RESEARCH ARTICLE

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Assessment of Mortality Rate in 10 Years and the Associated Risk Factors in Schizophrenia

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SUMMARY

Objective: The aim of the study was to explore the mortality rate and the associated risks factors in patients with schizophrenia during a10-year follow up period.

Method: We searched the records of patients with schizophrenia receiving treatment as outpatients and/or inpatients in the psychiatric clinic of a university hospital between 2004 and 2008 and determine the survival of these patients by the end of 2018. The results were compared with the all cause mortality rate in the general population during the same period. Also, the risk factors affecting the mortality rate among the patients were investigated.

Results: Out of a total of 626 registered patients 506 were included in the study. The mortality rate within 10 years was found to be 10.6%, with a mean age of 53.1 years at the time of death. The overall expected life expectancy was 73.4 years; varying between 66.6 years among the males and 77.6 years among the females; and 64.7 and 76.5 years among smokers and non-smokers, respectively. The overall standardized mortality rate (SMR) was 3.7, being 3.9 among the males and 3.3 among the females. The risk factors that were associated with the death were old age, male gender, smoking, not working, and early age of disease onset.

Conclusion: Smoking is a significant risk factor for mortality. Giving priority to programs for stopping smoking, and supporting rehabilitation services that enables patients to get involved in could help reducing the mortality risk.

Keywords: Schizophrenia, life expectancy, standardized mortality rate (SMR), smoking

INTRODUCTION

It is known that life expectancy of patients with schizophrenia is 10 to 20 years shorter than in the general population and shows a regional variation (Hjorthoj et al. 2017, Tanskanen et al. 2018). Also, the risk of mortality is reported to be 2 to 3 times (range 1.9-5) more than in the general population (Tanskanen et al. 2018, Oaklaey et al. 2018). The incidences of death are studied under two main groupings of natural expected causes such as comorbidites of cancer and cardiovascular diseases (CVD) constituting the majority of incidences or unnatural unexpected causes such as suicide and accidents (Tanskanen et al. 2018, Olfson et al. 2015, Ko et al. 2018).

The possible risk factors for death are reported to include advanced age, male gender, smoking, comorbid physical diseases including cancer, metabolic diseases, CVDs, respiratory diseases, suicide, side effects of antipsychotic drugs (APDs) used, and insufficient diagnosis and treatment of physical diseases due to low rates of benefiting from non-psychiatric health-care services (Kiselyet al. 2013, Piotrowski et al. 2017, Laursen 2019).

Smoking, known to be a risk factor for developing chronic obstructive pulmoner disease (COPD), CVD, and cancer (Crump et al. 2013), has a reported prevalence of 55-60% among schizophrenia patients (Kelly et al. 2011, Yildiz et al. 2010); and increasing amounts of daily smoking has been reported to be the greatest risk for death due to CVDs among these patients (Kelly et al. 2011).

In schizophrenia patients the risk of developing COPD is increased by 2.6-fold (Krieger et al. 2019) and the risk of developing pneumonia is 1.8 times higher (Chou et al. 2013). Factors such as insufficient self-care, homelessness and

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malnutrition may increase the risk of pneumonia (Copeland et al. 2007). Using psychotropic drugs is associated with pneumonia (Kuo et al. 2013) and with prolonged hospitalization (Lin et al. 2011). Increased compliance with antipsychotic drug treatment has been shown to be positively correlated with the risk of developing pneumonia and negatively correlated with the risk of death, revealing both the benefits and side effects of the therapy (Oakley et al. 2018).

CVDs constitute nearly half of all causes leading to early death in schizophrenia (Laursen et al. 2014, Kisely et al. 2013); with 3 times and 6 times raised incidenccs of mortality, respectively, at all ages and above the age of 60 as compared to the general population (Westman et al. 2018). Stroke, congestive heart failure and all cardiovascular diseases are more prevalent in this patient group (Fan et al. 2013).

The prevalence of diabetes mellitus (DM) in schizophrenia patients is 2.5-fold higher than in individuals without any psychiatric disorders (Stubbs et al. 2015). The frequency of diagnosing DM was found to be higher at all ages as compared to the general population, but the difference decreased with advancing age (Brink et al. 2018). Multiple complications associated with large and small vessel involvement in DM are thought to increase the risk of death.

The APD effect on death risk in schizophrenia can show duality next to the treatment of the psychiatric disorder, adverse side effects of weight gain and irregularities of lipid and sugar metabolism (Druss et al. 2018), increased risk of dose related sudden cardiac death (Ray et al. 2009) and increased risk of death from respiratory disorders at high doses (Torniainen et al. 2015) have been reported. Both in the newly started and chronic schizophrenia cases, the highest death risk was in the absence of APD use and the lowest risk was seen with the use of the second-generation long-acting injectable antipsychotic drugs (Taipale et al. 2018, Torniainen et al. 2015). The results have shown in general that the increased risk of death in schizophrenia is not associated with the APD use but with the lack of any APD therapy (Taipale et al. 2018).

There is significant increase in cancer related death risk in schizophrenia (Zhuo et al. 2017) which may be explained by the difficulties of gaining access to treatment services and poor quality of care (Chou et al. 2011, Beary et al. 2012). Lower participation in cancer screening, increased risk of metastasis due to delayed diagnosis and the resultant advanced stages of cancer may lead to a poor clinical course in this patient group (Cunningham et al. 2015, Mitchell et al. 2014).

The lifelong incidence of suicide in schizophrenia is about 5% (Palmer et al. 2005). Suicide related death risk is higher in the first years of the disease (Simon et al. 2018), particularly in the first year after hospitalization (Nordentoft et al. 2013). Severe psychotic symptoms, previous suicide attempts, lack of social support and regular relationships, and social withdrawal are the risk factors at the early stages of the disease (Ventriglio et al. 2016). The risk is reported to be lower in patients using APDs (Haukka et al. 2008).

Despite the numerous studies reported in the literature on the causes and increased risk of death in schizophrenia, there is not a published investigation on survival and death risk in schizophrenia in Turkey. The circulatory system diseases, particularly the CVDs and the respiratory system diseases including COPD were listed as the primary causes of death among 45 patients with chronic schizophrenia and death was also shown to be secondary to accidental falling and trauma (Ipekçioğlu and Kök Kendirlioğlu 2019).

The present study aimed at determining the mortality rate, life expectancy and the probable factors of death risk after a 10-year follow up in a cohort of schizophrenia patients monitored in a healthcare institution.

METHOD

The study consisted of reviewing the hospital records of the patients surviving at the end of 2008, who had been diagnosed with schizophrenia or schizoaffective disorder (SAD) on the criteria of the DSM-IV (American Psychiatric Association – APA-1994) at ≥16 years of age between January 1, 2004 and December 31, 2008 in Kocaeli University Medical School Psychiatry Clinics. An approval numbered 2019/04.2018 and dated 20/08/2019 was obtained from Kocaeli University Non-Interventional Clinical Trials Ethics Committee to conduct the study.

The files of the patients who consulted the clinic and were diagnosed with schizophrenia or SAD between the designated dates were reviewed retrospectively. Patients with a definitive diagnosis of schizophrenia or SAD in their epicrisis report, who had been treated as inpatients or by attending the dayclinic or as outpatients with a record of consulting the polyclinics minimally 3 times were enrolled in the study. Those patients without recorded citizen ID numbers when registering before 2007 and could not be reached by telephone were excluded from the study.

The death/survival status between 1 and 31 December 2018 of the patients included in the study were checked by using their citizen ID numbers recorded in their files. The ID numbers were also used on the Medula Pharmacy system which shows the drug prescription information of patients across Turkey for the previous 6 months. Those with a record of any medication on the Medula system were assumed to be alive and their current ages were recorded. The death/

survival status of the patients without any record on the Medula system were checked from the Central Population Administration System (MERNİS) to record the date of death and the age at death as the last age. Information was obtained on the health status of those patients without a recorded ID number in their hospital file, when they could be reached directly or through a relation by telephone. Some telephone numbers recorded in the hospital files were, however, not useful.

The required number of the participating patients to reflect the entire population was calculated using the formulation *'n=Nxt²x(pxq)/d²x(N-1)+t²x(pxq')* (Naing et al. 2006), where *n* is the number of individuals to be included in the sample and *N* is the number of people in the population. Accepting a prevalence of 0.6% for schizophrenia and a population count of 80 million in Turkey, the current number of schizophrenia patients was found to be 480.000. In the given formula, *p* is the incidence of the condition being studied and the accepted mortality rate estimated by previous studies was 10% *(p*=0.10*); q* is the prevalence of the studied condition and was calculated as 1-p (1-0.1=0.90); and *d* is the sampling error accepted by the investigator, which was suggested to be between 1% and 5% and accepted as 3% in our study (3%=0.03); *t* gives the agreed significance level, that is, type 1 (alpha) error level, which is 1.96, corresponding to the standard 5%. With this formula, the number of patients that need to be included in the sample to represent the number of patients with schizophrenia in Turkey was calculated to be at least 384 ($n=480000x(1,96)^2x0,1x0,9/(0,03)^2x479999+(1,96)^2x0,1x0,9=384$).

A control group, age and gender matched with the patients included in the study, was formed by using the data from Turkish Statistics Institude (TUIK 2019a) on randomly selected individuals living in Turkey in the the 2009-2018 period. Using the annually published TUIK mortality rate data specific for age and gender, the probability for each person in the control group to die between 2009 and 2018 was calculated. The mean general probability of death and the mean probabilities for females and males were calculated.

Statistical Analysis

Statistical analyses were carried out using the Statistical Package Program for Social Sciences (SPSS)-version 22. The initially recorded data in the file on patient age, disease onset age, disease duration, years of completed education, body mass index (BMI), number of cigarettes smoked daily, and the current age assessed in the last control were entered the SPSS as continuous variables. The data on patients smoking ≥5 cigarettes daily were included in the 'smoker's class' to be used as categorical variable. Data on BMI were divided as '(+) Obesity-BMI≥30' and '(-) Obesity-BMI<30' and classified as categorical data. In order to compare the patients at the early stage of disease and the chronically ill patients, the data on disease duration were divided as ≤5 years and >5 years and used as categorical variables. The categorical data were expressed in numbers and percentages and the numerical data on demographics and clinical details were expressed by the mean and the standard deviation. The Kolmogorov Simirnov test demonstrated the normal distribution of the variables. The T test and the Chi-Square test were used to analyse, respectively, the continuous and the categorical variables.

When evaluating 'employement status', students and those with employment were calssified as 'working' and the rest of the patients were classified as 'non-working'. Marital status was evaluated as the 'married' and the 'singles' which included the bachelors, the widowed, and the divorced. The p value of <0.05 was accepted to iadicate statistical significance.

For survival analyses, the life expectancy for each categorical variable was calculated by the Kaplan Meier method, taking *death* was the *event*, and the *last age* was the *time* factor. The Log Rank test was used to check the statistical significance of the differences between the variables. The Cox Regression analysis was used to determine the variables predicting death and smoking was evaluated separately in the *categories of yes/no* and in *numbers per day*. Checking on the Omnibus Test whether the variables entered the regression analysis fit the model indicated that the model was significant (p<0.05).

The probability of death and the life expectancy in the general population was estimated by forming a control group comprising randomly selected individuals matched one-to-one on the basis of age and gender with the patients by using the TUIK (2019a) data on the annual mortality rates during 2009-2018. The probability of death in this period for the controls on a general basis and also on female and male gender basis was calculated to be, respectively, 0.02882, 0.02484, and 0.03112. The expected counts of death were obtained by multiplying the number of individuals in each grouping with the probability values. The death count in the patient group was taken as the observed death count which, when divided by the expected death count, gave the standardized mortality rate (SMR).

RESULTS

The number of outpatients and/or inpatients diagnosed with and treated for schizophrenia and SAD between 2004 and 2008 was determined to be 626. Investigating retrospectively the hospital records of all patients, the data of 506 (80.8%) patients were reached at the end of 2018 after the10-year

Table 1. Comparison of Death/survival on the Basis of the Continuous Variables

Variables	Number	Alive (mean+SD) (range)	Dead (mean+SD) (range)	Total (mean+SD) (range)	t (df)	*P*
Age in the records	506	33.42±10.31 (17-64)	46.26±13.32(21-78)	34.79±11.37 (17-78)	-8.357 (504)	0.000
Last age	506	46.55±10.33 (29-79)	53.14±12.72(26-87)	47.26±10.79 (26-87)	-4.314 (504)	0.001
Disease onset age	462	24±7.24 (10-51)	26.94±9.08 (12-56)	24.33±7.51 (10-56	-2.650 (460)	0.008
Disease duration[a]	462	22.23±7.86 (5-60)	20.13±11.53 (1-45)	22±8.35 (1-60)	1.693 (460)	0.212
BMI	423	27.13±5.39 (16-54)	28.59±7.57 (18-60)	27.3±5.69 (16-60)	-1.695 (421)	0.196
Education years[a]	469	8.99±3.75 (0-17)	7.53±3.79 (0-16)	8.83±3.78 (0-17)	2.614 (467)	0.009
Daily smoking[b]	470	11.42±17.61 (0-100)	23.13±25.80 (0-80)	12.69±18.99 (0-100)	-4.233 (468)	0.003

BMI: Body mass index; SD: Standard deviation; [a]Year; [b]Number.

follow up period. Death had occurred in 54 (10.6%) patients with a mean age of the 53.1 years. Comparisons of the surviving and the deceased groups on the basis of continuous and categorical variables are given in Tables 1 and 2. The variables showing significant intergroup differences were patient age in the records, last recorded age, disease onset age, disease duration, daily smoking, education years, employment status, and marital status.

Life Expectancy

The Kaplan Meier analysis of survival showed life expectancy in all patients to be 73.4±1.673 years, the difference between the females (77.6±2.431) and the males (66.6±1.389) being statistically significant. Life expectancy was shortened in smokers. The data on life expectancy are given in Table 3.

Life expectancy was longer among the females than the males in both the control and the patient groups. The control

Table 2. Comparison of Death/survival on the Basis of the Categorical Variables

Variables		Total (n, %)	Dead (n, %)	Alive (n, %)	x^2 (df)	*P*
Diagnoses (n=506)	Schizophrenia	441 (87.2)	47 (9.3)	394 (77.9)	0.001 (1)	0.978
	SAD	65 (12.8)	7 (1.4)	58 (11.5)		
Disease duration (n=410)	≤5 year	162 (35.1)	6 (1.3)	156 (33.8)	13,748 (1)	0,000
	>5 year	299 (64.9)	45 (9.8)	254 (55.1)		
Gender (n=506)	Female	185 (36.6)	15 (3.0)	170 (33.6)	2.011(1)	0.156
	Male	321 (63.4)	39 (7.7)	282 (55.7)		
Smoking (n=471)	Yes	192 (41)	29 (6.4)	163 (34.6)	6.753 (1)	0.009
	No	278 (59)	22 (4.7)	256 (54.4)		
Obesity (421)	Yes	118 (28)	14 (3.3)	104 (24.6)	0.10 (1)	0.919
	No	304 (72)	35 (8.3)	269 (63.7)		
Employment status (n=466)	Employed	111 (23.8)	3 (0.69)	108 (23.2)	9.801 (1)	0.002
	Unemployed	355 (76.2)	47 (10.1)	308 (66.1)		
Suicide attempt (n=435)	Yes	106 (24.4)	13 (3.0)	93 (21.4)	0.216 (1)	0.642
	No	329 (75.6)	35 (8.0)	294 (72.9)		
Marital status (n=471)	Single	377 (80)	33 (7.0)	344 (73.0)	8.421 (1)	0.004
	Married	94 (20)	18 (3.8)	76 (16.1)		
Psychosis in family (n=460)	No	343 (74.4)	39 (8.5)	304 (65.9)	0.129 (1)	0.720
	Yes	118 (25.6)	12 (2.6)	106 (23)		

SAD: Schizoaffective disorder

Table 3. Life Expectancy on the Basis of the Categorical Variables

Variables		Life expectancy- Mean±SD (range)	Log	Rank
			X^2	*P*
Gender	Female	77.56±2.431 (72.80-82.33)	10.26	0.001
	Male	66.64±1.389 (63.91-69.36)		
Diagnosis	Schizophrenia	73.63±1.749 (79.20-77.06)	0.216	0.610
	SAD	65.11±1.553 (62.07-68.16)		
Disease duration	≤5 year	63.533±1.490 (60.61-64.00)	0.018	0.894
	>5 year	72.916±1.765 (69.45-76.37)		
Marital status	Married	69.03±1.552 (65.99-72.08)	0.012	0.913
	Single	74.97±1.953 (71.14-78.80)		
Employment Status	Employed	74.38±2.698 (69.09-79.67)	2.645	0.104
	Unemployed	72.59±1.813 (69.04-76.15)		
Suicide attempt	Yes	68.49±2.402 (63.78-73.19)	1.113	0.291
	No	73.14±1.945 (69.33-76.96)		
Smoking	Yes	64.74±1.399 (62.00-67.48)	11.135	0.001
	No	76.54±2.077 (72.47-80.61)		
Obesity	Yes	71.38±1.455 (68.53-74.23)	3.903	0.058
	No	71.00±2.261 (66.57-75.43)		
Psychosis in family	Yes	69.82±1.254 (67.36-72.28)	0.159	0.690
	No	72.19±3.330 (65.66-78.71)		

SAD: Schizoaffective disorder, SD: Standard deviation

group life expectancy was 82.1 years, this being 85.2 years for the females and 79.4 years for the males. As compared to the general population, the deficit in life expectancy in schizophrenia patients was approximately 9 years, this being 11 years for the males and 8 years for the females. The Cox regression analysis identified gender, patient age in the records, disease onset age, employment status and smoking as the statistically significant mortality risk factors. The numbers smoked per day included in the regression analysis, instead of the categorical smoking variable, resulted in a statistically significant positive correlation with the risk of death (Table 4).

Table 4. Cox Regression Analysis for Risk Factors Affecting Mortality Rate in Schizophrenia

Risk Factors	B	SD	Wald	df	*P*	Hazard Ratio (min-max)
Age in the records	0.106	0.016	45.713	1	0.000	1.112 (1.078-1.147)
Disease onset age	-0.045	0.021	4.620	1	0.032	1.046 (1.004-1.089)
Disease duration	-0.77	0.548	0.020	1	0.888	0.926 (0.316-2.708)
BMI	0.032	0.025	1.682	1	0.195	1.033 (0.986-1.085)
Smoking[a]	0.619	0.315	3.862	1	0.049	1.857 (1.002-3.441)
Daily smoking[b]	0.012	0.005	4.692	1	0.030	1.012 (1.001-1.023)
Marital status	0.423	0.329	1.655	1	0.198	1.527 (0.801-2.912)
Employment status	1.273	0.613	4.304	1	0.038	3.571 (1.073-11.883)
Gender (Male)	1.063	0.379	7.866	1	0.005	2.895 (1.377-6.084)

[a]Yes/no, [b]Number

Table 5. The Expected and the Observed Number of Deaths and the SMR on the Basis of the Demographic and Clinical Characteristics

Characteristics		Expected number of deaths	Observed number of deaths	Standardized mortality rate
Gender	Female	4.59	15	3.3
	Male	9.99	39	3.9
	Total	14.58	54	3.7
Disease duration	≤5 year	4.67	6	1.3
	>5 year	8.62	45	5.2
Diagnoses	Schizophrenia	12.71	47	3.7
	SAD	1.87	7	3.7
Marital status	Married	2.71	18	6.6
	Single	10.87	33	3.0
Employment status	Employed	3.20	3	0.9
	Unemployed	10.23	47	4.6
Suicide attempt	Yes	3.06	13	4.3
	No	9.48	35	3.7
Smoking	Yes	5.54	29	5.2
	No	8.01	22	2.7
Obesity	Yes	3.4	14	4.1
	No	8.8	35	4.0
Psychosis in family	Yes	3.40	12	3.5
	No	9.89	39	3.9

SAD: Schizoaffective disorder

Standardized Mortality Rate (SMR)

Mortality rates related with the demographic and clinical variables and the calculated SMR are given in Table 5.

DISCUSSION

The results of the study have shown that life expectancy in schizophrenia patients was shorter as compared to the general population, with smoking, male gender, unemployment, and early disease onset age being the risk factors for early death. Since the patients included in the study had a mean age of 35 at the 2004-2008 baseline and the mean disease duration was 22 years, the results are to be interpreted in the respective framework.

Mortality risk

The most significant result of this study was the demonstration of a mean 3.7 fold increase in the mortality risk among schizophrenia patients as compared to the general population, with this risk factor being 3.9 for the males and 3.3 for the females. These results are in agreement with the higher death risk in males reported in the literature; notably those in a meta-analysis of 34 studies on schizophrenia and other nonaffective psychotic disorders with an overall mean SMR of 3.1 (1.9-5.0), differing as 3.1 in males and 3.0 in females (Oakley et al. 2018), and confirming the reports by others (Brown et al. 2010, Tanskanen et al. 2018).

Life Expectancy

The life expectancy was calculated to be 82.1 years in the entire control group, varying as 85.2 years in females and 79.4 years in males. According to the data of Turkish Statistics Institude, life expectancy at birth in the general population of Turkey was 78.3 years in 2018, varying as 81.0 years in females and 75.6 in males (TUIK 2019b). Whereas the TUIK data give life expectancy at birth, our study included individuals ≥16 years of age. Therefore, the life expectancy results of our study were calculated for this age group which should explain the difference from the TUIK data. However, in agreement with the results reported in the literature, life expectancy of schizophrenia patients (73.4 years) was found approximately 9 years shorter than that of the general population (82.1 years); and, as expected, life expectancy of the males was 11 years shorter than that of the females.

A meta-analysis reported the general mean life expectancy in schizophrenia as 62.6 years, that varied as 59.3 years for males and 67.6 years for females, which were below our results and showed a 13-15-year deficit, exceeding our result, in comparison to the general population (Hjorthøj et al. 2017). There may be various factors underlying these discrepencies as suggested by the results of a 30-year follow-up study on schizophrenia in Finland that reported a 13-year deficit in life expectancy in comparison to the general population at the starting point but which was reduced to 7.4 years at the end of the 30-year period (Tanskanen et al. 2018). The reported differences from our results showing relatively longer life expectancy may be attributed to a history of disease duration longer than 5 years among 65% of the patient population of our study. Given that suicide incidences are relatively higher in the early stages of schizophrenia (Simon et al. 2018), the mean disease duration of 22 years in our patient group suggests the possibility of having missed the patients who died at earlier ages in the starting years of the disease. Another explanation could be the effect of the methodological differences between the studies reporting shortened life expectancy or lifespan in schizophrenia. For example, the mean age at death has been accepted as 'life expectancy' (Tanskanen et al. 2018). However, overall the results show that both average lifetime and life expectancy are shorter in schizophrenia patients than in the general population**.**

Smoking

It was found that death risk was approximately 2 times higher among the smoking patients compared to the non-smokers and 5 times higher in comparison to the general population. Determining that the risk of death increased as the number of cigarettes smoked per day increased is consistent with the reports in the literature (Brown et al. 2010, Kelly et al. 2011). Also, Dickerson et al. (2014) have shown that the risk of death due to natural causes was elevated 4.7 fold among the smokers as compared to non-smokers among schizophrenia patients which can be explained by the increases observed by Krieger et al. (2019) in the incidences of obesity, raised blood lipid levels, DM, congestive heart failure, and drug and alcohol abuse in this subgroup of schizophrenia patients. Hence, the demonstration of increased risk of death and shortened life expectancy by smoking is a significant contribution to the relevant literature.

Other Demographic Variables

Although life expectancy of the employed and unemployed schizophrenia patients did not differ significantly, the risk of death was 3.5 fold higher among the unemployed patients as compared to the employed patients and 4.6 fold higher than that in the general population, while the risk of death in the employed patients was lower than in the general population. It had been previously reported that death risk was higher among the schizophrenia patients without employment, unmarried and/or with a low socioeconomic level (Brown et al. 2010) which was confirmed in a small scale study carried out in India reporting that unemployment and low socio-economic status were more common among the deceased schizophrenia patients (Manjunatha et al. 2019). This finding that working lowers death risk stresses the importance of supporting the subject in future studies. Having a job while unemployment rate is as high as 14% (TUIK 2020) should be considered as an important achievement for schizophrenia patients which is probably associated with better self-care by the patient, expansion of social contact network and benefiting more from general healthcare services. Although being married or living with a partner is accepted to be a positive indicatior for the prognosis of schizophrenia (Remschmidt and Theisen 2012), marital status does not affect the shortened life expectancy in schizophrenia (Brown et al. 2010). In our study, regression analysis result showed that the initial observation of a relatively raised death risk in married patients was not statistically significant, suggesting that this can be the confounding effect of the other group differences, since the mean values of the disease onset age and the patient age in the records, which were determined as risk factors for early death and differed significantly between the death/survival groups, were also significantly different in the married and the single groups, being 30 and 42 years, respectively, for married patients and higher than the corresponding ages of 22 and 32 years, respectively, for the unmarried patients.

In our study, there were statistically significant differences between the deceased and surviving groups with respect to 'patient age in the records' or the age at the time of including the patients in the study and the disease onset age. The mean age of 46 in the records for the deceased patients exceeded the 32 years recorded for the survivors in 2018. The disease onset age was also higher in the deceased patients (27 vs. 24). Regression analysis showed that the increase in patient age in the records (HR=1.110) was associated with increased death rate and the increase in disease onset age (HR=1.40) correlated with decreased risk of death. The earlier death of the patients who started participating in the study at a more advanced age can be considered as a natural outcome. Other studies have also reported age as a risk factor for death in schizophrenia (Dickerson et al. 2014, Rantanen et al. 2009). The risk of death associated with the comorbidity of circulatory system diseases, cancer, and other physical diseases is thought to increase with advancing age in schizophrenia (Rantanen et al. 2009). Increased death risk with early disease onset age, when considered together with subsequent addition of physical diseases, requires serious attention. Early disease onset age is known to be a negative prognostic indicator in schizophrenia (Remschmidt and Theisen 2012) with a poor clinical course

that is exacerbated with lack of self-care, poor nutrition habits, sedentary living, less seeking of medical treatment, less compliance with treatment. The side effects of long term APD load, even with good treatment compliance, may lead to increased risk of death.

In this study, being obes was not found to be a significant death risk in the schizophrenia patients, which confirmed other reports showing that a raised BMI is not a marker for death risk in schizophrenia (Brown and Mitchell 2012). Investigation of increased death risk in schizophrenia has not directly linked BMI to death risk, despite noting that the prevalence of obesity and metabolic syndrome was higher in patients with schizophrenia than in the general population and was one of the reasons for raised incidence of CVD-related deaths in this patient group (Ringen et al. 2014).

Education status significantly differed between the death/survival groups in the initial evaluation but lost its significance when included in the Cox regression analysis. This result is consistent with those in the literature (Laursen et al. 2012).

In our study, disease duration was not determined to be a risk factor for death in schizophrenia. However, demonstrating that SMR was 4 times higher in patients with >5 years of disease duration as compared to the patients with disease duration of <5 years should be considered as an important finding.

On the basis of our results, a history of suicide attempt was not a factor increasing death risk. Although the total number of patients included in this study who died after suicide attempt was not known, it is noteworthy that 24% of the participating patients had a history of suicide attempt and a higher SMR was calculated for this subgroup. A significant relationship was not determined between having a history of suicide attempt and increased risk of death. However, new studies are needed to reach definitive results. Having a family history of psychosis was not found to have any effect on death risk.

Since data on the APDs used by the patients, the history of comorbidities and the level of access to medical treatment were not available, the effects of these factors on death rate could not be investigated in this study.

Our study is the first in Turkey to investigate the mortality rates, death risks, and life expectancies of schizophrenia patients. Although made with a smaller number of patients as compared to the national registry studies in other countries, our study presents comprehensive information on variables including gender, disease onset age, obesity, smoking, marital status, and employment status that affect the death risk and life expectancy in schizophrenia patients.

Not having adequate data on the patient comorbidities and causes of death, lacking a separate group of first episode patients although death risk and its causes are known to show differences in this group, including all housewives in the non-working classification since their functionality level was not known, lack of data on substance abuse and on drugs and doses used and, finally, being unable to calculate SMR by years are the major limitations of our study.

In conclusion, it is seen that death risk is increased in schizophrenia patients compared to the general population and that smoking is a reversible factor increasing this risk. Giving priority to programs for cessation of smoking as a preventable risk factor and planning studies on measures to include patients in work life are recommended.

REFERENCES

American Psychiatric Association (1994) Diagnosticand Statistical Manual of MentalDisorders- 4th Ed. American Psychiatric Association, Washington DC.

Beary M, Hodgson R, Wildgust HJ (2012) A critical review of major mortality risk factors for all-cause mortality in firstepisode schizophrenia: clinical and research implications. J Psychopharmacol 26 (Suppl 5):52-61.

Brown S, Kim M, Mitchell C et al (2010) Twenty-five-year mortality of a community cohort with schizophrenia. Br J Psychiatry 196:116-21.

Brown S, Mitchell C (2012) Predictors of death from natural causes in schizophrenia: 10-year follow-up of a community cohort. Soc Psychiatry Psychiatr Epidemiol 47:843-7.

Brink M, Green A, Bojesen AB et al (2018) Excess medical comorbidity and mortality across the lifespan in schizophrenia: a nationwide Danish register study. Schizophr Res 206:347-54.

Chou FH, Tsai KY, Chou YM (2013) The incidence and all-cause mortality of pneumonia in patients with schizophrenia: a nine-year follow-up study. J Psychiatr Res 47:460–6.

Chou FH, Tsai KY, Su CY et al (2011) The incidence and relative risk factors for developing cancer among patients with schizophrenia: a nine-year follow-up study. Schizophr Res 129:97–103.

Copeland LA, Mortensen EM, Zeber JE et al (2007) Pulmonary disease among inpatient decedents: impact of schizophrenia. Prog Neuropsychopharmacol Biol Psych 31:720–6.

Crump C, WinklebyMA, Sundquist K et al (2013) Comorbidities and mortality in persons with schizophrenia: A Swedish national cohort study. Am J Psychiatry 170:324-33.

Cunningham R, Sarfati D, Stanley J et al (2015) Cancer survival in the context of mental illness: a national cohort study. Gen Hosp Psychiatry 37:501-6.

Dickerson F, Stallings C, Origoni A et al (2014) Mortality in schizophrenia: clinical and serological predictors. Schizophr Bull 40:796-03.

Druss BG, Chwastiak L, Kern J et al (2018) Psychiatry's role in improving the physical health of patients with serious mental illness: a report from the American Psychiatric Association. Psychiatr Serv 69:254–6.

Fan Z, Wu Y, Shen J et al (2013) Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies. J Psychiatr Res 47:1549-56.

Haukka J, Tiihonen K, Ha¨rka¨nen T ve et al (2008) Associated between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. Pharmacoepidemiol Drug Saf 17:686–96.

Hjorthøj C, St€urup AE, McGrath JJ et al (2017) Years of potential life lost and lifeexpectancy in schizophrenia: asystematic review and meta-analysis. Lancet Psychiatry 4:295–01.

İpekçioğlu D, KökKendirlioğlu B (2019) Physical comorbidity and causes of death among schizophrenia patients: a retrospective descriptive study. Bakırköy Tıp Dergisi 15:103-9.

KellyDL, McMahon RP, Wehring HJ et al (2011) Cigarette smoking and mortality risk in people with schizophrenia. Schizophr Bull 37:832–8.

Kisely S, Preston N, Xiao J et al (2013) Reducing all-cause mortality among patients with psychiatric disorders: a population-based study. Can Med Assoc J 185:E50–6.

Ko SY, Tsai HC, Chi MH et al (2018) Higher mortality and years of potential life lost of suicide in patients with schizophrenia. Psychiatry Res 270:531-7.

Krieger I, Tzur Bitan D, Comaneshter D et al (2019) Increased risk of smoking-related illnesses in schizophrenia patients: A nationwide cohort study. Schizophr Res 212:121-5.

Kuo CJ, Yang SY, LiaoYT et al (2013) Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. Schizophr Bull 39: 648-57.

Laursen TM, Nordentoft M, Mortensen PB (2014) Excess early mortality in schizophrenia. Annu Rev Clin Psychol 10:425-48.

Laursen TM (2019) Causes of premature mortality in schizophrenia: a review of literature published in 2018. Curr Opin Psychiatry 32:388-93.

Laursen TM, Munk-Olsen T, Vestergaard M (2012) Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr Opin Psychiatry 25:83–8.

Lin HC, Huang CC, Chen SF et al (2011) Increased risk of avoidable hospitalization among patients with schizophrenia. Can J Psychiatry 56:171-8.

Manjunatha N, Kumar CN, Thirthalli J et al (2019) Mortality in schizophrenia: A study of verbal autopsy from cohorts of two rural communities of South India. Indian J Psychiatry 61:238-43.

Mitchell AJ, Pereira IE, Yadegarfar M (2014) Breast cancer screening in women with mental illness: comparative meta-analysis of mammography uptake. Br J Psychiatry 205:428-35.

Naing L, Winn T, Rusli BN (2006) Practical issues in calculating the sample size for prevalence studies. Archives of Orofacial Sciences 1:9-14.

Nordentoft M, Wahlbeck K, Hällgren J et al (2013) Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland, and Sweden. PLoS One 8:e55176.

Oakley P, Kisely S, Baxter A et al (2018) Increased mortality among people with schizophrenia and other nonaffective psychotic disorders in the community: A systematic review and meta-analysis. Psychiatr Res 102:245–53.

Olfson M, Gerhard T, Huang C et al (2015) Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatr 72:1172–81.

Palmer BA, Pankratz VS, Bostwick JM (2005) The lifetime risk of suicide in schizophrenia - a reexamination. Arch Gen Psychiatry 62:247–53.

Piotrowski P, Gondek TM, Królicka-Deręgowska A et al (2017) Causes of mortality in schizophrenia: An updated review of European studies. Psychiatr Danub 29:108-20.

Rantanen H, Koivisto AM, Salokangas RK et al (2009) Five-year mortality of Finnish schizophrenia patients in the era of deinstitutionalization. Soc Psychiatry Psychiatr Epidemiol 44:135-42.

Ray WA, Chung CP, Murray KT et al (2009) Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 360:225–35.

Remschmidt H, Theisen F (2012) Early onset schizophrenia. Neuropsychobiology 66:63-9.

Ringen PA, Engh JA, Birkenaes AB et al (2014) Increased Mortality in Schizophrenia Due to Cardiovascular Disease - A Non-Systematic Review of Epidemiology, Possible Causes, and Interventions. Front Psychiatry 26:137.

Simon GE, Stewart C, Yarborough BJ et al (2018) Mortality Rates After the First Diagnosis of Psychotic Disorder in Adolescents and Young Adults. JAMA Psychiatry 75:254-60.

Stubbs B, Vancampfort D, De Hert M et al (2015) The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. Acta PsychiatrScand 132:144–57.

Taipale H, Mittendorfer-Rutz E, Alexanderson K et al (2018) Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. Schizophr Res 197:274-80.

Tanskanen A, Tiihonen J, Taipale H (2018) Mortality in schizophrenia: 30-year nationwide follow-up study. Acta Psychiatr Scand 138:492–9.

Torniainen M, Mittendorfer-Rutz E, Tanskanen A et al (2015) Antipsychotic Treatment and Mortality in Schizophrenia. Schizophr Bull 41: 656-63.

Turkish Statistics Institude (2019a) Death Statistics: age specific death rate by gender 2009-2018. http://www.tuik.gov.tr/ Pre Tablo.do?alt_id=1060. Access date: 29.05.2020.

Turkish Statistics Institude (2019b) Life Tables. http://www.tuik.gov.tr/PreHaberBultenleri.do? id=30712. Access date: 29.05.2020.

Turkish Statistics Institude (2020) Labor Statistics. http://www.tuik.gov.tr/PreHaberBultenleri.do? id=33786. Access date: 29.05.2020.

Ventriglio A, Gentile A, Bonfitto I et al (2016) Suicide in the early stage of schizophrenia. Front Psychiatry 7:116.

Westman J, Eriksson SV, Gissler M (2018) Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. Epidemiol Psychiatr Sci 27:519-27.

Yıldız M, Yazıcı A, Böke Ö (2010) Demographic and clinical characteristics in schizophrenia: A multi center cross-sectional case record study. Turk Psikiyatri Derg 21:213-24.

Zhuo C, Tao R, Jiang R et al (2017) Cancer mortality in patients with schizophrenia: systematic review and meta-analysis. Br J Psychiatry 211: 7–13.