Mortality in patients addicted to opioids across 30-year follow-up

Mortalidad entre los pacientes adictos a opiáceos al cabo de 30 años de seguimiento

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Abstract

The maintenance of premature mortality among opioid users is a highly significant public health issue. The main objective is to study the causes and age of mortality recorded in the population of opiate addicts (n = 1,998) treated at the Cangas Drug Addiction Assistance Unit (Pontevedra) over more than 30 years. The causes of mortality are classified into 4 groups: overdose, disease, suicide and trauma. The average age of mortality of the patients is compared with that of the general population residing in the same health area. Throughout the study, the premature mortality of these patients remained high, although with a tendency to decrease over time: up to 1998, the mean age of death was 31.8 years compared to 47.7 years since 1998. The mean age of death was always lower than that of the general population. Disease is the most prevalent cause of mortality (84% of the deceased) with a great difference compared to the other 3 groups. Despite the reduction in infections associated with parenteral use, there are still factors associated with an unhealthy lifestyle that, together with the aging of this population, explain to a large extent why the average age of death of these patients is not equal to that of the general population, which seems to force us to review the objectives of health and social intervention.

Keywords: Opioid addiction; premature mortality; age; disease; overdose.

Resumen

El mantenimiento de la mortalidad prematura entre los consumidores de opiáceos es una cuestión de salud pública altamente significativa. El objetivo principal es estudiar las causas y edad de mortalidad registradas en la población de adictos a opiáceos (n = 1.998) atendida en la Unidad Asistencial de Drogodependencias de Cangas (Pontevedra) a lo largo de más de 30 años. Las causas de mortalidad se clasifican en 4 grupos: sobredosis, enfermedades, suicidio y trauma. La edad media de mortalidad de los pacientes se compara con la de la población general que reside en la misma área sanitaria. A lo largo del estudio la mortalidad prematura de estos pacientes se mantiene elevada, aunque con tendencia a disminuir con el paso del tiempo: hasta 1998, 31,8 años de edad media de fallecimiento frente a 47,7 años desde 1998. La edad media de fallecimiento siempre es inferior a la de la población general. La enfermedad es la causa de mortalidad más prevalente (84% de los fallecidos) con gran diferencia frente a los otros 3 grupos. Pese a la reducción de las infecciones asociadas al consumo por vía parenteral, persisten factores asociados a un estilo de vida poco saludable, que, unidos al envejecimiento de esta población, explican en buena medida que la edad media de fallecimiento de estos pacientes no se equipare a la de la población general, lo que parece obligar a revisar los objetivos de la intervención sanitaria y social.

Palabras clave: Adicción a opiáceos; mortalidad prematura; edad; enfermedad; sobredosis.

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According to data supplied to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by the Spanish Government Delegation for the National Plan on Drugs (DGPNSD), "the age-standardized mortality rate among users of cocaine and heroin, or only cocaine, is higher than that of the general population", and "the mortality rate induced by illegal drugs among adults (15 to 64 years) was 12.7 deaths per million in 2015, a figure lower than the average estimates in Europe, which was around 21.8 deaths per million" (EMCDDA, 2020).

In 2018 it was estimated that a heroin user in Europe had between 5-10 times more chances of dying than non-users of the same age and sex (EMCDDA, 2020). The average age of death was 42 years, heroin was involved in 78% of the deaths, and 8,300 deaths were recorded due to overdose, mainly of morphine derivatives. Of the deceased, 76% were male (EMCDDA, 2020).

Four groups of death causes can be considered in these patients: 1. overdose, 2. diseases, 3. suicide, 4. trauma (EMCDDA, 2020; Larney et al., 2020). Overdose has been considered both the most direct and the most frequent cause of death in these patients (Degenhardt et al., 2011; Onyeka et al., 2014; Onyeka et al., 2015). Other, more indirect causes such as suicide and trauma, related to intoxication and social and psychological deterioration derived from chronic use, result in 20-40% of deaths. Finally, less than 10% of deaths in the sample were caused by infectious diseases such as human immunodeficiency virus (HIV). Harm reduction measures, less intravenous use, and treatments for HIV and, more recently, for the hepatitis C virus (HCV) have reduced mortality from these infectious diseases (Giraudon, Vicente, Matias, Mounteney & Griffiths, 2012). However, not all studies agree with these prevalence rates, and some point to diseases as a whole, not just those of an infectious nature, as the most frequent cause of death in these patients (Bahji, Cheng, Gray & Stuart, 2020; Cruts, Buster, Vicente, Deerenberg & Van Laar, 2008).

Analyzed as a whole, it must be concluded that it is difficult to know the exact mortality data of these patients, since the different data collection methods regarding cause of death in the different countries and studies, together with the different designs used in the studies, are confounding factors which are difficult to surmount when research and data collection are not homogenized (Bahji, Cheng, Gray & Stuart, 2019; Bahji et al., 2020; Cruts et al., 2008; Degenhardt et al., 2011; Degenhardt, Hall & Warner-Smith, 2006; Dennis, 2021; Giraudon et al., 2012; Horon, Singal, Fowler & Sharfstein, 2018; Larney et al., 2020; Mathers & Degenhardt, 2014; Mathers et al., 2013; Molist et al., 2018; Onyeka et al., 2014; Onyeka et al., 2015; Slavova et al., 2019).

With regard to overdose, which is the main directly use-related cause of death in these patients, it is well known that heroin is the substance most closely linked to it (Horon, Singal, Fowler & Sharfstein, 2018; Martins, Sampson, Cerdá & Galea, 2015; Onyeka et al., 2015). However, since polydrug use is common among these patients, other substances such as alcohol, cocaine, cannabis and benzodiazepines are also involved in overdoses. The COPSIAD study may be taken as an example (Pereiro, Pino, Flórez, Arrojo & Becoña, 2013), carried out in the same healthcare setting as the present study. Carried out in the addiction treatment network of Galicia in 2010, this study showed that 63.9% of the 2,300 participants were polydrug users. In patients whose main substance of abuse was heroin, this figure increased to 79.1% (Pereiro et al., 2013). The risk of suicide attempts and trauma resulting from moments of intoxication were also increased by such polydrug use (Park et al., 2020).

Trauma is not only linked to intoxication, with the severity and hardship typical of social exclusion situations in which these patients find themselves also contributing to this type of mortality (EMCDDA, 2020; Larney et al., 2020).

With regard to suicide, the use of substances multiplies the risk of this type of death compared to the general population by 15. Comorbidity with depression markedly increases suicide risk in the addicted population (Bahji et al., 2020; Carrasco-Barrios et al., 2020; Larney et al., 2020).

Other causes of death that should also be taken into account, especially as these patients age, are cardiovascular disease, lung disease, and cancer. Although these diseases are also common in the general population as people age, addicted patients take less care of their health and smoke more, raising the likelihood of suffering from these diseases and dying prematurely as a result (Giraudon et al., 2012; Molist et al., 2018; Morris and Garver-Apgar, 2020; Pajusco et al., 2012).

It is therefore of special interest to study how mortality figures in opioid-using patients change in the long term so that design better intervention and prevention strategies to improve the survival expectancy of these patients may be designed (Colom et al., 2021; Hickman et al., 2018; Ma et al., 2019).

The objectives of this study are:

1. To calculate the mortality rates of the population of opioid users treated in a drug addiction care unit (DACU) from 1986 to 2020.
2. To compare the mortality rates of this DACU with those of the general population of the same geographic area (Pontevedra province).
3. To assess the attributed causes of mortality, divided into 4 groups of causes, according to the EMCDDA protocols (EMCDDA, 2020).
4. Link mortality in these patients to HIV/HCV infections.

The working hypothesis is as follows: Patients who use opioids will have a higher and premature mortality rate compared to that of the general population. The causes of death in these patients will remain stable over time, with the exception of diseases; in this last cause, the development of treatments for HIV and HCV will reduce mortality and delay the age of death.

Material and methods

Participants

Patients using opioids, confirmed through urinalysis, and treated at the Cangas Drug Addiction Care Unit (Pontevedra), from when it opened in 1986 until 2020.

The total population attended over this period was 1,988 patients (1,611 men, 377 women).

Procedure

Longitudinal study of all opioid-using patients who began treatment at the Cangas Drug Addiction Care Unit during the study period.

Assessment

The registered personal medical records in the care unit's own physical registry were used, supplemented by the electronic medical records of the health service of Galicia (IANUS). One of the authors (A.F.), in the capacity of the unit's medical professional, reviewed and collated the variables assessed in both registries to gather all the variables included in the study. This procedure was carried out on an annual basis.

The following variables were collected from all study participants:

- *Sociodemographic*: 1. sex; 2. date of birth and age.
- *Clinical*: 1. Use of opioids; 2. HIV serology; 3. HCV serology.

In addition, in all registered deaths (149) the cause of death and its date were determined, grouping them as follows: 1. Overdose, 2. Diseases, 3. Suicide or 4. Trauma.

Statistical analysis

The R package was used to analyze and verify the survival data of the studied population with the following statistical significance tests:

- The classic Kaplan-Meier method for constructing survival tables and their graphical expression, survival curves.
- Wilcoxon's non-parametric test, which makes it possible to establish whether or not a quantitative variable, such as the age of death, depends significantly on a qualitative factor with 2 levels.
- Cox regression (as a proportional hazards model), which allows the statistical significance of the effect of a factor on the survival curve to be established, and also calculates a measure of the effect in terms of relative risk.
- The Harrington-Fleming test, with the same purpose as the Cox regression of deciding whether or not the effect is significant, and being a general test, it has no additional requirements.

Death rates in each period were compared with each other over time. As an additional comparison method, the rate of deaths in the general population of the province of Pontevedra in the year 2020 was added, calculated from a random sample with the same n as the patient sample, according to the National Institute of Statistics (INE) (www.ines.es), and with the mortality rate in the general population taken as the gold standard.

The statistical significance criterion in all tests was $p < 0.05$, established as the maximum acceptable value for the probability of a type I error.

Results

The total population attended during the study period was 1,988 patients (1,611 men, 377 women, in a male/female ratio of 4/1 that remained stable throughout). This data reflects a similar proportion of the numbers of patients treated to the figures reported in European surveys (EMCDDA, 2020).

For the purposes of comparison, in 2020, 374 patients were treated (321 men and 73 women, 227 of which were in methadone maintenance programs and 10 in treatment with bupremorphine/naloxone), and polydrug substance use (alcohol, cocaine, cannabis and tobacco) was observed to be common practice (Pereiro et al., 2013).

Of the total number of deceased patients (149) registered in the medical records, the number of deceased men (127) is higher than that of women (Morris & Garver-Apgar, 2020); this proportion (85% men deceased, 15% women deceased) is slightly higher than that of the patients attended in the unit (81% men, 19% women) during the period of time studied, with no significant differences observed in the mean age between both sexes.

Disease caused the death of 125 patients (83.89%), 6 died due to overdose (4.02%), 5 due to suicide (3.35%), 8 died in accidents (5.36%) and 4 from unidentified causes (2.68%); the latter were excluded from the analysis.

Of the deceased patients, 57 (38.25%) were HIV positive and 103 (69.12%) were HCV positive.

1. Survival analysis by mortality cause

Given that most of the patients died as a result of disease, the survival analysis by cause of mortality was carried out following two different strategies. First, data on death by disease was compared to the other three groups together. Subsequently, the four causes were studied separately.

Disease versus other causes

The survival curves (Figure 1) following the classic Kaplan-Meier method overlap, indicating that the other causes (overdose, accident, suicide) did not present an age of death significantly lower or different from that corresponding to the majority group of deaths from disease. It must be remembered that the median age of death was practically the same (disease at 41 years, other causes at 40 years).

The Wilcoxon test (P value = 0.5783) indicates that the age of death was not related to the cause (disease or other causes).

The value of the Cox regression (z = 0.5, P = 0.612) also indicates that the age of death was not different for the different causes of death (disease or other causes such as suicide, accident or overdose).

The four causes of death separately

Again, the survival curves (Figure 2) following the classic Kaplan-Meier method overlap, indicating the absence of significant differences.

The estimated median age of death was slightly higher (44.5 years) in the accident group, and lower in the suicide group (36 years, practically indistinguishable from the overdose group, 37 years).

The Cox regression value when comparing the four causes of death is not statistically significant (P = 0.338), probably due to the very small size of three of the four groups.

The differences do not appear to be significant, although all groups have negative coefficients, i.e., a better survival rate, compared to group 1 (overdose) used as a reference. The median survival ages were similar, and the curves intersect (overdose, 37 years, and suicide, 36 years, slightly below accident, 44 years, and slightly above the mean found in the majority group, disease, 42 years).

2. Survival analysis by time period, taking the general population of Pontevedra province as reference group

In the sample, the data was divided into four periods by date of death: (1) prior to 2000; (2) 2001-2010; (3) 2011-2017; (4) 2018-2020; this last period was created to study the most recent trend as the sample size was considered sufficient to find significant effects. The data from these four periods were compared to a fifth group with random data from the 2020 census of Pontevedra province; this allowed the treatment groups of the care unit to be compared to the normal reference population.

In the Cox regression, this last group is used as the reference level, with the other periods compared to it. As can be seen in Table 1, all the regression coefficients are positive, indicating that the probability of death was higher in each of the groups compared to the reference group. Of more interest is the interpretation of the exponential of the coefficient, in the second column of the table, which shows the relative risk (RR): in the period up to 2000, the risk of death of addicts, for any age, was 696 times that of the general population; in the most recent period 2018-2020 that risk was 27.6 times higher. This shows a rapid, positive change of relative risk over time, although it remains very high in the most recent years.

The last column of the table shows the P values of the significance tests. All of them have a value of practically zero, which means that the effects described are statistically significant, and so is the model as a whole, as indicated by the three general tests at the foot of the table.

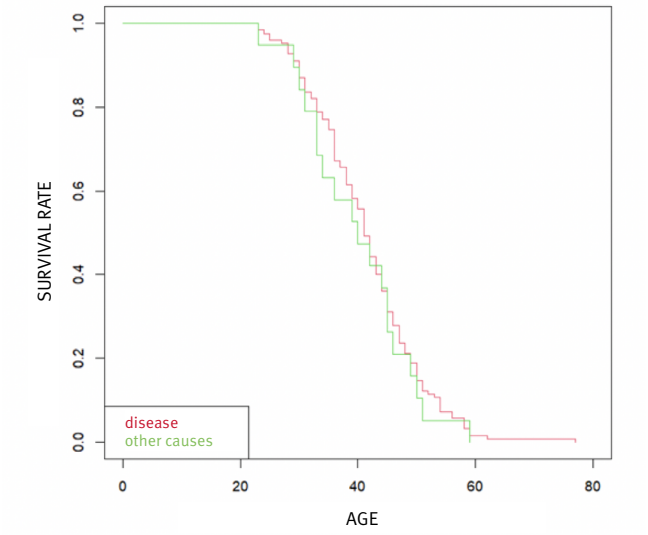

Figure 1. Survival analysis by cause of mortality. Combined minority causes of mortality (other causes) versus disease.

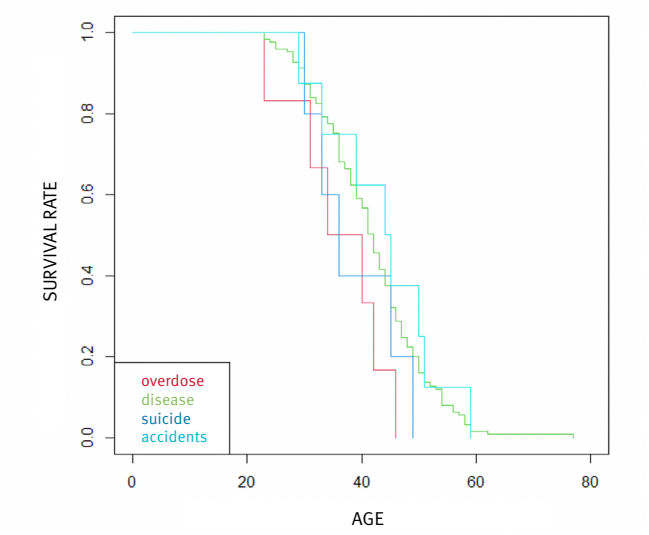

Figure 2. Survival analysis by cause of mortality. Each cause of mortality is analyzed individually.

Table 1. *Cox regression model applied to temporal survival in the Cangas Drug Addiction Care Unit.*

Comparison of periods	Regression coefficient	Relative risk	se	z	P
Period 1 versus 5	6.54	696.06	0.48	13.52	‹ 0.000001
Period 2 versus 5	4.81	122.76	0.44	10.72	‹ 0.000001
Period 3 versus 5	4.50	90.18	0.47	9.48	‹ 0.000001
Period 4 versus 5	3.31	27.62	0.42	7.77	‹ 0.000001

Note. Likelihood ratio test = 357 in 4 degrees of freedom, p = ‹2e-16; Wald test = 197.4 in 4 degrees of freedom, p = ‹2e-16, Score (logrank) test = 412.3 in 4 degrees of freedom, p = ‹2e-16.

Figure 3 shows the described effects, representing the survival curves for the five groups. The curve corresponding to the general population is clearly higher (i.e., better survival rate), and the other groups have clearly lower survival the older the period.

The median survival age in each period (1 = 31.5, 2 = 41, 3 = 45, 4 = 51, and control group 5 = 86) rises steadily for patients as the follow-up period progresses.

The mean age of death is clearly influenced by the follow-up period analysed. Until 1998 it was 31.8 (median 31), rising to 47.47 (median 47) after 1998. Applying the non-parametric Wilcoxon statistical test, a p close to 0 (W = 298.5; 2.831e-11) was obtained, indicating high statistical significance.

A scatter plot shows that the change is continuous over time; the average age, represented by the adjustment line, has risen steadily, at a constant rate, from 25 years before 1990 to more than double, 52 years, after 2015.

A regression model between age and year of death allows further analysis. The regression coefficient between age and year is clearly significant (t = 13.28; P value = 2e-16), and its estimated value of 0.77 can be interpreted as the increase in age at death, 0.77 years, for each passing year throughout the period studied.

The linear model is adequate (the graph shows a clearly linear relationship), and the coefficient of determination R-squared, 0.54, indicates that the advances represented by the passage of time explain 54.4% of the variability in the age of death. The model is also significant (F = 145.4, P value = 2.2e-16).

Sex does not have a significant influence (P = 0.39 in the sex variable regression coefficient) in this relationship between the age of death and the period in question. The age at death of men and women is not significantly different.

When observing the deaths in each period by cause, the following results were obtained: (1) 2 from overdose (33.33%), 38 from disease (30.4%), 0 from suicide (0%) and 1 from trauma (12.5%); (2) 3 from overdose (50%), 48 from disease (38.4%), 2 from suicide (40%) and 2 from trauma (25%); (3) 1 from overdose (16.66%), 20 from disease (16%), 3 from suicide (60%) and 3 from trauma (25%); (4) 0 from overdose (0%), 19 from disease (15.2%), 0 from suicide (0%) and 2 from trauma (25%). Given the low prevalence of overdose, it is not possible to determine whether these changes are statistically significant (although a clear downward trend is observed as of 2010); the same applies to suicide and trauma (no clear trend is observed for these causes). For disease, however, a clearly significant decrease is observed as of 2010 with respect to the previous period ($p \leq 0.001$). However, there are no significant differences in the prevalence of disease between periods 3 and 4.

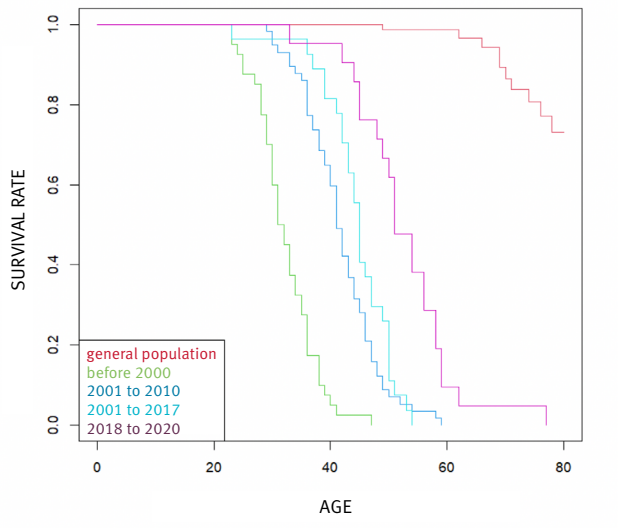

Figure 3. Time-period survival curves. Comparison of the 4 follow-up periods with the general population.

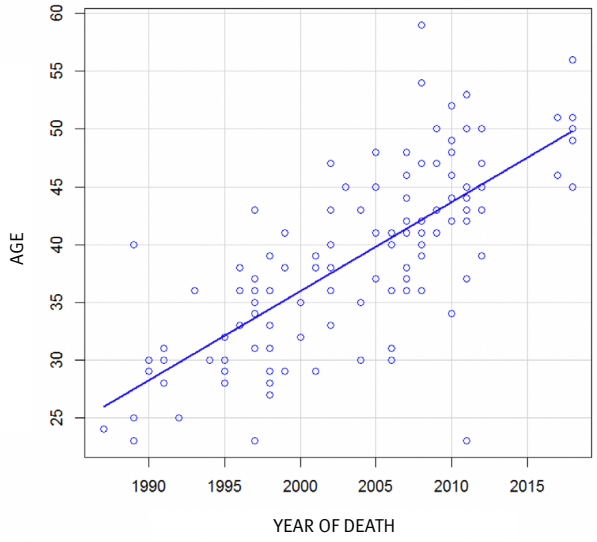

Figure 4. Dispersion graph of changes in sample mortality over time.

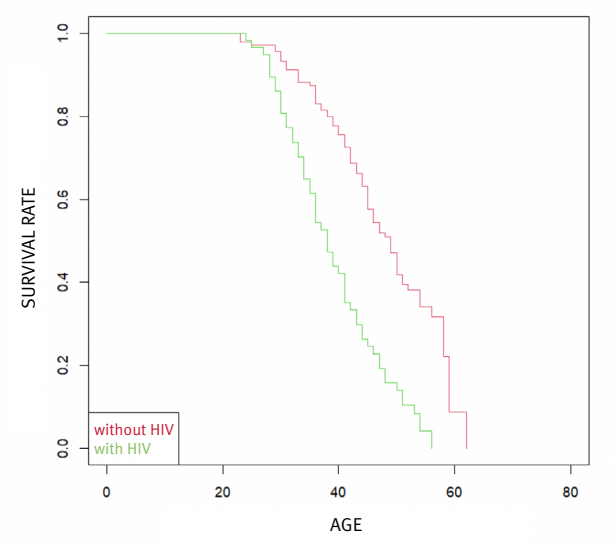

Figure 5. Survival curves by HIV infection.

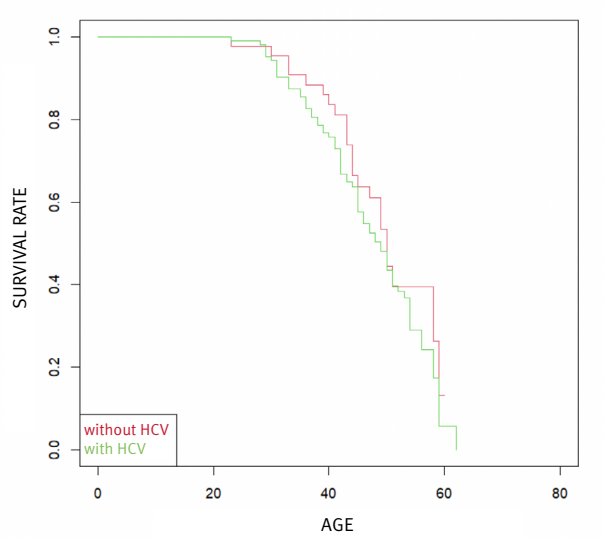

Figure 6. Survival curves by HCV infection.

3. Mortality in relation to HIV/HCV infections

The Cox regression model for HIV, with survival as a function of HIV, had a P value < 0.001, indicating a clearly significant effect. The hazard ratio was 2.78, indicating that the risk of death within this group was 2.78 higher among those who had HIV compared to those who did not. Figure 5 shows a consistently lower curve, for any age, for HIV patients.

However, results changed when performing the same analysis considering three different time periods: until the year 2000, from 2000 to 2010, and from 2011 to 2020. With this temporal division, the presence of HIV was no longer significant (p = 0.82 for the first period, p = 0.99 for the second, and p = 0.37 for the third period). This is the result of a significant fall in the proportion of HIV over time, with HIV patients in this sample mostly concentrated in the initial periods of the study. In these initial periods, life expectancy of the group of patients in treatment was the lowest, as already shown in the previous analyses (Figure 3), with all causes of mortality at their strongest.

For HCV, the Cox regression model, with survival as a function of HCV, has a P value = 0.357, indicating a non-significant effect. Mortality does not seem be dependent on HCV, as can be seen in Figure 6.

Discussion

The data presented in the results section allows the following conclusion to be quickly drawn: The addicted patients who participated in this study have a lower survival age than that of the general population in the same geographical area, although this age has been rising over time, from 1986 to 2020.

The premature death of patients participating in this study has been a common finding in this type of population, as highlighted in different studies of patients addicted to substances, particularly heroin (Bahji et al., 2020; Cruts et al., 2008; Degenhardt et al., 2011; EMCDDA, 2020; Giraudon et al., 2012; Jiménez-Treviño et al., 2021; Jiménez-Treviño et al., 2011; Mathers et al., 2013). This premature mortality is sustained even despite the rise in age of death in recent years.

The results of the study reflect a mixed reality of care. On the one hand, the survival age has been rising, as could in part be expected given the increase in the age of patients in treatment who were incorporated at the beginning of the study. This statistically significant fact points to the positive effect that methadone/buprenorphine maintenance programs have had, the decrease in use of the parenteral route, and the universalization of the treatment of concomitant HIV and HCV infections (Bahji et al., 2019; Kimber, Larney, Hickman, Randall & Degenhardt, 2015; Krawczyk et al., 2020; Lozano, Domeque, Perálvarez, Torrellas & Gonzalo, 2019; Mathers & Degenhardt, 2014; Sordo et al., 2017). Nevertheless, the survival age of these patients has not reached that of the general population, despite all the advances mentioned, and this undoubtedly indicates that there are harmful factors associated with substance addiction that have not yet been fully neutralized in these patients (Bahji et al., 2020).

Another clear result of this study is that the attribution of mortality in the sample of patients is linked to clinical

disease in general (84%), and to a lesser extent (16%), to another group of causes (overdose, suicide or trauma). This result, as already indicated in the introduction, is unusual in mortality studies involving such patients, although previous studies already indicate that this distribution of mortality is common in samples of older patients (Stenbacka, Leifman & Romelsjö, 2010). In our opinion. this difference is related to the design of the study; when carrying out a prospective study, with a very comprehensive follow-up of patients and access to the general clinical records, numerous cases of death from disease are detected that go unnoticed in other types of study (Bahji et al., 2020; Cruts et al., 2008; Mathers et al., 2013). As will be discussed below, this exhaustive follow-up was accompanied by intense health, psychological, and social treatment that also influenced the results, and could explain why mortality rates in Spain are lower than those in Europe (EMCDDA, 2020).

The influence of HIV as a factor generating diseases and mortality is reflected in the results. HIV is associated with higher mortality globally, but when performing the analysis by time period this significance is lost since HIV infections were more prevalent in the first years of the study, when mortality was at its highest in these patients. However, the relationship between the presence of HIV/HCV and the main cause of mortality, disease, is clear throughout the study. Of the 125 patients who died from this cause, 97 were HIV or HCV positive (77.66%, $p \leq 0.001$).

Initially, it could be considered that viral infections, in fact, all infections typical of parenteral drug use, would explain the results of this study. HIV infection, and since the end of the 1990s, the infectious liver diseases HCV and hepatitis B virus (HBV), which have doubled their prevalence compared to HIV (29), are the main infectious threat of the parenteral route, but not the only one; bacterial and fungal abscesses, embolisms, and endocarditis are also highly prevalent in users of this route.

The large-scale abandonment of the parenteral route, and the advances in treating these infections could explain the improvement observed in the present study in relation to the survival age of patients, and above all through a decrease in the prevalence of death by disease after 2010.

This development is clearly seen in a study carried out between 2005 and 2010 in patients from all drug addiction care units in Galicia, including the one in which this study was performed, which thus involved a very similar sample. This study analyzed the new requests for heroin addiction treatment (Flórez et al., 2015). In the 1,655 patients analyzed, the presence of HIV was found in 7.4% of the sample, and HCV in 19.9%. These data correlated with low use of the parenteral route, only present in 15.6% of the sample (Flórez et al., 2015), and contrasted with previous longitudinal studies indicating the presence of HIV in 47.2% of heroin addicts, and HCV, together with HBV, in 81.1% (Giraudon et al., 2012). This reduction in viral infections would also affect the other infections, bacterial or fungal, typical of the parenteral route, a fact that would also contribute to reducing mortality.

On the other hand, and despite these favourable aspects of care, it is noted that this improvement is not strong enough to allow comparisons of patient survival age to that of the general population; this is confirmed by the absence of a significant difference in the prevalence of deaths from disease between periods 3 and 4. Undoubtedly, other factors continue to be involved that prevent this gap from being closed. Unhealthy habits, such as sedentary lifestyle and poor diet, together with polydrug use, especially tobacco, alcohol and stimulants, typical of this population, would explain why the difference to the general population continues (Morris & Garver-Apgar, 2020; Pajusco et al., 2012). In addition, polydrug use reduces adherence to treatment in general, and to antiretrovirals in particular (González-Álvarez, Madoz-Gurpide, Parro-Torres, Hernández-Huerta & Ochoa Mangado, 2019). The aforementioned COPSIAD study serves as an example. Of the 805 patients (35% of the total) whose main substance of abuse was heroin, 43.1% were also addicted to cocaine, 30.7% were addicted to cannabis and 19.2% to alcohol (Pereiro et al., 2013). Furthermore, the COPSIAD study also indicated the high comorbidity of heroin addicts in Galicia with other non-addictive psychiatric disorders (7.6% psychotic disorders, 20.6% mood disorders, 11.9% anxiety disorders and 26.5% personality disorders). It is well known that non-addictive psychiatric disorders also have a high comorbidity with physical illnesses related to unhealthy lifestyles. Thus, it is clear that this comorbidity, or dual pathology, contributes to maintaining this significant difference in life expectancy in the present sample with respect to the general population, where these disorders are not as prevalent (Pereiro et al., 2013), as previous studies have already indicated (Fridell et al., 2019).

Tobacco use is also very prevalent in this population, with studies indicating a prevalence of over 80% and great difficulty in quitting (Morris & Garver-Apgar, 2020; Pajusco et al., 2012). Therefore, smoking and its morbidity and mortality also contribute to maintaining a significant difference between the study population and the general population with regard to life expectancy.

It is easy to conclude that it is this unhealthy lifestyle, resulting from polydrug use and psychiatric comorbidity, together with the ageing suffered by the participants in this study, which, compared to the general population, has increased the risk of presenting certain diseases, especially oncological and cardiovascular, which in turn has kept diseases as the main cause of death in the study. In addition, these diseases have counteracted the beneficial effect of control of infectious diseases associated with the parenteral route, so prevalent in this population, and have

prevented the disappearance of the significant differences in survival age compared to the general population, as shown by the evolution of the prevalence of deaths by disease. Despite this, the beneficial effect of the intense health control carried out in this population is evident when observing a clear improvement in the survival age over time, and in the low rates of death by suicide, overdose or accident. It should be remembered that in these latter cases, the presence of an effective public health system capable of responding urgently makes a very significant difference (Bahji et al., 2020; Cruts et al., 2008; Degenhardt et al., 2006).

The results of this study must be interpreted within the healthcare context in which the data were collected. Participants attended a treatment program with health, psychological and social coverage, reducing mortality due to suicide, overdose and trauma. In addition, the presence of a permanent emergency public health intervention service also helps reduce mortality from suicide, overdose and trauma. The decline in the prevalence of injecting, coupled with decreasing purity of available heroin has also contributed to reduced overdose mortality. All these factors have also helped, as the results of this study indicate, to reduce mortality from disease, but unhealthy lifestyles are generating morbidity and mortality linked to various infectious, cardiovascular, endocrinological or oncological diseases that increase with age and explain the evolution of the data in this study.

Finally, it should be noted that there is a tendency for men to have higher mortality compared to women in the present study, but without a significant difference in the mean age of death. Taken together, the results indicate a risk that is higher for men, but not as intense as in other studies (Brugal et al., 2016; Onyeka et al., 2015).

Limitations

This study has some limitations worthy of note. Although the study participants were originally mainly from the Morrazo and Vigo health area, with hardly any patients coming from places outside the study area, it is possible that undetected movement occurred and that some of these patients from outside the health area died without the cause of death being recorded. Nevertheless, it can be noted that the percentage of patients with missing cause of death data throughout the study was less than 1%.

It must be taken into account that all data in this study were collected by the same researcher, which improves internal validity; however, cause of death was not determined on the basis of a common prior protocol for the entire health area, but was rather based on the records of the daily activity of the health professionals involved. This fact is important when discriminating between accidental overdoses and suicides, but it does not significantly affect deaths from disease.

As the study was conducted in a health setting, it is possible that deaths caused by causes other than disease which were not recorded directly by health personnel were underestimated.

With regard to sample size, a larger sample would have made it possible to obtain results with higher statistical power.

Finally, the causes of mortality occurring in the sample throughout the study period (1986-2020) were compared with the causes of death in the general population of the Pontevedra health area that occurred in 2020. Although it is the case that the general population encompasses the study sample, it is possible that the causes of death in the general population have changed over the years. Nevertheless, life expectancy in the general population has done nothing but improve throughout the study, and this fact indicates that there is no significant bias in how the comparison of life expectancy developed in the study patients compared to the general population.

Conclusions

1. The opioid-addicted population followed in this study had a higher premature mortality rate, maintained over time, than the general population in the same area, the province of Pontevedra, with a steady reduction over recent years. This positive development is the result of the intense multidisciplinary treatment to which these patients have free access.
2. Despite this intense multidisciplinary treatment, the unhealthy lifestyle of these patients generated a higher prevalence of risk factors for various diseases than in the general population. This has led to the appearance of a 'plateau' effect in the deaths from disease prevalence, and thus in the overall mortality of patients, which prevented them from having a life expectancy similar to that of the general population.
3. The opioid-addicted population followed in this study presented the same causes of premature mortality as the usual causes referred to in the EMCDDA studies (1): 1. Overdose / 2. Diseases / 3. Suicide / 4. Trauma, disease being the primary cause of mortality.

Conflict of interests

The authors declare no conflicts of interest in relation to the study, its authorship, and/or the publication of this manuscript.

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