

Epidemiology, management and costs of sepsis in Spain (2008-2017): a retrospective multicentre study

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Abstract

Objective: To update the profile of patients attended with sepsis in specialised care centres in Spain, to analyse in-hospital mortality, disease management and costs between 2008 and 2017.

Methods: Admission records registered between 1 Jan 2008 and 31 Dec 2017 obtained from a Spanish National hospital discharge database for public and private hospitals. Centres are responsible for data codification, evaluation and confidentiality. The database is validated internally, and is subjected to periodic audits. Files corresponding to patients with sepsis and septic shock were selected by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version and 10th version codes. These criteria claimed 311,674 records of 288,211 patients. Direct medical costs of secondary healthcare include expenses derived from the admission: examination, medication, treatment and costs of nutrition, personnel, medical equipment and resources.

Results: More than 53% of all patients were males, with a mean age of 73.0 years. Fifty-one per cent of the identified admissions were due to a sepsis without organ dysfunction, 21.5% to sepsis with organ dysfunction, and 27.3% registered a septic shock. The incidence of sepsis increased 2.7 folds between 2008 and 2017, reaching a hospital incidence of 5.7 per 10,000 inhabitants in 2017. Case fatality rate (CFR) was 23.2% and 35.0% in patients without and with organ dysfunction in 2017, respectively, and 42.9% in patient with septic shock, decreasing over time. Mean annual direct medical costs of specialised care over the study period were €6,664 and €8,084 per patient in patients with sepsis without and with organ dysfunction, respectively, and €11,359 per patient in those with septic shock.

Conclusions: The social and economic burden of sepsis in Spain continues to grow (incidence, total costs). Despite its general decreasing trend, CFR remains elevated, thus, patients could benefit from further research and protocol revision.

Keywords: Sepsis; Septic shock; Population characteristics; Hospital costs; Spain.

Short title: Epidemiology, management and costs of sepsis in Spain (2008-2017).

Word count: 4,401

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [1]. Sepsis can be caused by a wide range of organisms, and have varied origins, principally respiratory, abdominal or urinary [2]. It is a major cause of morbidity and mortality, remaining a challenge for clinicians and healthcare systems. Sepsis is assumed to represent a significant burden worldwide, with a global incidence of 43.7 per 10,000 persons-year, with several studies indicating an increasing trend over the past decades [3,4].

In Spain, the incidence of sepsis has been evaluated several times over the past decades, revealing a similar trend and an incidence of 8.7 per 10,000 persons between 2006 and 2011, as evaluated in the Spanish national hospital discharge database including sepsis diagnosed in patients hospitalised for other reasons [5,6]. On the contrary, mortality appears to be decreasing, which serves as an indicator of the success of recent awareness campaigns and updated treatment guidelines [6]. Globally, the implementation of specific sepsis treatment guidelines and protocols has been critical for the decrease in sepsis-related mortality. The guidelines developed by the Surviving Sepsis Campaign (SSC) published in 2004 and updated in 2016 have been associated with improved outcomes worldwide [7]; these focused on a series of bundles to be completed within 3 or 6 hours after the admission including blood culture, the administration of broad spectrum antibiotics and treatment to control hypotension and the repeated examination of vital signs and cardiovascular function [7,8,9]. Similarly, Sepsis-3 recommends the use of the Sequential Organ Failure Assessment (SOFA), which correlates with an increased probability of mortality, to

clinically characterise patients [1,10]. These criteria have provided a tool for early recognition that needs to be continuously updated [11,12].

The revision and improvement of protocols is one of the applications of epidemiology revisions, hence the growing interest on obtaining detailed and updated epidemiological data including sepsis and septic shock. Via this study, we aim to provide updated data regarding the characteristics of patients attended with sepsis in hospitals and specialised care centres in Spain, incidence, in-hospital mortality, disease management and costs, and to evaluate any temporal trends between 2008 and 2017.

Methods

Study design and setting

Admission records of patients admitted in specialised care centres (hospitals and ambulatory) were analysed in a retrospective multicentre study, with a study period set from 1 Jan 2008 to 31 Dec 2017. Records were obtained from a Spanish National discharge database including public and private hospitals, which covers 90% of hospitals in Spain and is representative of all Spanish regions. The database includes anonymised admission data with diagnoses codified by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD9) prior to 2016 and 10th version (ICD10) the years 2016 and 2017. Data codification is achieved at the hospital level by specialised doctors by using the Spanish ICD codification guides made available to health professionals. Hospitals are responsible for data codification, evaluation and confidentiality. The database is validated internally, and is subjected to periodic audits. In this process, errors and unreliable data are eliminated. Data inclusion was limited to admissions explicitly registered as sepsis or septic shock cases.

Data extraction

Files corresponding to admissions with sepsis or septic shock as primary diagnosis (cause of admission) were selected via the ICD9 codes: 038.0, 038.1x, 038.2, 038.3, 038.4x, 038.8, 038.9, 995.91, 995.92, 785.52, and ICD10 codes: A40.x, A41.x, R65.2x. A total of 311,674 records complied with these criteria, corresponding to 288,211 patients that were classified according to sepsis severity: with or without organ dysfunction (without septic shock), and those that registered septic shock during the admission. Subsequently cases were classified according to the pathogen into streptococcal sepsis, staphylococcal sepsis, sepsis due to anaerobes, sepsis due to other Gram-negative organisms, other specified sepsis (i.e. sepsis due to *Enterococcus*) and sepsis due to unspecified organisms.

Study variables

The database codifies hospital discharge data on the patient profile and admission details: patients' sex and age, Spanish region, date of admission, type of admission, date of discharge, type of discharge (including death), service that discharged the patient, length of stay, readmission rate, admission motive, secondary diagnoses registered during the admission, medical procedures performed and cost of the admission.

Data analysis

Single-patient data, obtained grouping recurrent admissions per each single patient, was used to characterise the population and calculate case fatality rate (CFR) defined as the proportion of in-hospital deaths registered in the study population. Sepsis age-adjusted incidence was extracted from the ministry of health database and was measured as the proportion of sepsis cases registered in specialised care centres within the population adjusted per age. All admission files were used to analyse the nature of admissions, length of stay, readmission (understood as a subsequent admission for the same cause within 30-

days after discharge), medical procedures and costs. All the registered secondary diagnoses were identified by using ICD9 and ICD10 codes.

Descriptive values are presented in mean (standard deviation [SD]), length of stay is presented in mean (standard error [SE]). Odds ratio (OR) with a 95% confidence interval (CI) were calculated for deceased patients, using non-deceased patients as the reference group. Two-tailed T-student or one-way analysis of variance were used as appropriate and two-sample Z tests were used to test for differences in sample proportions, with a $p < 0.05$ considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Released 2011 (IBM Corporation, Armonk, NY, USA) and Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

Direct medical costs of specialised healthcare were calculated based on admission costs indicated in the database; these are calculated according to the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health, which includes all expenses derived from the admission: examination, medication, treatment and costs of nutrition, personnel, medical equipment and resources.

This study did not involve human participants and the database contains anonymised data with no identifying parameters, complying with the principles of Good Clinical Practice and the Declaration of Helsinki. In this context the Spanish legislation does not require patient consent and ethics committee approval [13].

Results

The 288,211 patients admitted with sepsis and septic shock over the ten year period were included in the analysis of patient characteristics (Table 1). Across all groups, more than

50% of the patients were males, with a mean age of 73.0 years. Over 51% of all registered admissions were due to a sepsis without organ dysfunction, 21.5% to sepsis with organ dysfunction without septic shock and 27.3% registered a septic shock. In most of the cases the pathogen was not specified; when specified, gram-negative organisms were predominant. The patients with a streptococcal sepsis (principally *E. coli* and *Streptococcus pneumoniae*) were the youngest.

Sepsis incidence measured in specialised care facilities was 5.7 per 10,000 persons in 2017, increasing 2.7 folds over the study period (Figure 1A). Most of the cases were registered among patients aged 70 to 90 years (Figure 1B).

CFR was 23.2% and 35.0% in patients without and with organ dysfunction in 2017, respectively, and 42.9% in patient with septic shock. CFR decreased significantly over the study period in patients with organ dysfunction and septic shock (2008 vs. 2017, $p<0.001$) (Figure 2A). CFR was higher in older patients throughout the study period (Figure 2B).

Secondary conditions diagnosed upon admission are listed in Table 2. Acute conditions associated with organic dysfunction were predominant. Chronic conditions as essential hypertension, diabetes mellitus and malignant neoplasms, were found in between 20 and 30% of admissions, with slight differences between patient groups. In addition, potential associations appeared in the group of deceased patients versus the remaining population. Acute respiratory failure was more common in deceased patients (OR=2.4; 95%CI 2.3-2.4); similar differences were observed for acute renal disease (OR=2.1; 95%CI 2.1-2.2), heart failure (OR=1.6; 95%CI 1.6-1.7), disorders of fluid electrolyte and acid-base balance (OR=2.2; 95%CI 2.1-2.2), malignant neoplasms (OR=1.7; 95%CI 1.7-1.8) and chronic ulcers of skin (OR=1.9; 95%CI 1.8-1.9).

In terms of healthcare use, over 96% of admissions in all groups were due to emergencies and attended by internal medicine departments in 63.5%, 67.1% and 47.1% of the cases in patients admitted due to sepsis without and with organ dysfunction and septic shock, respectively (Table 3). Mean length of stay was of 10.7 (SE=0.03) in patients without organ dysfunction and increased to 11.8 (SE=0.05) days in patients with organ dysfunction ($p<0.001$). In admissions that registered septic shock this was of 14.3 (SE=0.06) days (septic shock vs. no septic shock, $p<0.001$). Deceased patients registered a mean length of stay of 8.6 days (SE=0.04) (deceased patients vs. non deceased, $p<0.001$). The 30-day readmission rates oscillated between the 10 and 25%.

The estimated mean annual direct costs of specialised care of sepsis were €6,664 and €8,084 per patient in patients with sepsis without and with organ dysfunction, respectively, and €11,359 per patient in those with septic shock (between groups, $p<0.001$) (Table 4), which, considering all patients ($N=288,211$), equalled a total of €247,412,912 per year. Overall, costs per patient decreased between 2011 and 2014 and increased again between 2014 and 2017 (Figure 3). Mean admission cost was €7,940 over the study period and varied with the length of hospital stay. Mean admission cost per stays up to Q1 and longer than Q3 were €5,825-7,779; €6,703-10,132; and €8,035-17,735 in admissions due to sepsis without or with organ failure and septic shock, respectively (within groups, $p<0.001$).

Discussion

Several studies worldwide have described an increasing trend in the number of sepsis cases, which has correlated with an increasing interest in analysing its incidence, nature, management and costs.

The incidence of sepsis has been previously evaluated in Spain, covering a period of 14 years (2000-2013) [5,6]. Data showed an increase that went from 3.3 per 10,000 persons-year (2000-2004) to 4.5 (2010-2013), similarly to estimations in a global scale [2,6,14]. The same trend has been observed in smaller studies focused on patient subpopulations as those diagnosed with type 2 diabetes mellitus [15]. Herein the incidence per 10,000 was 2.1 in 2008, increasing to 5.7 in 2015. A small decrease was observed the year 2016 after the introduction of ICD10, which limits comparability; yet, between 2016 and 2017 the increasing trend continued. Overall, this increase in incidence could be explained by the improved coding of sepsis that has been demonstrated in certain European countries, as Germany, as well as the increased sepsis awareness [16].

On the contrary, data confirms a decrease in mortality, measured as the reduction of CFR. This parameter was 45.4% in Spain in 2006, and decreased to 40.2% in 2011 [5]; our data estimated a CFR of 23.2% and 35.0% in patients without and with organ dysfunction in 2017, respectively, and 42.9% in patients with septic shock, overall, decreasing over the study period presumably due to the improved treatment algorithms and guidelines promoted at the European and global level [1,7,8]. In Spain, European protocols are used, with compliance rates that have increased considerably since 2008 directly affecting health outcomes, reducing mortality rates in patients with severe sepsis and septic shock [17-20]. In addition, an effect of the increased register of sepsis cannot be discarded.

Regarding patients' profile, mean age registered upon admission was 73.0 (18.6) years. Data from the period 2000-2013 showed a significant temporal increase of patients' age, that in that case averaged 69.7 (20.0) years [6].

A predominance of cases caused by Gram-negative bacteria, principally *E. coli*, would coincide with previous estimations, while the origin of the infection could not be directly

evaluated [5,21]. Most admissions registered symptoms of organ dysfunction, although chronic conditions including hypertension and diabetes were also present. Renal, cardiac and respiratory symptoms were associated with in-hospital mortality, as well as the disorders of fluid electrolyte and acid-base balance and malignant neoplasms. On the other hand, even though liver dysfunction is considered a common symptom of sepsis, liver affectation was not depicted clearly in this population [22]; the lack of laboratory test results impeded a formal analysis of laboratory abnormalities.

Most of the admissions were not scheduled, with hospital stays over the 10 days. Relatively high 30-day readmission rates have been previously described in patients with sepsis, attributed primarily to infections and pulmonary complications [23].

These factors had an influence on the medical costs of the disease in specialised care, known to correlate with age, severity, admission and attention characteristics [24,25]. Overall, the mean annual cost per patient in the study period was €6,664 and €8,084 in patients with sepsis without and with organ dysfunction, respectively, and €11,359 per patient in those with septic shock; whereas in the period 2000-2013 average costs reached the €9,090 following an increasing trend [6]. Herein, cost per patient appeared to decrease between the years 2011 and 2014, likely to be an effect of the economic crisis that had great effects on the Spanish medical and pharmaceutical expenditure in that period [26,27]. Data suggest a recovery of the increasing trend after 2014. As expected, admission costs increased with longer hospital stays.

A series of factors limited the results of this study. The update of the database codification to ICD10 in 2016 generated inconsistencies in the data, likely to derive from centres not adhering to the new system. Incidence was calculated using only patients admitted with sepsis in specialised care centres; this could origin an underestimation of this rate. Data

selection method should be taken into account for data interpretation. Finally, the lack of laboratory test results in admission files hampered the evaluation of organ dysfunction and overall severity of the symptoms.

Conclusions

Sepsis is a major cause of mortality in Spain and represents a significant economic burden that continues to grow. Patients with sepsis with organ dysfunction and septic shock present elevated case fatality rates (35.0% and 42.9% in 2017), despite its globally decreasing trend presumably due to the successful application and revision of clinical protocols. Research to corroborate and update these results will be necessary in the upcoming years.

Transparency section

Declaration of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of financial and other interest

The authors declare that they have no competing interests.

Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at <https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm>

Author contributions

JD contributed to the investigation by analysing and interpreting the burden associated to sepsis in Spain and was a major contribution in the intellectual content revision. AM

analysed the current situation of sepsis in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of patients admitted with sepsis (2008-2017).

Patient cluster	Admissions, N	Patients, N	Males, %	Age (SD)
All files	311,674	288,211	53.7	73.0 (18.6)
Sepsis without organ dysfunction	159,343	145,155	53.1	72.6 (20.5)
Streptococcal sepsis	7,519	7,127	59.0	62.6 (27.3)
Staphylococcal sepsis	6,534	6,120	59.8	68.6 (21.3)
Sepsis due to anaerobes	944	879	55.2	73.4 (17.5)
Sepsis due to other Gram-negative organisms	42,935	39,175	50.2	73.4 (17.7)
Other specified sepsis	5,455	4,870	57.8	71.8 (20.9)
Sepsis of unspecified organism	95,956	86,984	53.1	73.5 (20.8)
Sepsis with organ dysfunction	67,146	62,851	53.0	75.9 (15.9)
Streptococcal sepsis	3,507	3,369	59.5	68.3 (19.9)
Staphylococcal sepsis	2,666	2,544	60.6	72.3 (17.0)
Sepsis due to anaerobes	378	353	54.1	74.4 (16.4)
Sepsis due to other Gram-negative organisms	13,865	12,957	50.1	74.9 (15.4)
Other specified sepsis	3,642	3,436	53.9	74.8 (17.0)

Sepsis of unspecified organism	43,088	40,192	52.8	77.2 (15.3)
Septic shock	85,185	80,205	55.5	71.4 (16.6)
Streptococcal sepsis	5,209	5,064	62.6	62.9 (19.5)
Staphylococcal sepsis	3,541	3,436	61.6	67.1 (17.3)
Sepsis due to anaerobes	567	546	52.2	68.7 (16.6)
Sepsis due to other Gram-negative organisms	18,641	17,808	52.8	70.8 (15.6)
Other specified sepsis	4,471	4,293	56.9	70.5 (16.9)
Sepsis of unspecified organism	52,756	49,058	55.2	72.9 (16.1)

Table 2 Secondary conditions diagnosed in >10% of admissions in patients with sepsis (2008-2017).

Diagnosed conditions	Sepsis without organ dysfunction, %	Sepsis with organ dysfunction, %	Septic shock, %	Deceased patients, %
Acute conditions	-	-	-	-
Acute heart disease	43.9	62.0	55.7	62.9
<i>Heart failure</i>	10.7	19.8	15.6	18.4
<i>Atrial fibrillation</i>	16.7	20.6	18.2	22.1
Infection of the urinary system	38.1	31.6	25.0	25.7
Acute renal disease	20.9	72.8	63.1	62.9
<i>Acute kidney failure</i>	19.6	52.7	47.6	43.5
Disorders of fluid electrolyte and acid-base balance	19.1	31.8	28.1	32.6
Acute respiratory failure	9.8	29.4	26.9	30.1
Bacterial pneumonia	11.3	17.9	16.4	17.3
Chronic conditions	-	-	-	-
Hypertension	34.0	32.6	28.9	31.8
Diabetes mellitus	29.8	30.7	24.2	28.4
Malignant neoplasms	23.3	23.5	25.6	32.1
Chronic ulcer of skin	22.4	24.0	15.7	29.1

Anaemia	17.8	18.8	14.1	13.9
Hyperlipidaemia and hypercholesterolemia	16.8	15.7	13.1	13.3
Chronic kidney disease	15.3	18.8	13.9	17.7
Chronic obstructive pulmonary disease	14.2	15.6	13.7	14.1
Cerebrovascular disease	10.7	11.7	7.8	12.5

Table 3 Admission details and case fatality rate (CFR) for sepsis (2008-2017).

Patient cluster	Emergency admissions, %	Length of stay, mean (SE)	Readmission rate, %	CFR, %
Sepsis without organ dysfunction	96.4	10.7 (0.03)	18.2	21.4
Streptococcal sepsis	91.3	12.9 (0.15)	15.8	11.3
Staphylococcal sepsis	89.8	17.0 (0.28)	24.6	20.2
Sepsis due to anaerobes	89.8	14.9 (0.62)	22.7	15.0
Sepsis due to other Gram-negative organisms	87.9	11.0 (0.05)	18.5	9.4
Other specified sepsis	86.1	11.9 (0.17)	21.1	17.3
Sepsis of unspecified organism	87.6	9.9 (0.03)	17.6	27.9
Sepsis with organ dysfunction	97.1	11.8 (0.05)	18.4	42.8
Streptococcal sepsis	92.2	15.2 (0.30)	12.2	27.1
Staphylococcal sepsis	92.8	18.5 (0.37)	22.6	41.4
Sepsis due to anaerobes	90.7	15.6 (0.73)	23.5	33.3
Sepsis due to other Gram-negative organisms	90.6	13.1 (0.12)	18.5	24.1
Other specified sepsis	91.3	13.1 (0.30)	21.3	42.0
Sepsis of unspecified organism	90.8	10.5 (0.06)	18.3	50.2
Septic shock	96.5	14.3 (0.06)	18.0	47.3
Streptococcal sepsis	96.4	20.0 (0.33)	11.7	31.3

Staphylococcal sepsis	94.5	22.0 (0.41)	21.1	47.8
Sepsis due to anaerobes	96.3	20.4 (1.05)	22.9	33.6
Sepsis due to other Gram-negative organisms	96.6	16.5 (0.14)	18.5	27.5
Other specified sepsis	95.4	15.5 (0.30)	18.3	43.7
Sepsis of unspecified organism	96.7	12.3 (0.07)	18.1	56.2

Table 4 Direct medical costs of specialised care associated with sepsis (2008-2017).

Patient cluster	Annual cost	Cost per patient
Sepsis without organ dysfunction	€ 103,015,558	€ 6,664
Streptococcal sepsis	€ 5,193,776	€ 7,036
Staphylococcal sepsis	€ 4,819,885	€ 7,489
Sepsis due to anaerobes	€ 642,211	€ 6,955
Sepsis due to other Gram-negative organisms	€ 26,538,863	€ 6,347
Other specified sepsis	€ 3,633,741	€ 6,728
Sepsis of unspecified organism	€ 62,187,082	€ 6,701
Sepsis with organ dysfunction	€ 52,006,723	€ 8,084
Streptococcal sepsis	€ 3,234,226	€ 9,565
Staphylococcal sepsis	€ 2,485,410	€ 9,502
Sepsis due to anaerobes	€ 320,357	€ 8,438
Sepsis due to other Gram-negative organisms	€ 10,546,086	€ 8,067
Other specified sepsis	€ 2,915,835	€ 8,156
Sepsis of unspecified organism	€ 32,504,810	€ 7,870
Septic shock	€ 92,390,630	€ 11,359
Streptococcal sepsis	€ 7,086,419	€ 13,801

Staphylococcal sepsis	€ 4,991,391	€ 14,279
Sepsis due to anaerobes	€ 728,305	€ 13,008
Sepsis due to other Gram-negative organisms	€ 20,378,961	€ 11,321
Other specified sepsis	€ 5,127,978	€ 11,505
Sepsis of unspecified organism	€ 54,077,576	€ 10,909

Figures

Figure 1 (A) Annual age-adjusted incidence of sepsis and (B) age-specific case rate (2008-2017).

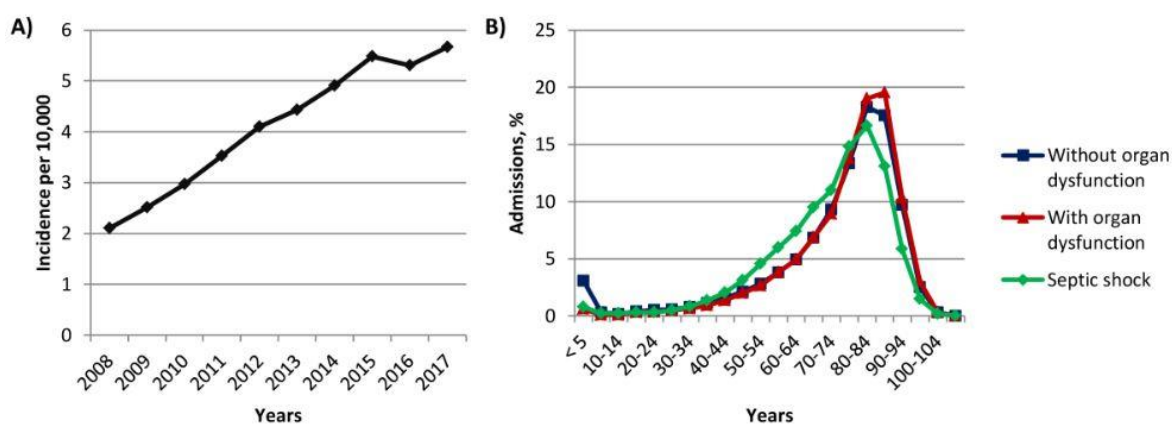


Figure 2 (A) Annual case fatality rate (CFR) by sepsis severity and (B) age specific CFR by sepsis severity (2008-2017).

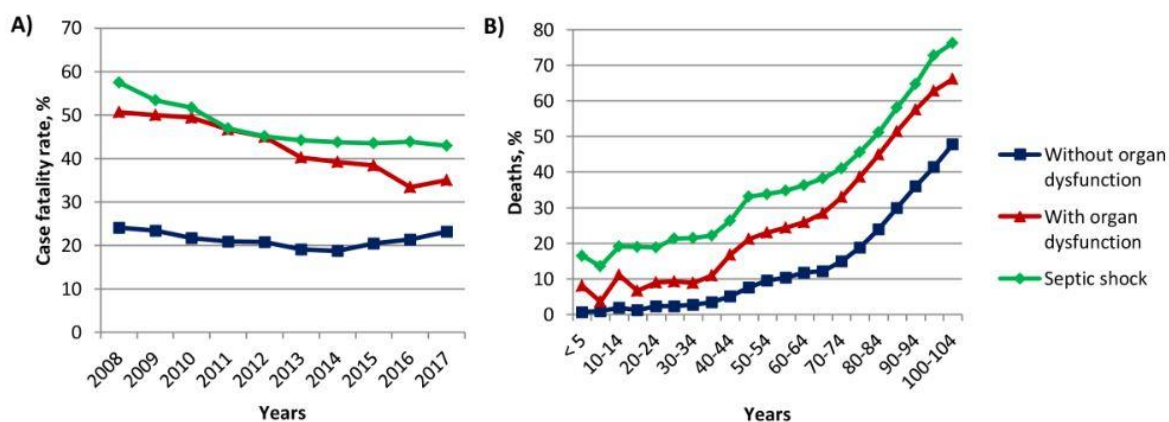


Figure 3 Annual medical cost per patient by sepsis severity (2008-2017)

