ORIGINAL ARTICLE

The increase of sepsis-related mortality in Italy: a nationwide study, 2003–2015

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Abstract

The true burden of sepsis is largely unknown. Conventional underlying cause of death (UCoD) statistics largely underestimates sepsis-related mortality. This study aims to analyze all the conditions mentioned in the death certificates (multiple causes of death—MCoD) to estimate the nationwide burden of sepsis-related mortality in Italy, to investigate time trends and main comorbidities in sepsis-related deaths. All death certificates mentioning sepsis from 2003 to 2015 were analyzed. Age-standardized mortality rates were calculated for sepsis as both UCoD and MCoD, by gender and broad age groups. The ratio of the age-standardized proportions of any mention of sepsis in the presence/absence of associated chronic diseases (ASPR) was computed. The number of certificates reporting sepsis increased from 18,939 in 2003 to 49,010 in 2015 (from 3 to 8% of all deaths). The increase in sepsis mortality rates was larger for UCoD (males, + 200%; females, + 175%) than for MCoD-based figures (+ 100%; + 90%); MCoD rates remained noticeably higher than UCoD rates (2015, 87.3 per 100,000 vs. 16.3 for males; 54.9 vs. 11.8 for females). The largest increase was observed among the very elderly. The association between sepsis and chronic diseases was stronger for subjects aged less than 75 years. The increased awareness within the medical community in addition to the growing susceptible elderly population and the spread of antimicrobial resistance could have contributed to the sepsis-related mortality increase. MCoD statistics could help in recognizing sepsis not only as a clinical challenge, but also as a major public health issue.

Keywords Sepsis · Mortality · Multiple causes of death · Italy

Introduction

Sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1], is the subject of increasing interest for clinicians, policy makers, patients, and researchers. The Surviving Sepsis Campaign, World Sepsis Day, and mandatory reporting rules are examples of ongoing initiatives raising awareness about sepsis. Within this context, accurate data are needed on sepsis incidence, characteristics, outcomes, and whether these are changing over time [2].

Despite these knowledge needs, the true burden of disease arising from sepsis remains largely unknown, both in terms of incidence and mortality. The most common source for sepsis surveillance at the population level is represented by hospital discharge records; however, they are undermined by uncertainties due to the different approaches followed to track sepsis using discharge diagnoses. Different methods lead to very different estimates of sepsis rates, but all the studies on discharge records report an increasing trend, with codes for sepsis being used more frequently over time and thus capturing an increasing fraction of the septic population [3]. Nevertheless, a recent report from the US showed that the increasing trend in sepsis incidence registered through discharge data was not confirmed when clinical criteria assessed through the analysis of electronic health records were considered [4]. Increasing trends from administrative claims may be due to increased reimbursement for sepsis encouraging hospitals to be more careful about coding for sepsis; moreover, improved awareness and recognition contribute to increased documentation of sepsis over time; lastly, estimates of sepsis-related mortality based on hospital data are biased by taking into account only deaths occurring in health-care facilities [5].

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An additional data source is represented by cause of death registers; however, conventional statistics based on the underlying cause of death (UCoD) largely underestimate the true burden of sepsis-related mortality. This problem is compounded by the fact that sepsis is treated as a "garbage code" in the Global Burden of Disease statistics (GBD) [3]. Improving the coding of sepsis and establishing a proper accounting in those statistics are essential steps envisaged by the World Health Assembly (WHA) on May 24, 2017 [6]. UCoD statistics, in accordance with the definition of underlying cause of death, usually emphasize the burden of chronic illness, and understate the role of infectious diseases in the terminal phase leading to death [7, 8]. A solution is represented by the analysis of all the conditions mentioned in the death certificate (multiple causes of death—MCoD). In the GBD 2017 cycle, analyses on MCoD for some important intermediate causes such as sepsis will be included [9]. The MCoD approach to analyze the burden of sepsis-related mortality has been adopted in few countries with diverging results: sepsis-related mortality rates were reported to be stable from 1999 to 2005 in the USA [10], and from 2001 to 2010 in England [11], while a steep increase was registered in Brazil [12] from 2002 to 2010 and in the Czech Republic [13] from 1998 to 2011. To date, the only report from Italy referred to a single region and a short time period, and showed increasing sepsis-related mortality rates [14].

Aim of the study is to analyze the national database of MCoD in Italy to estimate sepsis-related mortality rates, to investigate recent time trends and to assess the main comorbidities mentioned in sepsis-related deaths.

Materials and methods

All analyses were carried out on the mortality data routinely collected by the Italian National Cause of Death Register, managed by the Italian National Institute of Statistics (ISTAT) [15]. Data are based on the information reported on death certificates; all the diseases mentioned in the certificate (MCoD) are coded according to the International Classification of Diseases, 10th Revision (ICD-10) [16]. Part I of the death certificate reports the causal sequence from a single underlying cause which initiated the train of morbid events leading directly to death, to intermediate causes, to the immediate cause of death; part II of the certificate includes other significant conditions contributing to death. The UCoD is selected basing on an internationally adopted set of rules and generally corresponds to the underlying cause stated by the certifier, but it could also be another disease reported elsewhere in part I or in part II, or a condition obtained by combining the selected UCoD with other causes reported on the death certificate (application of modification rules). There is no restriction in the number of causes coded and recorded in

the Register's database. Causes of death are automatically coded with the Micar-ACME system (2009 version, Centre for Disease Control and Prevention). Micar is the module operating the multiple cause coding while ACME performs the selection of the UCoD. About 80% of death certificates are automatically coded. The remaining certificates, where multiple cause codes are not attributed, are manually coded and the UCoD selection is performed by ACME. For external cause deaths and deaths following medical or surgical procedures, the UCoD is manually selected.

All deaths from January 1, 2003 to December 31, 2015 of subjects resident in Italy were analyzed. Mention of sepsis was searched among MCoD records to retrieve sepsis-related deaths, corresponding to the ICD-10 codes A02.1 (Salmonella septicaemia), A32.7 (Listerial septicaemia), A40 (Streptococcal septicaemia), A41 (Other septicaemia, including unspecified septicemia and septic shock), B37.7 (Candidal septicaemia), and P36 (Bacterial sepsis of newborn). The selection of these specific ICD codes was made in order to allow the comparison with previous studies which investigated the burden of sepsis-related deaths [10–14]. As it has been already shown [11, 13], the codes A40–A41 identify almost all sepsis-related deaths in official mortality statistics. Age- and gender-specific mortality rates were computed for sepsis as both UCoD and MCoD. Time trends of sepsis-related mortality rates were investigated by age-standardized rates (European standard population) [17]. As a measure of the underestimation of the role of sepsis in UCoD-based mortality statistics, the standardized ratio of the multiple to the underlying cause (SRMU) was computed, defined as the ratio between the age standardized multiple cause mortality rate and the age standardized underlying cause death rate [18].

Chronic diseases at risk of sepsis were selected a priori based on previous evidence of an increased cause-specific mortality from sepsis and other infections among cohorts of affected subjects, or according to multiple causes of death analyses. Therefore, death certificates with mention of diabetes (ICD-10 E10-E14), chronic renal failure (N18.5, N18.9), dementia, Alzheimer, and Parkinson's disease (F01–F03, G30, G20), rheumatoid arthritis (M05-M06), and hematological malignancies (C81-C96) were identified. The age standardized proportion of any mention of sepsis was compared between deaths with and without the above-mentioned chronic conditions. To measure the excess proportion of having sepsis mentioned in the death certificate in association with the selected chronic diseases, a relative risk indicator, the Age-Standardized Proportion Ratio (ASPR) with 95% confidence interval (CI) was computed as the ratio of the age-standardized proportions of any mention of sepsis in the presence or in the absence of associated chronic diseases [19]. ASPR significantly greater than unity indicates that the frequency of sepsis is higher in the death certificates mentioning the selected chronic diseases than that in the death certificates that do not

mention the selected chronic diseases. Shortly, the indicator measures the propensity of sepsis to act as a cause of death in presence of the selected chronic diseases. The ASPR provides a measure of the excess mortality related to specific conditions comparing proportions of deaths and then needing only mortality data without the population at risk.

Results

The number of death certificates reporting sepsis as MCoD increased from 18,939 in 2003 to 49,010 in 2015 (from about 3 to 8% of all deaths), while the number of death certificates with sepsis selected as UCoD increased from 2490 to 9729. In the same period, sepsis age-standardized death rates increased remarkably both in males and in females (Fig. 1a). The increase was exceptionally large for UCoD, which between 2003 and 2015 showed a percent change of about + 200% in males and 175% in females, while the increase observed in rates calculated on MCoD data was + 100% for males and 90% for females. Rates increased noticeably in 2015 when an excess in overall mortality was observed in Italy, as in other European countries [20]. The difference between UCoD- and MCoD-based figures is also reflected in the decrease of the SRMU observed both in males and females (Fig. 1b). However, rates still remained noticeably higher for MCoD than for UCoD-based analyses: in 2015, the SRMU was 5.3 in males (rates, 87.3 per 100,000 vs. 16.3) and 4.6 in females (rates, 54.9 per 100,000 vs. 11.8). Sepsis-related mortality was higher in males than in females throughout the study period, being 1.6 the ratio of male to female death rates based on MCoD and 1.4 the ratio based on the UCoD.

The largest burden of sepsis-related mortality was observed at older ages (in the study period, about 70% of deaths with sepsis were registered among subjects aged ≥ 75 years). The analysis by age at death (Table 1) showed that MCoD-based rates rise with age (in 2015, from 22.5 per 100,000 in the age class 0–74 years to 986.8 per 100,000 in the age class 85 years and over), and the strongest increase over the study period was observed among the very elderly (percent change + 143% for the age class ≥ 85 years compared to + 101% for the age class 75–84 years). The same pattern was confirmed also by UCoD data. The peak in 2015 with respect to 2014 was remarkable for both UCoD (from + 16.5% for the 0–74 years age group to + 28.4% for the 85 years and over age group) and MCoD (from + 10 to + 20.9%) rates.

The proportion of sepsis-related deaths that occurred in hospitals (Table 2) rose from 84% in 2004 (first year with available data by place of death) to 87.7% in 2015, i.e., more than double with respect to that observed for overall deaths (42.9% in 2004 and 41.2% in 2015). The quota of sepsis deaths that occurred at home decreased from 6.8 to 3.8%.

The conditions most frequently mentioned among MCoD in association with sepsis (Fig. 2) are other heart diseases (i.e., other than ischemic heart diseases, reported on 25.5% of death certificates with mention of sepsis in the period 2010–2015), diseases of kidney and ureter (23.2%), influenza and pneumonia (20.3%), cerebrovascular diseases (15.6%), and diabetes mellitus (14.8%). Among the most mentioned associated causes, the increase in the proportion on total sepsis-related deaths from 2003–2009 to 2010–2015 was particularly pronounced for other heart diseases, influenza and pneumonia, hypertensive diseases, dementia, and Alzheimer's disease, while a reduction was observed for cerebrovascular diseases and blood diseases. Among cancers, the most frequently reported were leukemia (reported on 3% of sepsis-related deaths), cancer of colon, rectum and anus (3%), Hodgkin diseases and lymphomas (2%), and cancer of trachea, bronchus, and lung (2%).

The proportion of death certificates with any mention of sepsis in the presence/absence of chronic diseases and the corresponding ASPR estimates by age group (Table 3) showed as the association between sepsis and the chronic diseases selected a priori as risk factors for sepsis was stronger for ages less than 75 years. The relative risk for deaths in this age group was greater than 2 all over the study period (ASPR = 2.11, 95% CI 2.05–2.17 in the last observation year), and did not show any significant change over time. A statistically significant reduction of ASPR in 2015 with respect to 2003 was instead observed for the age group 75 years and over—1.23 (95% CI 1.20–1.25) vs. 1.58 (95% CI 1.52–1.64).

Discussion

This study provides an estimate of the burden of sepsis-related mortality on a nationwide scale in Italy and analyses its recent time trends, age, and gender patterns. The use of MCoD data allowed for accurate and internationally comparable estimates of sepsis-related mortality and for investigating the role of some associated chronic diseases. The percentage of death certificates reporting sepsis on the total number of deaths in Italy (about 8% in the more recent years) is consistent with previous studies carried-out on MCoD in the Italian region of Veneto (8%) [14] and in the USA (6%) [5, 10], while it is higher than the estimate for the Czech Republic (3%) [13]. The time trend analysis showed a remarkable increase of sepsis-related mortality during the period 2003–2015, similar to that observed in the Czech Republic [13]: in the comparable period 2003–2011 (the Czech study covered the period 1998–2011), a 6% annual increase was observed in Italy compared to an 8–9% increase in the Czech Republic. The strong increase of the mortality rates for sepsis in 2015, as for the overall mortality, could be related to the extreme cold spell and seasonal transmission of influenza during the winter

Fig. 1 Time trend of sepsis mortality: age-standardized mortality rates by gender, multiple (MCoD) vs underlying cause of death (UCoD), values per 100,000 residents (**a**); Standardized Ratio of the Multiple to the Underlying cause (SRMU) (**b**). Years 2003–2015
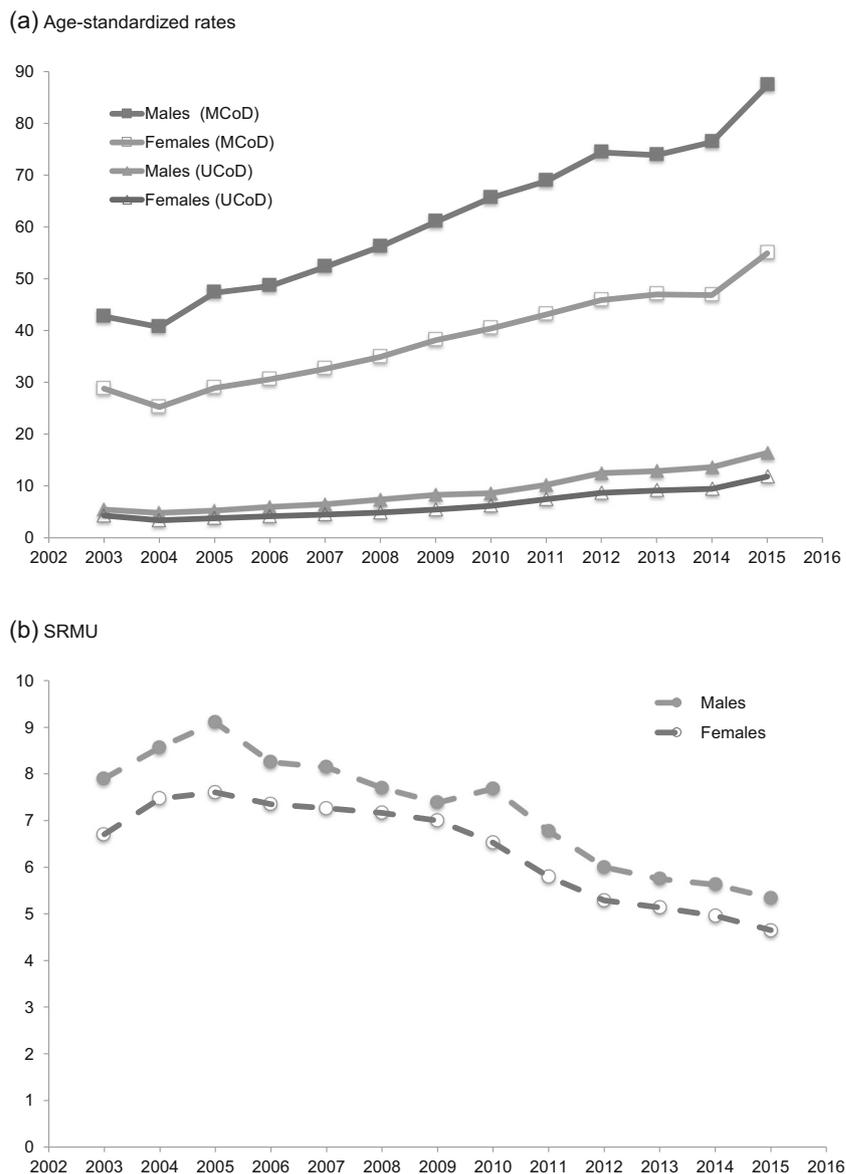
season that could have led to an increase of diseases of the respiratory tract, which represent a common associated site of infection [20], including pneumonia.

A possible explanation of the increasing mortality rates for sepsis is the aging of the population, strictly connected with multi-chronicity, polypharmacy, repeated hospitalizations, malnutrition, functional loss, and age-related immune-senescence [21]. Actually, the observed increase in the burden of sepsis-related mortality was particularly strong at very old ages and was mostly accounted by hospitalized elderly patients. The study also highlights a strong association with selected chronic conditions that, according to the literature findings, are associated to the risk of infection both due to dysfunction of the immune system, and to the need for invasive procedures and immunosuppressive medications. Among those, diabetes represents a worldwide epidemic with increasing prevalence both in

high and low-middle income countries; the association with a raised risk of infection is multifactorial, possibly mediated by short- and long-term hyperglycemia, microangiopathy, renal dysfunction, and other comorbidities. In a recent study carried out on a large cohort of diabetic patients, the risk of death from septicemia increased tenfold in type 1 and twofold in type 2 diabetes [22]. Patients receiving chronic hemodialysis are well known to be at increased risk of infection, bacteremia, and sepsis due to exposure to invasive procedures; more recently, an increased risk of death from infection has also been reported among patients with pre-dialysis chronic kidney disease [23]. In the present study, Parkinsonism and other neurodegenerative disorders were included among risk factors for sepsis because of reduced mobility and respiratory impairment; an analysis on MCoD found an association between Parkinson's diseases, pneumonia, and sepsis in death certificates from Northern

Table 1 Sepsis mortality by age-class: age-standardized rates, years 2003–2015. Multiple (MCoD) vs underlying cause of death (UCoD), rates per 100,000 residents

Year	UCoD				MCoD			
	Age-class				Age-class			
	0–74 years	75–84 years	85 years and over	All ages	0–74 years	75–84 years	85 years and over	All ages
2003	1.7	24.0	66.8	4.8	14.4	174.9	406.0	34.6
2004	1.5	19.6	50.5	3.9	14.2	159.2	327.7	31.5
2005	1.5	21.4	62.1	4.3	15.2	183.3	424.7	36.4
2006	1.7	23.6	71.5	4.9	15.4	190.9	458.8	37.9
2007	1.8	26.9	75.1	5.2	16.1	207.6	496.3	40.6
2008	1.9	28.7	87.8	5.8	16.9	223.5	544.8	43.5
2009	2.1	31.8	101.0	6.5	18.1	240.6	606.9	47.3
2010	2.1	36.7	111.8	7.1	18.4	260.5	673.9	50.5
2011	2.3	44.2	140.2	8.5	19.5	275.9	707.7	53.4
2012	2.9	52.2	162.8	10.1	20.5	296.6	775.0	57.3
2013	2.8	56.7	172.9	10.6	20.1	303.5	792.6	57.8
2014	3.0	56.4	182.6	11.0	20.5	301.1	816.5	58.6
2015	3.5	69.6	234.4	13.6	22.5	351.0	986.8	68.0
Percent change 2014–2015	+ 16.5%	+ 23.4%	+ 28.4%	+ 23.8%	+ 10.0%	+ 16.6%	+ 20.9%	+ 16.0%
Percent change 2003–2015	+ 108.6%	+ 190.7%	+ 251.0%	+ 185.4%	+ 56.4%	+ 100.7%	+ 143.0%	+ 96.4%

Italy [24]. Rheumatoid arthritis was also included as a known risk factor because it represents the most common autoimmune disease requiring immunosuppressive therapy, with an already demonstrated increased risk of hospitalization for sepsis [25]. Lastly, among death certificates with mention of sepsis, a neoplasm is often reported [14], especially hematologic malignancies leading to neutropenia and other immune disorders. The present analysis confirms a role of the above chronic conditions, recognized risk factors for developing sepsis, especially among younger decedents (aged < 75 years). However, the

Table 2 Distribution of deaths by place of death, years 2004 and 2015

Place of death	2004[a]		2015	
	n	%	n	%
Sepsis-related deaths	17,606		49,010	
Hospital	14,783	84.0	42,971	87.7
Home	1195	6.8	1886	3.8
Other	741	4.2	3034	6.2
n.a.	887	5.0	1119	2.3
All deaths	545,051		646,048	
Hospital	234,002	42.9	266,307	41.2
Home	227,641	41.8	247,926	38.4
Other	50,996	9.4	111,120	17.2
n.a.	32,412	5.9	20,695	3.2

[a] The information on place of death is available from 2004

mention of sepsis increased over time also in death certificates not reporting these conditions. As a consequence, the increasing prevalence of underlying chronic diseases is unlikely to fully account for the observed rise in sepsis-related mortality.

An increase in sepsis-related mortality might be due to a genuine rise in incidence, to an increasing recognition of previously missed cases due to a raised awareness of physicians, or to a change in death certification practices [26]. The second mechanism has probably a relevant role in the observed increasing time trend. More than 85% of certificates with mention of sepsis are filled by hospital physicians (with a rising proportion through the study period), who are supposed to pay more attention to the condition also due to ongoing initiatives such as the surviving sepsis campaign [27, 28]. As a consequence of the increased awareness in hospitals, the role of sepsis in the morbid process leading to death might also be more often reported in death certificates. The present study showed that the mortality increase was larger for rates based on sepsis selected as the UCoD, and this finding probably reflects a higher importance attributed to the condition by the cause-of-death certifying physicians. Actually, the selection of the UCoD depends on the position where a disease is mentioned on the death certificate, and sepsis on average was reported in part I in 94% of certificates; moreover, the percentage reporting sepsis in the underlying cause position increased from 8% in 2003 to 14% in 2015.

In the Emilia Romagna Region of Italy, the crude population-based rate of bacteremia based on microbiology records increased by two-fold through the period 2005–2015; the growth

Fig. 2 Top 20 conditions reported among multiple causes (MCoD) in the death certificates with mention of sepsis[a]. Percent proportions on total sepsis-related deaths, periods 2003–2009 and 2010–2015. For each cause ICD-10 codes are reported in brackets
[a]The group of "Other heart diseases (I30-I51)" does not include the ICD-10 categories I46 (Cardiac arrest) and I49.0 (Ventricular fibrillation and flutter)
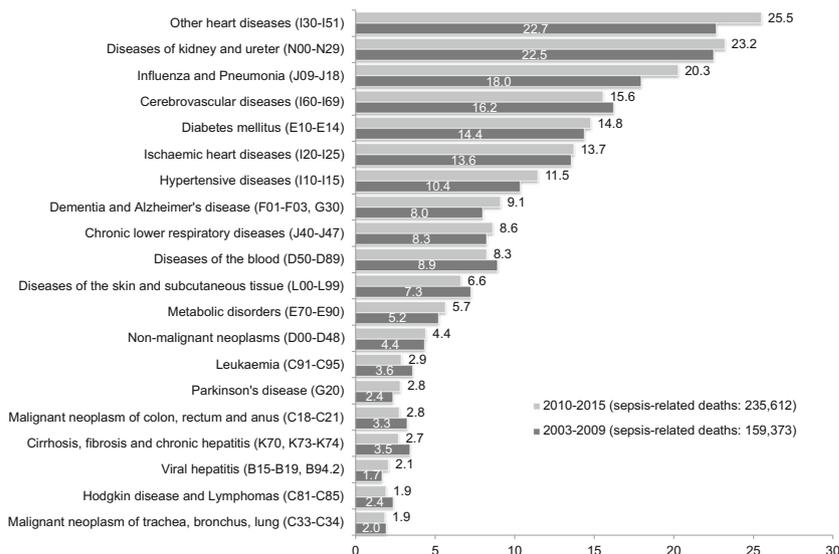
was more pronounced for selected Gram-negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae* [29]. To which extent, these findings might be attributed to an increased diagnostic activity among hospitalized patients is difficult to assess. In addition, figures on antimicrobial resistance reported by the European Antimicrobial Resistance Surveillance Network [30] show an unfavorable pattern for countries in Eastern and Southern Europe, including Italy, and the spread of carbapenem-resistant *Enterobacteriaceae* involved especially Mediterranean countries such as Italy, Cyprus, and Greece [31].

As a consequence, the spread of antimicrobial resistance and the consequent paucity of effective antibiotic treatments might have had an impact on aging population affected by multi-chronicity and with an increased need for invasive procedures.

Coding practices can also play a role in the observed sepsis mortality rates, impairing international comparability and time trend analysis. The ICD-10 has been updated in the last years in order to include recommendations from experts, with significant effect on the selected UCoD. In the present study, such updates have not been used in coding and the reported trends are

Table 3 Proportion of death certificates with any mention of sepsis among deaths with/without mention of associated chronic diseases [a](age-standardized [b]percent values) and ASPR with 95% confidence interval (CI), by age class. Years 2003–2015

Year	0–74 years		75 years and over		0–74 years		75 years and over	
	% on deaths with associated chronic diseases	% on deaths without associated chronic diseases	% on deaths with associated chronic diseases	% on deaths without associated chronic diseases	ASPR	95% CI	ASPR	95% CI
2003	7.1	3.3	3.8	2.4	2.15	(2.04–2.26)	1.58	(1.52–1.64)
2004	7.7	3.4	3.4	2.4	2.26	(2.14–2.37)	1.44	(1.39–1.50)
2005	8.6	3.7	4.1	2.8	2.34	(2.23–2.45)	1.48	(1.43–1.53)
2006	9.1	3.9	4.5	3.1	2.36	(2.26–2.47)	1.44	(1.39–1.49)
2007	10.1	4.1	4.8	3.4	2.45	(2.35–2.55)	1.42	(1.37–1.46)
2008	10.1	4.5	5.2	3.7	2.25	(2.16–2.35)	1.40	(1.36–1.44)
2009	10.2	4.9	5.5	4.1	2.10	(2.02–2.18)	1.34	(1.30–1.38)
2010	10.7	5.0	6.1	4.7	2.13	(2.05–2.22)	1.30	(1.26–1.34)
2011	11.8	5.4	6.5	5.0	2.19	(2.11–2.27)	1.30	(1.26–1.33)
2012	12.3	5.7	6.9	5.5	2.18	(2.10–2.26)	1.26	(1.23–1.29)
2013	12.4	5.8	7.4	6.0	2.14	(2.06–2.21)	1.23	(1.20–1.26)
2014	12.9	6.1	7.7	6.2	2.13	(2.06–2.20)	1.24	(1.22–1.27)
2015	13.9	6.6	8.5	7.0	2.11	(2.05–2.17)	1.23	(1.20–1.25)

[a] Diabetes (E10–E14), Chronic renal failure (N18.5, N18.9), Dementia (F01–F03), Alzheimer's disease (G30), Parkinson's disease (G20), Rheumatoid arthritis (M05, M06), Malignant neoplasms, of lymphoid, hematopoietic and related tissue (C81–C96)
[b] The age distribution of total deaths in the year 2015 has been used as standard

consistent both for multiple and underlying cause, but a change in the UCoD is expected with the adoption of ICD-10 fifth edition for 2016 data [32] that also introduces the codes R65 (Systemic Inflammatory Response Syndrome [SIRS]) and R57.2 (Septic shock). Such codes will be included in future updates of the present analyses, to allow for comparisons across different versions of the ICD-10. Post-procedural sepsis codes (T80.2, T81.4) were not considered in the study, but they represented only a negligible proportion of death certificates with mention of sepsis in Italy (about 1%). The use of MCoD guarantees the consistency of comparison, since it takes into account all relevant information reported without the effect of changes in selection rules.

The main limitations of mortality data derived from death certificates are well known: death certificate completion is entrusted to the medical knowledge of the certifying physician, and therefore, it can suffer from a lack of specificity and/or underreporting. Despite these limitations, our study showed as mortality statistics based on MCoD that data can provide a major contribution to quantifying the nationwide burden of sepsis and its increase over time. Although increased awareness within the medical community might have contributed to increasing sepsis-related mortality rates in recent years, this tendency is sustained also by other long-term trends represented by a growing susceptible elderly population and by the spread of antimicrobial resistance. Monitoring of official mortality statistics could help in recognizing sepsis not only as a clinical challenge, but also as a major public health issue and therefore as a priority for planning resource allocation for its prevention, early recognition and treatment.

Compliance with ethical standards

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