THE SPECTRUM OF INFECTIOUS DISEASES HOSPITAL MORTALITY BY HIV STATUS

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ABSTRACT

Introduction: *Although there is a declining in infectious diseases mortality all over the world, there is still no area on the globe were mortality rate completely disappeared through these diseases. Despite available vaccination, there are still challenges related to various infectious diseases such as enterocolitis, tuberculosis, malaria or infection with human immunodeficiency virus (HIV).*

Materials and methods*: Analysis of death causes based on clinical, biological and anatomo-pathological examinations was performed among patients admitted in Constanta Clinical Infectious Diseases Hospital, from January 2008 to December 2017, by their HIV status.*

Results*: In a period of 10 years, in Constanta Clinical Infectious Diseases Hospital, 184 inpatients died. Mostly deaths were related with HIV infection/AIDS (n=134; 72.82%), while others (n=50; 27.18%) were caused by other infectious diseases among non-HIV infected patients. The mean age of HIV group was 31.72 years +/-13.458, versus 56.27 years +/- 21.114 in non-HIV group. The risk of death in HIV group was 6.43 times higher for tuberculosis (OR = 6.43), 12.135 higher for candidiasis (OR = 12.135) and 3.84 times higher for respiratory infections (OR = 3.845), 6.99 lower for cardiovascular disease (OR = 0.143) and 2.48 lower for sepsis (OR = 0.402) compare to non-HIV group. The risk of death was equal between groups regarding liver cirrhosis, and brain infections.*

Conclusion*: We found a higher risk of death by candidiasis, tuberculosis, or respiratory infections and a lower risk of death by cardiovascular disease or sepsis in HIV group comparative with non-HIV group of patients. Therefore, it is very important to know the main conditions that can influence the mortality rate of HIV and non-HIV patients because the proper management of these conditions can reduce the risk of mortality.*

Keywords: *mortality, HIV, tuberculosis, respiratory infections, malignancies.*

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Introduction

After 2000, an accelerated decline of morbidity and mortality caused by various infectious diseases has been observed for high-income countries, but not in middle- and small-income countries. Despite available vaccination, there are still challenges related to various infectious diseases such as diarrhea, tuberculosis (TB), malaria or human immunodeficiency virus (HIV) infection - acquired immunodeficiency syndrome (AIDS)[(1)].

In an over 100 year- study, performed in US, researchers found the trend of mortality, caused by different infectious diseases, decreased from 800‰ in 1900 to 46‰ in 2014, although several entities started to slightly increased their rate of mortality like Spanish influenza in 1918, HIV-AIDS epidemic in 1995, West Nile meningoencephalitis in 1999, and, more recently, acute enterocolitis with Clostridium difficile in 2014[(2)]. The top five most common causes of death caused by infectious diseases, reported by World Health Organization, in 2002, were lower respiratory infections with 3 871 000 deaths, followed by HIV-AIDS with 2 866 000 deaths, diarrhea with 2 001 000 deaths, tuberculosis with 1 644 000 cases and malaria with 1 124 000 deaths[(3)].

Worldwide, in 2008, infectious disease caused 68% of the estimated deaths in children younger than 5 years. The first three leading cause of mortality in children less than 5 years were pneumonia (18%), followed by diarrhea (15%) and malaria (8%)[4].

According with Eurostat data the number of deaths in Romania has remained steady over the last 20 years, ranging from 240,000 to 260,000 deaths annually. The average death rate recorded by Romania is above the European Union (EU) mortality rate, namely 13 deaths per one thousand inhabitants, compared to the EU average of 10 deaths per one thousand inhabitants. From total deaths, mortality by infectious diseases varies between 4-5%[5]. Constanta County located in southeastern Romania is one of the counties most affected by pediatric HIV infection in the early 1990s. In this area, there is an important cohort of HIV-positive patients, made up of former surviving children and of newly diagnosed cases over time in adulthood. The mortality recorded in this cohort of patients is either related to the late diagnosis of the disease or as a result of therapeutic abandonment, thus appearing a series of opportunistic infections and neoplasia. From opportunistic infectious TB is one of the most spread disease. In our area, there is also a high mortality through TB regardless HIV coinfection or not. From the total cases of TB registered in Constanta County, deaths represent 51% from the total cases of TB, with an overall fatality rate of 2.7%[6].

Our study evaluate the risk of death by HIV status among 71,711 patients, who were hospitalized from January 2008 to December 2017, in Clinical Infectious Diseases Hospital of Constanta, the main city from Southeastern Romania.

Materials and methods

We performed a 10- year survey analysis of deceased patients charts in Constanta Clinical Infectious Diseases Hospital (January 2008-December 2017). Whereas the majority of deaths were HIV patients, presenting comorbidities, analysis took into consideration the main cause of death and only two important lethal comorbidities. Regarding the cause of death, all clinical, biological and even pathological data provided by autopsy were assessed among 184 dead cases. Autopsy was performed in 67.46% HIV cases (n=77/134) and 50% of non-HIV ones (n=25/50).

Statistical analysis included descriptive statistics, nonparametric statistical tests (association test χ^2, the relationship between two categorical variables), with determination in some situations of the risk / chance ratio, OR and the relative risk - RR, Chi-squared test for the comparison of two proportions, Mann-Whitney Test, considering statistical significance when $p < 0.05$.

Although in some situations such as meningitis, TB or some neoplasms the death diagnosis was obvious, the main limitation of the study design is that anatomo-pathological evaluation were not available in all patients. Another important limitation of the study is the numerical inequality of the two compared groups of patients.

Results

In a period of 10 years (January 2008 – December 2017), in Constanta Clinical Infectious Diseases Hospital, there were registered 71,711 inpatients and reported 184 deaths, 72.82% (n=134) HIV/AIDS- related. The mean age of HIV group was 31.72 years +/-13.458, versus 56.27 years +/- 21.114 in non-HIV group. While the median age for the HIV patient group was 27 years and the interquartile range (IQR) was 17.5 years, for the non-HIV group the median value was 60.5 years with the IQR 24.5 years. The distribution of age (years) is not the same across categories of group (Mann-Whitney Test $p<0.001$) (Figure 1).

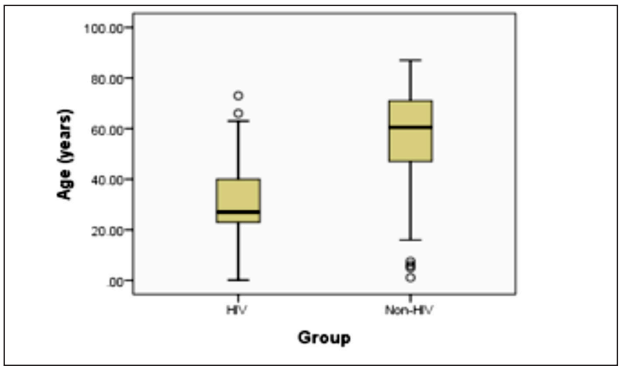

Figure 1: Distribution age, represented by box plot, between HIV group and non-HIV group of patients.
(Abbreviation: HIV= human immunodeficiency virus)

The peaks of deaths were registered in HIV infected patients 2014 (n=18), followed by years 2011 (n=17) and 2009 (n=16), as we can see in figure 2. The frequency of deaths among non-HIV cases was high and almost equal in years 2010 (n=11) and 2009 (n=10). Comparing the proportion of annually reported deaths between both groups of patients, there was no significant difference ($p>0.05$).

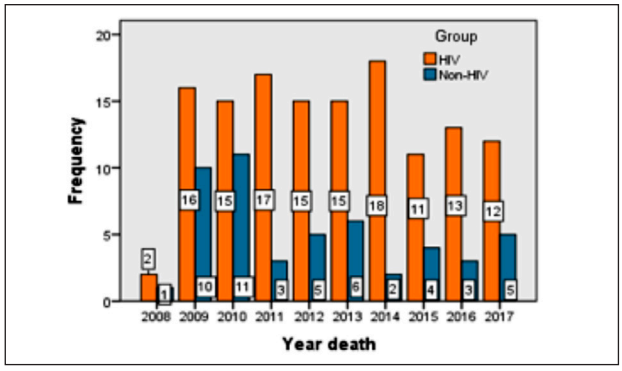

Figure 2: The frequency of deaths per year studied compared for the HIV group and non-HIV group of patients.
(Abbreviation: HIV= human immunodeficiency virus)

The risk of death is higher among males (n=116/184; 63%) (Figure 3), with a gender ratio male/female of 1.68 (84 male/50 female) in HIV group and 1.77 (32 male/18 female) in non-HIV group, but without any statistical significance (p = 0.870).

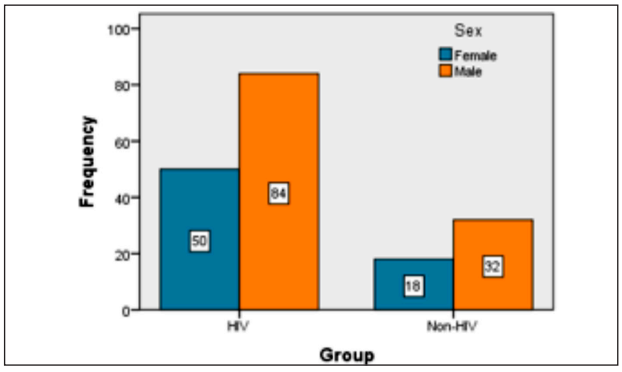

Figure 3: Repartition by sex (male or female) for the HIV group and non-HIV group of patients.
(Abbreviation: HIV= human immunodeficiency virus)

Most dead patients lived in urban areas of Constanta county (59.7% in HIV group and 68% in non-HIV group) with no statistical significance (p = 0.302) (Figure 4).

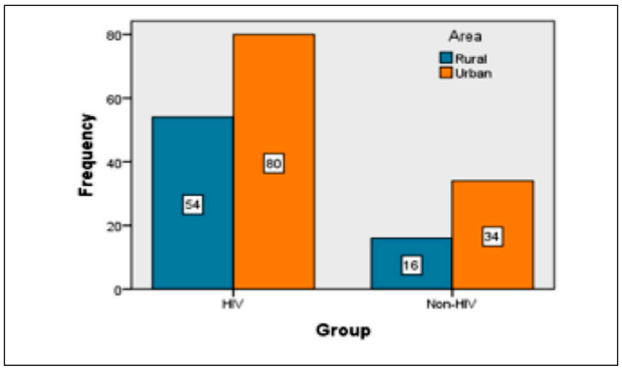

Figure 4: Repartition by environmental area (urban area or rural area) for the HIV group and non-HIV group of patients.
(Abbreviation: HIV= human immunodeficiency virus)

In the HIV-group, the most frequent infectious causes of death were tuberculosis (TB) with 39 cases, followed by HIV-HBV coinfection (n=27), and pneumonia with Pneumocystis jiroveci (n=21). Other causes of death were progressive multifocal leukoencephalopathy (PML) and HIV encephalopathy (n=24/134; 17.9%) and also malignancies associated HIV (n=23/134; 17.1%) including non-Hodgkin lymphoma (NHL) (n=7/23; 30.43%), pulmonary malignancies (n=4/23; 17.4%), Kaposi Sarcoma (n=4/23; 17.4%), hepatocellular carcinoma (n=1/23; 4.3%) and cervical cancer (n=1/23; 4.3%). Two patients died in the first 24 hours of hospitalization before HIV infection first diagnosis confirmation.

Among non-HIV dead patients, death was caused by brain infections (n=11), liver cirrhosis (n=10), bronchopneumonia (n=7), malignancies (n=5), pulmonary or extra-pulmonary TB (n=3) and tetanus (n=1). Non-infectious causes of death were represented by acute myocardial infarction (n=5), mesenteric infarction (n=3), pulmonary thromboembolism (n=3) and intestinal occlusion (n=2).

TB was the most frequent cause of opportunistic infections that led to death among HIV infected patients (n=39/134; 29.1%) compare to non-HIV group (n=3/50; 6%). The risk of one HIV infected patient to die by TB is 6.43 higher than in cases without HIV [OR = 6.43; 95% IC for OR = (1.88, 21.89); RR=4.85; chi2=10.97, p< 0.001].

Candidiasis is one of the most common opportunistic infections in HIV patients (95.7%) compare to non-HIV cases (4.3%). The risk of death caused by candidiasis is 12.135 higher in HIV group comparative with non-HIV group [OR = 12.135; 95% IC for OR = (2.820, 52.211)].

Respiratory infections diagnosed in HIV group (n=77/134; 57.5%) consisting in Pulmonary TB - 25 cases, Pneumocystis jirovecii Pneumonia (PJP)- 21 cases and Bronchopneumonia - 31 cases, while in non-HIV group (bronchopneumonia -7 cases, followed by pulmonary tuberculosis- 1 case) represented less (n=8/50; 16%). The risk of death by respiratory infections was 3.84 higher in HIV group, comparative with non-HIV group [OR = 3.845; 95% IC for OR = (1.874, 7.889)].

Sepsis as the prior cause of sudden death was recorded in 20 cases (n=12/134; 8.9% in HIV group and n=8/50; 16% in non-HIV group), with a risk of death 2.48 (1/0.402) times lower in HIV cases [OR = 0.402; 95% IC for OR = (0.192, 0.841)].

Another disease, present in small proportion, but with influence upon the mortality rate in both groups

was enterocolitis with 5 cases – 45.5 % in HIV group and 6 cases – 54.5% in non-HIV group. The risk of death by enterocolitis was 2.48 (1/0.284) times lower in the HIV group compared to non-HIV group [OR = 0.284; 95% IC for OR = (0.083, 0.977)]. Enterocolitis caused by Clostridium difficile was present in 2 non-HIV cases and one HIV patient.

Brain infections in HIV group (n=33/134; 24.6%) and in non-HIV group (n=11/50; 22%) had an equal risk of death in both studied groups [OR = 1.158; 95% IC for OR = (0.533, 2.517)]. Brain infections for HIV group were PML – 14 cases, HIV encephalopathy – 10 cases, cerebral toxoplasmosis, TB meningoencephalitis, bacterial meningoencephalitis in 3 cases each respectively. Among non-HIV patients, brain infections consisted in Meningococcal meningoencephalitis (n=5), Pneumococcal meningoencephalitis (n=2) and West Nile meningoencephalitis (n=4).

Malignant tumors had almost 2 times higher frequency in HIV group of younger adults (n=23/134; 17.2%) compare to non-HIV older cases (n=5/50; 10%) but the risk of death was equal in both groups [OR = 1.865; 95% IC for OR = (0.668, 5.209)].

Although the proportion of patients who died by cardiovascular disease was equal (50% for each group) in both studied groups, the risk of dying from a cardiovascular disease is 6.99 (1/0.143) times lower in the HIV group compared to the non-HIV group [OR = 0.143; 95% IC for OR = (0.069, 0.295)]. When we analyze both groups regarding chance of developing myocarditis, we notice that this risk is equal [OR = 0.516; 95% IC for OR = (0.198, 1.350)]. Contrarily the risk of dying by cardiomyopathy is 4.87 (1/0.205) times lower in the HIV group compared to the non-HIV group [OR = 0.205; 95% IC for OR = (0.102, 0.414)].

When comparing liver cirrhosis mortality by HIV status, the percentage of deaths in the HIV group (76.7%) was higher compare to non-HIV group (23.3%), but, statistically, the risk of disease is equal in both studied groups [OR = 1.307; 95% IC for OR = (0.589, 2.899)]. In HIV group, liver cirrhosis was a consequence of co-infection with hepatitis B virus (HBV) in 25 cases, with hepatitis C virus (HCV) in 6 cases and with triple infection HIV+ HBV + HDV (hepatitis Delta virus) in other 2 cases. In non-HIV patients, liver cirrhosis was related to HCV infection (n=2), to HBV infection (n= 4), alcoholism (n=3) and autoimmune hepatitis (n=1).

Discussion

In a study performed by Florescu et al., in a tertiary hospital of infectious diseases from Bucharest, the number of patients deceased during two consecutive years (437 deaths out of 36745 patients, with a mortality rate of 1.18%) was 4 times higher than in our hospital (184 deaths out of 71,711 inpatients with a mortality rate of 0.256%)[7]. In our study, the highest number of deaths was related to HIV status (n=134/184; 72.8%) comparing with the study of Florescu et al, which revealed sepsis (n=153/437; 35%) as the most frequent cause of death and HIV as the second cause (n=54/437; 12.35%)[7].

In immunocompromised HIV or non-HIV patients, TB seems to be the most frequent infections in Romania, but also in other countries[8-10]. In a study performed by Pettit et al., the risk of death in HIV population, after the initiation of the antiretroviral therapy, was twice higher in AIDS group compared to non-AIDS cases[11]. Considering TB, PJP and NHL as AIDS specific causes of deaths we noticed that 50% of deaths were by AIDS related disease because the majority of deaths were noticed in non-adherent patients to antiretroviral regimens. Pulmonary TB in HIV positive patients can cause decreased lung function evidenced by decreased in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, and single-breath diffusion capacity of the lung for carbon monoxide (DLCO). The high mortality caused by the pulmonary TB could be influenced by the decreased lung function: (FEV1/FVC <70 and DLCO<60% predicted) in HIV patients (12), as found even in the recently diagnosed, treatment-naive nonsmokers[13, 14]. This reflects the more frequent exacerbations[15] that correlates in lung diseases with the low quality of life[16]. As TB infection is one of the main causes of death between HIV positive patients, with atypical manifestation and sometimes very difficult to be recognized in their condition, an alternative way of diagnosis in these patients is evaluation of adenosine deaminase (ADA) in pleural effusion. Studies regarding ADA determination have shown promising results in the diagnosis of TB pleural effusion, all these studies evidenced high value of ADA in TB cases[17].

In a study performed by Zhang et al. they noticed that in HIV/AIDS patients, TB occur within 1 year of follow-up after HIV diagnosis. In this study, the risk of death is associated with age, non-sexually transmitted infections, no antiretroviral therapy, and low first CD4 count, in patients with double infection[18].

In another study performed by Teng J, HIV transmission route, tuberculosis severity, accepts of antiviral therapy and specific treatment time are related factors affecting death of coinfection with mycobacterium tuberculosis and HIV[19]. In Constanta area in hospital mortality caused by TB active diseases is still high, TB remaining one of the most important cause of death in a tertiary care pneumophthisiology hospital - 51% of the total cases[6].

AIDS related malignancies causing death represented 17.2%, lower than the results obtained by Oprea C. et al. (62.6%), similar frequency of non-Hodgkin's lymphoma (30.43% in our study and 34.06% in their study) and Kaposi sarcoma (17.39% in our study and 18.68% in study of Oprea and col.), and less cervical cancer in our study (4.34%) comparative with results of the mentioned study (9.8%)[20]. The importance of protocols and procedures is major in detecting and monitoring cancer, lymphoma, the screening of cervical cancer[21-24] and even occupational disorders associated with malignancies[25-27].

In the same period, another study was performed, in Romania, by Jugulete et al. regarding meningococcal infections[28]. It seems to be a big difference between mortality rates in different geographical areas from Romania. In our study, there were 5 deaths reported in children, but, in Bucharest, in a similar hospital of infectious diseases, there were registered 13 deaths from the total of 31 cases with meningococcemia[28].

In non -HIV patients, we found a mortality rate by bronchopneumonia of about 14% similar with Florescu et al. who reported a mortality rate of 12.1%[7]. Although TB is considered a risk factor for lung cancer development even in never smokers, our study found no kind of overlapping.

Mortality by brain infectious, some of the most serious infectious diseases, in non-HIV group 11 deaths were reported (22%), while in Florescu study there were more cases (n=33) but lower frequency (7.55%)[7].

Although there are reported HIV infections complicated by myocarditis and dilated cardiomyopathy (29), our study evidenced an equal risk of death induced by myocarditis was noticed in both groups and a higher risk of dying by cardiomyopathy in non-HIV cases (older than HIV patients). Another rare situation evidenced by our study was an extensive myocardial infarction of left ventricle with dilated cardiomyopathy causing death of an 11 years old HIV infected girl. It seems pediatric HIV cases monitoring should be focused on cardiovascular and metabolic comorbidities in order to prevent an early death.[30].

Conclusion

Despite the limitations of the study, given that it has been conducted over a period of 10 years, the results regarding the causes of death for HIV and non-HIV patients are somewhat similar to other data from literature. Our study evidenced that the first three common cause of death for HIV infected patients were TB, brain infections and HIV+HBV co-infection. For the patients from non-HIV group the main three cause of deaths were noninfectious causes followed by the brain infections, and liver cirrhosis.

According with our data, we found a higher risk of death by candidiasis, TB, and respiratory infections and a lower risk of death by cardiovascular disease or sepsis in HIV group of patients comparative with non-HIV group of patients. Therefore, it is very important to know the main conditions that can influence the mortality rate of HIV and non-HIV patients because the proper management of these conditions can reduce the risk of mortality.

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Author contributions

All authors contributed equally to the content and design of this review and have read and approved the final version.

Cambrea Simona Claudia - substantial contribution to the conception of the work and data acquisition, final approval of the version to be published;

Popescu Gilda Georgeta – interpretation of data and revising the work critically for important intelectuall content, final approval of the version to be published;

Resul Ghiulendan - substantial contribution to autopsy reports and specific interpretation, final approval of the version to be published.

Petcu Lucian Cristian - substantial contribution by providing statistical analysis and data interpretation, final approval of the version to be published

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