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Sudden cardiac arrest in patients with schizophrenia: A population-based study of resuscitation outcomes and pre-existing cardiovascular disease

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ABSTRACT

Objective: Individuals with schizophrenia carry a high burden of cardiovascular disease and elevated rates of sudden cardiac arrest (SCA), but little published data is available regarding survival from SCA in this population. The authors compared cardiovascular disease burden and resuscitation outcomes following SCA in individuals with and without schizophrenia.

Methods: Case-control analysis drawn from a prospective community-based study of SCA in a large community. The authors defined cases as having a pre-SCA history of schizophrenia, and controls as individuals with SCA without a history of schizophrenia. SCA cases with schizophrenia were compared to a 1:5 age- and sex-frequency-matched sample of SCA cases without schizophrenia.

Results: The 103 SCA schizophrenia cases were as likely as the 515 cases without schizophrenia to have resuscitation attempted (75% vs. 80%; $p = 0.24$) and had a shorter 911 call mean response time (5.8 min vs. 6.9 min, $p < 0.001$). However, they were significantly less likely to present with a shockable rhythm (ventricular fibrillation/pulseless ventricular tachycardia 16% vs. 43%, $p < 0.001$), and less likely to survive to hospital discharge (3% vs. 14%, $p = 0.008$). Pre-arrest cardiovascular disease burden was similar in patients with and without schizophrenia.

Conclusions: Despite comparable resuscitation characteristics and cardiovascular disease burden, patients with schizophrenia had significantly lower rates of SCA survival. The paucity of previous research into this phenomenon warrants further investigation to identify factors that may improve survival.

1. Introduction

Individuals with schizophrenia are more likely to suffer sudden cardiac arrest (SCA) compared to the general population [1–3]. This increased risk may be attributed to a number of factors, including a higher burden of cardiovascular disease associated with smoking, poor diet, lack of exercise, limited access to health care services [4–6], barriers to effective treatment for existing cardiovascular disease [7–9], and medications [2,3,10]. Little is known regarding survival outcomes following SCA among individuals with schizophrenia. A 2019 study from Denmark reported that out-of-hospital SCAs among individuals with overall psychiatric illness have lower rates of shockable rhythm and worse 30-day survival following SCA [11]. Thus, it is possible that patients with schizophrenia also have worse resuscitation outcomes compared to the overall population. Pre-existing cardiovascular disease in general can also influence resuscitation outcomes [12] and this could potentially be relevant for schizophrenia.

Our objective was to address gaps in the literature by performing a simultaneous evaluation of pre-existing cardiovascular disease burden and resuscitation outcomes following SCA in individuals with and without schizophrenia. Using matched SCA cases as a basis for comparison, we analyzed the prevalence of cardiovascular disease in

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patients presenting with schizophrenia and SCA.

2. Methods

This study was approved by the Institutional Review Boards of Oregon Health and Science University and all participating hospital systems. All survivors of cardiac arrest provided written informed consent; for non-survivors this requirement was waived.

2.1. Study population

The ongoing Oregon Sudden Unexpected Death Study (Oregon SUDS) identifies individuals with out-of-hospital SCA in the Portland, OR metropolitan area (population ≈1 million) from the region's emergency medical services (EMS) system, hospitals, and the state medical examiner; detailed methods have been previously published [13,14]. For this analysis, cases age ≥ 18 identified from Feb. 1, 2002 through Jan. 31, 2016 were included if adequate pre-arrest medical history was available from EMS records or archived medical records (97% of adult case population).

2.2. Data definitions and adjudication of SCA

We obtained the following records for each SCA case: detailed arrest circumstances and outcomes from EMS reports at the time of SCA, pre-arrest medical records, and autopsy and medical examiner reports when available. Demographic variables collected included age, sex, and race/ethnicity.

SCA was defined as a sudden, unexpected pulseless condition of likely cardiac origin if the arrest was witnessed; for unwitnessed cases, as a sudden, unexpected death if the patient was seen within 24 h of the SCA in their normal state of health [15]. Cases were excluded if they had a terminal medical condition (e.g., cancer), a traumatic cause of SCA, other non-cardiac cause of death, or if emergency responders or physician notes indicated that the SCA occurred due to a possible drug overdose.

Individuals were defined as having schizophrenia based on diagnosis noted in medical records and/or medical history as recorded by paramedics. Clinically recognized comorbidities and history of cardiovascular risk factors and disease were determined from physician-noted health history in medical charts or from medical history as reported to paramedics. Pre-arrest coronary artery disease was defined as a history of myocardial infarction, revascularization, or ≥ 50% stenosis on coronary angiogram before SCA. Medication use was determined from the physician visit closest to arrest, and from the list of medications noted by EMS personnel at the time of arrest.

We obtained resuscitation circumstances from detailed EMS pre-hospital care reports based on the Utstein-style guidelines [16]. Initial rhythm was defined as the cardiac rhythm first recorded by EMS and categorized as shockable (ventricular fibrillation/pulseless ventricular tachycardia; VF/VT) or non-shockable (pulseless electrical activity (PEA) or asystole). We determined survival to hospital discharge by review of EMS pre-hospital care reports, medical records from the SCA event, and state vital statistics records.

2.3. Statistical analysis

During the study period, we identified 4544 SCA cases age ≥ 18; for this analysis, we included 4387 (97% of the total) with adequate health history available from physician records, EMS records, or medical examiner records. Initial demographics comparisons were between all SCA cases with a documented history of schizophrenia (n = 103) vs. all remaining SCA cases (n = 4284).

For further detailed analyses, we used 5:1 frequency-matching by age and sex to select 5 SCA cases without a history of schizophrenia matched to each schizophrenia case. The resulting dataset consisted of the 103 people with SCA and a history of schizophrenia and 515 people with SCA without a history of schizophrenia, each group 62.1% male and matched by 5-year age categories.

Analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). Independent samples *t*-tests were used to compare continuous variables, presented as mean ± SD, and $\chi 2$ to compare categorical variables. A complete-case analysis approach was used for missing data; results tables present the number with available data for each comparison. Differences with two-tailed P values < 0.05 were considered significant.

3. Results

Cases with a history of schizophrenia (n = 103) represented 2.2% of the total 4387 SCA cases identified from Feb. 1, 2002 to Jan. 31, 2016. The majority of SCAs among individuals with schizophrenia occurred before age 65; the mean age at the time of SCA was 60.8 ± 13.5 years (range 23.8 to 85.8 years), significantly younger than cases without a history of schizophrenia (66.2 ± 16.3 years, p < 0.001; Table 1). There were no significant differences by sex or race/ethnicity between cases with and without schizophrenia (Table 1).

3.1. Circumstances and outcomes of sudden cardiac arrest

Compared to the age- and sex-matched subset of SCA cases without schizophrenia, SCA cases with schizophrenia were more likely to have an SCA in a care facility, and less likely to have one at a private home (p < 0.001; Table 2). However, when the care facility was assumed to be the primary residence of individuals with schizophrenia, there was no difference in arrest location (p = 0.47). Individuals in the schizophrenia and comparison group were equally likely to have a witnessed arrest, bystander CPR, and resuscitation attempted (Table 2), while the mean 911 call response time was shorter for individuals with schizophrenia than individuals without schizophrenia (5.8 ± 2.3 vs. 6.9 ± 3.6 min, p < 0.001) (Table 2). Despite having comparable circumstances of arrest, the initial recorded rhythm was shockable (ventricular fibrillation/tachycardia; VF/VT) in 16% of the schizophrenia group compared to 43% of the comparison group (p < 0.001). The schizophrenia group was significantly less likely to experience a return of spontaneous circulation (ROSC) (p = 0.04); and survival to hospital discharge was achieved in 3% of schizophrenia cases vs. 14% of comparison cases (p = 0.008) (Table 2).

Table 1
Demographics of SCA cases with schizophrenia compared to all other SCA cases aged ≥ 18 in Oregon Sudden Unexpected Death Study (SUDS) Feb. 1, 2002 – Jan. 31, 2016.

	Schizophrenia Cases (n = 103)	All other cases (n = 4284)	P-value
Male	64 (62%)	2848 (66%)	0.36
Age (years)	60.8 ± 13.5	66.2 ± 16.3	<0.001
Age categories			0.002
18 – 34	4 (4%)	166 (4%)	
35 – 64	59 (57%)	1813 (42%)	
65 – 79	31 (30%)	1309 (31%)	
≥80	9 (9%)	996 (23%)	
Race / ethnicity			0.10
White	83 (83%)	3509 (84%)	
Black	12 (12%)	334 (8%)	
Asian	5 (5%)	124 (3%)	
Hispanic	0	105 (3%)	
Other	0	83 (2%)	
Missing	3	129	

Table 2
Circumstances and outcome of arrest among SCA cases with schizophrenia and an age- and sex-matched group of SCA cases without schizophrenia in Oregon SUDS 2002–2016.

	SchizophreniaCases (n = 103)	Matched cases (n = 515)	P-value
Arrest location[a]			<0.001
Home	40 (39%)	318 (62%)	
Care Facility	40 (39%)	50 (10%)	
Public	16 (16%)	99 (19%)	
ED / Outpatient Clinic	6 (6%)	27 (5%)	
Other	1 (1%)	16 (3%)	
Witnessed arrest[b]			0.72
Witnessed	46 (45%)	234 (46%)	
Witnessed by EMS	4 (4%)	29 (6%)	
Not witnessed	53 (51%)	249 (49%)	
Bystander CPR	28 (27%)	181 (35%)	0.12
Response time (minutes)[c]	5.8 ± 2.3	6.9 ± 3.6	<0.001
Do Not Resuscitate (DNR) Order	9 (9%)	31 (6%)	0.31
Resuscitation attempted[d]	73 (75%)	400 (80%)	0.24
Initial rhythm[e,f]			<0.001
VF/VT	11 (16%)	157 (43%)	
PEA	20 (29%)	83 (23%)	
Asystole	38 (54%)	116 (32%)	
Other	1 (1%)	7 (2%)	
Return of spontaneous circulation[e,g]	20 (29%)	158 (42%)	0.04
Survival to hospital discharge[e,h]	2 (3%)	55 (14%)	0.008

PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/ventricular tachycardia.

[a] Arrest location data missing for 5 non-schizophrenia cases.

[b] Witnessed arrest data missing for 3 non-schizophrenia cases.

[c] Response time data missing for 12 schizophrenia and 88 non-schizophrenia cases.

[d] Data for whether resuscitation was attempted was missing for 6 schizophrenia and 18 non-schizophrenia cases.

[e] Among those with resuscitation attempted and without DNR orders (70 schizophrenia and 382 non-schizophrenia cases).

[f] Initial rhythm missing for 19 non-schizophrenia cases among those with resuscitation attempted and without DNR orders.

[g] Return of spontaneous circulation data missing for 2 non-schizophrenia cases among those with resuscitation attempted and without DNR orders.

[h] Survival data missing for 1 schizophrenia case and 1 non-schizophrenia case among those with resuscitation attempted and without DNR orders.

3.2. Clinical history

Few differences in the prevalence of traditional cardiovascular risk factors were observed between SCA cases with and without schizophrenia, including body mass index, diabetes mellitus, hypertension, and hyperlipidemia (Fig. 1). The schizophrenia group was more likely to be current smokers ($p = 0.02$) and to have recreational drug use recorded in their medical history ($p = 0.003$), though documented current heavy alcohol use (22%) was the same for both groups. The group with schizophrenia also had a higher prevalence of COPD ($p < 0.001$), and seizure disorder ($p < 0.001$).

3.3. Cardiac history

The two groups were similar in their history of myocardial infarction and congestive heart failure (Table 3). However, the schizophrenia group was less likely to have documented coronary artery disease, broadly defined as a history of myocardial infarction, revascularization, or ≥ 50% stenosis on coronary angiogram before SCA. The schizophrenia group had a 20% prevalence of coronary artery disease while the comparison group had 34% ($p = 0.008$). Compared to their counterparts without a history of schizophrenia, the schizophrenia group was also less likely to have a history of revascularization ($p = 0.006$) or a history of atrial fibrillation/flutter ($p = 0.05$) (Table 3). A pre-arrest cardiac work-up with an angiogram (8% of schizophrenia cases and 11% of comparison cases) or echocardiogram (28% of each group) was similarly uncommon, while individuals with schizophrenia were more likely to have a pre-arrest ECG available in medical charts (62% vs 44%). Findings from pre-arrest angiograms and echocardiograms regarding extent of coronary disease and left ventricular size and function were not significantly different between the two groups, though schizophrenia cases had somewhat less cardiac dysfunction or remodeling, based on left ventricular ejection fraction and left ventricular size (Table 3). The schizophrenia group had a faster heart rate on ECG (92 vs. 81 bpm in the comparison group, $p < 0.001$) and a shorter QRS duration, 92 vs. 102 ms respectively, $p = 0.005$. QTc interval was similar between the two groups, while left ventricular hypertrophy by ECG was somewhat less prevalent in individuals with schizophrenia.

3.4. Medication use prior to arrest

Data on medication use was available from the time of arrest for 35% of SCA cases, and within the year prior to arrest for 80% of SCA cases; timing did not differ by history of schizophrenia ($p = 0.18$). The schizophrenia group was less likely than the comparison group to be taking several medications for chronic conditions, including statins, lipid lowering drugs, ACE inhibitors, and diuretics (Table 4), but was more likely to be taking beta-2 agonists, and significantly more likely to be taking QT-prolonging drugs, 87% vs. 49% ($p < 0.001$) (Table 4). Among the subset of individuals diagnosed with diabetes, hypertension, or hyperlipidemia, medication use for those conditions was similar in the two groups, except that in individuals with hypertension, diuretics were less often used in the schizophrenia group than the comparison group ($p = 0.04$; Table 4).

Among SCA cases with schizophrenia, 82% were taking antipsychotic drugs, with the most common type (77% of users) being atypical (second-generation) antipsychotics. A total of 14% of the individuals with schizophrenia were taking more than one type of antipsychotic drug, most commonly a first-generation with an atypical antipsychotic. We evaluated whether antipsychotic type was associated with presenting rhythm and found no significant association between presentation with shockable vs. non-shockable rhythm and use of atypical antipsychotics ($p = 0.17$) or first-generation antipsychotics ($p = 0.14$) (data not shown). More than a third of SCA cases with schizophrenia were also taking antidepressants (38%), though this frequency did not differ significantly from comparison SCA cases (33%; $p = 0.38$) (Table 4). Nearly a quarter (23%) of schizophrenia SCA cases were taking benzodiazepines, vs. 12% of those without schizophrenia ($p = 0.005$).

3.5. Autopsy findings

From the frequency-matched dataset, autopsies were available for 13 of 103 schizophrenia cases (13%) and 70 of 515 comparison cases (14%). Of those with autopsy available, 85% of schizophrenia and 81% of comparison cases were male. There were no differences between the two groups in findings of myocardial infarction at the time of arrest; evidence of past myocardial infarction; burden of coronary disease; hypertrophic cardiomyopathy; or left ventricular hypertrophy.

4. Discussion

In this community-based study, 2.2% of all out of hospital SCA cases had a history of schizophrenia. Compared to an age- and sex-matched subset of the SCA cases without schizophrenia, SCA cases with schizophrenia were significantly less likely to be found with a shockable rhythm, to achieve return of spontaneous circulation during resuscitation, and to survive to hospital discharge. The schizophrenia group had shorter response times and a comparable rate of witnessed arrests and bystander CPR, indicators that the “chain of survival” [17] including

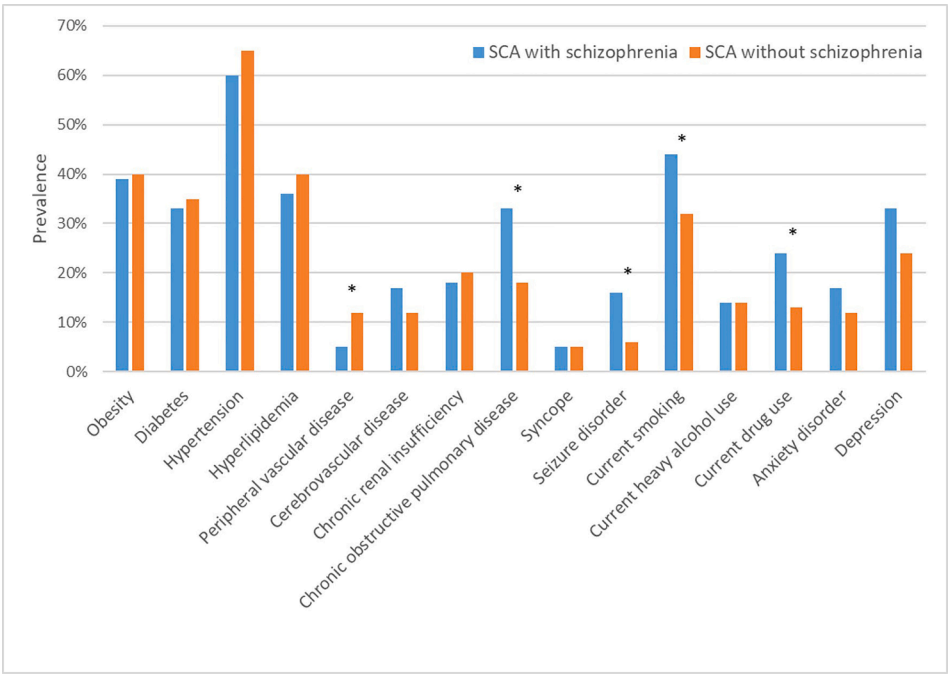

Fig. 1. Clinical profile prior to SCA among individuals with schizophrenia (n = 103) and an age- and sex-matched group of other SCA cases (n = 515), Oregon SUDS 2002 – 2016. Bars indicate prevalence of cardiovascular risk factors, clinical comorbidities, and risk behaviors. Due to missing data, sample sizes were smaller for obesity: individuals with schizophrenia n = 69, other cases n = 379. Asterisks indicate statistically significant differences with $p < 0.05$.

Table 3
Cardiac history prior to SCA among SCA cases with schizophrenia and an age- and sex-matched group of other SCA cases, Oregon SUDS 2002–2016.

	Schizophrenia cases (n = 103)	Matched cases (n = 515)	p-value
Documented pre-arrest coronary artery disease	21 (20%)	173 (34%)	0.008
History of myocardial infarction	16 (16%)	111 (22%)	0.17
History of revascularization	3 (3%)	62 (12%)	0.006
Congestive heart failure	20 (19%)	130 (25%)	0.21
Atrial fibrillation / flutter	10 (10%)	82 (19%)	0.05
Angiogram findings			
≥1 coronary artery with ≥ 50% stenosis	11 (58%)	117 (74%)	0.14
Echocardiogram findings			
Left ventricular hypertrophy	6 (30%)	54 (50%)	0.09
Ejection fraction	22	76	0.11
≥55%	(76%) 5	(56%) 32	
36–54%	(17%) 2	(24%) 28	
≤35%	(7%)	(21%)	
ECG Parameters	61 with data	219 with data	
Heart rate (bpm, mean ± SD)	92 ± 25	81 ± 18	<0.001
QTc (Bazett's, ms, mean ± SD)	459 ± 27	468 ± 40	0.09
QRS duration (ms, mean ± SD)	92 ± 17	102 ± 26	0.005
LVH by ECG[a]	4 (7%)	35 (16%)	0.06

Angiograms, ECGs, and echocardiograms were not available in all subjects. Sample sizes for variables derived from angiograms, echocardiograms, and ECGs were smaller: angiogram: 19 schizophrenia cases, 158 non-schizophrenia cases; LVH by echo: 20 schizophrenia cases, 107 non-schizophrenia cases; LVEF by echo: 29 schizophrenia cases, 136 non-schizophrenia cases; heart rate: 61 schizophrenia cases, 218 non-schizophrenia cases; QTc: 44 schizophrenia cases, 167 non-schizophrenia cases; QRS duration: 60 schizophrenia cases, 218 non-schizophrenia cases.

[a] LVH by ECG: Left ventricular hypertrophy by Sokolow-Lyon or Cornell voltage criteria.

early EMS activation, CPR, defibrillation, and advanced life support measures was at least as robust in the schizophrenia group as in the group without schizophrenia. Contrary to our hypothesis, the prevalence of cardiovascular risk factors was similar in SCA cases with and without schizophrenia, and documented cardiovascular disease was somewhat lower among cases with schizophrenia than the comparison group.

Our observed lower-than-expected shockable rhythm among individuals with schizophrenia is consistent with findings from two recently-published studies, and also may partly explain the low survival among SCA cases with schizophrenia, since presentation with a shockable rhythm is a strong determinant of survival from SCA [18].

From a Danish registry of over 27,000 out-of-hospital SCA cases from 2001 to 2015, individuals with a history of serious psychiatric illness in the 10 years prior to SCA (17.3% of total cases) were less likely to have a shockable rhythm (16.8% vs 32.3%) and had lower 30-day survival (6.0% vs 10.6%) [11]. While this study combined psychiatric illnesses, including depression, survival results were consistent in the smaller schizophrenia subgroup. In a study in Tokyo, 2631 out-of-hospital SCAs included 157 (6.0%) with severe mental illness (schizophrenia or mood disorders); this subgroup had significantly less shockable rhythm (5.7% vs 18.8%) but no difference in survival was reported (7.6% vs 10.2%) [19].

Our finding that 2.2% of all SCA cases in a single large community had a diagnosis of schizophrenia may be novel, and this proportion is considerably higher than the prevalence of schizophrenia in the general population, which is in the range of 0.5% [20]. This discrepancy may be partly explained by Oregon's relatively high state-level prevalence of serious mental illness [21], but a complete explanation likely takes into account schizophrenia as a risk factor for SCA.

A strength of our study is the simultaneous evaluation of detailed cardiac arrest circumstances, survival outcomes, and medical history for both survivors and those who died of SCA, with large enough numbers of carefully adjudicated cases from a single, well-defined community to include more than one hundred cases of SCA with a history of schizophrenia.

Both groups had a similar chart history of prior myocardial infarction

Table 4
Medication use prior to arrest among SCA cases with schizophrenia and an age- and sex-matched group of other SCA cases, Oregon SUDS 2002 – 2016.

	Schizophrenia cases (n = 100)	Matched cases (n = 420)	p-value
Among all patients			
Beta blockers	31 (31%)	170 (40%)	0.08
Statins	24 (24%)	150 (36%)	0.03
Lipid lowering drugs	25 (25%)	154 (37%)	0.03
Anti-anginal drugs	11 (11%)	65 (15%)	0.25
Anti-coagulants	4 (6%)	52 (12%)	0.07
ACE inhibitors	26 (26%)	158 (38%)	0.03
Diuretics	21 (21%)	163 (39%)	0.009
Digoxin	2 (2%)	31 (7%)	0.05
Beta-2 agonists	32 (32%)	92 (22%)	0.03
Opiates	21 (21%)	127 (30%)	0.07
QT-prolonging drugs	87 (87%)	206 (49%)	<0.001
Among diabetics			
Anti-diabetic use	25 (74%)	119 (70%)	0.72
Insulin	15 (44%)	70 (41%)	0.77
Among hypertensives			
ACE inhibitors	23 (38%)	145 (48%)	0.15
ARBs	4 (7%)	36 (12%)	0.23
Calcium channel blockers	14 (23%)	73 (24%)	0.86
Diuretics	20 (33%)	144 (47%)	0.04
Beta blockers	24 (39%)	153 (50%)	0.12
Among hyperlipidemics			
Lipid lowering drugs	22 (59%)	118 (60%)	0.93
Psychotropic medications			
Anti-psychotics	82 (82%)	31 (7%)	<0.001
Number of antipsychotics	18	389	<0.001
0	(18%) 68	(93%) 27	
1	(68%) 14	(6%) 4	
2	(14%)	(1%)	
Anti-depressants	38 (38%)	140 (33%)	0.38
Anxiolytics	5 (5%)	15 (4%)	0.50
Lithium	8 (8%)	3 (1%)	<0.001
Benzodiazepines	23 (23%)	51 (12%)	0.005

Table excludes 3 schizophrenia and 95 non-schizophrenia cases who were missing information regarding medication use.

and congestive heart failure, conditions with obvious symptoms. However, schizophrenia cases were less likely to have had a revascularization prior to SCA that could have addressed underlying coronary disease, and less likely to have recognized stable heart disease. While autopsy data was only available in ~ 14% of cases overall, no difference in burden of heart disease was observed between those with and without schizophrenia. We should note one distinction between the schizophrenia group and their comparators: individuals with schizophrenia had their SCA an average of six years younger than the overall SCA population, indicating earlier-onset heart disease. Premature cardiovascular disease (CVD) is a common cause of death in individuals with schizophrenia [6]. CVD is more likely to be undiagnosed in individuals with schizophrenia than in individuals without schizophrenia [22], and less access to preventive medical care may mean cardiovascular risk factors are underdiagnosed and undertreated among individuals with schizophrenia.

Regarding non-cardiac findings, schizophrenia cases were more likely to be current smokers, and to have COPD and seizure disorder, conditions associated with increased risk of SCA. The findings regarding smoking and COPD are consistent with patterns in the population as a whole: individuals with schizophrenia have higher smoking rates [23] and prevalence of COPD [24] than individuals without schizophrenia. The Danish study of SCA also reported a higher prevalence of COPD (22.1% vs 12.3%) and epilepsy (7.0% vs 1.4%) in SCA cases with psychiatric illness than in SCA cases without such history [11]. Sudden unexpected death in epilepsy (SUDEP) is a common cause of epilepsy-related death [25]. Both epilepsy and schizophrenia have been linked to low levels of adenosine, a neuromodulator with cardioprotective qualities [26]. Taken together, these findings indicate that these conditions, or medications used to treat them, could play a role in SCA among individuals with schizophrenia. Finally, hypoxia associated with COPD could partly explain the higher likelihood of nonshockable rhythm in SCA among individuals with schizophrenia, as hypoxia is an established predictor of PEA [27].

The differences in medication use we report may also partly explain the lower likelihood of shockable initial rhythm, as antipsychotics have been associated with non-shockable rhythm in SCA [28]. In a Danish registry of nearly 30,000 individuals with out of hospital cardiac arrest, antipsychotic medication use was the strongest predictor of presentation with non-shockable rhythm (OR 2.30) [29]. Among 222 patients with SCA in Finland, individuals using antipsychotics had increased odds (OR 4.27) of presenting with non-shockable rhythm, adjusting for age, sex, and underlying cardiac disease [30]. Furthermore, fourteen percent of SCA cases with schizophrenia were taking more than one type of antipsychotic; this may reflect current prescription practices supported by data indicating lower hospitalization rates among individuals with schizophrenia taking more than one anti-psychotic [31]. However, many atypical antipsychotic drugs prolong the QT interval and have a possible or conditional risk of Torsades de Pointes (TdP) [10], which could deteriorate into ventricular fibrillation. Different classes of antipsychotic medications are associated with different degrees of risk for both QT_c prolongation and TdP, with the highest risks on both counts being thioridazine and IV haloperidol, whereas the lowest risks were risperidone, olanzapine, and quetiapine [32]. It is not clear why drugs with risk of TdP are also associated with increased likelihood of presentation with a non-shockable rhythm. In our dataset, we did not find a difference in presentation with shockable rhythm between those taking atypical antipsychotics versus those taking other types. Other medications may also play a role: among cases with schizophrenia, one-third were also taking antidepressants, which have also been associated with non-shockable rhythms in some studies [29]. Evidence from the Netherlands and Denmark suggests that use of non-cardiac QT prolonging drugs may have a higher risk of out of hospital SCA compared to cardiac QT prolonging drugs [33]. Finally, polypharmacy was more prevalent among schizophrenia cases than comparison cases, which may increase risk of SCA via QT-prolongation or other mechanisms. The combined evidence suggests that the benefits of combining multiple anti-psychotic and other drugs must be weighed against their risks.

Additional factors potentially influencing both risk of SCA and survival following SCA may include genetic causes underlying both schizophrenia and cardiovascular disease or arrhythmogenic substrates [34]. For example, in a study using a "genetic-pleiotropy-informed" method for new gene discovery, 25 loci associated with schizophrenia were identified, and of these, 10 were also associated with cardiovascular disease risk factors [35]. More specifically for arrhythmia risk, ion channel mutations are known to play a role in risk of sudden cardiac death [36] and increasing evidence suggests that they are also important in susceptibility to schizophrenia [37,38]. Finally, non-genetic factors such as an unfavorable metabolic profile, decreased peak oxygen uptake [39] and systemic inflammation in schizophrenia may also increase risk for early circulatory mortality [40].

Some risk factors and clinical conditions, including smoking, COPD, and seizure disorder were more prevalent among individuals with schizophrenia and may play a role in both increasing risk of SCA overall and in risk of presentation with a nonshockable rhythm. Future research is warranted to evaluate other potential factors such as gene-environment interactions.

4.1. Limitations

Our community-based study was reliant on the availability of individual medical records. While availability of medical records did not differ between schizophrenia and comparison cases, our findings may not account for under-diagnosed comorbidities in the schizophrenia

group [22,41]. In our study, schizophrenia cases were more likely than other SCA cases to have a history of recreational drug use. However, it is unlikely that drug use played an immediate role in the SCAs included in this study because our adjudication process excluded any SCA that occurred due to a likely overdose based on EMS, medical examiner, or physician assessment, or if illicit drugs were detected on toxicology screen. Because the population included in this study was approximately 80% white European descent, it is possible that findings would not be generalizable to more racially or ethnically diverse populations.

4.2. Conclusions

Individuals with schizophrenia who suffered SCA had significantly worse post-arrest survival outcomes than individuals with no history of schizophrenia who suffered SCA despite having similar arrest circumstances and pre-arrest clinical profile. The poor survival outcomes with schizophrenia are at least partly due to a much higher presentation with non-shockable rhythms. Most cardiovascular risk factors were similar, while existing cardiovascular disease was less prevalent among SCA cases with schizophrenia. There has been little previous research into this phenomenon, and further investigation to identify factors that may improve survival is warranted.

Disclosures

All authors have no financial interests to disclose.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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