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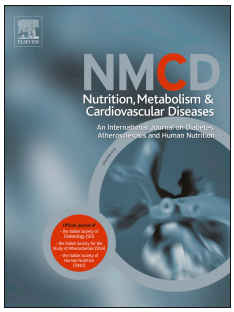


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# MORTALITY FROM INFECTIOUS DISEASES IN DIABETES

*Running title: infections and diabetes mortality*

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## ABSTRACT

**Background and Aims:** to investigate the risk of mortality from infections by comparing the underlying causes of death versus the multiple causes of death in known diabetic subjects living in the Veneto Region, Northern Italy.

**Methods and Results:** 185,341 diabetic subjects aged 30-89 years were identified in the year 2010 and causes of death were assessed from 2010 to 2015. Standardized Mortality Ratios (SMR) with 95% confidence intervals were computed with regional mortality rates as reference. The underlying causes of death and all the diseases reported in the death certificates were scrutinized. At the end of the follow-up, 36,382 subjects had deceased. We observed an increased risk of death from infection-related causes in subjects affected by diabetes with a SMR of 1.83 (95 % CI, 1.71-1.94). The SMR for death from septicemia was 1.91 (95 % CI, 1.76-2.06) and from pneumonia 1.47 (95 % CI, 1.36-1.59). The use of the multiple causes of death approach emphasized the contribution of infectious diseases to mortality.

**CONCLUSION:** the results of the present study demonstrate an excess mortality from infection-related diseases in patients affected by diabetes and, more interestingly, show a possible underestimation of the impact of these conditions by routine mortality analyses.

## INTRODUCTION

The prevalence of diabetes is steadily rising, and therefore it constitutes a consistent challenge for health care systems worldwide [1]. In patients affected by diabetes, the main burden in terms of morbidity and mortality is represented by cardiovascular diseases [2], nevertheless infections are increasing both in frequency and severity in these patients [3]. Subjects with diabetes have higher rates of impaired immunity [4,5] and an increased risk for various types of infections when compared with those without diabetes [6] The impact of infectious diseases is particularly high in older patients as recently shown [7,8]. The association of diabetes and infections has been reported in the past and at least two important studies have observed an increased frequency of bacteriuria and bacteremia in adult women with diabetes versus those without it [9,10]. Besides bacteremia, diabetes has shown to increase the risk of pneumonia, tuberculosis, urinary tract infections, severe gram-positive and hospital acquired post-operative infections [3,11].

It has been reported that 28-day mortality rate is higher among patients affected by diabetes with MRSA pneumonia compared to patients without diabetes [12]. Nevertheless, other studies did not report an increased risk of mortality from community acquired pneumonia in patients with diabetes [13]. An important Australian study, that involved 1,108,982 individuals with diabetes, reported an increased risk of mortality from various infections compared to the general population [14]. The risk of mortality was higher in type 1 patients compared to type 2 patients [14].

The excess risk of death from infectious diseases in patients with diabetes may be multifactorial. An important role is played by the presence of microangiopathy and renal failure [15]. The other important factor is hyperglycemia: hyperglycemia on admission has been shown to increase the risk of pneumonia-related mortality [16].

Considering the important emerging role of infectious diseases in the clinical outcomes of diabetes, in the present study we analyzed the impact of infections on the risk of mortality in patients with

diabetes by using both the underlying cause of death (UCOD) and the multiple causes of death (MCOD) approaches [17]. Through the MCOD approach, it is likely to obtain a more realistic estimate of mortality burden from infection-related causes [17].

## METHODS

### Identification and follow-up of a cohort of diabetic subjects

In the Veneto Region (North-Eastern Italy), hospital care is free of charge, while patients contribute to out-of-hospital care and drug costs. However, after the certification by a specialist and the enrollment in an electronic list of subjects with diabetes maintained by Local Health Units, out-of-hospital care related to diabetes (both type 1 and type 2) is free of charge. The electronic regional archive of subjects with copayment exemption for diabetes is estimated to include about 80% of subjects identified as diabetics by multiple data sources [18]; therefore it does not include all the affected residents in the Region because, for example, elderly patients with an income below an official threshold have access to free outpatient care even if not listed as diabetic subjects. However, such archive can be the source for the identification of a large cohort of patients; in a previous survey in the Veneto Region, the positive predictive value of the archive was 98% for the diagnosis of diabetes in a sample of people aged 18–65 years [19].

For the purpose of this study, we identified in the electronic archive of the Veneto Region a cohort of diabetic patients aged 30-89 years with copayment exemption for diabetes in January 2010 and linked them with the archive of causes of deaths occurred in the period 2010-2015. Based on copayment exemptions, selected comorbidities affecting patients with diabetes were also identified: cancer, chronic renal failure, heart diseases (congestive heart failure, ischemic and hypertensive heart diseases), respiratory diseases (chronic respiratory failure, asthma), rheumatoid arthritis, Parkinson's disease, and having received an organ transplant. The study was carried out by using health records previously submitted to a standardized anonymization process assigning to each

subject a unique code allowing record linkage between electronic archives, without any possibility of retrieving the identities of patients. Each subject was followed-up from January 1, 2010, either until death, or 90 years of age, or December 31, 2015, whichever came first.

**Analysis of causes of death**

A copy of death certificates of all residents in the Veneto Region is centrally transmitted to the Regional Epidemiological Department for coding of causes of death according to the International Classification of Diseases, 10th Edition (ICD-10). Since 2008 the electronic regional archive of mortality includes not only the underlying cause of death, but all diseases mentioned in the death certificate (MCOD), both in Part I (i.e. conditions involved in the causal chain of events leading to death), and in Part II (i.e. other significant conditions contributing to death). The selection of the UCOD is performed by means of the Automated Classification of Medical Entities, which is a computer program developed by the US National Center for Health Statistics to standardize assignment of the underlying cause [20].

To assess mortality in the study cohort, common causes of death routinely reported in mortality statistics were investigated, including certain infectious diseases (ICD-10 A00-B99), sepsis (A40-A41), and pneumonia (J12-J18). Furthermore, to obtain a broader picture of infections-related deaths, the following causes were included in a single category: certain infectious diseases (A00-B99, with the exclusion of viral hepatitis B15-B19), respiratory infections (J10-J22, J69, J85-J86), and urinary infections (N10-N12, N136, N15, N390). Mention of infection diseases was searched both limited to the UCOD, and among MCOD of the period 2010–2015.

Since all analyses were carried out on routinely collected anonymized health records, the study was deemed exempt from approval by the Local Ethical Committee.

**Statistical analysis**

Standardized Mortality Ratios (SMR) with 95% confidence intervals based on the Poisson distribution were computed as the ratios between deaths observed in the diabetic cohort, and those expected according to age- and gender-specific regional mortality rates. SMRs were computed for both total mortality and the main nosologic categories based on the underlying cause of death. SMRs were assessed in the whole cohort of diabetic subjects, separately by gender and three classes of age, and stratified by the presence of comorbidities.

Furthermore, the proportional mortality (share of overall mortality accounted by a specific cause) for infectious diseases was analyzed by follow-up period (2010-2012 and 2013-2015), both through the UCOD and the MCOD approaches.

## RESULTS

In the present study, 185,341 patients with diabetes were included out of 191,301 identified on January 2010: 5,960 were excluded for the age limits (< 30 yrs or ≥ 90 yrs). Less than 1 % of patients were lost during the years of follow-up. At the end of the follow-up 36,382 (24.7 %) patients had deceased. The main cause of death, in quantitative terms, was represented by cardiovascular diseases (as shown in table 1), nevertheless the risk of dying from infection-related causes was quite high, with a SMR of 1.83 (95 % CI, 1.71-1.94). The SMR for death from septicemia was 1.91 (95 % CI, 1.76-2.06) and that from pneumonia 1.47 (95 % CI, 1.36-1.59), respectively. It is worth noting that the highest SMRs, with a two-fold increased risk of mortality with respect to the general population, were observed for sepsis as well as for few already well-known causes of death in diabetic subjects: ischemic heart diseases, liver and pancreatic cancer, and chronic liver diseases.

Table 2 reports the number of deaths and SMRs for infection-related deaths stratified by sex and age. In general, SMRs decreased with increasing age in all conditions and the peaks of SMRs were seen in the group aged 30-64 yrs in both sexes. Females showed higher SMRs, especially in the

younger age group. The highest risk of dying from infection-related causes was for sepsis, with a 3 and about 5 fold increase in males and females, respectively, aged 30-64 yrs (table 2). The SMRs for pneumonia in the same age group was 2.18 (95 % CI, 1.16- 3.73) for males and 3.53 (95 % CI, 1.25- 7.68) for females. Of note, figure 2 shows the prevalence of infectious diseases when selected as the UCOD, or as any mention in the death certificate (MCOD). This figure emphasizes that infections may largely be underestimated as causes of death. A large difference between UCOD and MCOD could be observed especially during the second triennium of follow-up for which sepsis was the main contributor (figure 2). From 2013 to 2015, infectious diseases were selected as the UCOD in 6.0% of overall deaths, whereas they were mentioned in 20.6% of all death certificates in diabetic subjects. Table 3 shows the SMRs for common infections and sepsis stratified according to the comorbidities. The increased risk of death from infections persisted after stratification for the comorbidities. Some subgroups in the sepsis analysis have few events, but it is still shown that the trend of SMRs indicates an increase in the risk of mortality.

## DISCUSSION

The main results of this study were: 1) patients with diabetes experienced an excess mortality from infectious diseases that persisted even when the comorbidities were accounted for by stratified analysis, 2) excess mortality peaked in younger patients (between 30-64 yrs) and declined afterwards, 3) SMRs of mortality were higher in females, and 4) the burden of infectious diseases on mortality became substantial when the MCOD approach was adopted; therefore the use of UCOD may lead to an underestimation of infectious diseases as cause of death. In the second triennium of follow-up there was an increase in infection-related mortality and sepsis was the major contributor to this increase.

Notably, about 20% of patients with diabetes could not be included in the study, mainly elderly patients with low economic income. This may represent a selection bias that limits the generalization of our results. However, this bias may also lead to a further underestimation of the impact of infectious diseases on total mortality.

During the recent years, infectious diseases have turned out to be a major health problem probably due to the emergence of multi-resistant bacteria [11,12,13], and the growing number of patients with altered immune function. Diabetes may compromise the immune system activity at several levels [3,21].

A retrospective study on 218,805 elderly patients with diabetes showed an high incidence of community acquired infection (lower respiratory tract and urinary tract infections, sepsis) with many of them requiring hospitalization [7]. In England, between 2000-2001 and 2010-2011, hospital admission rates for community-acquired infection more than doubled [8]. Our results showed an increase in infectious diseases in the interval 2013-2015 compared to 2010-2012. The increase for sepsis was impressive, maybe related both to a real increase and to more careful recording of the condition in death certificates [17].

In the younger age group (30-64 yrs), the risk of dying from sepsis or pneumonia was 3-5 and 2-3.5 fold higher in patients with diabetes, with higher relative risks observed in the female gender. Eventually, the risk of dying from infection-related causes decreased with age. Diabetes is associated with an increased risk of mortality from different infectious diseases [14] and infections caused by specific agents such as Pseudomonas aeruginosa [22] or Acinetobacter baumannii [23] .

Our results are in agreement with a recent and large population-based study from Australia [14]. This Australian study found comparable SMRs for sepsis , while SMRs for pneumonia were higher in the present study. The Australian study is also important because the authors were able to distinguish between type 1 and type 2 diabetes, observing higher risks in type 1 diabetes.

However, instead of recoding the causes of death and conducting a successive analysis as in the Australian study [14], we analyzed any mention of infections in death certificates. We believe that this latter approach can better estimate the global burden of infectious diseases on mortality, contributing also to emphasize the underestimation of the real impact of these diseases on mortality as shown by our results (figure 2) [17].

Community-acquired pneumonia, despite modern treatment modalities, still confers a high in-hospital and 30-day risk of mortality [24]. Diabetes is one among all the comorbidities that can increase the risk of mortality in these patients [24]. Moreover, the 28-day mortality in patients with diabetes affected by nosocomial pneumonia caused by methicillin-resistant microorganisms was higher compared to patients without diabetes [12]. The risk of death was sixth-fold higher among patients with diabetes who were receiving chronic renal dialysis [12].

The relationship among diabetes, immune system function and infections may be mediated by multiple factors, but at least three of them deserve attention: microangiopathy, renal dysfunction and other comorbidities, as well as short and long-term hyperglycemia.

Microangiopathy along with hyperglycemia may alter both the permeability and the structure of glycolipid moiety in the microcirculation [25] increasing the risk of bacteremia [3].

Renal dysfunction seems to be a critical factor of infection-related mortality, as reduced glomerular filtration rate has been associated to an increased risk (more than double when GFR falls below 30 ml/min/1.73m$^2$) of mortality from infection-related conditions [26] . Even the pre-existence of chronic kidney disease is associated with an increased short-term risk of mortality following pneumonia and sepsis [27].

Comorbidities may play an important role in causing the excess mortality from infectious diseases; a retrospective cohort study found an increased risk for infection-related mortality in adults with diabetes and reported that the increased risk could be mediated by congestive heart failure [28].

However, our study seems to indicate that the risk of mortality from infections was increased even after stratification by comorbidities (table 3).

Hyperglycemia was shown to impair the chemotaxis of neutrophils, phagocytosis, superoxide production and killing activity of Staphylococcus aureus [29]. Also short-term episodes of hyperglycemia may impair IL-6 expression in intermediate monocytes and IL-17A expression, both of which are responsible for immune dysfunction in critically ill patients [30]. However, the relationship between glycemia and sepsis is not straightforward. In recent studies it has been shown that while diabetes mellitus behaves somehow as a protective factor in sepsis patients, hyper- or hypoglycemia status on admission, and increased blood glucose variability during hospital stay, were independently associated with an increased risk of mortality [31].

Through all the above mechanisms, patients affected by diabetes are at increased risk of mortality from infection-related diseases. Our results may have important clinical relevance as they show that the impact on mortality from infectious diseases, including sepsis, may be largely underestimated if confined to the UCOD. In fact, the UCOD usually emphasizes the impact of chronic illnesses and understates the role of infections in the terminal phase leading to death, while MCOD, by analyzing all conditions reported in the death certificate, may reveal a more realistic picture of the impact of infections as a cause of mortality [17].

Our study may have important clinical implications as it suggests that infectious diseases greatly increase the risk of a worse prognosis in patients affected by diabetes. Even though the absolute risk based on the UCOD is quite small, it should be emphasized that the real impact of infectious diseases on mortality may be largely underestimated, as the use of MCOD seems to indicate.

The present study has different strengths: standardized coding of death certificates, inclusion of deaths in non-hospitalized patients, the large number of subjects, and the use of both UCOD and MCOD for classifying infection-related causes of death. Limitations of the study are the use of a

single source of identification of diabetes, the lack of distinction between type 1 and type 2 diabetes and, finally, the absence of clinical variables such as severity of diabetes, diabetes duration, glycated hemoglobin and type of hypoglycemic treatment that are difficult to obtain by administrative databases.

In conclusion, the results of the present study demonstrate an excess mortality from infection-related diseases in patients affected by diabetes and, more interestingly, show a possible underestimation of the impact of these conditions in causing mortality.

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Specific author contributions: UF and ES designed the study, collected and analyzed the data; GZ designed the study, revised the results and wrote the manuscript; EB, MD, GT, and MCC critically revised the manuscript. All authors have seen and approved the final version of the submitted manuscript.

**CONFLICT OF INTEREST**: none to declare

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**Table 1**. Number of deaths and standardized mortality ratio (SMR) with 95% Confidence Interval (CI) in a cohort of 185,341 patients with diabetes according to the underlying cause of death. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

| | n deaths | SMR (CI) | % all deaths |
|---|---|---|---|
| Certain infectious and parasitic diseases (A00-B99) | 1,022 | 1.83 (1.71-1.94) | 2.8% |
| Septicemia (A40–A41) | 641 | 1.91 (1.76-2.06) | 1.8% |
| Neoplasms (C00-D48) | 10,870 | 1.31 (1.28-1.33) | 29.9% |
| Malignant neoplasms of colon, rectum and anus (C18-C21) | 1,048 | 1.24 (1.17-1.32) | 2.9% |
| Malignant neoplasm of liver (C22) | 1,194 | 2.26 (2.14-2.40) | 3.3% |
| Malignant neoplasm of pancreas (C25) | 1,159 | 1.85 (1.74-1.96) | 3.2% |
| Malignant neoplasms of trachea, bronchus and lung (C33-C34) | 2,058 | 1.17 (1.12-1.22) | 5.7% |
| Malignant neoplasm of breast (C50) | 526 | 1.26 (1.15-1.37) | 1.4% |
| Endocrine, nutritional and metabolic diseases (E00-E90) | 4,814 | 5.17 (5.03-5.32) | 13.2% |
| Diabetes mellitus (E10-E14) | 4,518 | 6.08 (5.90-6.26) | 12.4% |
| Mental and behavioural disorders (F00-F99) | 822 | 0.98 (0.92-1.05) | 2.3% |
| Dementia (F00-F03) | 785 | 1.02 (0.95-1.09) | 2.2% |
| Diseases of the nervous system (G00-G99) | 914 | 0.90 (0.84-0.96) | 2.5% |
| Diseases of the circulatory system (I00-I99) | 12,282 | 1.53 (1.50-1.55) | 33.8% |
| Hypertensive diseases (I10-I15) | 1,261 | 1.26 (1.19-1.33) | 3.5% |
| Ischemic heart diseases (I20-I25) | 5,085 | 1.80 (1.75-1.85) | 14.0% |
| Other heart diseases (I00-I09, I26-I51) | 2,855 | 1.49 (1.43-1.54) | 7.8% |
| Cerebrovascular diseases (I60-I69) | 2,707 | 1.41 (1.35-1.46) | 7.4% |
| Diseases of the respiratory system (J00-J99) | 2,088 | 1.26 (1.21-1.31) | 5.7% |
| Pneumonia (J12-J18) | 665 | 1.47 (1.36-1.59) | 1.8% |
| Chronic lower respiratory diseases (J40–J47) | 752 | 1.13 (1.05-1.21) | 2.1% |
| Diseases of the digestive system (K00-K93) | 1,618 | 1.72 (1.64-1.80) | 4.4% |
| Diseases of liver (K70-K76) | 799 | 2.31 (2.15-2.48) | 2.2% |
| Diseases of the genitourinary system (N00-N95) | 550 | 1.66 (1.52-1.80) | 1.5% |
| External causes of mortality (V01-Y84) | 910 | 1.30 (1.22-1.39) | 2.5% |
| **All causes** | 36,382 | 1.53 (1.51-1.54) | 100.0% |

**Table 2**. Number of deaths and standardized mortality ratio (SMR) with 95% Confidence Interval (CI) in patients with diabetes, by gender and age class according to the underlying cause of death. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | n | SMR (CI) | % all deaths | n | SMR (CI) | % all deaths |
| All causes | | | | | | |
| 30-64 yrs | 2,209 | 2.18 (2.09-2.27) | - | 729 | 2.47 (2.29-2.65) | - |
| 65-74 yrs | 5,644 | 1.72 (1.67-1.76) | - | 2,349 | 1.95 (1.88-2.04) | - |
| 75-89 yrs | 13,159 | 1.35 (1.33-1.38) | - | 12,292 | 1.48 (1.46-1.51) | - |
| Sepsis | | | | | | |
| 30-64 yrs | 30 | 3.00 (2.02-4.28) | 1.4% | 16 | 4.98 (2.84-8.08) | 2.2% |
| 65-74 yrs | 90 | 2.44 (1.96-3.00) | 1.6% | 52 | 3.67 (2.74-4.81) | 2.2% |
| 75-89 yrs | 233 | 1.63 (1.43-1.85) | 1.8% | 220 | 1.72 (1.50-1.96) | 1.8% |
| Pneumonia | | | | | | |
| 30-64 yrs | 13 | 2.18 (1.16-3.73) | 0.6% | 6 | 3.53 (1.29-7.68) | 0.8% |
| 65-74 yrs | 57 | 1.91 (1.45-2.47) | 1.0% | 33 | 3.21 (2.21-4.51) | 1.4% |
| 75-89 yrs | 306 | 1.38 (1.23-1.55) | 2.3% | 250 | 1.37 (1.20-1.55) | 2.0% |
| Common infections* | | | | | | |
| 30-64 yrs | 70 | 1.96 (1.53-2.48) | 3.2% | 38 | 4.02 (2.84-5.51) | 5.2% |
| 65-74 yrs | 205 | 1.79 (1.55-2.05) | 3.6% | 113 | 2.42 (1.99-2.91) | 4.8% |
| 75-89 yrs | 753 | 1.33 (1.23-1.43) | 5.7% | 692 | 1.30 (1.20-1.40) | 5.6% |

*Common infections: some infectious diseases A00-B99 - with the exclusion viral hepatitis B15-B19; respiratory infections J10-J22, J69, J85-J86; urinary infections N10-N12, N136, N15, N390

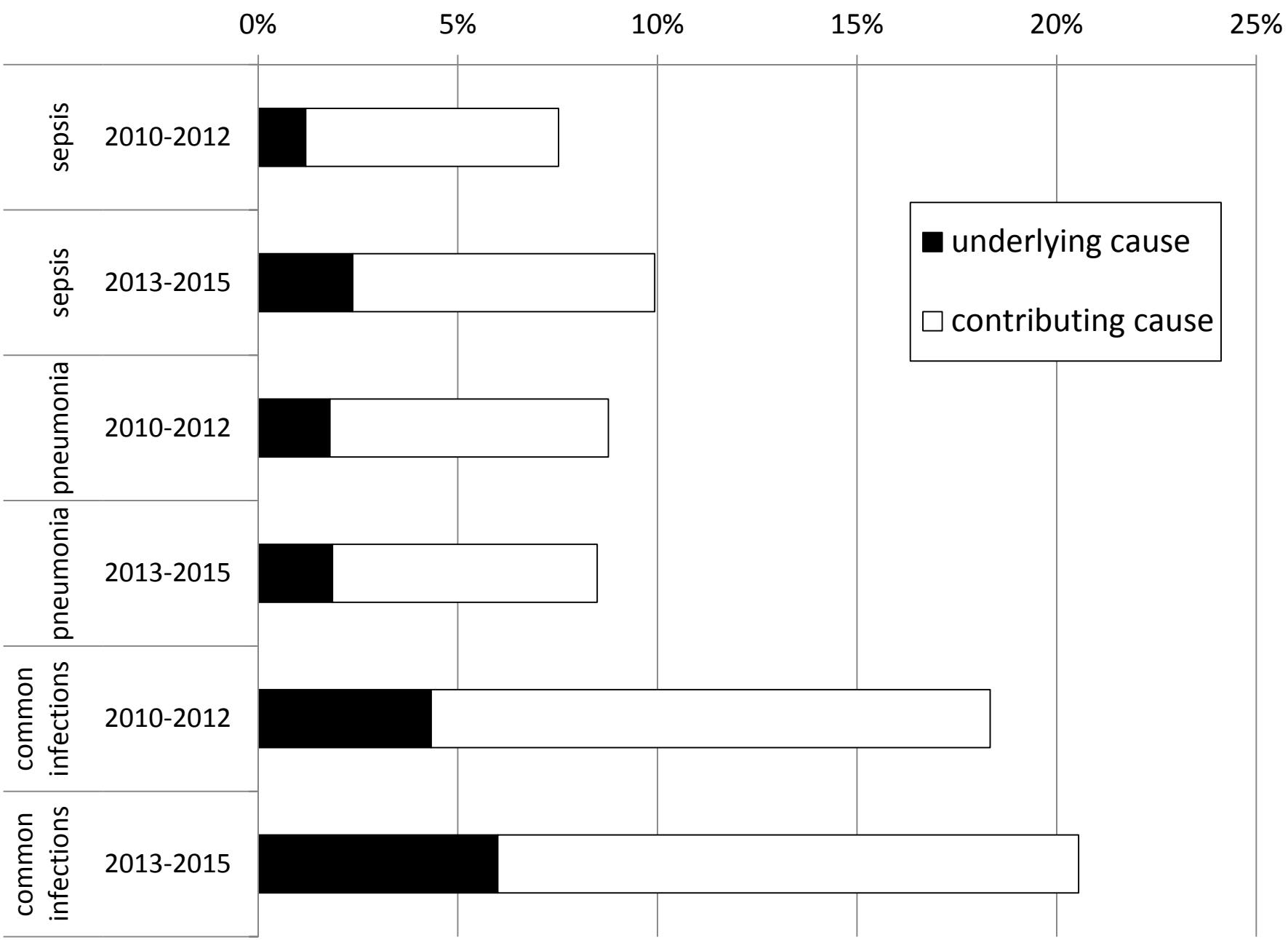
Table **3**. Number of deaths and standardized mortality ratio (SMR) with 95% Confidence Interval (CI) in patients with diabetes, by gender and comorbidities according to the underlying cause of death. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

| | Males | | Females | |
|---|---|---|---|---|
| | N | SMR (CI) | n | SMR (CI) |
| **Common infections*** | | | | |
| No comorbidities | 540 | 1.25 (1.14-1.36) | 478 | 1.22 (1.11-1.33) |
| Any comorbidity | 488 | 1.71 (1.57-1.87) | 365 | 1.85 (1.67-2.05) |
| Cancer | 123 | 1.35 (1.12-1.61) | 85 | 1.50 (1.19-1.85) |
| Chronic renal failure | 47 | 4.09 (3.00-5.44) | 28 | 5.17 (3.44-7.48) |
| Heart diseases | 344 | 1.71 (1.53-1.90) | 260 | 1.88 (1.66-2.12) |
| Respiratory diseases | 29 | 1.96 (1.31-2.81) | 21 | 2.25 (1.39-3.44) |
| Rheumatoid arthritis | 14 | 4.39 (2.40-7.36) | 15 | 2.36 (1.32-3.90) |
| Parkinson's disease | 13 | 2.98 (1.58-5.09) | 9 | 2.24 (1.02-4.26) |
| Transplant | 8 | 9.27 (3.99-18.3) | 5 | 22.8 (7.35-53.2) |
| **Sepsis** | | | | |
| No comorbidities | 188 | 1.63 (1.41-1.88) | 165 | 1.69 (1.45-1.97) |
| Any comorbidity | 165 | 2.21 (1.88-2.57) | 123 | 2.55 (1.12-3.04) |
| Cancer | 42 | 1.76 (1.27-2.37) | 23 | 1.62 (1.03-2.43) |
| Chronic renal failure | 18 | 5.87 (3.48-9.28) | 15 | 11.3 (6.30-18.6) |
| Heart diseases | 119 | 2.25 (1.87-2.70) | 90 | 2.69 (2.16-3.31) |
| Respiratory diseases | 4 | 1.04 (0.28-2.66) | 6 | 2.55 (0.93-5.55) |
| Rheumatoid arthritis | 5 | 5.87 (1.89-13.7) | 3 | *1.88 (0.38-5.48)* |
| Parkinson's disease | 3 | *2.64 (0.53-7.72)* | 5 | 5.23 (1.68-12.2) |
| Transplant | 3 | *11.5 (2.30-33.5)* | 2 | *30.0 (3.37-108)* |

*Common infections: some infectious diseases A00-B99 - with the exclusion viral hepatitis B15-B19; respiratory infections J10-J22, J69, J85-J86; urinary infections N10-N12, N136, N15, N390

## FIGURE LEGENDS

Figure 1. Contribution of infectious diseases selected as the underlying cause of death (UCOD), or contributing causes of death, among 36,382 decedents from a cohort of 185,341 patients with diabetes. The results are stratified by the two triennial periods of the follow-up.



**Highlights**

Infections are growing as a major problem in diabetes.

The risk of dying from infections in diabetes is quite high.

Septicemia and pneumonia are major threatens.

Multiple causes of death approach may give a more realistic estimate of mortality.