Mortality risk in a population of patients treated for gambling disorders: results of a follow-up study

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ORIGINAL ARTICLES AND REVIEWS

Abstract
Aims. To examine mortality risk and causes of death in a cohort of a population of patients treated for gambling disorders in northern Italy from 1992 to 2019.
Methods. Cohort study.
Results. Half of the patients were diagnosed with psychiatric disorders, substance use disorder or alcohol dependence. The excess mortality compared to the general population (SMR) was 1.16 (0.85-1.58), more elevated among females aged 40 to 59 and males aged 20 to 29. Females had higher SMRs for all cancers and suicide; males for malignant neoplasm of liver, of lung, of prostate, and of bladder.
Conclusions. Despite patients increasing, subjects who most turn to the services are the most serious ones, in older age, with comorbid mental disorders and with a compromised health status. This is reflected in the high risk of death for all cancers.

INTRODUCTION

Pathological gambling (PG) is characterized by the presence of persistent and recurrent maladaptive gambling behaviour the person is unable to adequately control [1]. Problem gambling is a term used when an individual has developed some problems related to gambling but does not fulfil the PG diagnostic criteria [2].

First recognized in DSM-III [3], PG was classified as a disorder of impulse control in DSM-5 [4] and the disorder was moved to the chapter on substance-related and addictive disorders [5]. To reduce the stigma attached to the term pathological gambling, there is now a tendency to use the term gambling disorders (GD) [6].

There are strong associations between gambling participation and problem gambling [7]. Adult problem gambling prevalence rates worldwide in the past 12 months are mostly within a range of 0.5% and 3.0%, with three to four times as many people reporting subclinical problems and harm [8, 9] and is highly comorbid with other mental disorders [10], substance dependence [11], alcohol dependence [12], and cigarette smoking [13]. In Italy, the estimate of the prevalence of problem gamblers in the general population (15-64 years) was

estimated from 0.5% to 2% in 2019 [14]. Furthermore, given the differences in the diagnostic criteria for PG and GDs (as defined in DSM-5), it is possible that future studies could yield slightly higher prevalence rates, as a GD diagnosis requires one less diagnostic criterion than PG [15].

A significant percentage of gamblers develops clinically relevant gambling problems [16], but only 10% seek treatment in clinic-based programs [17]. Many surveys found that approximately half of people classified as "life-time" pathological or problem gamblers did not report experiencing problems currently, implying that a substantial proportion cease having problems [18].

The increasing prevalence of gamblers in recent years [19-21], and the fact that a significant percentage of them do not seek treatment in clinic-based programmes, make it necessary to study morbidity in this population and mortality linked to the emergence of social and health problems. In particular, cohort studies are needed about overall mortality risk and causes of death.

GD are associated with several medical disorders,

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particularly tachycardia, angina, cirrhosis and other liver disease [22], arteriosclerosis and any heart condition [23], chronic medical conditions and obesity [24, 25]. Furthermore, it was reported that PGs suffer from physical symptoms, such as fatigue, headaches, gastric pain, nausea [26], heartburn, and backache [27].

As for suicide, an association between gambling problems and suicidal ideation [28], suicide attempts [29] and suicide completed was found [30, 31] and pathological gambling should be seen as a chronic condition with a similar risk for suicidal ideation and behaviour as with other mental illnesses [32].

As regards the risk of death, there is only one study on general mortality in patients with a GD diagnosis, in which the first cause of death was suicide, followed by all cancers and diseases of the circulatory system [33]. A mortality excess with respect to the general population of 1.8 (95% CI 1.4-2.2) was reported, higher among females and also among subjects aged 29 to 49, more elevated for suicide.

In Italy, PGs can seek treatment in Services Dedicated to Drug Addicts (SERD), in Community Mental Health Centres (CMHC) or in hospital wards. In these three different public settings, treatment is covered by the National Health Service and is voluntary cohorts.

The aim of this study was to examine mortality risk and causes of death in a cohort of patients treated for GD in residents in the Emilia-Romagna region (northern Italy), over a 27-year follow-up period (from 1992 to 2019). Our aims were to estimate overall crude mortality rates and excess mortality by age, gender, substance use disorders, alcohol dependence, and psychiatric diagnoses

METHODS

We selected subject resident in the Emilia-Romagna region, aged over 17 years, referred for the first time to hospitals, SERDs and CMHCs with an ICD-9 (312.31) (ICD: International Classification of Diseases) or ICD-10 (F 63.0) diagnosis of pathological gambling in the period from 01/01/1992 to 31/12/2018. The cases were selected from the IT systems of SERDs (9 units), CMHCs (11 units), and hospitals (10 facilities). Each person may have sought treatment in all these services and the information was collected at the first contact.

Data were retrospectively collected from the various digitalized archives: the PG diagnosis in SERDs could be made at the first contact or in the subsequent periods, in CMHCs and hospitals it could have been concomitant with other psychiatric diagnoses. The date of first access considered in this study refers to the first PG diagnosis.

To be noted that DSM diagnosis was not recorded in the digitalized archives and services did not use ICD-11 codes during the study period.

The cohort was made up of 826 subjects, 20% female, 12% non-native, with an average age at first admission of 47.6 years.

All the variables were drawn from the electronic databases: age, gender, country of birth, residence, diagnoses, services addressed, date of first contact, and of diagnostic assessments.

To identify any other mental disorder, drug dependence, or alcohol dependence in the entire period, the cohort was cross-checked with the electronic data available for all subjects referring, respectively, to the hospitals, the SERDs, and the CMHCs in the metropolitan area of Bologna, and ICD-9 CM psychiatric diagnoses at first admission were included.

Person years (PY) were calculated from the first documented episode to 31 December 2019 or up to the date of death. The patients lost at follow-up were included in person-years until the date they moved out of their last known stable place of residence.

Based on the ICD9 (until 2008) and ICD10 (from 2009) codes, mortality was verified at the registry offices of the municipality where the patients were living at the end of the study period (i.e. 31 December 2019) or at death; personal identifiers were used following the rules of privacy regulation.

In keeping with Italian privacy regulations, the study design was approved by the local research ethics committee (Cod. CE: 19131).

Continuous and categorical variables were analysed with Student's t and chi-squared test, respectively. Crude mortality rates (CMRs) per thousand PY and relative confidence intervals (CI) at 95% were calculated.

In order to compare the mortality of PGs with that of the general population, the standardized mortality ratios (SMR) and the exact 95% relative confidence intervals specific for cause and sex – using as standard the relative specific mortality rates of the population of the Emilia Romagna Region – have been calculated as well. The SMR, adjusted according to age and calendar year was calculated overall and for all specific causes represented.

A Poisson regression analysis was performed to analyse the combined effect of gender, age, any psychiatric diagnosis, substance use disorders, alcohol dependence and interval from first registration on mortality risk.

Data analyses were performed using the STATA 15.1 statistical software program.

RESULTS

Follow-up continued until 31 December 2019, or until the date of death for 99% of the subjects (eight subjects were lost to follow-up). There were 4,672 at-risk PY (885 female, 3,787 male) and 39 deaths, the first of which occurred in 2003.

The number of patients has been increasing over time and 75% of subjects accessed services after 2012. As regards the first service accessed, 88% were referred to a SERD, 9% to a CMHC, and 3% to an hospital. Overall, half of them had another diagnosis: 41% were diagnosed for any psychiatric disorder (mainly neurotic and somatoform syndromes, personality and behavior disorders, depression), 10% for substance use disorders, and 8% for alcohol dependence *(Table 1)*.

In this cohort, 4.7% (39 subjects) died. Twenty-six were male (3.9% of all males), and 13 were female (7.9% of all females). Cancers (62% of all deaths) and diseases of the circulatory system (13%) were the main causes of death. We highlight five deaths for neoplasm of liver (13%), three for neoplasm of bronchus and lung (8%), and two for intentional self-harm (5%).

Table 1
Problematic gambling: patients diagnosed from 1992 to 2018 in the metropolitan area of Bologna

		Total (826)		Males (661)		Females (165)		P
		N	%	N	%	N	%	
Country of birth	Natives	724	87.7	573	86.7	151	91.5	0.092
	Non-natives	102	12.3	88	13.3	14	8.5	
Age at first admission	Mean (± standard deviation)	47.6±13.8		45.9±13.3		54.7±13.4		<0.0001
Period of first access	% ≤2000	7	0.9	7	1.1	-	-	0.110
	% 2001/2006	52	6.3	44	6.7	8	4.9	
	% 2007/2012	146	17.7	108	16.2	38	23.0	
	% 2013/2018	621	75.1	502	76.0	119	72.1	
First access	Public service for addictions	726	87.9	587	88.8	139	84.2	0.015
	Hospital	26	3.1	15	2.3	11	6.7	
	Mental Health Service	74	9.0	59	8.9	15	9.1	
Other diagnoses	Substance use disorders	80	9.7	73	11.0	7	4.2	0.008
	Alcohol dependence	68	8.2	56	8.5	12	7.3	0.616
	Any psychiatric diagnosis	337	40.8	244	36.9	93	56.4	<0.0001
Psychiatric diagnosis	Schizophrenia and other functional psychosis	36	4.4	30	4.5	6	3.6	0.612
	Mania and bipolar affective disorders	37	4.5	29	4.4	8	4.9	0.798
	Depression	89	10.8	65	9.8	24	14.6	0.194
	Neurotic and somatoform syndromes	158	19.1	108	16.3	50	30.3	<0.0001
	Personality and behavior disorders	92	11.1	67	10.1	25	15.2	0.067
	Other psychic disorders	62	7.5	47	7.1	15	9.1	0.388

The CMR for 1,000 PY were 8.35, higher for females (14.7) and for the oldest patients (<30 years CMR 3.50, 95% CI 0.49-24.85; 30/59 years CMR 3.42, 95% CI 1.90-6.18; ≥60 years CMR 23.05, 95% CI 15.80-33.60).

As regards the causes of death, the CMR in both genders was higher for all cancers, followed by diseases of the circulatory system, and external causes of death, particularly suicide *(Table 2)*.

The excess mortality compared to the general population was 1.16 (0.85-1.58), and it was not statistically significant among males or among females. We highlight elevated and statistically significant SMRs for all cancers and among subjects aged less than 30 years *(Table 3)*.

Regarding gender, females had higher statistically significant SMRs for all cancers (malignant neoplasm of the pancreas) and suicide; males had higher statistically significant SMRs for malignant neoplasm of liver, of lung, of prostate, and of bladder *(Table 2)*.

Among males, SMRs were elevated and statistically significant among subjects aged less than 30; among females, SMRs were elevated and statistically significant among patients aged from 40 to 59 *(Table 3)*.

Furthermore, we highlighted elevated statistically significant SMRs for patients with a diagnosis of schizophrenia, and personality and behavior disorders.

The combined effect of gender, age, any psychiatric diagnosis, substance use disorders, alcohol dependence and interval from registration was obtained from a Poisson regression analysis. A higher risk of death was found for patients aged more than 60 (<45 years RR 1; 45-60 years RR 2.47, 95% CI 0.70-8.75; >60 years RR 13.14, 95% CI 3.80-45.45), more elevated in the year of first contact and decreasing after three years (<1 year RR 1; 1-3 years RR 0.42, 95% CI 0.14-1.26; >3 years RR 0.13, 95% CI 0.04-0.39).

DISCUSSION

This is one of the first cohort studies, characterized by a 27-year follow-up duration, showing all the causes of death in a population of subjects treated for GD.

Our data suggest several interesting observations: the number of PGs has been increasing over time and half of them were diagnosed with psychiatric disorders, substance use disorder or alcohol dependence; all cancers are the most common cause of death, followed by diseases of the circulatory system; excess mortality compared to the general population is more elevated among females aged 40 to 59 and males aged 20 to 29.

Psychiatric comorbidity is the rule and not the exception for PGs [34], and mood/anxiety disorders, substance use disorders, impulse control disorders, and

Table 2
Crude Mortality Rates and Standardized Mortality Ratios for the most commons causes of death

	O/E	CMR	95% CI	SMR	95% CI
All causes	39/33.7	8.35	6.10-11.43	1.16	0.85-1.58
Infectious and parasitic diseases	2/1.12	0.43	0.11-1.71	1.79	0.45-7.15
Tumours/Neoplasms	24/11.6	5.14	3.44-7.66	2.07	1.38-3.08
Malignant neoplasm of stomach	2/0.11	0.43	0.11-1.71	17.41	4.35-69.60
Malignant neoplasm of liver and intrahepatic bile ducts	5/0.11	1.07	0.45-2.57	45.17	18.80-108.52
Malignant neoplasm of pancreas	2/0.15	0.43	0.11-1.71	13.22	3.31-52.87
Malignant neoplasm of bronchus and lung	3/0.42	0.64	0.21-1.99	7.07	2.28-21.91
Malignant neoplasm of prostate	3/0.09	0.64	0.21-1.99	35.43	10.46-100.57
Malignant neoplasm of bladder	2/0.07	0.43	0.11-1.71	29.93	7.49/119.67
Mental and behavioural disorders	2/1.5	0.43	0.11-1.71	1.37	0.34-5.49
Diseases of the circulatory system	5/10.2	1.07	0.45-2.57	0.49	0.20-1.18
External causes of morbidity and mortality	3/13.7	0.64	0.21-1.99	0.22	0.07-0.68
Intentional self-harm (suicide)	2/0.6	0.43	0.11-1.71	3.32	0.83-13.26
	O/E	**CMR**	**95% CI**	**SMR**	**95% CI**
Males	26/24.0	6.87	4.67-10.08	1.08	0.74-1.59
Infectious and parasitic diseases	1/0.8	0.26	0.04-1.87	1.28	0.18-9.06
Tumours/Neoplasms	14/8.8	3.70	2.19-6.24	1.59	0.94-2.68
Malignant neoplasm of liver and intrahepatic bile ducts	5/0.1	1.32	0.55-3.17	52.69	21.93-126.60
Malignant neoplasm of bronchus and lung	2/0.4	0.54	0.13-2.11	5.67	1.42-22.66
Malignant neoplasm of prostate	3/0.1	0.79	0.26-2.46	35.56	11.47-110.24
Malignant neoplasm of bladder	2/0.1	0.53	0.13-2.11	33.22	8.31-132.83
Mental and behavioural disorders	2/1.1	0.53	0.13-2.11	1.79	0.45-7.14
Diseases of the circulatory system	4/6.8	1.06	0.40-2.81	0.59	0.22-1.56
External causes of morbidity and mortality	2/9.8	0.53	0.13-2.11	0.20	0.05-0.81
Intentional self-harm (suicide)	1/0.6	0.26	0.04-1.87	1.79	0.25-12.69
	O/E	**CMR**	**95% CI**	**SMR**	**95% CI**
Females	13/9.7	14.70	8.53-25.31	1.34	0.78-2.30
Infectious and parasitic diseases	1/0.34	1.13	0.16-8.03	2.98	0.42-21.15
Tumours/Neoplasms	10/2.8	11.30	6.08-21.01	3.57	1.92-6.64
Malignant neoplasm of pancreas	2/0.0	2.26	0.57-9.04	47.48	11.88-189.86
Diseases of the circulatory system	1/3.4	1.13	0.16-8.03	0.30	0.04-2.12
External causes of morbidity and mortality	1/3.9	1.13	0.16-8.03	0.26	0.04-1.84
Intentional self-harm (suicide)	1/0.0	1.13	0.16-8.03	22.91	3.23-162.61

PY: person year; O: observed deaths; E: expected deaths; CMR: crude mortality ratio for 1000 PY; SMR: standardized mortality ratios; CI: confidence interval.

personality disorders are frequently comorbid with GD [10-12].

The CMRs for 1,000 PY were 8.35, more elevated among females and the oldest patients. Mortality rates were higher for all cancers, followed by diseases of the circulatory system and suicide. These data can be justified by the fact that they involve older subjects with high physical and psychological comorbidity. In fact, the multivariate analysis documents a higher risk of death in the year of first access to the service and for patients aged over 60.

SMRs for all causes of death were much lower than those reported by the literature regarding alcohol dependence [35], cocaine use [36] heroin use [37], and psychiatric outpatients [38]. Moreover, SMRs were lower than those reported by Karlsson and Håkansson [33], both among males and females, than for subjects aged 20 to 49.

Regarding psychiatric diagnosis, in our study SMRs were higher for patients with a diagnosis of schizophrenia and personality disorders. Notably, while SMRs of people with personality disorders is consistent with oth-

Table 3
Standardized Mortality Ratios for sex, age-group, first access service, substance disorders, alcohol dependence, psychiatric diagnosis

		Total		Males		Females	
		SMR	95% CI	SMR	95% CI	SMR	95% CI
Age-group	<30 years	7.71	1.09-54.70	7.93	1.12-56.27	-	-
	30/39 years	2.30	0.32-16.34	2.44	0.34-17.33	-	-
	40/49 years	2.22	0.83-5.91	1.80	0.58-5.59	7.21	1.02-51.18
	50/59 years	1.54	0.69-3.43	0.87	0.28-2.71	6.49	2.09-20.12
	≥ 60 years	0.98	0.67-1.43	0.98	0.62-1.56	0.99	0.51-1.90
Other diagnosis	Substance use disorders	1.48	0.48-4.60	1.68	0.54-5.21	-	-
	Alcohol dependence	1.75	0.66-4.67	2.59	0.97-6.91	-	-
	Psychiatric diagnosis	1.34	0.89-2.02	1.34	0.81-2.22	1.34	0.67-2.69
Psychiatric diagnosis	Schizophrenia and other functional psychosis	6.00	2.86-12.59	4.64	1.93-11.14	22.72	5.68-90.86
	Mania and bipolar affective disorders	1.99	0.50-7.95	2.33	0.58-9.32	-	-
	Depression	0.99	0.44-2.19	1.21	0.51-2.92	0.59	0.07-3.61
	Neurotic and somatoform syndromes	1.57	0.89-2.77	1.25	0.56-2.77	2.12	0.95-4.73
	Personality and behaviour disorders	2.72	1.30-5.71	2.20	0.92-5.29	6.66	1.67-26.64
	Other psychic disorders	1.72	0.77-3.82	1.35	0.34-5.42	1.99	0.75-5.29

SMR: standardized mortality ratios; CI: confidence interval.

er studies conducted on psychiatric outpatients, PGs with schizophrenia had higher SMRs [39].

Regarding mortality risk for diseases of the circulatory system, from various studies, it emerges that GD are associated with any heart condition, particularly arteriosclerosis [26], tachycardia, and angina [25].

Regarding suicide, mental and behavioral disorders, chronic pain, alcohol and drug abuse are the main risk factors [40, 41] and many studies have shown a high mortality risk among PCs [30-32]. Among the OCSE countries, Italy has one of the lowest suicide mortality rates [42], and crude mortality rate for suicide in 2016 in Italy (8.20 per 100,000 population) was much lower than Sweden (14.80 per 100,000) [43]. Nevertheless, mortality excess for suicide in our cohort was much lower than in the Swedish study and SMRs were statistically significant only for females, being suicide mortality risk very low for females in the general population.

Regarding mortality risk for all cancers, we highlight that GD are associated with liver disease [22], chronic medical conditions and obesity [24, 25], and PGs suffer from gastric pain, nausea [26], and heartburn [27]. Furthermore, particular lifestyles associated with GD, such as alcohol use and cigarette smoking, may have affected cancer mortality [44, 45]. Thus, changes in lifestyle (alcohol and tobacco use) must be a further relevant message for patients treated for GD.

Such as all researches based on large population, this study presents some limitations: the data used are those available from the first admission and data on the evolution of gambling habit are lacking. Moreover, data relating to alcohol use and tobacco smoking are lacking.

CONCLUSIONS

An elevated excess of mortality compared to the general population for older females and for younger males emerges from this study. Despite patients increasing, subjects who most turn to the services are the most serious ones, in older age, with comorbid mental disorders and with a compromised health status. This is reflected in the high risk of death for all cancers.

Moreover, suicide-related mortality is higher in females.

Further follow-up studies are necessary to confirm these evidences.

Author's contribution

Pavarin R designed the study, analyzed data and drafted the manuscript; Turino E, Marani S, Domenicali M and Caputo F collected the data and analyzed the literature; all Authors revised the manuscript for intellectual content.

Conflict of interest statement

All Authors declare that they have no conflicts of interest.

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