Sepsis Among Medicare Beneficiaries:

3. The Methods, Models, and Forecasts of Sepsis, 2012–2018*

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Objective: To evaluate the impact of sepsis, age, and comorbidities on death following an acute inpatient admission and to model and forecast inpatient and skilled nursing facility costs for Medicare beneficiaries during and subsequent to an acute inpatient sepsis admission.

Design: Analysis of paid Medicare claims via the Centers for Medicare & Medicaid Services DataLink Project (CMS) and leveraging the CMS-Hierarchical Condition Category risk adjustment model.

Setting: All U.S. acute care hospitals, excepting federal hospitals (Veterans Administration and Defense Health Agency).

Patients: All Part A/B (fee-for-service) Medicare beneficiaries with an acute inpatient admission in 2017 and who had no inpatient sepsis admission in the prior year.

Interventions: None.

Measurements and Main Results: Logistic regression models to determine covariate risk contribution to death following an acute inpatient admission; conventional regression to predict Medicare beneficiary sepsis costs. Using the Hierarchical Condition Category risk adjustment model to illuminate influence of illness on outcome of inpatient admissions, representative odds ratios (with 95% CIs) for death within 6 months of an admission (referenced to beneficiaries admitted but without the characteristic) are as follows: septic shock, 7.27 (7.19–7.35); metastatic cancer and acute leukemia (Hierarchical Condition Category 8), 6.76 (6.71–6.82); all sepsis, 2.63 (2.62–2.65); respiratory arrest (Hierarchical Condition Category 83), 2.55 (2.35–2.77); end-stage liver disease

(Hierarchical Condition Category 27), 2.53 (2.49–2.56); and severe sepsis without shock, 2.48 (2.45–2.51). Models of the cost of sepsis care for Medicare beneficiaries forecast arise approximately 13% over 2 years owing the rising enrollments in Medicare offset by the cost of care per admission.

Conclusions: A sepsis inpatient admission is associated with marked increase in risk of death that is comparable to the risks associated with inpatient admissions for other common and serious chronic illnesses. The aggregate costs of sepsis care for Medicare beneficiaries will continue to increase. (*Crit Care Med* 2020; 48:302–318)

Key Words: forecast; methods; models; sepsis

Sepsis analyses vary widely in their reports of occurrence and of outcome. Although some of that variation is attributed to differences in definitions of sepsis and in the populations studied, differences in analytic methods (such as procedures of data extraction, curation, and imputation of missing elements) also can lead to differences in results and subsequent forecasts (1–6). Such differences confound comparisons among studies and complicate aggregation of studies into a coherent description of the national and international experience.

Medicare is the U.S. federal healthcare coverage for people 65 years old or older; certain people under 65 years old with disabilities; and people of any age with end-stage renal disease. Beneficiaries may choose coverage either through the Original Medicare Program or through a Medicare Advantage (MA) Plan. The former, often referred to as “Traditional” or “Fee-For-Service” (FFS) Medicare, includes at least two parts: part A and part B. Part A is hospital insurance and covers inpatient hospital, inpatient skilled nursing facility, hospice, and some home health services. Part B is medical insurance and covers physician services, outpatient care, durable medical equipment, home health services, and many preventive services. In contrast, MA plans are covered under part C and provide all part A and part B services and may also provide additional services (7–9). The first report in this set described the mortality and costs of sepsis among Medicare beneficiaries (1). The second report in this set described the trajectories of those beneficiaries into and out of their sepsis inpatient admissions (10).

We sought to create, report, and freely disseminate the method we used in those first two reports to generate reliable summary statistics on sepsis. Our purpose is to enable a common reporting structure, fair comparison, and aggregation of summary sepsis statistics from diverse public agencies and private entities without communication of their constituents’ personal health information.

We further sought to use the products obtained from this methodology in three ways. First, we sought to revise the prior reports of the national costs of sepsis care to produce a contemporary lower-bound estimate while awaiting complementary analyses of current costs from other public agencies and from private sector entities (11). Second, we sought to evaluate the contributions of preexisting conditions (Hierarchical Condition Categories [HCCs]) and other covariates associated with sepsis

generally and with different sepsis severities in order to illuminate their relative effects on sepsis mortality among Medicare beneficiaries. Third, we sought to create simple yet informative models predicting future Medicare sepsis costs based on the most recent data reported in the first article of this set (1).

METHODS

For health outcome modeling, the study population is restricted to Medicare FFS inpatient admissions with an admission date in 2017 to avoid any potential complication that could arise from the *International Classification of Diseases*, 9th Edition (ICD-9) to *International Classification of Diseases*, 10th Edition (ICD-10) coding transition. We studied only beneficiaries having continuous enrollment in Medicare parts A and B (FFS), but not C (MA), for the 12 months prior to the admission. We further required continuous enrollment in Medicare parts A and B for the subsequent 6 months or until their date of death (whichever came first). We compared patient-level variables of patients admitted during 2017 who did and who did not have sepsis code during an inpatient admission. Please refer to the first article in this set for definitions of explicit sepsis used in this study set.

To isolate the effects of an initial sepsis event rather than recurrences of an infection, we analyzed each beneficiary’s first sepsis admission in 2017 and further required that the beneficiary have no prior inpatient sepsis admissions in the 12 months leading up to their admission date. (Acute inpatient admissions that did not gain an explicit sepsis code were allowed.) This restriction echoes the diagnostic prevalence study reported in the second article of this set. There were a total of 1,122,863 inpatient admissions with a sepsis diagnosis code in 2017 that reflected 915,083 unique beneficiaries. We are reporting on 736,189 unique beneficiaries with an initial sepsis admission in 2017 who had no sepsis admissions during the prior year and were enrolled in Medicare parts A and B (FFS), but not C (MA).

We used HCCs to estimate the influence of comorbidities on outcomes of the acute inpatient admission. Center for Medicare and Medicaid Services (CMS)-HCC risk adjustment models are generally used to calculate risk scores that predict individual beneficiaries’ healthcare expenditures relative to an average beneficiary. The associated comorbidities list for each inpatient admission was constructed using inpatient, outpatient, and professional claims from 12 months prior to, and inclusive of, the index admission. Additional healthcare utilization and outcomes following the inpatient admission were assessed using claims and reports during the 12 months following the index admission’s inpatient hospital discharge date.

STATA (Stata Statistical Software: Release 15; StataCorp LLC, College Station, TX) was used for logistic regression analyses. SAS (SAS software, Version 9.4 of the SAS System for Windows; SAS Institute, Cary, NC) was used for financial forecasting.

We began by using the STATA logistic function to specify a regression model for the indicated binary outcome (e.g., death at 6 mo) on these input predictors: sepsis severity tiers, HCCs, demographic characteristics, and preceding claims in 1 week

TABLE 1. Predictor Variable Summary in Sepsis and Nonsepsis Populations

Predictor Variables	Sepsis Inpatient Admission <i>n</i> (%)	Nonsepsis Inpatient Admission <i>n</i> (%)
Age group		
> 65	125,089 (17.0)	1,147,051 (16.9)
65–74	210,367 (28.6)	2,137,261 (31.4)
75–84	220,784 (30.0)	2,063,604 (30.3)
85+	179,949 (24.4)	1,455,699 (21.4)
Medicare eligibility		
ESRD	44,716 (6.1)	342,677 (5.0)
Non-ESRD	691,473 (93.9)	6,460,938 (95.0)
Dual enrollment		
Dual	238,576 (32.4)	1,768,268 (26.0)
Not dual	497,613 (67.6)	5,035,347 (74.0)
Gender		
Male	357,836 (48.6)	3,009,419 (44.2)
Female	378,353 (51.4)	3,794,196 (55.8)
Race		
White	615,454 (83.6)	5,759,059 (84.6)
Black	82,611 (11.2)	778,411 (11.4)
Asian	13,897 (1.9)	87,043 (1.3)
Hispanic	17,706 (2.4)	130,442 (1.9)
North American Native	6,521 (0.9)	48,660 (0.7)
Preceding claims 1 wk prior to inpatient admission		
Preceding home health claim	89,450 (12.2)	741,947 (10.9)
Preceding nonacute inpatient claim	59,345 (8.1)	497,339 (7.3)
Preceding nursing care (skilled or unskilled)	54,053 (7.3)	243,623 (3.6)
Preceding hospice claim	2,649 (0.4)	16,089 (0.2)
HCCs		
HCC85: congestive heart failure	196,758 (26.7)	1,810,994 (26.6)
HCC111: chronic obstructive pulmonary disease	182,632 (24.8)	1,591,625 (23.4)
HCC96: specified heart arrhythmias	180,090 (24.5)	1,659,249 (24.4)
HCC18: diabetes with chronic complications	157,230 (21.4)	1,282,711 (18.9)
HCC135: acute renal failure	130,337 (17.7)	955,215 (14.0)
HCC108: vascular disease	106,669 (14.5)	1,005,581 (14.8)
HCC84: cardiorespiratory failure and shock	101,469 (13.8)	748,120 (11.0)
HCC19: diabetes without complication	84,617 (11.5)	777,454 (11.4)
HCC48: coagulation defects and other specified hematologic disorders	64,760 (8.8)	510,184 (7.5)
HCC21: protein-calorie malnutrition	64,435 (8.8)	376,315 (5.5)
HCC22: morbid obesity	57,176 (7.8)	513,322 (7.5)
HCC40: rheumatoid arthritis and inflammatory connective tissue disease	43,045 (5.8)	382,328 (5.6)
HCC79: seizure disorders and convulsions	41,203 (5.6)	327,511 (4.8)

ESRD = end-stage renal disease, HCC = Hierarchical Condition Category.

These frequentist statistics report the number and percentage of sepsis or nonsepsis inpatient admissions having the predictor variable. For the categories of age group, Medicare eligibility, dual enrollment, gender, and race, totals are 100%. Beneficiaries may have more than one HCC. The unabridged table is given in Supplement 2 (Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>).

prior to hospital admission. We report the output from this logistic model specification, including the odds ratios (ORs) for the predictors. In order to further illuminate the influence of the covariates, we compute and report them as average marginal effects. The statistic reported is the adjusted average probability. This approach avoids the theoretical construct of an “average beneficiary” with mean values in favor of evaluating the influence of a predictor over the actual heterogeneity of the population. Technically, we used the “margins” function in STATA, with the “asobserved” option and not the “asmeans” option.

Influencers are presented in tabular form relative to the logistic regression models. One table type includes average marginal effects, providing a population average of predicted change in probability of the model outcome variable (in our tables, death) when the explanatory variable of interest increases by one unit while holding the other variables constant. In marginal effect tables, percent risks of death are additive versus baseline and are listed as average percentage change in outcome, with 95% CIs given. A second table type lists the outcomes of those marginal effect differences when certain groups are directly compared. A third table type presents ORs. The ratio of the odds of an outcome (e.g., mortality) in the exposed group (group 2) versus the basis (or reference) group (group 1) is calculated according to the usual convention:

$$\text{Odds Ratio} = \frac{\frac{\text{Probability of outcome with group 2}}{1 - \text{Probability of outcome with group 2}}}{\frac{\text{Probability of outcome with group 1}}{1 - \text{Probability of outcome with group 1}}}$$

The ORs were obtained from logistic regression by exponentiating the coefficient (or β) for each explanatory variable. The ORs are further annotated with SES, chi-square calculations for the contribution of each predictor variable in a logistic regression calculation (and associated p value), and the 95% CI for the OR of the specific predictor variable. ORs are related to but not synonymous with relative risk (12).

Comparative analyses are performed for clinical situations commonly of interest such as whether sepsis is present on admission, and for more specific situations such as whether sepsis occurred in association with hospital-acquired conditions (HACs): performance of major operations on the bowel,

use of ventilatory support, and exposure to extracorporeal membrane oxygenation (ECMO).

Care should be taken when considering statistical versus operational significance: some internal comparator groups are quite small and calculated differences (i.e., those with “significant” p values) may not always reflect clinically meaningful deviations from reference populations.

For financial forecasting, the foundational data included the Medicare FFS inpatient and skilled nursing facility claims data reported in the first article of this set. We used generally accepted strategies to design, evaluate, test, and project the cost burdens of sepsis using two- and three-parameter models. Regressions were used to create the models. We used conventional linear regression ($Y = \alpha + \beta x$) for the two-parameter model predicting the moving 12-month sum, where x is the sum for the prior 12 months, beginning with the sum January–December 2012. For the month-specific predictions, we added a phasic term, regressing and minimizing the error

of $Y = \alpha + \beta x + \gamma \cos\left(2\pi\left[\frac{x}{12}\right]\right)$, where x is the month number

and January 2012 begins month 0. For each model, residuals were plotted for direct inspection and further analyzed by quantile (Q-Q) analysis to visualize the normality of their distributions. For each model type, a preliminary version (withholding the final year of data) was tested with respect to its ability to forecast the last year. Finally, we used each model type to project sepsis costs 1 year into the future.

This analysis and publication is exempt from institutional review board oversight. It was performed as a health-care quality improvement analysis. CMS is a covered entity. Deidentification methods were implemented in accordance with CMS policy, Privacy Act of 1974 (5 U.S.C. § 552a) and HIPAA (45 Code of Federal Regulations Part 160 and Subparts A and E of Part 164) requirements.

Acknowledging the complexity of the analyses in this and in the two companion reports, we have prepared a companion methodology enabling programmers and analysts to reproduce and apply the data extraction, curation, and analytic methods to different populations. Application of the method to related datasets should yield summary tables that can be directly compared with the experiences of Medicare beneficiaries reported in this and in the other two articles of this set (1, 10) (Supplement 1, Supplemental Digital Content 1, <http://links.lww.com/CCM/F249>).

TABLE 2. Distribution of Hierarchical Condition Categories in Sepsis and Nonsepsis Inpatient Hospital Admissions

Admission Type	Average HCCs	Minimum HCCs	HCC Percentile Distribution							Maximum HCCs
			Fifth	10th	25th	50th	75th	90th	95th	
Nonsepsis inpatient admission	2.7	0	0	0	0	2	4	6	8	21
Sepsis inpatient admission	3.0	0	0	0	1	2	5	7	8	20

HCC = Hierarchical Condition Category.

TABLE 3. Death Within 1 Week of Inpatient Discharge, Predicted Values

Model: Death Within 1 wk of Inpatient Discharge Model With Sepsis Admission Predictor	
Predicted Probability	Average Predicted Probability, %
Predicted probability of death within 1 wk of inpatient discharge on average for a sepsis admission	17.5
Predicted probability of death within 1 wk of inpatient discharge on average for a nonsepsis admission	4.3
Model: Death Within 1 wk of Inpatient Discharge Model With Sepsis Tier Predictor	
Predicted Probability	Average Predicted Probability
Predicted probability of death within 1 wk of inpatient discharge on average for a septic shock admission	38.8
Predicted probability of death within 1 wk of inpatient discharge on average for a severe sepsis admission	15.5
Predicted probability of death within 1 wk of inpatient discharge on average for an unspecified sepsis admission	11.1
Predicted probability of death within 1 wk of inpatient discharge on average for other sepsis (organism identified) admissions	7.4
Predicted probability of death within 1 wk of inpatient discharge on average for nonsepsis admission	4.3
Model: Death Within 1 wk of Sepsis Admission Discharge Model With Sepsis Tier and Sepsis Present on Admission Predictors	
Predicted Probability	Average Predicted Probability
Predicted probability of death within 1 wk of inpatient discharge on average for a septic shock admission	39.8
Predicted probability of death within 1 wk of inpatient discharge on average for a severe sepsis admission	17.7
Predicted probability of death within 1 wk of inpatient discharge on average for an unspecified sepsis admission	12.5
Predicted probability of death within 1 wk of inpatient discharge on average for other sepsis (organism identified) admissions	8.4
Predicted probability of death within 1 wk of inpatient discharge on average for a present on admission sepsis admission	17.6
Predicted probability of death within 1 wk of inpatient discharge on average for a hospital-acquired sepsis admission	35.1
Model: Death Within 1 wk of Inpatient Discharge for Admissions With Metastatic Cancer and Acute Leukemia, Lung and Other Severe Cancers or Lymphoma and Other Cancers HCCs With Sepsis Admission Predictor	
Predictor Variables	Average Predicted Probability
Predicted probability of death within 1 wk of inpatient discharge on average for a sepsis admission	28.5
Predicted probability of death within 1 wk of inpatient discharge on average for a nonsepsis admission	9.2
Model: Death Within 1 wk of Inpatient Discharge for Admissions With Metastatic Cancer and Acute Leukemia, Lung and Other Severe Cancers or Lymphoma and Other Cancers HCCs With Sepsis Tier Predictor	
Predictor Variables	Average Predicted Probability
Predicted probability of death within 1 wk of inpatient discharge on average for a septic shock admission	51.4
Predicted probability of death within 1 wk of inpatient discharge on average for a severe sepsis admission	27.0
Predicted probability of death within 1 wk of inpatient discharge on average for an unspecified sepsis admission	20.2
Predicted probability of death within 1 wk of inpatient discharge on average for other sepsis (organism identified) admissions	13.6
Predicted probability of death within 1 wk of inpatient discharge on average for nonsepsis admission	9.2

HCC = Hierarchical Condition Category.

These average predicted probabilities of death within a week of discharge account for the following covariates: HCCs, demographic characteristics, and preceding claims in 1 wk prior to hospital admission.

RESULTS

Modeling the Risks of Sepsis

Comparing the sepsis admission population with the comparator nonsepsis admission population, sepsis admission patients were older, more likely to be Medicare-Medicaid (“Duals”) dual-eligible (32.4% vs 26.0%), and to have prior home health skilled nursing care or reside in a skilled nursing facility in the week prior to hospital admission. The sepsis admission population was more likely to have diabetes with chronic complications (HCC 18, 21.4% vs 18.9%) and protein-calorie malnutrition (HCC 21, 8.8% vs 5.5%). They were more likely to experience acute renal failure (HCC 135, 17.7% vs 14.0%) and cardiorespiratory failure and shock (HCC 84, 13.8% vs 11.0%). Although these data suggest predisposition, they are not precise indicators of relative risk given the condition (Table 1) (the unabridged form is given in Supplement 2, Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>).

Overall, patients destined for a sepsis inpatient admission had more hierarchical care conditions than the patients destined for a nonsepsis inpatient admission, average 3.0 versus 2.7, signifying a greater level of chronic illness (Table 2).

A sepsis admission carried an average adjusted 17.5% average predicted probability of mortality during hospitalization or 1 week following discharge versus the reference nonsepsis admission group in which 4.3% an average adjusted predicted probability of mortality was estimated. Breaking the risk down by severity tier, septic shock carried a 38.8% risk, severe sepsis carried a 15.5% risk, unspecified sepsis carried an 11.1% risk, and other sepsis (where the organism was identified) carried a 7.4% risk of 1-week mortality. Major small and large bowel procedures were associated with a 30.9% average predicted probability of death within 1 week of discharge if associated with hospital-acquired sepsis. Those procedures carried only 2.7% probability of death within one week of inpatient hospital discharge if sepsis was not associated with that inpatient

TABLE 4. Death Within 1 Week of Inpatient Discharge, Predicted Values in Setting of Common Intervention Diagnosis-Related Groups

Model: Death Within 1 wk of Inpatient Discharge for Non-POA and Nonsepsis Admissions With “Major Small and Large Bowel Procedures” Admission DRG	
Predictor Variables	Average Predicted Probability, %
Predicted probability of death within 1 wk of inpatient discharge on average for a hospital-acquired sepsis admission	30.9
Predicted probability of death within 1 wk of inpatient discharge on average for a nonsepsis admission	2.7
Model: Death Within 1 wk of Inpatient Discharge for Non-POA and Nonsepsis Admissions With “Respiratory System Diagnosis With Ventilator Support” Admission DRG	
Predictor Variables	Average Predicted Probability, %
Predicted probability of death within 1 wk of inpatient discharge on average for a hospital-acquired sepsis admission	62.1
Predicted probability of death within 1 wk of inpatient discharge on average for a nonsepsis admission	33.8
Model: Death Within 1 wk of Inpatient Discharge for Non-POA and Nonsepsis Admissions With “ECMO or TRACH W MV >96 HRS OR PDX EXC FACE, MOUTH & NECK W MAJ O.R.” admission DRG	
Predictor Variables	Average Predicted Probability, %
Predicted probability of death within 1 wk of inpatient discharge on average for a hospital-acquired sepsis admission	33.8
Predicted probability of death within 1 wk of inpatient discharge on average for a nonsepsis admission	21.6
Model: Death Within 1 wk of Inpatient Discharge for Non-POA and Nonsepsis Admissions With Surgical Procedures Admission DRG	
Predictor Variables	Average Predicted Probability, %
Predicted probability of death within 1 wk of inpatient discharge on average for a hospital-acquired sepsis admission	31.0
Predicted probability of death within 1 wk of inpatient discharge on average for a nonsepsis admission	2.3

DRG = diagnosis-related group, POA = present on admission.

These average predicted probabilities of death within a week of discharge are not simple averages but rather account for the following covariates: sepsis severity tiers, hierarchical condition categories, demographic characteristics, and preceding claims in 1 wk prior to hospital admission.

TABLE 5. Death Within Time Horizons After Inpatient Discharge for Sepsis Admissions, Adjusted Odds Ratios

ORs for Death Following Sepsis vs Nonsepsis Inpatient Admissions	Death < 1 wk	Death < 6 mo	Death < 1 yr
Age group (vs < 65)			
65–74	1.36	1.62	1.66
75–84	1.92	2.57	2.68
85+	3.38	5.19	5.77
POA vs non-POA sepsis			
Hospital-acquired sepsis	3.08	2.57	2.40
Sepsis tier (vs organism identified)			
Septic shock	8.68	4.53	3.96
Severe sepsis	2.51	1.70	1.61
Unspecified sepsis	1.61	1.27	1.23
Medicare eligibility (vs non-end-stage renal disease)			
End-stage renal disease	1.23	1.48	1.66
Dual enrollment (vs non-dual)			
Dual status	0.88	1.13	1.21
Gender (vs female)			
Male	0.98	1.07	1.11
Race (vs White)			
Black	1.07	1.15	1.13
Asian	0.96	0.84	0.82
Hispanic	0.94	0.83	0.80
North American Native	0.92	0.87	0.87
Preceding claims 1 wk prior to inpatient admission (vs no claims)			
Preceding home health claim	0.79	1.05	1.13
Preceding hospice claim	2.19	3.97	4.75
Preceding nonacute inpatient claim	1.34	1.26	1.17
Preceding nursing care (skilled or unskilled)	1.50	1.84	1.86

OR = odds ratio, POA = present on admission.

hospital admission (**Tables 3 and 4**). (Similar data for 6-mo and 1-yr mortality appear in Supplement 2 [Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>].)

We assessed the effect of time on the ORs of death. Reference groups are indicated in the table (**Table 5**).

Age has the expected effect, and impact is more pronounced over time in the oldest beneficiaries. Hospital-acquired sepsis has its worst effects early, but substantial effect persists out to a year or more. Sepsis severity effects taper over time as expected,

but do not converge illustrating that severity of sepsis may be a marker for the severity of chronic illness and risk. The impact of end-stage renal disease increases over time. Of special note are duals, who appear to be protected from early mortality (possibly because they are younger), but who have progressive excess mortality at 6 months and 1 year. This points to special vulnerability and an opportunity to test mitigation strategies. Men, Black beneficiaries, and those who required skilled or unskilled nursing care prior to their sepsis episode all experience increasing risk over the 1-year trajectory following the index admission, again possibly related to their chronic health status.

Age effects tended to be more pronounced when sepsis tiers specifically were accounted for in the logistic regression model. For example, a model that simply noted a 6-month risk of death to have a composite OR of 2.63 (95% CI, 2.62–2.65) (vs a nonsepsis admission) had ORs for the age groups of 65–74, 75–84, and 85+ of 1.56 (1.54–1.57), 2.51 (2.49–2.53), and 5.37 (5.32–5.41), respectively. When the logistic regression model was tiered according to septic shock, severe sepsis, unspecified sepsis, and other sepsis, with ORs of 7.27 (7.19–7.35), 2.48 (2.45–2.51), 1.88 (1.87–1.90), and 1.45 (1.43–1.48), respectively, the effect of advanced age sharpened somewhat, with ORs of 1.56 (1.55–1.57), 2.54 (2.54–2.56), and 5.49 (5.44–5.53), respectively, for the three age groups.

Logistic regression suggested that the impact of chronic health conditions was relatively unchanged whether the model lumped all sepsis admissions or split sepsis into severity tiers. As expected in this age group, a leukemia or metastatic cancer diagnosis led the hierarchical care conditions associated with increased risk of mortality at 6 mo following an inpatient admission (**Table 6**) (an unabridged version is given in Supplement 2 [Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>]).

Reciprocally, we determined the influence of a sepsis, age, eligibility, and other features on outcome of an inpatient admission among patients with HCCs 8 or 9 or 10, namely metastatic cancer, acute leukemia, lung, lymphoma, or other severe cancers. Among such patients, a sepsis admission more than doubled the risk of death, and a septic shock admission increased the probability of death 4.47 times (**Table 7**) (the unabridged form is given in Supplement 2 [Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>]). These mirroring models (influence of severe illness on sepsis outcome and influence of sepsis on severe illness outcome) illustrate the complex relationships among sepsis and other HCCs.

We next determined how the severities of sepsis, not present on admission status, “duals” status and hierarchical care conditions exhibited relative effects on sepsis mortality. Here, the reference admission cohorts are admissions with the least severe sepsis (other sepsis), admissions in which sepsis was present on admission, and admissions with non-dual status, with the ORs calculated separately for each of those groups and for admissions. The impact of severe cancer is lessened when impact is assessed within the sepsis cohort alone (**Table 8**) (an unabridged version is given in Supplement 2 [Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>], along with similar analyses for 1 wk and 1 yr).

TABLE 6. Death Within 6 Months of Inpatient Discharge, Odds Ratios

Predictor Variables	Model 1: Base Model With Sepsis Inpatient Admission Predictor				Model 2: Base Model With Sepsis Severity Tier Predictor			
	OR	SE	95% CI		OR	SE	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Sepsis admission	2.63	0.01	2.62	2.65	NA	NA	NA	NA
Sepsis tier								
Septic shock	NA	NA	NA	NA	7.27	0.04	7.19	7.35
Severe sepsis	NA	NA	NA	NA	2.48	0.02	2.45	2.51
Unspecified sepsis	NA	NA	NA	NA	1.88	0.01	1.87	1.90
Other sepsis (organism identified)	NA	NA	NA	NA	1.45	0.01	1.43	1.48
Age group								
65–74	1.56	0.01	1.54	1.57	1.56	0.01	1.55	1.57
75–84	2.51	0.01	2.49	2.53	2.54	0.01	2.52	2.56
85+	5.37	0.02	5.32	5.41	5.49	0.02	5.44	5.53
HCCs								
HCC8: metastatic cancer and acute leukemia	6.76	0.03	6.71	6.82	6.84	0.03	6.78	6.90
HCC9: lung and other severe cancers	2.57	0.01	2.55	2.60	2.58	0.01	2.56	2.61
HCC83: respiratory arrest	2.55	0.11	2.35	2.77	2.48	0.10	2.28	2.69
HCC27: end-stage liver disease	2.53	0.02	2.49	2.56	2.51	0.02	2.47	2.54
HCC80: coma, brain compression/anoxic damage	1.91	0.02	1.88	1.95	1.91	0.02	1.88	1.95
HCC28: cirrhosis of liver	1.70	0.01	1.68	1.73	1.69	0.01	1.66	1.72
HCC10: lymphoma and other cancers	1.68	0.01	1.66	1.70	1.69	0.01	1.66	1.71
HCC84: cardiorespiratory failure and shock	1.54	0.00	1.53	1.55	1.53	0.00	1.52	1.54
HCC166: severe head injury	1.54	0.15	1.27	1.85	1.55	0.15	1.28	1.87
HCC46: severe hematologic disorders	1.50	0.01	1.48	1.53	1.50	0.01	1.48	1.53
HCC99: cerebral hemorrhage	1.48	0.01	1.46	1.51	1.49	0.01	1.46	1.52
HCC85: congestive heart failure	1.36	0.00	1.35	1.36	1.35	0.00	1.35	1.36
HCC112: fibrosis of lung and other chronic lung disorders	1.31	0.01	1.29	1.33	1.31	0.01	1.29	1.34
HCC135: acute renal failure	1.29	0.00	1.28	1.30	1.28	0.00	1.27	1.29
HCC111: chronic obstructive pulmonary disease	1.20	0.00	1.19	1.21	1.21	0.00	1.20	1.21

HCC = Hierarchical Condition Category, NA = not applicable, OR = odds ratio.

The ORs here compare the risk versus index inpatient admissions that did not include the reference characteristic. The ratios are adjusted for covariates ("adjusted OR").

Forecasting the Costs of Sepsis

We created two- and three-parameter models aimed at distilling the progressive sepsis costs into a framework that would allow not only predictions but also early recognition of deviation from those predictions and, thus, an early alert that something has changed. We began by focusing on the inpatient costs associated with Medicare FFS beneficiaries.

Inspection of the data shows a general linear trend with superimposed seasonal variation corresponding to the clinically familiar wintertime "respiratory season" during which influenza, pneumonia, and similar respiratory ailments increase in prevalence. To get a sense of the rate of growth of costs, we began by evaluating a 12-month moving average across the entire 2012–2018 FFS inpatient cost dataset and observed an

TABLE 7. Death Within 6 Months of Inpatient Discharge for Admissions With Metastatic Cancer and Acute Leukemia, Lung and Other Severe Cancers, or Lymphoma and Other Cancers Hierarchical Condition Categories, Adjusted Odds Ratios

Predictor Variables	Model 1: Base Model With Sepsis Admission Predictor				Model 2: Base Model With Sepsis Tier Predictor			
	OR	SE	95% CI		OR	SE	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Sepsis admission	2.02	0.02	1.99	2.05	NA	NA	NA	NA
Sepsis tier								
Septic shock	NA	NA	NA	NA	4.47	0.08	4.32	4.63
Severe sepsis	NA	NA	NA	NA	1.95	0.04	1.88	2.03
Unspecified sepsis	NA	NA	NA	NA	1.57	0.02	1.53	1.60
Other sepsis (organism identified)	NA	NA	NA	NA	1.27	0.03	1.21	1.32
Age group								
65–74	1.23	0.01	1.21	1.25	1.23	0.01	1.21	1.25
75–84	1.41	0.01	1.38	1.44	1.41	0.01	1.38	1.44
85+	1.82	0.02	1.78	1.87	1.84	0.02	1.79	1.88
Medicare eligibility								
End-stage renal disease	0.95	0.02	0.92	0.98	0.94	0.02	0.91	0.97
Dual enrollment	0.99	0.01	0.97	1.00	0.99	0.01	0.97	1.00
Gender								
Male	1.16	0.01	1.14	1.17	1.16	0.01	1.14	1.17

NA = not applicable, OR = odds ratio.

The reference cohort is the set of inpatient admissions in which beneficiaries had Hierarchical Condition Category (HCC)8 (metastatic cancer and acute leukemia) and/or HCC9 (lung and other severe cancers) and/or HCC10 (lymphoma and other cancers).

average cost increase of around 4.7% per year, rising substantially faster than the annual consumer price index over the same interval (range, 0.1–2.2% annually).

Next, we performed regression modeling. We began with a two-parameter (slope and intercept, “line”) model, ($Y = \alpha + \beta x$). The two-parameter model regresses the 12-month payment sum on a particular month. The intercept predicts that the 12-month payment sum ending on month 0 (February 2011–January 2012) would have been \$17,025,619,739 with an SE of \$77,462,307. Increasing the month number by one increments the total estimated payment by \$69,651,082, with that increment having an SE of \$1,651,127. Similar to a moving average approximation, this model accounts for seasonal variation by creating a time series that shifts the 12-month sum 1 month into the future. That accounting does not, however, provide for a monthly estimate of claims.

To account for the seasonal variation, we added a phasic (cosine) term linked to the month number. The independent variable for this model is the month versus the 12-month sum in the prior model. This three-parameter model, “a line and

a cosine” ($Y = \alpha + \beta x + \gamma \cos\left(2\pi\left[\frac{x}{12}\right]\right)$), is therefore specified

by an intercept, a slope, and a coefficient-weighted periodic function (cosine) capturing the impact of seasonal variation. The intercept, \$1,452,104,837 with SE \$18,459,625, predicts the (monthly) payment in month 0 (January 2012) without the seasonal variation term. The seasonal variation term is at its maximum in winter ($\cos 0 = 1$) and adds \$116,607,170. The slope, \$5,702,403 with a SE of \$425,205, indicates the modest month-over-month increase without the large seasonal variation imposed. (The slope here may be compared with the slope of the two-parameter model by multiplying by 12.) The impact of seasonal variation is substantial, fluctuating $\pm \$116,607,170$ (the cosine function oscillates between +1 and –1) with a SE of \$13,204,447 over each year (peaks in January [$\cos(0, 2\pi, 4\pi, \dots) = 1$], troughs in July [$\cos(\pi, 3\pi, 5\pi, \dots) = -1$]) around the linear trend.

Inspection of the models shows that the studentized residuals (i.e., residuals divided by the sample SD) are nonrandom in the two-component models, but nearly random in the three-component models. The quantile

TABLE 8. Death Within 6 Months of Inpatient Discharge for Sepsis Admissions, Adjusted Odds Ratios

Predictor Variables	Model 3: Sepsis Admission Model With Sepsis Tier and Sepsis POA Predictors			
	OR	SE	95% CI	
			Lower Bound	Upper Bound
Age group				
65–74	1.62	0.02	1.59	1.65
75–84	2.57	0.03	2.52	2.62
85+	5.19	0.06	5.08	5.30
POA vs non-POA sepsis				
Hospital-acquired sepsis (not present on admission)	2.57	0.03	2.52	2.62
Sepsis tier				
Septic shock	4.53	0.04	4.44	4.62
Severe sepsis	1.70	0.02	1.67	1.74
Unspecified sepsis	1.27	0.01	1.25	1.29
Medicare eligibility				
End-stage renal disease	1.48	0.02	1.44	1.52
Dual enrollment	1.13	0.01	1.12	1.15
Gender				
Male	1.07	0.01	1.06	1.08
HCCs				
HCC8: metastatic cancer and acute leukemia	5.16	0.07	5.03	5.30
HCC27: end-stage liver disease	2.39	0.05	2.29	2.49
HCC9: lung and other severe cancers	2.17	0.03	2.10	2.23
HCC83: respiratory arrest	2.00	0.21	1.62	2.47
HCC28: cirrhosis of liver	1.71	0.04	1.64	1.80
HCC80: coma, brain compression/anoxic damage	1.63	0.04	1.55	1.72
HCC46: severe hematologic disorders	1.58	0.04	1.51	1.66
HCC158: pressure ulcer of skin with full thickness skin loss	1.55	0.03	1.49	1.61
HCC157: pressure ulcer of skin with necrosis through to muscle, tendon, or bone	1.54	0.05	1.45	1.63
HCC106: atherosclerosis of the extremities with ulceration or gangrene	1.48	0.03	1.42	1.54
HCC10: lymphoma and other cancers	1.44	0.03	1.38	1.49
HCC84: cardiorespiratory failure and shock	1.40	0.01	1.38	1.43
HCC85: congestive heart failure	1.25	0.01	1.23	1.27
HCC135: acute renal failure	1.25	0.01	1.23	1.27

HCC = Hierarchical Condition Category, OR = odds ratio, POA = present on admission.

(Q-Q) plots deviate from the line of identity for the two-parameter model, whereas hewing more closely to the line of identity for the three-component model. We conclude that the three-parameter model reasonably captures the seasonal variation, although the costs incurred during December and January each year always exceed the model

prediction. We return to this point in the *Discussion* section (**Fig. 1**).

We first used the models to forecast inpatient sepsis costs for FFS beneficiaries only. We trained the models on the interval January 2012–April 2017 and then forecast the interval May 2017–April 2018. We estimated the model (in)accuracy

Figure 1. Models of payments, Medicare fee-for-service, inpatient only. *Left column*, two-parameter (linear) model regressing on sum of prior 12-mo payments. *Right column*, three-parameter model incorporating a phasic term ("line and a cosine") to account for seasonal variation regressing on the monthly payment. *Top row*, model and actual data. *Middle row*, studentized residuals by month. Note the obvious nonrandom pattern of residuals by month from the two-parameter model, compare with the apparently random pattern of residuals by month from the three-parameter model. *Bottom row*, Q-Q plots showing the distributions of residuals versus a normal distribution. The closer the data fall on the line of identity, the closer the distribution of residuals lies to a normal (random) distribution. The three-parameter model captures the essential features of payments.

as the root mean square error (RMSE) for both the training and the forecast period—all of which were in the range of 1–2% of the actual value, observing that the ratio of the

RMSE for the test/training period was greater for the two-component model versus the three-component model (2.225 vs 1.626). We then used the models to forecast the 2019 costs,

TABLE 9. Comparison of Model Predictions for Fee-for-Service Inpatient Sepsis Payments in General and for 2019

Model	Training Data (January 2012 to April 2017)		Test Data (May 2017 to April 2018) RMSE ^b	Test RMSE/ Training RMSE	2019 FFS Inpatient Payment Projections ^a		
	Adjusted R^2	RMSE ^b			Projection	95% Lower Bound	95% Upper Bound
Model 1: regress 12-mo payment sum on month	0.9653	\$223,800,609	\$497,884,906	2.225	\$23,642,472,567	\$23,111,097,216	\$24,173,847,918
Model 2: regress monthly payment on month with seasonal adjustment	0.7842	\$252,214,391	\$410,122,611	1.626	\$23,549,639,139	\$22,961,052,155	\$24,138,226,123

	Projection	95% Lower Bound	95% Upper Bound
Model 1: 2019 FFS inpatient payment projections ^a /2017 FFS inpatient payment	1.087	1.063	1.112
Model 2: 2019 FFS inpatient payment projections ^a /2017 FFS inpatient payment	1.083	1.056	1.110

FFS = fee-for-service, RMSE = root mean square error.

^a95% prediction intervals are reported. Note that the reported intervals for model 1 are expected to underestimate the actual prediction intervals due to the correlations in the errors in model 1.

^bThe RMSE for model 2 has been multiplied by a factor of $\sqrt{12}$ to make it comparable to the RMSE for the running 12-mo payment sums.

which ranged from \$23.550 to 23.642 billion. (Recall that the actual 2017 inpatient cost for Medicare FFS patients was \$21.741 billion [Table 9].)

The analyses in the first article of this set showed that encounter data claims submitted on behalf of Medicare part C (MA) beneficiaries were indistinguishable from claims paid on behalf of Medicare FFS patients. We, therefore, used the encounter data from the MA population to model and project the total inpatient costs of Medicare beneficiaries in 2019 using each of the models. Those projections for the 2019 inpatient sepsis costs for all Medicare (FFS and MA) beneficiaries ranged from \$35.425 to 35.499 billion (Fig. 2 and Table 10). Additional detail is given in Supplement 3 (Supplemental Digital Content 3, <http://links.lww.com/CCM/F251>).

Finally, we compiled the skilled nursing facility (SNF) claims paid on behalf of the FFS beneficiaries and inferred that SNF admissions for MA beneficiaries obtained from the minimum data set would have similar costs. That compilation provided a basis to model and further to project the total inpatient and SNF costs for both FFS and MA beneficiaries for 2019 to be in the range of \$44.575–\$44.718 billion, around \$9 billion more than the total inpatient costs alone (Fig. 3 and Table 11).

DISCUSSION

We observed that Medicare beneficiaries who have an inpatient admission linked with sepsis diagnosis are distinct from beneficiaries admitted without having sepsis at admission or acquired during the hospital admission; they are slightly older and have (on average) more comorbidities defined by the number of HCCs. Once a sepsis diagnosis is made, the likelihood of death within 6 months is associated with the severity of sepsis at the time of the index admission, the age of the patient, and the specific comorbidities, most notably advanced

cancers. Effective treatment of such advanced cancers may, therefore, depend on prevention, early detection, and effective treatment of sepsis. Certain HACs, such as major surgery on the small or large intestine; need for mechanical ventilation; and ECMO appear to act in synergy with the sepsis diagnosis to identify beneficiaries at especially high risk of death. (For further information, see Supplement 2 [Supplemental Digital Content 2, <http://links.lww.com/CCM/F250>].)

We further observed that the costs associated with care of Medicare beneficiaries appeared to change in ways amenable to modeling using linear combinations of few parameters. Although a two-parameter model offered insight into annual total costs, a three-parameter model reasonably accounted for the seasonal variation in sepsis occurrence and associated changes in monthly claims. The forecasts enabled by these models are not intended to be official cost projections of the U.S. government. Rather, our purposes in developing these models and making forecasts are to enable detection of departures from the forecasts and thereby call attention to processes and events not captured in the models. For example, we observed qualitative matching between the annual deviations from forecast during the winter respiratory seasons (13, 14). We observed in the residuals plots for inpatient and SNF costs an outlier, even beyond the seasonal variation, for January 2018. The 2017–2018 winter respiratory season was reported by the Centers for Disease Control and Prevention (CDC) to be especially impactful on the U.S. population, attributable at least in part to a virulent influenza A H3N2 variant virus (15). Secondary pneumonia commonly underlies sepsis. We suggest that near-real-time FFS sepsis claims that deviate from the model might be used as an early warning system around clinically significant outbreaks. We further suggest that public health measures taken against influenza (including but not limited to consistently high

Figure 2. Models of payments, Medicare fee-for-service and Medicare Advantage, inpatient only. Medicare advantage payments based on encounter data. Models and explanations identical to Figure 1.

rates of vaccination with the most current vaccine and early antiviral treatment) may be important to reduce seasonal sepsis “spikes.”

Figure 3 extended the models to include both FFS and MA beneficiaries and to include their inpatient and SNF costs. For 2019, that care alone is projected to be approximately \$45 billion. Those extensions invite rough-order-of-magnitude (ROM) estimates of the total costs of sepsis care in the United States. Although our data do not reflect the costs of inpatient or skilled nursing facility care in the private sector, the analysis by Torio and Moore (11) of inpatient costs of septicemia

derived from the Agency for Healthcare Research and Quality’s Healthcare Cost and Utilization Project (AHRQ-HCUP) project suggested that Medicare beneficiaries accounted for \$14.551 billion/23.663 billion total equals to 61.5% of the national inpatient costs in 2013.

We observed that the predicted 2-year growth rates varied not only by model but also by what was being modeled. For example, using Model 1 (Regression of 12-month Payment Sum on Month), we observed the ratio of the 2019 prediction to the 2017 actuals to be as follows: for FFS inpatient only, 1.087; FFS SNF only, 1.139; FFS and MA inpatient only, 1.129; and

TABLE 10. Comparison of Model Predictions for Fee-for-Service and Medicare Advantage Inpatient Sepsis Payments in General and for 2019

Model	Training Data (January 2012 to April 2017)		Test Data (May 2017 to April 2018) RMSE ^b	Test RMSE/ Training RMSE	2019 FFS and MA Inpatient Payment Projections ^a		
	Adjusted R ²	RMSE ^b			Projection	95% Lower Bound	95% Upper Bound
Model 1: regress 12-mo payment sum on month	0.9823	\$345,850,356	\$466,086,001	1.348	\$35,499,060,056	\$34,768,534,563	\$36,229,585,549
Model 2: regress monthly payment on month with seasonal adjustment	0.8873	\$341,105,301	\$603,946,233	1.771	\$35,425,492,442	\$34,601,705,356	\$36,249,279,528
					Projection	95% Lower Bound	95% Upper Bound
Model 1: 2019 FFS and MA inpatient payment projections ^a /2017 FFS and MA inpatient payment					1.129	1.106	1.152
Model 2: 2019 FFS and MA inpatient payment projections ^a /2017 FFS and MA inpatient payment					1.127	1.100	1.153

FFS = fee-for-service, MA = Medicare Advantage, RMSE = root mean square error.

^a95% prediction intervals are reported. Note that the reported intervals for model 1 are expected to underestimate the actual prediction intervals due to the correlations in the errors in model 1.

^bThe RMSE for model 2 has been multiplied by a factor of sqrt(12) to make it comparable to the RMSE for the running 12-mo payment sums.

FFS MA inpatient and SNF, 1.137. The cost per case of FFS inpatient care is declining but is still offset by the rise in FFS enrollees. The rate of rise of MA enrollees is faster than that of SNF enrollments. SNF costs are not declining as fast as inpatient costs. Thus, the ratios represent growth in different cost blends. The best near-term estimate using this model is likely the fully blended cost, rising ~13.7% over the 2-year interval.

Given the rise in the number of Medicare beneficiaries relative to the general population, it is reasonable to increase that cost proportion from 61.5% to approximately 2/3, an approximation that reflects both growth in the Medicare population as a whole and the fact that the growth in numbers has occurred at the lowest age bands where occurrence, severity, and costs are proportionately lower. That 2/3 cost approximation means that the private sector would add half again as much to the total. Similarly, MA patients are half again as many as the FFS cohort. Looking at inpatient costs alone, we have projected for 2019 that the care for FFS beneficiaries will reach \$23.5 billion. Adding half this number for the MA beneficiaries, we arrive at \$35.25 billion for the entire Medicare population. Adding half again for patients cared for in the private sector, the cost of inpatient care is estimated to be \$53 billion. We have confidence in an estimate of the use and costs of skilled nursing facility care on behalf of Medicare (FFS and MA) beneficiaries, which adds around \$9 billion. The total cost then exceeds \$62 billion annually.

This estimate is incomplete. It omits professional fees (such as physician costs during the inpatient admission) incurred treating sepsis. It further omits: 1) all skilled nursing facility care costs for private sector patients suffering from sepsis and 2) all costs incurred by beneficiaries of the nation's federal

hospital systems operated by the Department of Veterans Affairs and by the Defense Health Agency. Thus, the ROM estimate of \$62 billion is an extremely conservative lower bound that omits significant real inpatient costs of sepsis to the nation.

Furthermore, that \$62 billion ROM estimate includes no outpatient costs (including office visits, durable medical equipment costs, medication costs) and no home healthcare costs (e.g., skilled nursing visits, physical therapy, aides) or custodial care in a nursing home. That estimate further does not account for secondary costs such as loss of employment, loss of productivity by the patient or family members, and many others. Thus, the \$62 billion ROM estimate can and must be revised upward as the listed unaccounted costs are systematically analyzed and reported.

This lower-bound ROM estimate of the national cost of sepsis differs substantially from the \$23.66 billion reported by Torio and Moore (11), an estimate widely cited by many observers. We note the following differences. First, the estimate by Torio and Moore (11) was derived from 2013 data, and Americans have aged toward increasing sepsis vulnerability. Second, Torio and Moore (11) examined inpatient costs only, whereas we also included skilled facility costs. Third, Torio and Moore (11) examined only ICD-9 code 038 ("septicemia") that is contained in—but does not span—the usual explicit sepsis diagnostic codes. Fourth, the costs of each episode of care have changed over the interval 2012–2018. Those differences notwithstanding, we observe that the projected 2019 cost of inpatient sepsis care alone (not including SNF) for Medicare FFS beneficiaries alone (not including MA) is \$23.5 billion, which is approximately equal to the national inpatient cost

Figure 3. Models of payments, Medicare fee-for-service and Medicare Advantage, inpatient and skilled nursing facility. Medicare Advantage payments for inpatient care based on encounter data. Medicare Advantage payments for skilled nursing facility care assume similar utilization and similar payments per episode. Models and explanations identical to Figure 1.

TABLE 11. Comparison of Model Predictions for Fee-for-Service and Medicare Advantage Inpatient and Skilled Nursing Facility Sepsis Payments in General and for 2019

Model	Training Data (January 2012 to April 2017)		Test Data (May 2017 to April 2018)	Test RMSE/ Training RMSE	2019 FFS and MA Inpatient and SNF Payment Projections ^a		
	Adjusted R^2	RMSE ^b			Projection	95% Lower Bound	95% Upper Bound
Model 1: regress 12-mo payment sum on month	0.9818	\$461,958,323	\$780,360,571	1.689	\$44,717,521,586	\$43,704,237,708	\$45,730,805,463
Model 2: regress monthly payment on month with seasonal adjustment	0.8932	\$431,509,173	\$776,305,272	1.799	\$44,574,961,755	\$43,530,326,535	\$45,619,596,974
					Projection	95% Lower Bound	95% Upper Bound
Model 1: 2019 FFS and MA inpatient and SNF payment projections ^a /2017 FFS and MA inpatient and SNF payment					1.137	1.111	1.162
Model 2: 2019 FFS and MA inpatient and SNF payment projections ^a /2017 FFS and MA inpatient and SNF payment					1.133	1.106	1.160

FFS = fee-for-service, MA = Medicare Advantage, RMSE = root mean square error, SNF = skilled nursing facility.

^a95% prediction intervals are reported. Note that the reported intervals for model 1 are expected to underestimate the actual prediction intervals due to the correlations in the errors in model 1.

^bThe RMSE for model 2 has been multiplied by a factor of $\sqrt{12}$ to make it comparable to the RMSE for the running 12-mo payment sums.

for “septicemia” reported for Torio and Moore (11) for 2013 (\$23.7 billion), and neither of those figures includes any costs of care rendered to Department of Veterans Affairs (VA) or Defense Health Agency (DHA) beneficiaries. Furthermore, neither the report by Torio and Moore (11) nor this report estimate professional fees that might be attributed to diagnosis or treatment of sepsis.

The true cost of sepsis care in the United States is thus not currently known. We only can be certain that this cost has risen rapidly, in part to due to the expansion of the Medicare population outpacing the reductions in cost per case. There is, nevertheless, a need to estimate to total cost burden in order to provide a rational basis for ongoing investment in research and development.

There are several limitations to the methods, results, and projections. The influencer analysis and financial forecasts ultimately depend on the administrative codes assigned. A different code set, such as a selection of code combinations including, for example, phlebotomy for blood culture and various organ failure codes, would have produced different results. As telegraphed in the first article of this set, we will not debate the merits of a particular definition of sepsis. Our purpose in this initial set of articles was to use a reliable and reproducible approach spanning the ICD-9→ICD-10 transition. The observed impacts of admission stratification into a hierarchy of sepsis severity and of age and of comorbidities on ORs of mortality likely will have face validity among clinicians who deal regularly with sepsis independent of the definition debate. We caution that the tables of influencers (marginal

effects, ORs, and so on) are tables based on univariate analyses. Comparisons across studies may suggest interactions. However, formal interaction analyses (e.g., metastatic cancer $\times$ age $\times$ sepsis severity) have not yet been performed.

We are aware that ICD-11 specifies Sepsis-3 as the data-driven definition of sepsis, namely ICD-11 codes for sepsis without septic shock (1G40) and for sepsis with septic shock (1G41). We note that although ICD-11 was announced in mid-2018 by the World Health Organization and will be open for adoption by member states beginning 2022, the United States historically has been a late adopter of successor ICD editions. (We observe that ICD-10 was announced in 1992, and implemented by many World Health Organization member states as early as 1998. In the United States, the Department of Health and Human Services (HHS) did not propose that medical professionals use ICD-10 for reporting diagnoses and procedures on healthcare transactions in the United States until 2008. Although HHS published a final rule in 2009 declaring ICD-10 to be the new national standard, preparing for the transition took more than 6 yr, finally occurring in 2015 [16].) Reasonably, many stakeholders will work from the ICD-10–based definitions of sepsis for the foreseeable future, although progressive use of definitions is likely toward those that are more clinically refined, such as Sepsis-3 and the CDC’s Adult Sepsis Event.

National reporting of sepsis data invites international comparisons and comprehensive assessment of global burdens. The need for reproducible methodology toward uniform coding and contemporary assessment is apparent. In the interim, the hierarchy of septic shock, severe sepsis, and the organism

specific and unspecified forms of sepsis without the threshold organ dysfunction described in Sepsis-3 may continue to provide insight into the different trajectories and incurred costs of Medicare beneficiaries, and perhaps other patients as well.

The financial forecasts are based on current (not constant) dollars. Forecasts, therefore, implicitly account for growth not only in patient numbers and severity but also of inflation. None of these can be determined with certainty. For example, we observe that financial forecasts are influenced strongly by catastrophic events; appearance of a global pandemic such as the 1918 “Spanish Flu” would incur costs far in excess of financial forecasts generated by the models discussed. Indeed, the January 2018 anomaly hints at the scale of the potential cost impact of widespread serious infection.

We reiterate that the lower-bound ROM figure for the national cost is known to significantly underestimate the aggregate costs because certain large cost sectors (e.g., the costs of sepsis within the VA and DHA systems) currently are not known, and other large cost sectors (private payers and state-run Medicaid programs) lag a couple of years in reporting (via the AHRQ HCUP project) in comparison to the more current Medicare data. Indeed, our purpose in preparing and freely disseminating the analytic framework and algorithm specification is to encourage acceleration of reporting, sharing of data, and comparison across different sectors to arrive at more accurate estimates of the national burdens and trajectories of sepsis.

CONCLUSIONS

We offered a method of data extraction and summarization that protects protected health information at the source and yet encourages reliable comparisons among sepsis populations. We used logistic regression to illuminate the effects of severity, demographics, “duality,” and healthcare conditions on immediate and early mortality. We developed multiparameter models that offer companion and convergent forecasts around Medicare costs related to the sepsis burden. We now know the actual national expenditures for sepsis to far exceed widely cited contemporary estimates. The question is “exceed by how much”? Answering this question requires new public-private partnerships that harmonize definitions of sepsis, that facilitate internal analyses and preparation of comparable summary data, and above all that promote the sharing of those summary data into the public space. Only when we understand the burdens, the trajectories, the predispositions, and the costs of sepsis can the nation fairly and prudently allocate the resources necessary to solve sepsis.

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