies indicate similar findings. Although one earlier study showed opposite findings (earlier age of onset was associated with lower rates of comorbidity among schizophrenia patients [59]), other and more recent studies on specific diagnoses show similar results to our findings; substance use disorder (notably cannabis) [60–63], OCD [9,64], depression [12] and personality disorders [65] have all been associated with an earlier age of onset among schizophrenia patients. This finding is also in line with previous research indicating that psychiatric comorbidity among schizophrenia patients is associated with more severe psychopathology [9], as well as poorer outcome of illness [66,67]. This highlights the need for early treatment interventions among individuals with schizophrenia and comorbid psychiatric disorders.

Among the different comorbid diagnoses identified, the most prevalent were SUDs, bipolar disorders, personality disorders, depressive disorders and OCD. The finding of an increased presence of SUDs, depressive disorders and OCD among schizophrenia patients are in line with findings of previous studies [8–12]. Substance use disorders have been found to be the most prevalent comorbid psychiatric disorders among schizophrenia patients; with a lifetime prevalence of about 50% [9,13,14]. Depression is also widely associated with schizophrenia, with a modal frequency of 25% [9]. The prevalence of OCD among individuals with schizophrenia varies between studies, and has been shown to be between 5% [11] to 23% [9]. The literature regarding comorbidity between schizophrenia and personality disorders seems to be scant. As it has been suggested that personality disorders may worsen the short and long-term outcomes of different psychiatric

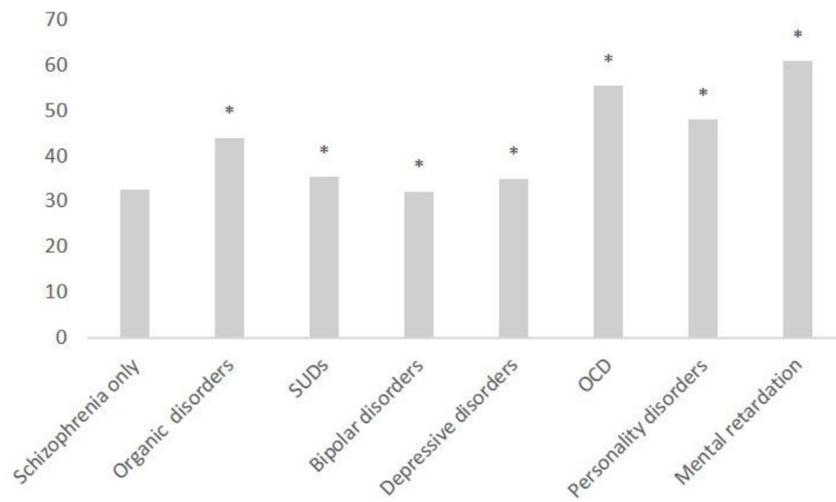
disorders [68], this may be particularly important. Perhaps partially due to the diagnostic complexity of the co-diagnosis of schizophrenia and a manic episode/bipolar disorder [9], little literature exists regarding the comorbidity between the two entities. Our results on comorbidity between schizophrenia and personality and bipolar disorders, therefore, represent data on relatively under-studied diagnoses with clinical impact.

We found that among individuals with schizophrenia, comorbid psychiatric diagnoses were associated with more hospitalizations, and that the greater the number of comorbid diagnoses, the greater the number of hospitalizations. This is in line with previous studies focusing on specific comorbid psychiatric disorders. For example, drug and alcohol abuse have been found to be associated with relapse among schizophrenia patients, [30,69,70] and are probably the most studied comorbid state associated with clinical deterioration leading to subsequent admission. Depression, or depressive symptoms, has also been linked to relapse among schizophrenia patients [9,71,72]. The little research done on the association of OCD among schizophrenia patients with relapse and rehospitalizations, has shown contradictory results [73,74]. The role of anxiety is not clear as well; while according to one study, anxiety related disorders among schizophrenia patients were shown to not be associated with rehospitalizations [75], another study found that panic attacks among schizophrenia patients was associated with higher mental health service utilization [76]. Despite these reports focusing on specific disorders, our findings indicate a general trend, in which all comorbid disorders were associated with increased hospitalization, and the more diagnoses, the greater the increase. Rehospitalizations among schizophrenia patients are an indicator of symptoms relapse, which is associated with a wide variety of negative consequences. Therefore, the understanding of the potential factors associated with this phenomenon is of clinical importance.

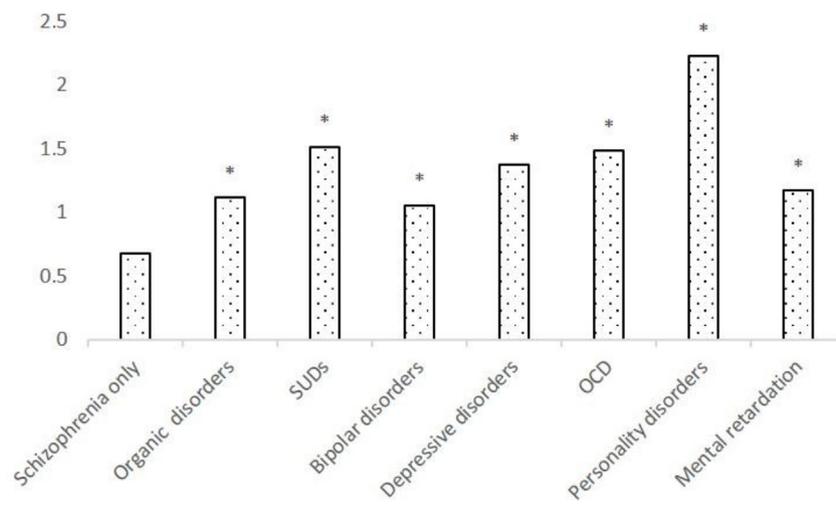
We further found that having any additional comorbid diagnosis, and having an accumulative number of diagnoses, was associated with longer LOS. Though previous reports indicate that among individuals with psychiatric disorders, medical comorbidities were correlated with longer hospitalizations [77], while psychiatric comorbidity was found to be associated with longer general hospital length of stay [78], less is known regarding particular factors associated with increased LOS in schizophrenia. Previous findings focus on the role of SUDs in LOS among schizophrenia patients, reporting that cocaine use disorder was found to be associated with a shorter LOS [79], while cannabis and alcohol consumption with longer admissions [80,81]. Our findings



a



b



c

expand on previous reports and indicate that all comorbid psychiatric diagnoses are associated with increased LOS among schizophrenia patients. This may be especially important among schizophrenia patients, who have a life-long debilitating disease, characterized by repeated relapses leading to admissions. Understanding of the determinants associated with LOS among these patients, therefore, presents a prominent issue for patients and their families, clinicians and policy makers.

Lastly, we found that among individuals with schizophrenia, comorbid psychiatric diagnoses were associated with more psychiatric ER visits, and that the greater the number of comorbid diagnoses, the greater the number of ER visits. Furthermore, our findings suggest that having at least one diagnosis beyond schizophrenia, was associated with an increased incidence of being discharged after the ER visit (possibly an indication of higher emergency service utilization). Though these are in line with findings from previous studies focusing on specific psychiatric disorders, indicating that individuals with comorbid personality disorders and depression, as well as anxious symptoms and self-harm behaviors, are high utilizers of psychiatric ERs [38,82,83], less is known regarding comorbid psychiatric disorders among schizophrenia patients. While individuals with schizophrenia have been found to be high utilizers of the psychiatric ER [38–40], this has been explored mainly in the context of comorbid substance abuse [38,41]. To our knowledge, other specific comorbid states among these patients, and their association to high ER utilization have not been explored.

As high utilizers of the psychiatric ER are often a small group that account for a disproportionate amount of visits [43,83] and have less stable means of treatment and follow-up in the community [84], a better understanding of their profiles may have substantial clinical and financial implications.

There are several possible explanations for the increased number and length of hospitalizations, as well as psychiatric ER visits, among schizophrenia patients with psychiatric comorbidity. Psychiatric comorbidity among these individuals is linked with worst psychopathology and outcomes [9]. This may be reflected by patients who suffer from more frequent exacerbations or present a complex clinical picture which is more challenging to contain in community-based settings. Furthermore, the complexity of diagnoses may require appropriate and unique pharmacological and psychotherapeutic interventions, which may be lacking due to overlooking of the comorbid states or attributing them to the clinical picture of the psychotic disease (a widespread remnant of the hierarchical approach [8,9,12,50]), or the less data available regarding these clinical pictures. All these, in turn, may result in increased ER visits leading to frequent hospitalizations, though these potential mechanisms were beyond the scope of the current study.

Several limitations of the study should be acknowledged. First, the data in this study were based on registries and on clinical diagnoses, not structured validated tools. Nevertheless, all diagnoses were assigned by senior, experienced, board-certified psychiatrists, who use ICD-10 diagnostic criteria, and who may have frequently had the advantage of observing the patients over time and multiple hospitalizations. Furthermore, studies have shown that registry-based clinical diagnoses of major psychiatric diagnoses, such as schizophrenia and mood disorders [85–88], OCD [89] and tic disorders [90], have high concordance rates with research diagnoses. Second, the comorbid diagnoses included in the study were not inclusive of all psychiatric diagnoses, and therefore, perhaps some potential comorbidity states may have been overlooked. Third, we frequently refer to categories of diagnoses (e.g., anxiety disorders). The use of broad, general diagnostic categories when describing psychiatric comorbidities among schizophrenia patients has been implemented in past studies on this subject [8,9,11]. Further research focusing on additional, specific comorbidities is needed. Regarding the comorbid diagnoses that were compared to schizophrenia

only, it should be mentioned that the diagnoses were not exclusive, as explained in the methods section. Further study of specific comorbid diagnoses and their association with hospitalization factors may therefore be needed. Fourth, it should be noted that the generalizability of the results may be limited, as the rates of different psychiatric disorders (excluding schizophrenia) are found to be lower in Israel [51–58]. Accordingly, data regarding the rates of psychiatric comorbidity among schizophrenia patients may differ from those in other high-income countries. Last, patients still hospitalized during the time the study was performed were excluded, suggesting that some chronic patients with very long hospitalizations were excluded. However, as our study covers a 20-year time-span, several chronic patients discharged during this period were included in our analyses.

5. Conclusions

In conclusion, comorbid psychiatric disorders among schizophrenia patients were found to be associated with an increase in the mean number and length of psychiatric hospitalizations as well as the mean number of psychiatric emergency room visits. In addition, we found that the greater the number of comorbid diagnoses, the higher this increase among all factors explored.

A prominent percent of schizophrenia patients suffers from comorbid psychiatric disorders [10–12], which may not be addressed properly. Clinicians should be alert to the possibility of comorbid diagnoses (which may be overlooked in the presence of the principal diagnosis [50]) and previous studies have suggested the implementation of validated assessment tools for this purpose [10,91]. Clinicians should also properly choose the treatment modalities for these patients. Examples of interventions which have previously been shown to be effective include an integrated approach of treatment for comorbid schizophrenia and SUDs [92], anti-depressant medication for schizophrenia patients who suffer from depression or obsessive-compulsive symptoms [91,93,94], and cognitive behavioral treatments for those with a comorbid diagnosis of PTSD [95,96].

Frequent hospitalizations and ER visits, as well as prolonged hospitalization may pose a financial burden on the health care system. Better understanding of the association between psychiatric comorbidities among individuals with schizophrenia is an important issue for the patients and their families, clinicians and policy makers alike. Future research should focus on assessing specific comorbidities as risk factors for adverse hospital-related outcomes, as well recognizing specific clusters of diagnoses that are most associated with these outcomes among highly comorbid individuals.

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Conflict of interest

None.

Shaul Lev-Ran MD is Deputy Director, Lev Hasharon Medical Center and a Senior Lecturer at the Sackler Faculty of Medicine, Tel Aviv University. He completed his MD degree at Tel-Aviv University, Israel; psychiatric residency at the Shalvata Mental Health Centre, Tel-Aviv University, Israel; and a fellowship in Addiction Psychiatry at the Centre for Addiction and Mental Health, University of Toronto, Canada. Dr. Lev-Ran's research focuses on the psychiatric outcomes of drug and alcohol use. Particularly, Dr. Lev-Ran focuses on the study of

Fig. 4. Comparison of hospitalization-related factors based on type of comorbid diagnoses: mean annual number of hospitalizations (a), mean annual length of hospitalizations (in days) (b) and mean annual number of psychiatric emergency room visits (c). The different groups were compared to the “no comorbid diagnosis” group. The bars represent the collected data, the statistical analysis was performed on log transformed data. SUDs, substance use disorders; OCD, obsessive compulsive disorder. * $p < 0.001$.

psychiatric outcomes of cannabis use and the interface between pain, addiction and psychiatric disorders.

Tal Kessler MD is a resident in psychiatry at Lev Hasharon Medical Center, affiliated with Tel Aviv University. Dr. Kessler completed her MD degree at the Hebrew University Hadassah Medical School.

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