Epidemiology of sepsis in cancer patients in Victoria, Australia: a population-based study using linked data

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Sepsis may be defined as life-threatening organ failure caused by a dysregulated host response to infection.[1] It is a recognised major public health concern with global estimates of 31.5 million sepsis cases annually, including 19.4 million severe cases, potentially resulting in 5.3 million deaths.[2] In Australia, in-hospital care of all infections accounted for 4.8% of the total hospital admitted patient expenditure in 2012–2013 (approximately $2.16 billion) and has increased by 65% since 2004.[3] Sepsis may have both short-term and long-term consequences for patients. Patients with sepsis experience severe illness, long hospital stays and high risk of death,[4] with mortality rates of 10–80% depending on sepsis severity. Survivors of sepsis may experience persistent cognitive decline associated with functional disability resulting in a diminished capacity for independent living.[5]

Cancer is the most common disease diagnosis in the Australian population, with more than 130,000 new diagnoses in 2017.[6] Cancer in Australia accounts for 35% of the total fatal burden and 19% of the total burden of disease.[7] Cancer is a recognised risk factor for the development of sepsis,[8] with cancer patients at an estimated 10-fold risk of sepsis compared with non-cancer patients.[9] This increased sepsis risk is multifactorial and includes tumour location with risk of obstruction or perforation, older age, higher rates of invasive procedures or in-dwelling catheters and immunosuppression; with the

Abstract

Objective: To determine the clinical characteristics, outcomes and longitudinal trends of sepsis occurring in cancer patients.

Method: Retrospective study using statewide Victorian Cancer Registry data linked to various administrative datasets.

Results: Among 215,763 incident cancer patients, incidence of sepsis within one year of cancer diagnosis was estimated at 6.4%. The incidence of sepsis was higher in men, younger patients, patients diagnosed with haematological malignancies and those with de novo metastatic disease. Of the 13,316 patients with a first admission with sepsis, 55% had one or more organ failures, 29% required care within an intensive care unit and 13% required mechanical ventilation. Treatments associated with the highest sepsis incidence were stem cell/bone marrow transplant (33%), major surgery (4.4%), chemotherapy (1.1%) and radical radiotherapy (0.6%). The incidence of sepsis with organ failure increased between 2008 and 2015, while 90-day mortality decreased.

Conclusions: Sepsis in patients with cancer has high mortality and occurs most frequently in the first year after cancer diagnosis.

Implications for public health: The number of cancer patients diagnosed with sepsis is expected to increase, causing a substantial burden on patients and the healthcare system.

Key words: cancer, sepsis, epidemiology

latter due both to the cancer itself[10,11] and the cancer treatments.[12,13]

While the epidemiology of sepsis in hospitalised patients has been well described in a number of studies, including a study of patients in Victoria,[14,15] the epidemiology of sepsis in hospitalised cancer patients is less commonly described in recent literature.[9,16] To our knowledge, the epidemiology of sepsis in cancer patients in Australia has not been previously described. Using data from the Victorian Cancer Registry linked to administrative datasets we aimed to describe

sepsis incidence and mortality over time and relate the timing of sepsis incidence with cancer treatment in Victorians diagnosed with cancer between 2008 and 2015.

Methods

Victoria is Australia's second-most populous state, with a population of 6.18 million in 2017.[17] As part of Australia's health care and funding processes, comprehensive data is collected on all in-patient hospital admissions and the data for Victorian hospital admissions

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are contained within the Victorian Admitted Episodes Dataset (VAED). Cancer registries are also maintained in each of the Australian states, with the Victorian Cancer Registry (VCR) collecting data on all cancer diagnoses in Victorian residents. Deaths in Australia are notified to state registries and collated nationally.

Data sources

The VCR includes all pathology-confirmed diagnoses of cancer in Victoria. It collects data on patient demographics and tumour details (site, morphology, grade, behaviour, date of diagnosis). Data for patients diagnosed between 1 January 2008 and 31 December 2015 were included in the present analysis.

The VAED includes demographic and clinical data for in-patient admissions to any public or private Victorian hospital. Clinical diagnosis data are recorded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM). Multiple codes may be recorded for each admission according to co-morbidities, hospital discharge diagnoses and in-patient procedures. Procedures, coded using the Australian Classification of Health Interventions, include surgery and parenterally-administered chemotherapy, but not oral chemotherapy. For the purpose of this study, admissions including transfers were considered as a single admission. Data corresponding to admissions between 1 July 2006 and 31 December 2016 were included.

The Victorian Radiotherapy Minimum Data Set (VRMDS) includes any radiotherapy provided in public and private Victorian radiotherapy centres. Data related to radiotherapy courses provided between 1 July 2010 and 31 December 2016 were included. Complete data on radiotherapy data prior to July 2010 were not available.

The Victorian Registry of Births, Deaths and Marriages records all deaths that occur in Victoria. The Australian National Death Index (NDI) uses data from Registrars of Births, Deaths and Marriages in each jurisdiction, the National Coronial Information System and the Australian Bureau of Statistics to record all deaths that occur in Australia. The VCR internally linked deaths from the NDI (complete up to 31 December 2015 in the study data) prior to linkage with the other datasets. Deaths from the VDI (up to 31 December 2016) were included by central data linkage.

Data linkage between the VCR, VAED, VRMDS and VDI was performed by the Centre for Victorian Data Linkage (CVDL) using an iterative deterministic linkage process with fuzzy matching on selected fields that enabled the matching of patients, treatments and outcomes.

Patients with cancer were defined as any patient included on the VCR with a newly diagnosed cancer between 2008 and 2015. Tumours reported by death certificate only (n=5,331 tumours) were excluded. Only the first cancer diagnosis was included for patients with more than one cancer diagnosis. Patients were considered 'metastatic at diagnosis' if any hospital admission within four months of diagnosis included an ICD-10-AM metastatic disease code (C78, C79).

An episode of sepsis was defined based on ICD-10-AM diagnosis codes for an admitted episode of care (see Supplementary File 1).[18] We sought to identify patients in whom the treating clinicians(s) had recorded a clinical diagnosis of 'sepsis', with this expected to represent a patient with an infection and who is systemically unwell. To this end, we limited the definition to ICD-10-AM codes that included the word 'sepsis'. Both community-acquired and hospital-acquired sepsis were included in our sepsis definition. Severity was categorised as sepsis without organ failure (where there is a sepsis discharge code but no ICD-10-AM code for any organ failure) and sepsis with organ failure (a discharge including ICD-10-AM codes for sepsis and at least one organ failure [see Supplementary File 2] or the code for severe sepsis [R65.1] or septic shock [R57.2]).

Sepsis within the first year of diagnosis included any sepsis admission within one year post cancer diagnosis date or within one month prior to the diagnosis. The latter enabled inclusion of patients for whom the sepsis presentation may have been the result of an undiagnosed cancer and allowed for uncertainty in diagnosis dates.

ICU use was defined as ICU duration of ≥1 hour and use of mechanical ventilation was defined as a duration of mechanical ventilation ≥1 hour.

Statistical methods

Incidence of sepsis within one year of cancer diagnosis was estimated using the competing risk framework, taking death into account as competing risk using the 'timereg' package.[19] Predictors of sepsis within one year of cancer diagnosis were assessed using multivariable

logistic regression analysis, including explanatory variables sex (male, female), age at diagnosis (<15, 15–24, 25–49, 50–59, 60–69, 70–79, 80+), tumour type (solid, haematological) and metastatic disease status at diagnosis (non-metastatic, metastatic). Differences in in-hospital mortality, 90-day mortality, length of stay and ICU use between sepsis cases with and without organ failure were tested using chi-squared and Wilcoxon-Mann-Whitney tests. The proportion of treatment episodes and patients followed by sepsis within two weeks of treatment was calculated for major surgery (identified using ACHI block codes), chemotherapy and radiotherapy (with or without chemotherapy) as crude percentage with associated binomial confidence interval. All analyses were performed using R version 3.4.3 (R Core Team [2017]).

Results

Between 2008 and 2015, a total of 215,763 Victorians were diagnosed with an incident cancer. These patients were linked to 3.5 million hospital admissions (cancer and non-cancer related), including 32,832 admissions with sepsis codes in 24,774 patients (11.5% of all patients). The rate of admission for sepsis was low prior to cancer diagnosis, was highest in the year following cancer diagnosis and then decreased to pre-cancer level after seven years (Figure 1). Overall, 13,316 patients had 16,029 sepsis-related admissions in the year following diagnosis. There were 1,256 (9.4%) cancer patients who had more than one sepsis episode in the year following cancer diagnosis. Sepsis incidence within one year of cancer diagnosis was estimated at 6.4% (95% confidence interval 6.2-6.5). The likelihood of admission with sepsis within a year of diagnosis was higher for men, younger and older patients (with the exception of patients aged 80 and over), patients with haematological cancers and those with metastatic disease at diagnosis (Table 1). Sepsis incidence varied among tumour streams ($p<0.001$; Table 2).

Organ failure was present in 7,321 (55.0% [95%CI 54.1-55.8]) first sepsis episodes in the year following diagnosis (Table 3). Compared to patients with sepsis without organ failure, those with organ failure had higher mortality (in-hospital mortality 31.9% [95%CI 30.8-33.0] vs 14.1% [95%CI 13.2–15.0]; $p<0.001$; 90d mortality 40.1% [95%CI 39.0–41.2] vs. 25.2% [95%CI 24.1–26.3]; $p<0.001$); longer length

of stay (median 18 vs 9 days; $p<0.001$); and were more likely to have an ICU stay with and without mechanical ventilation (23.7% [95%CI 22.8–24.7] vs 8.3% [95%CI 7.6–9.0] and 1.0% [95%CI 0.8–1.3] vs 22.2% [95%CI 21.1–23.1]; both $p<0.001$). The most common organ failures were cardiovascular, renal and haematological.

Timing of sepsis in relation to cancer treatment

The proportion of patients with sepsis within two weeks of cancer treatment was highest following stem cell or bone marrow transplant (29.4%; Table 4), followed by major surgery (4.8%), chemoradiation (3.6%) and chemotherapy alone (1.0%). Two-week sepsis incidence following chemotherapy was highest for the first chemotherapy episode (2.5%), declining with each subsequent episode. Overall, 6.1% of all patients who had one or more admissions for chemotherapy in the first year following diagnosis were admitted with sepsis.

Trends over time – incidence and mortality

Sepsis incidence increased from 5.8% in 2008 to 7.8% in 2015. This increase was mostly due to the increase in sepsis with organ failure over this period (2.7% in 2008 to 4.4% in 2015; p linear trend <0.001; Figure 2). Incidence of sepsis without organ failure decreased between 2008 and 2012 with an increase in more recent years (p quadratic trend <0.001). Ninety-day mortality following sepsis was high but has decreased since 2008, for sepsis with and without organ failure (p linear trend <0.001 and p linear trend =0.02, respectively; Figure 2).

Discussion

We show that 6.4% of Victorians diagnosed with cancer between 2008 and 2015 were hospitalised with sepsis within a year of their cancer diagnosis. Sepsis incidence increased over that period, occurred mainly within one year of cancer diagnosis and was often within two weeks of cancer treatment. Stem cell or bone marrow transplants had the highest risk of sepsis, followed by major surgery, chemotherapy and radiotherapy. Organ failure was present in more than half of the sepsis episodes. The median length of stay was nine and 18 days for sepsis without and with organ failure, respectively. ICU stay occurred in 45.9% of sepsis cases with organ

failure. In-hospital mortality rates significantly under-estimate total mortality risk associated with sepsis following cancer diagnosis. Mortality following sepsis diagnosis was 25.2% and 40.1% for sepsis without and with organ failure and has decreased over the study period.

The incidence of sepsis in cancer patients has been described sparsely in recent reports. Danai et al.[9] reported a sepsis incidence (with and without organ failure) of 1,465 per 100,000 cancer patients based on US

Figure 1: Percentage of patients with a sepsis admission for six-month time intervals relative to the date of cancer diagnosis.
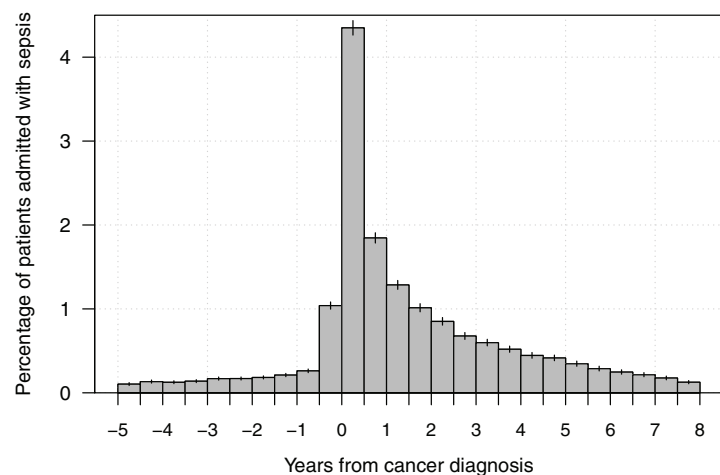
Notes:
Bars represent 95% binomial confidence intervals. Victorians diagnosed with cancer between 2008 and 2015 who were alive at the start of each time interval were included for the calculation of each bar. Patients with multiple sepsis episodes were included in multiple intervals, but only once per interval. (0 = time of cancer diagnosis).

Table 1: Characteristics of cancer patients with sepsis.

Characteristic	All cancer patients (n=215,763) Number (% of all cancer patients)	Cancer patients with sepsis[a] (n=13,316) Number (%)	Adjusted odds ratio [95% confidence interval]
Sex			
Female	98,030 (45.4)	5,136 (5.2)	1.00[b]
Male	117,733 (54.6)	8,180 (6.9)	1.32 [1.28-1.37]
Age at diagnosis			
Under 15	1,270 (0.6)	288 (22.7)	2.62 [2.27-3.02]
15-24	1,698 (0.8)	189 (11.1)	1.40 [1.19-1.64]
25-49	27,096 (12.6)	1,280 (4.7)	0.80 [0.75-0.86]
50-59	37,093 (17.2)	1,833 (4.9)	0.83 [0.78-0.88]
60-69	57,566 (26.7)	3,513 (6.1)	1.00[b]
70-79	51,451 (23.8)	3,730 (7.2)	1.13 [1.07-1.18]
80 and over	39,589 (18.3)	2,483 (6.3)	0.93 [0.88-0.99]
Metastatic disease present at diagnosis			
No	181,495 (84.1)	9,808 (5.4)	1.00[b]
Yes	34,268 (15.9)	3,508 (10.2)	2.60 [2.49-2.72]
Cancer type			
Solid	194,810 (90.3)	9,966 (5.1)	1.00[b]
Haematological	20,953 (9.7)	3,350 (16.0)	4.18 [4.00-4.38]

Notes:
a: Cancer patients who developed sepsis within one year of their cancer diagnosis
b: Reference category

hospitalisation data between 1979 and 2001, while Williams et al.[16] report incidence of sepsis with organ failure of 1,640 per 100,000 cancer patients based on 1999 US hospitalisation data. Our observed incidence of sepsis in Victoria is substantially higher (6,200 per 100,000 cancer patients), even though we restricted our analysis to sepsis episodes within the first year following cancer diagnosis. Various factors could contribute to this difference. First, the US estimates are more than a decade old, and it has been

reported that sepsis incidence has increased over the past few decades.[20] Second, both US estimates were based on hospitalisation data only, which required the cancer to be coded in the sepsis admission in order to assign a sepsis case to a cancer patient. In our data, cancer was coded in only 48.7%

of sepsis cases that occurred within the first year following diagnosis, and in only 76.9% of sepsis cases that occurred within two weeks of chemotherapy (data not shown). Thus, using only hospitalisation data may underestimate sepsis incidence in cancer patients.

That sepsis admissions peak around time of diagnosis has not been previously described (to our knowledge) but is consistent with septic complications of a cancer leading to the initial detection of cancer and the combination of treatments in the months following diagnosis (surgery, chemotherapy, radiotherapy, invasive lines) predisposing cancer patients to infection and sepsis. Indeed, sepsis often occurs within 14 days of cancer treatment. Lower sepsis incidence in patients diagnosed aged 80 or older is consistent with the less aggressive cancer treatment that this group may receive. Risk of sepsis persists for cancer patients even years following their initial diagnosis, possibly due to additional treatment for recurrent cancers or development of chronic conditions in this population, which have previously been shown to be associated with increased risk of sepsis.[21]

Our estimate of in-hospital mortality in cancer patients with sepsis with organ failure is comparable to that for all patients with sepsis (31.9% vs. 31.1%), but mortality for sepsis without organ failure was higher for cancer patients than all patients (14.1% vs 10.2%).[14] These findings are favourable compared to the previously reported 37.8% in-hospital mortality following severe sepsis in cancer patients based on two-decade old hospitalisation data from the US.[16] More importantly, the total mortality following sepsis is underestimated by in-hospital mortality. Our data shows relatively high risk of death after hospital discharge with 90-day mortality rates of 40.1% and 25.2% compared to in-hospital mortality rates of 31.9% and 14.1% for sepsis with and without organ failure, respectively.

The increase in sepsis incidence over time was mainly attributable to the steady increase in sepsis with organ failure over the study period. There was a sudden increase in sepsis without organ failure for patients diagnosed with cancer in 2015 that may have been driven by changes in coding practices. In July 2015, the ninth edition of ICD-10-AM was introduced and included changes to the definition of sepsis, which could have increased the identification of sepsis cases. Specifically, prior to July 2015 a diagnosis of urosepsis, without further qualification, was coded as urinary tract infection (UTI); post-July 2015 this could have two codes assigned, one for sepsis and one for UTI. It is unlikely that sepsis with organ failure incidence was affected by this, as severe sepsis cases would

Table 2: Sepsis incidence within one year following cancer diagnosis by tumour type for patients diagnosed between 2008 and 2015.

Tumour stream	Number of new cancer diagnoses (% of total cancer population)	Number of patients with sepsis (crude %)	Sepsis incidence (% [95% confidence interval])
Head and neck	5,607 (2.6)	249 (4.4)	4.5 [4.0–5.1]
Stomach	4,207 (1.9)	386 (9.2)	9.6 [8.7–10.6]
Bowel	27,309 (12.7)	1,984 (7.3)	7.5 [7.2–7.9]
Pancreas	5,271 (2.4)	792 (15.0)	16.3 [15.2–17.4]
Lung	18,543 (8.6)	1,344 (7.2)	7.5 [7.1–7.9]
Melanoma	17,824 (8.3)	188 (1.1)	1.1 [0.9–1.2]
Breast (female)	29,660 (13.7)	671 (2.3)	2.3 [2.1–2.5]
Uterus	4,873 (2.3)	120 (2.5)	2.5 [2.0–3.0]
Ovary	3,159 (1.5)	167 (5.3)	5.4 [4.6–6.2]
Prostate	36,343 (16.8)	1,018 (2.8)	2.8 [2.7–3.0]
Kidney	5,486 (2.5)	219 (4.0)	4.1 [3.5–4.6]
Bladder	4,816 (2.2)	551 (11.4)	12.2 [11.1–13.2]
Thyroid	3,857 (1.8)	34 (0.9)	0.9 [0.6–1.2]
Lymphoma	10,666 (4.9)	1,220 (11.4)	12.1 [11.4–12.9]
Leukaemia	6,267 (2.9)	1,528 (24.4)	27.9 [26.4–29.5]
Other	31,875 (14.8)	2,845 (8.9)	9.3 [9.0–9.7]
All tumour streams	251,763 (100)	13,316 (6.2)	6.4 [6.2–6.5]

Table 3: Characteristics of the first sepsis admission within a year of cancer diagnosis by sepsis severity (n = 13,316 patients).

	Cancer patients admitted with sepsis without organ failure N = 5,995 patients	Cancer patients admitted with sepsis and organ failure ("severe sepsis" and "septic shock") N = 7,321 patients
In-hospital death in sepsis episode	844 (14.1%)	2,334 (31.9%)*
Death within 90 days	1,510 (25.2%)	2,937 (40.1%)*
Length of stay (days) median [IQR]	9 [5-20]	18 [8–36]*
Intensive Care Unit stay*		
No	5438 (90.7%)	3963 (54.1%)
ICU stay without mechanical ventilation	497 (8.3%)	1736 (23.7%)
ICU stay with mechanical ventilation	60 (1.0%)	1622 (22.2%)
Number of failing organs		
0	5,995 (100%)	266 (3.6%)ᵃ
1		3,883 (53.0%)
2-3		2,572 (35.1%)
4 or more		600 (8.2%)
Organ failure type		
Respiratory		1,660 (22.7%)
Cardiovascular		3,188 (43.5%)
Renal		3,088 (42.2%)
Hepatic		84 (1.1%)
Haematologic		2,126 (29.0%)
Metabolic		820 (11.2%)
Neurologic		1,471 (20.1%)

Notes:

a: 3.6% of patients with the severe sepsis code (R65.1) had no details regarding organ failures specified

* P-value comparing sepsis cases with and without organ failure <0.001

IQR = interquartile range

always have been coded as sepsis cases. The trend of increasing sepsis incidence with decreasing sepsis mortality found in cancer patients matches patterns seen in the general population of various western countries.[20] The total number of sepsis cases is expected to grow in the future due to continuing population growth, an increase in cancer incidence and the increasing sepsis incidence in cancer patients.

The use of administrative data for research purposes is often criticised because the data are mainly collected for the reimbursement of hospital activity, rather than for research purposes.[22] Clinical coders, when under the pressure of financial incentives, may seek complete documentation to support the coding of some conditions and not others (e.g. code sepsis instead of local infection). These biases may affect research outcomes. For example, an analysis using US clinical data found sepsis incidence did not increase, while claims data on the same patients suggested an increase in sepsis incidence.[23] It is unknown to what extent these limitations have affected our results, however, regular audits on various aspects of the VAED are carried out to minimise over-coding for financial incentives.[24] Furthermore, mortality following sepsis diagnosis could be influenced by other underlying health conditions. Nationally-agreed coding rules during the study period resulted in underreporting of comorbidities and hence these associations were not estimated.

There are several strengths to this study; most are related to the use of linked administrative data, which enables the inclusion of variables beyond a single hospital (hospitalisations and treatments at other health services, deaths outside hospitals) and provides cost effectiveness, as the data are already collected.

In summary, sepsis in cancer patients is common and has high associated mortality. In-hospital mortality rates significantly underestimate total mortality risk associated with sepsis following cancer diagnosis. Sepsis occurs most frequently in the first year after diagnosis and within two weeks of cancer treatment. Incidence of sepsis with organ failure appears to be increasing over time. The number of cancer patients diagnosed with sepsis in the future is expected to increase, placing a substantial burden on patients and the healthcare system.

Table 4: Occurrence of sepsis within 14 days of cancer treatment episode per treatment episode and per patient. Treatment episodes were restricted to one month prior to one year post cancer diagnosis.

Treatment[a]	Number of episodes	Proportion of treatment episodes following sepsis	Proportion of patients with sepsis
Biopsy only[b]	124,167	2.3%	2.6%
Bone marrow or stem cell transplant (all)	1,739	29.4%	32.7%
Autologous	1,294	26.0%	28.6%
Allogeneic	410	40.7%	42.8%
Cancer removal or debulking surgery (any)	167,023	1.7%	2.1%
Major excision	38,937	4.8%	5.0%
Other excision	128,086	0.8%	1.0%
IV chemotherapy only	615,255	1.0%	6.1%
1st admission	64,271	2.5%	2.5%
2nd admission	59,852	1.7%	1.7%
3rd admission	56,958	1.4%	1.4%
4th admission	54,121	1.2%	1.2%
5th or later admission	388,744	0.9%	4.3%
Radiotherapy only	37,002 courses	1.2%	1.3%
Radical	24,039 courses	0.6%	0.6%
Other	12,963 courses	2.5%	2.8%
Radiotherapy combined with IV chemotherapy	11,012 courses	3.6%	3.7%
Radical	8,290 courses	3.8%	3.8%
Other	2,722 courses	3.3%	3.5%

Notes:

a: Incidence reported as the proportion of treatment events with sepsis reported within 14 days of the treatment episode. Units of assessment are each biopsy, each surgery, each chemotherapy infusion, and each radiotherapy course started within the first year post cancer diagnosis. No data on oral chemotherapy were available. IV = intravenous.

b: Includes scoping procedures during which a biopsy was performed (e.g. colonoscopy with excision)

Figure 2: Sepsis incidence (%) and 90-day crude mortality (%) based on sepsis cases within the first year of cancer diagnosis (2008 to 2015). Bars represent 95% confidence intervals.
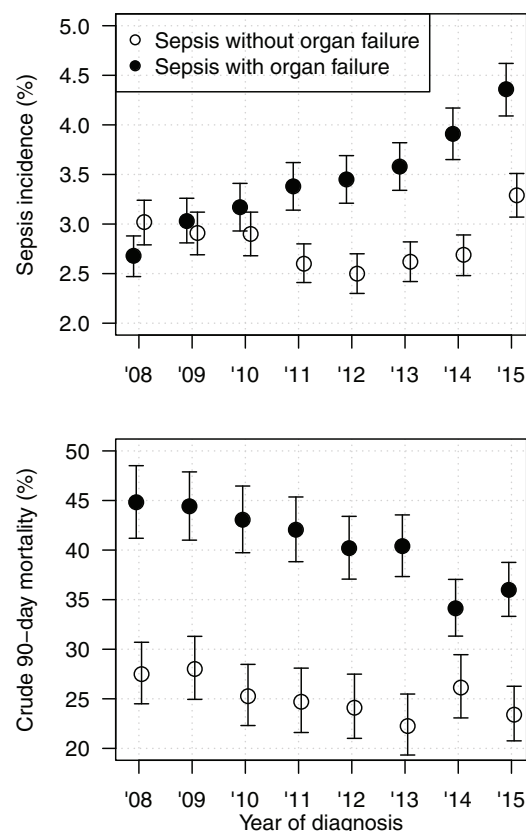
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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary File 1: Sepsis related ICD-10-AM diagnosis codes used in this study.

Supplementary File 2: ICD-10-AM diagnosis codes for organ failure used in this study.