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Association Between Psychiatric Comorbidities and Mortality in Epilepsy

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ABSTRACT

Objective: To explore the impact of psychiatric comorbidities on all-cause mortality in adults with epilepsy from a cohort of patients admitted for video-electroencephalogram monitoring (VEM) over two decades.

Methods: A retrospective medical records audit was conducted on 2709 adults admitted for VEM and diagnosed with epilepsy at three Victorian comprehensive epilepsy programs from 1995-2015. 1805 patients were identified in whom the record of a clinical evaluation by a neuropsychiatrist was available, excluding 27 patients who died from a malignant brain tumour known at the time of VEM admission. Epilepsy and lifetime psychiatric diagnoses were determined from consensus opinion of epileptologists and neuropsychiatrists involved in the care of each patient. Mortality and cause of death were determined by linkage to the Australian National Death Index and National Coronial Information System.

Results: Compared to the general population, mortality was higher in people with epilepsy (PWE) with a psychiatric illness (standardised mortality ratio [SMR] 3.6) and without a psychiatric illness (SMR 2.5). PWE with a psychiatric illness had greater mortality compared to PWE without (hazards ratio 1.41, 95% confidence interval 1.02-1.97) after adjusting for age and sex. No single psychiatric disorder by itself conferred increased mortality in PWE. The distribution of causes of death remained similar between PWE with psychiatric comorbidities and those without.

Conclusion: The presence of comorbid psychiatric disorders in adults with epilepsy is associated with increased mortality, highlighting the importance of identifying and treating psychiatric comorbidities in these patients.

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SUMMARY BOX

- Adults with epilepsy with comorbid psychiatric illness have an elevated risk of mortality on top of that conferred by having epilepsy alone, in the drug resistant epilepsy population.
- Adults with epilepsy with and without comorbid psychiatric illness have a similar distribution of cause of death.
- Sudden unexplained death in epilepsy (SUDEP) remains a major cause of death in the drug resistant epilepsy population.

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INTRODUCTION

People with epilepsy (PWE) face an increased risk of mortality compared to the general population,[1-6] with a standardised mortality ratio (SMR) of 2.3 reported by population-based studies.[2] Epilepsy is associated with high rates of psychiatric comorbidities and suicide,[7-11] traditionally attributed to the psychosocial impact, stigmatisation and mental anguish relating to experiencing seizures.[12 13] However, it is increasingly being recognised that psychiatric comorbidities have a neurobiological connection with the epileptic condition, with growing evidence suggesting a bidirectional relationship.[14-20]

The detrimental impact of psychopathology in PWE extends beyond the subjective experience of poorer quality of life. Patients with psychiatric disorders prior to epilepsy diagnosis are more likely to develop drug-resistant epilepsy.[21] Similarly, higher scores of neuropsychiatric symptoms predict poorer response to antiepileptic medication in adherent patients independent of other clinical predictors, including seizure frequency prior to commencing treatment, epilepsy syndrome and epileptiform abnormalities on electroencephalography (EEG).[22]

PWE with psychiatric comorbidities represent a potentially vulnerable subpopulation with greater risk of mortality, however this has been little explored, with existing research focussing on premature causes of death.[10] This study utilises a large cohort of adult inpatients admitted at three video-EEG monitoring (VEM) units over 20 years to: a) investigate all-cause mortality in PWE with psychiatric comorbidities, and b) identify psychiatric diagnoses that may benefit from more careful management because of an increased risk of mortality.

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METHODS

Study population and design

We performed a retrospective analysis from a cohort of 5508 patients consecutively admitted for VEM to one of three comprehensive epilepsy programs in Melbourne, Victoria, Australia; The Royal Melbourne Hospital (n=2306), St Vincent's Hospital (n=1244), and Austin Hospital (n=1958) between 1st January 1995 and 31st December 2015.

Patients were admitted either for definitive diagnosis of an undiagnosed uncontrolled seizure disorder or for further characterisation of difficult to control epilepsy to guide further management, including potential surgery. Data collection was performed by review of the medical records of each patient's admission.

Epilepsy diagnosis

All patients were routinely evaluated with thorough examinations of their clinical history, 1-3 weeks of continuous VEM, and neuroimaging using a 1.5T/3.0T magnetic resonance imaging (MRI) with an epilepsy sequence protocol. Single photon emission tomography and fluorodeoxyglucose positron emission tomography studies were also performed when clinically indicated to aid localisation of epileptic focus. Epilepsy diagnoses were made at weekly multidisciplinary meetings by consensus opinion of experienced epileptologists in accordance with the International League Against Epilepsy (ILAE) guidelines[23 24] on the basis this evaluation. Captured seizures during VEM with ictal EEG recording were not required for the diagnosis of epilepsy to be made, although ictal and or inter-ictal epileptiform EEG discharges were recorded in the majority of patients in whom epilepsy diagnosis was made. Epilepsies were classified in accordance with the 2017 ILAE classification system[25] into epilepsy types defined as 1) focal, 2) multifocal, 3) generalised

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and 4) combined focal and generalised epilepsy, as well as into epilepsy syndromes of temporal lobe epilepsy (TLE), extra-temporal lobe epilepsy (ETLE), genetic generalised epilepsy (GGE), and epileptic encephalopathy (EE) where enough diagnostic information was available. Epilepsies were further classified according to lesionality. Lesional epilepsy was defined as the presence of a potentially epileptogenic structural lesion on MRI. Mesial temporal sclerosis (MTS) was used to describe lesional epilepsy in patients with TLE who had compatible MRI findings. Non-lesional epilepsy was defined by the absence of imaging evidence of pathology but clear epilepsy syndrome localisation on VEM.

Psychiatric diagnosis

All patients were routinely referred for neuropsychiatric assessment with the aim of identifying psychiatric comorbidities that would affect management or confound an epilepsy diagnosis. Patients were formally assessed by a neuropsychiatrist prior to the weekly multidisciplinary VEM meeting. Psychiatric diagnoses were informed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) -IV and DSM-V. Psychiatric diagnoses were categorised into a lifetime history of depressive, anxiety, psychotic, substance misuse, and personality disorders with supervision by a neuropsychiatrist (DV). Psychotic disorders included post-ictal and inter-ictal psychoses, and excluded ictal psychoses.

Exclusion criteria

Patients were excluded from analyses if they did not have a formal epilepsy diagnosis after comprehensive evaluation (n=2116), were under 18 years at time of admission (n=683), died from a high-grade brain tumour known at admission (n=27), or if they had incomplete neuropsychiatric assessment data (n=877). Reasons for incomplete neuropsychiatric data included declined assessments, unsuitability for assessment due to intellectual disability or

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mutism, discharge prior to assessment, time constraints leading to incomplete assessment, and lost reports. Patients under 18 years at admission were excluded to maintain consistency within the cohort as two of the three centres are exclusively adult hospitals that do not routinely admit children for VEM, and these patients are likely to represent a more severe group with refractory epilepsy in childhood. After exclusion criteria were applied, 1805 patients were included for analysis. This cohort overlapped with that included in a recent report from our group focussing on mortality in patients with psychogenic non-epileptic seizures.[6]

Ascertainment of mortality

Subjects were followed up from their VEM admission until June 2018. Mortality and cause of death were ascertained by linkage at this date to the Australian National Death Index (NDI), a database listing all deaths in Australia since 1980. Underlying causes of death extracted from the NDI were reported as International Classification of Diseases (ICD) -10 codes derived from the primary cause of death listed on Australian death certificates. The cohort was also linked to the Australian National Coronial Information System (NCIS), a database of complete coronial, autopsy, and toxicology reports for all patients with reportable deaths since 1st July 2000 under The Coronial Act. Where subjects received a post-mortem examination, cause of death was refined based on data from the NCIS. Cases of sudden unexpected death in epilepsy (SUDEP) were reviewed independently by two epileptologists (TOB and PP) and classified according to Nashef et al [26] criteria.

Statistical analyses

For calculation of SMRs, expected number of deaths were estimated from applying published age-, sex- and year-specific mortality rates in 1995 to 2015 from the Australian Bureau of

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Statistics (ABS).[27] For patients who died after 2015, the 2015 general population mortality rates were applied.

Multivariable Cox proportional hazards regression was performed to assess the hazard ratio (HR) of mortality between PWE with psychiatric comorbidities and PWE without, adjusting for age at VEM and sex. This was also used to compare mortality between PWE with specific categories of psychiatric comorbidities and PWE with no history of a psychiatric disorder.

Statistical significance level was set at $p<0.05$. All statistical tests were performed by using *Stata* version 15 (StataCorp, College Station, TX).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Human Research Ethics Committees of St. Vincent's Hospital, Melbourne Health and Austin Health (HREC/15/SVHM/110). For data linkage to the NDI, approval was granted by the Australian Institute of Health and Welfare Ethics Committee (EO2016/1/226). Access to the NCIS was granted by the Justice Human Research Ethics Committee (CF/16/8896).

Data Availability

Data used in analysis is available from the corresponding author upon request from any qualified researcher for a period of 12 months following publication.

RESULTS

Demographics

Demographics of the study population (n=1805) and categorisation of patients with a lifetime history of a psychiatric disorder are summarised in table 1. 52% of patients had a history of a

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psychiatric disorder. Demographics of patients included for analyses compared to patients who were excluded due to lack of complete neuropsychiatric data are presented in the supplementary material (table e-1, http://links.lww.com/CPJ/A300).

Mortality of PWE with psychiatric comorbidities

Mortality of PWE with (SMR 3.6, 95% confidence interval [CI] 2.9-4.4; table 2) and without a lifetime history of a comorbid psychiatric disorder (SMR 2.5, 95% CI 1.9-3.2; table 2) were both greater than that of the general population. On direct comparison using Cox regression analysis adjusting for the effects of age and sex, mortality remained elevated in PWE with comorbid psychiatric disorders compared to PWE without (HR 1.41, 95% CI 1.02-1.97; table 3; figure 1A). In patients where the epilepsy type (n=1624) and syndrome (n=1537) were known, mortality remained elevated in PWE with comorbid psychiatric disorders compared to PWE without after additional adjustment for epilepsy type and lesionality (HR 1.54, 95% CI 1.05-2.24; table e-2, http://links.lww.com/CPJ/A300), and epilepsy syndrome and lesionality (HR 1.51, 95% CI 1.03-2.20; table e-3, http://links.lww.com/CPJ/A300). A subgroup Cox regression analysis (n=417) adjusting for the lifetime presence of tonic-clonic seizures (TCS), which encompassed generalised TCS in patients with GGE and bilateral TCS in patients with forms of epilepsy other than GGE, demonstrated no elevated mortality in PWE with comorbid psychiatric disorders (table e-4, http://links.lww.com/CPJ/A300).

On examination of relative risk (RR) of mortality stratified by age groups, there was evidence of increased mortality in PWE with a lifetime history of a psychiatric comorbidity compared to PWE without in the under 30 age group (figure e-1, http://links.lww.com/CPJ/A300), however this did not reach the predefined statistical threshold. Within PWE with a lifetime history of psychiatric comorbidity, the RR of mortality in the under 30 age group was significantly greater than the RR of mortality in the 40-49, 50-59 and over 60 age groups (figure e-1, http://links.lww.com/CPJ/A300). Within PWE with no lifetime history of

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psychiatric comorbidity, the RR of mortality in the under 30 age group was significantly greater than the RR of mortality in the 50-59 and over 60 age groups (figure e-1, http://links.lww.com/CPJ/A300).

Mortality of PWE with specific psychiatric comorbidities

On Cox regression and survival analyses of the effect on mortality of specific psychiatric comorbidities in epilepsy, PWE with a single comorbid depressive, anxiety, psychotic, substance misuse or personality disorder had no increased risk of mortality compared to PWE with no psychiatric comorbidity (table 3; figures 1B, 1C, 1D, 1E, 1F). In patients where the epilepsy type and syndrome were known, no difference was observed between PWE with a single psychiatric comorbidity compared to PWE with no psychiatric comorbidity, after adjusting for the effects of epilepsy type, syndrome and lesionality (tables e-2, e-3, http://links.lww.com/CPJ/A300). When the effect of specific psychiatric comorbidities on mortality regardless of the presence of other psychiatric comorbidities was examined, no significant difference was observed in mortality between PWE with a specific comorbid psychiatric disorder and PWE without (tables e-5A, e-5B, e-5C, e-5D, e-5E, http://links.lww.com/CPJ/A300).

Cause of death

Of 147 deceased PWE over the study period, 87 had a lifetime history of a psychiatric disorder. Diseases of the nervous system were the most common cause of death, followed by neoplasms and external causes of mortality for both PWE with a psychiatric comorbidity and PWE without (table 4). 36 patients met criteria for either definite (n=29) or probable SUDEP (n=7), with the majority of these deaths (89%) occurring in patients aged under 50. The rates of definite or probable SUDEP were 1.62 and 2.49 cases per 1000 person-years in PWE with

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no lifetime psychiatric comorbidity and in PWE with psychiatric comorbidity respectively, however the difference did not reach statistical significance.

DISCUSSION

This study demonstrates that a lifetime history of any comorbid psychiatric disorder confers a significantly greater risk of mortality in PWE on top of the risk due to epilepsy alone. The subgroup analyses suggest that this is irrespective of epilepsy type, syndrome or lesionality.

Interestingly, there was no diagnostic category of psychiatric disorders (depressive, anxiety, psychotic, substance misuse or personality disorders) which specifically conferred an increased risk of mortality in PWE with a single comorbid psychiatric diagnosis (table 3). This discrepancy may be due to smaller sample sizes and the heterogeneity of presentations within these categories. Additionally, there may be factors other than psychiatric diagnosis that may increase mortality in PWE, such as severity of psychiatric illness or having multiple comorbid psychiatric disorders, which should be explored in future studies.

Consistent with previous studies,[28 29] neoplasms and diseases of the circulatory system were among the four most common causes of death in both PWE with and without psychiatric comorbidities. We report a higher prevalence of deaths from diseases of the nervous system than previous studies. This likely reflects our hospital-based cohort which selects for more severe, drug-resistant epilepsy compared to community-based cohorts of most previous studies. We also found several cases of deaths that were reported as diseases of the nervous system only after coronial examination. It is possible that previous studies that did not have access to coronial or autopsy data may have underestimated the true prevalence of diseases of the nervous system in PWE.

The prevalence of external causes of death (i.e. accidental deaths or suicides) in both PWE with and without psychiatric comorbidities was considerably greater than previous mortality

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studies in PWE, which have largely been community-based. Although both groups had comparable rates of death from external causes (table 4), PWE with psychiatric comorbidities had five cases of confirmed suicide and one case of potential suicide compared to only two cases of confirmed suicide in PWE without psychiatric comorbidities. This consistent with a recent study conducted by Fazel et al[10] demonstrating an increased risk of death due to suicide in PWE with psychiatric disorders compared to PWE without. Our findings show that accidents remain an important and major cause of death in patients with treatment refractory epilepsy, and confirm that PWE with psychiatric comorbidities remain at especially high risk of death from suicides. Moreover, suicides were still more common in PWE with comorbid psychiatric illness despite extensive psychiatric evaluation, highlighting the importance of timely psychiatric management and follow up.

Overall, 24% of deaths in our cohort were due to definite or probable SUDEP, accounting for the majority of deaths from diseases of the nervous system. The rate of SUDEP in our cohort is consistent with the range of 1.2-6.3 cases per 1000 person-years reported in previous studies.[2] We found a trend for the rate of definite or probable SUDEP per 1000 person-years in PWE to be higher in those with a lifetime history of psychiatric comorbidity (2.49) compared with those without (1.62). No previous SUDEP studies have examined the effects of psychiatric comorbidities. Only one previous study investigating the prevalence of SUDEP in PWE has been based mainly on autopsy findings, which reported the highest incidence of SUDEP (6.3 per 1000 person-years).[30] However this study only examined patients referred for epilepsy surgery, potentially reflecting a population with more severe epilepsy, while our cohort included both patients referred for surgery and patients referred for further medical management. Our cohort is more than 8 times larger with over double the length of follow up time. Consistent with previous literature, the prevalence of SUDEP was greatest in ages 20-40 years.[31 32] Our results confirm the danger of SUDEP in drug resistant epilepsy, in particular those with a history of psychiatric comorbidities, and the importance of addressing this risk in this vulnerable group of patients.

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Otherwise, we found that both PWE with psychiatric comorbidities and PWE without had a similar distribution of causes of death. This finding raises the question of whether the presence of a psychiatric comorbidity may augment epilepsy via shared underlying pathological mechanisms such as common changes in neuroanatomy or neurotransmitter disturbance, genetic susceptibility or environmental factors. Several previous studies have established a complex bidirectional relationship between epilepsy and psychiatric disorders, whereby psychiatric illness may represent a marker of decreased seizure threshold and/or the presence of seizures may increase one's susceptibility to develop psychiatric illness.[16 17 30 33-38] We did not explore this relationship as data relating to the age of onset of epilepsy and psychiatric disorders were not systematically available.

The key strengths of our study include its large sample size, utilisation of VEM and specialist evaluation, which is considered to be gold standard for epilepsy diagnosis. Mortality data was accurate and complete through linkage to the NDI and NCIS. Psychiatric diagnoses were determined by full neuropsychiatric assessment. While previous studies have found some psychiatric diagnoses, such as anxiety, to be under-detected without the use of structured diagnostic instruments,[39] clinical neuropsychiatric assessment may be more sensitive in detecting atypical symptoms in other psychiatric diagnoses which are not uncommon in PWE.

Limitations of our study include its retrospective nature, number of deceased patients despite our sizeable cohort, an average follow up time of 10 years, and that patients admitted for VEM evaluation often have drug-resistant epilepsy, so results may not be generalisable to a community-based population. A significant proportion of patients were excluded from analyses due to lack of neuropsychiatric data. Of note, there was a greater representation of focal epilepsies in those who had neuropsychiatric data available compared to those who did not. There is thus a potential selection bias for patients who were referred for epilepsy surgery. Excluded patients may represent a more unwell population due to the higher proportion of generalised epilepsy who are non-surgical candidates, which may also explain

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the substantially larger proportion of deaths in this group. Additionally, although our exclusion of individuals under 18 at the time of admission does not exclude childhood-onset epilepsy patients presenting in adulthood, extrapolation of results to patients with refractory epilepsy in childhood is limited.

We used the lifetime presence of TCS as a surrogate marker for epilepsy severity, however as this variable was only available for a quarter of the total cohort, it was only adjusted for in a subgroup analysis (table-4). Although the findings of this analysis suggest that the effect of epilepsies that manifest as TCS may be a potential confounder, the lifetime presence of TCS is a relatively poor surrogate for epilepsy severity, especially at the time of death. A number of other potential confounding variables were not adjusted for in our analysis, such as whether remission had been achieved, number of previously failed antiepileptic medications (which may be more robust markers of epilepsy severity) and medical comorbidities including those associated with psychiatric conditions. The potential confounding effect of polypharmacy, i.e. whether particular combinations of antiepileptic drugs and psychotropic agents may increase or decrease seizure threshold, is poorly understood and is worth exploring in future studies.

In conclusion, this study found that the presence of comorbid psychiatric disorders in adult PWE is associated with increased all-cause mortality, with a quarter of patients dying of SUDEP. These findings highlight the importance of identifying and treating psychiatric comorbidities in PWE.

APPENDIX 1: AUTHORS

Name	Location	Contribution
Gerard Tao, MD	The University of Melbourne	Acquisition of data, interpretation of data, drafting of the manuscript

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		for intellectual content
Clarissa Auvrez, MD	The University of Melbourne	Acquisition of data, interpretation of data, drafting of the manuscript for intellectual content
Russell Nightscales, BSc(Hons)	Monash University, Melbourne	Major role in acquisition of data, interpretation of data
Sarah Barnard, MIPH	Monash University, Melbourne	Major role in acquisition of data, interpretation of data
Lara McCartney, MBBS	The University of Melbourne	Acquisition of data, interpretation of data, revised the manuscript for intellectual content
Charles B. Malpas, PhD	The University of Melbourne	Oversight of study design, interpretation of data, revised the manuscript for intellectual content
Piero Perucca, MD	Monash University, Melbourne	Role in study design, data collection and interpretation, revised the manuscript for intellectual content, reviewed NCIS data to classify categories of sudden death

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Zhibin Chen, MBiostat, PhD	Monash University, Melbourne	Statistical analysis of data and production of figures
Sophia Adams, MBBS	The University of Melbourne	Major role in acquisition of data, interpretation of data, revised the manuscript for intellectual content
Anne McIntosh, PhD	The University of Melbourne	Oversight of study design, interpretation of data, revised the manuscript for intellectual content
Sophia Ignatiadis, MSc	The University of Melbourne	Acquisition of data, interpretation of data
Patrick O'Brien, MBBS	The University of Melbourne	Acquisition of data, interpretation of data
Mark J. Cook, MD	The University of Melbourne	Role in study design, revised the manuscript for intellectual content
Patrick Kwan, MD	The University of Melbourne	Role in study design, revised the manuscript for intellectual content
Samuel F. Berkovic, MD	The University of Melbourne	Principle investigator, oversight of study design, interpretation of data, revised the manuscript for

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		intellectual content
Wendyl D'Souza, MBChB, PhD	The University of Melbourne	Principle investigator, oversight of study design, interpretation of data, revised the manuscript for intellectual content
Dennis Velakoulis, MBBS	The University of Melbourne	Principle investigator, oversight of study design, interpretation of data, revised the manuscript for intellectual content
Terence J. O'Brien, MD	Monash University, Melbourne	Principle investigator, oversight of study design, interpretation of data, drafting of the manuscript for intellectual content, reviewed NCIS data to classify the categories of sudden death

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TABLES

Table 1

Patient demographics by presence of a psychiatric comorbidity (n=1805)

	Patients who had a complete neuropsychiatric evaluation (n=1805)						
Psychiatric comorbidity status	**No Psychiatric Disorder**	**Any Psychiatric Disorder**	**Depressive Disorder**	**Anxiety Disorder**	**Psychotic Disorder**	**Substance Misuse Disorder**	**Personality Disorder**
Number (%)	868 (48)	937 (52)	670 (37)	231 (13)	135 (7)	214 (12)	121 (7)
Age at VEM, median (IQR), years	35 (26-46)	37 (29-47)	38 (30-48)	36 (29-47)	37 (30-47)	35 (27-43)	35 (26-45)
Sex – Female (%)	465 (54)	534 (57)	392 (59)	165 (71)	65 (48)	88 (41)	67 (55)
Follow up duration, median	9 (4-14)	9 (5-13)	9 (5-13)	8 (5-12)	10 (4-15)	8 (5-12)	11 (7-16)

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(IQR), years							
Number deceased	60	87	63	16	15	19	14

VEM, video-encephalogram monitoring; IQR, interquartile range

Table 2

Age-sex-year specific standardised mortality ratios

Psychiatric Diagnosis	**Sex**	**Observed Death**	**Expected Death**	**Standardised Mortality Ratio (95% CI)**
No Psychiatric Disorder	F	26	9.6	2.7 (1.9 – 4.0)
	M	34	15	2.3 (1.6 – 3.2)
	Total	**60**	**24**	**2.5 (1.9 – 3.2)**
Any Psychiatric Disorder	F	41	12	3.3 (2.4 – 4.5)
	M	46	12	3.8 (2.9 – 5.1)
	Total	**87**	**24**	**3.6 (2.9 – 4.4)**

CI, confidence interval

Table 3

Cox proportional hazards model of time to death by psychiatric disorders

	Hazard Ratio (95% CI)					
	Any Psychiatric	**Depressive Disorder**	**Anxiety Disorder**	**Psychotic Disorder**	**Substance Misuse**	**Personality Disorder**

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	Disorder (n=1805)	**(n=1235)**	**(n=933)**	**(n=923)**	**(n=928)**	**(n=912)**
Psychiatric comorbidity status vs No psychiatric disorder	1.41 (1.02 – 1.97)	1.45 (0.96 – 2.21)	0.77 (0.24 – 2.47)	1.66 (0.72 – 3.86)	1.26 (0.50 – 3.14)	1.35 (0.58 – 3.16)
Age at VEM	1.04 (1.02 – 1.05)	1.04 (1.02 – 1.05)	1.03 (1.01 – 1.05)	1.03 (1.02 – 1.05)	1.04 (1.02 – 1.05)	1.04 (1.02 – 1.06)
Male sex	1.54 (1.11 – 2.13)	1.58 (1.06 – 2.36)	1.45 (0.88 – 2.39)	1.60 (0.98 – 2.61)	1.38 (0.84 – 2.26)	1.49 (0.91 – 2.43)

CI, confidence interval; VEM, video-encephalogram monitoring

Table 4

Distribution of cause of death by psychiatric comorbidity

	Number of deceased (% of deceased of each subpopulation)		
Cause of death according to ICD-10-CM Chapter Codes	**No Psychiatric Disorder**	**Any Psychiatric Disorder**	**Total**
I Certain infectious and parasitic diseases	0 (0)	1 (1)	1 (1)
II Neoplasms	11 (18)	13 (15)	24 (16)
IV Endocrine, nutritional and metabolic diseases	0 (0)	5 (6)	5 (3)

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V Mental and behavioural disorders	2 (3)	1 (1)	3 (2)
VI Diseases of the nervous system	20 (33)	28 (32)	48 (33)
SUDEP (definite or probable)	*14 (23)*	*22 (25)*	*36 (24)*
IX Diseases of the circulatory system	7 (12)	12 (14)	19 (13)
X Diseases of the respiratory system	3 (5)	3 (3)	6 (4)
XI Diseases of the digestive system	2 (3)	0 (0)	2 (1)
XIV Diseases of the genitourinary system	3 (5)	0 (0)	3 (2)
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2 (3)	7 (8)	9 (6)
XIX Injury, poisoning and certain other consequences of external causes	0 (0)	1 (1)	1 (1)
XX External causes of morbidity and mortality	10 (17)	16 (18)	26 (18)
Unintentional causes of death	*8 (13)*	*10 (11)*	*18 (12)*
Confirmed suicide	*2 (3)*	*5 (6)*	*7 (5)*
External cause of death of undetermined intent	*0 (0)*	*1 (1)*	*1 (1)*
Total number of deceased patients	60	87	147

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FIGURE TITLES AND LEGENDS

Figure 1. Kaplan Meier plots of survival comparing PWE with and PWE without psychiatric comorbidities.

(A-F) The navy line represents the cumulative probability of death for PWE with no psychiatric comorbidities admitted for video-encephalogram monitoring (VEM) over a period of 20 years. The maroon lines represent the cumulative probability of death in the groups of PWE with any psychiatric comorbidity, PWE with only depressive disorders, PWE with only anxiety disorders, PWE with only psychotic disorders, PWE with only substance misuse disorders, and PWE with only personality disorders admitted for VEM over a period of 20 years in parts A-F respectively. Univariable Cox proportional hazards regression was used to compare the mortality between PWE with no psychiatric comorbidities and the respective group in each part.

(A) In comparison to PWE with no psychiatric comorbidities, a significantly increased hazard ratio of mortality was observed in PWE with any psychiatric comorbidity (hazard ratio [HR] 1.41, 95% confidence interval [CI] 1.02-1.97).

(B) In comparison to PWE with no psychiatric comorbidities, no significant difference was observed in the hazard ratio of mortality in PWE with comorbid depressive disorders only (HR 1.45, 95% CI 0.96-2.21).

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(C) In comparison to PWE with no psychiatric comorbidities, no significant difference was observed in the hazard ratio of mortality in PWE with comorbid anxiety disorders only (HR 0.77, 95% CI 0.24-2.47).

(D) In comparison to PWE with no psychiatric comorbidities, no significant difference was observed in the hazard ratio of mortality in PWE with comorbid psychotic disorders only (HR 1.66, 95% CI 0.72-3.86).

(E) In comparison with PWE with no psychiatric comorbidities, no significant difference was observed in the hazard ratio of mortality in PWE with comorbid substance misuse disorders only (HR 1.26, 95% CI 0.50-3.14).

(F) In comparison with PWE with no psychiatric comorbidities, no significant difference was observed in the hazard ratio of mortality in PWE with comorbid personality disorders only (HR 1.35, 95% CI 0.58-3.16).

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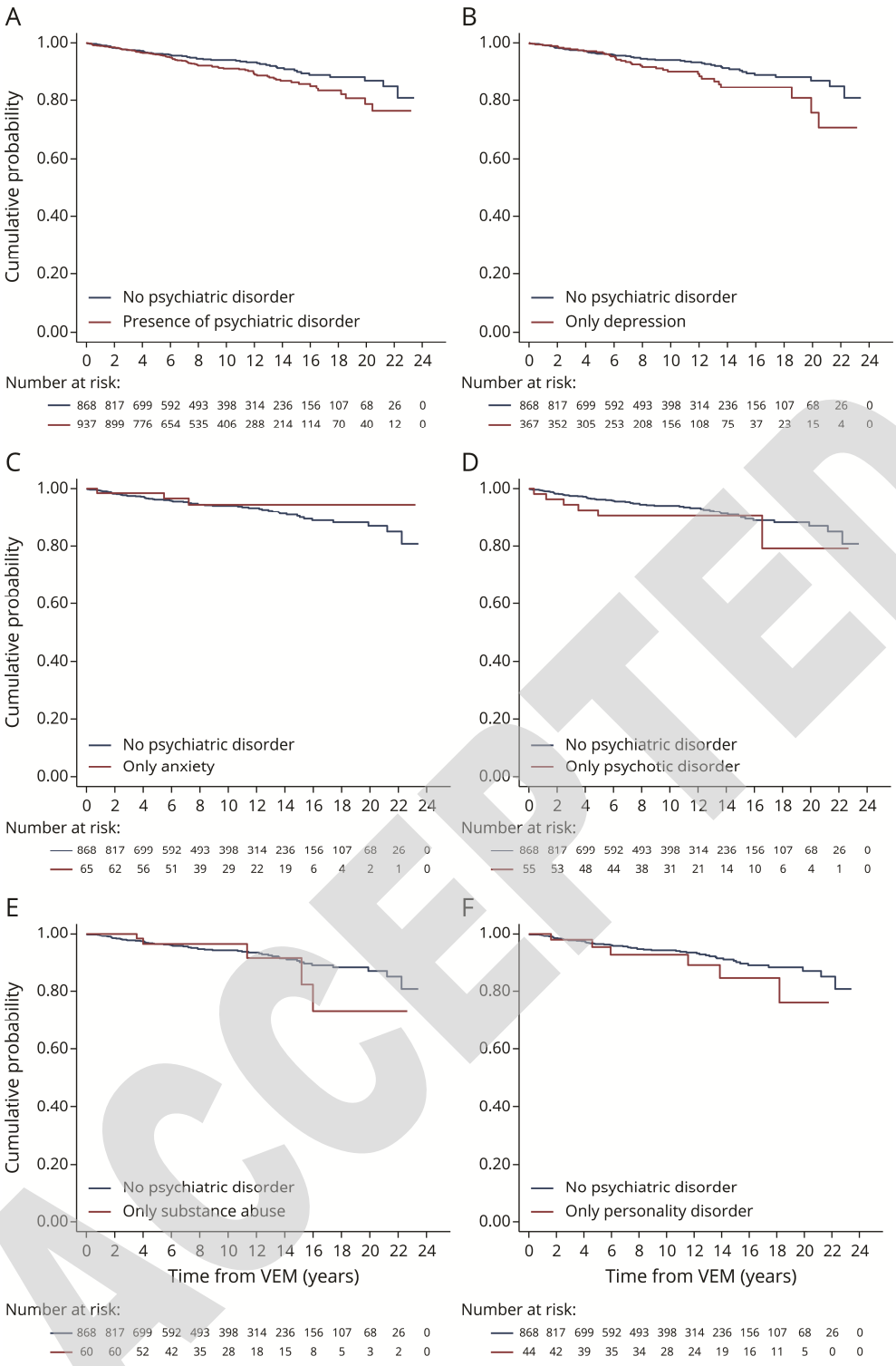

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