Effects of Compliance With the Early Management Bundle (SEP-1) on Mortality Changes Among Medicare Beneficiaries With Sepsis

A Propensity Score Matched Cohort Study

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e-Table 1: Description of SEP-1 Measure

A case was identified as compliant, or passed SEP-1 measure, when it received all the following:

Received within three hours of presentation of severe sepsis:
1. Initial lactate level measurement, and
2. Broad spectrum or other antibiotics administered, and
3. Blood cultures drawn prior to antibiotics

Received within six hours of presentation of severe sepsis:
1. Repeat lactate level measurement only if initial lactate level is elevated
2. If Septic Shock present, received within three hours of presentation of septic shock:
3. Resuscitation with 30 ml/kg crystalloid fluids
4. If hypotension persists after fluid administration, received within six hours of presentation of septic shock:
5. Vasopressors

If hypotension persists after fluid administration or initial lactate greater than or equal to 4 mmol/L, received within six hours of presentation of septic shock:
1. Repeat volume status and tissue perfusion assessment consisting of either:
    A. A focused exam including:
        •   Vital signs, and
        •   Cardiopulmonary exam, and
        •   Capillary refill evaluation, and
        •   Peripheral pulse evaluation, and
        •   Skin examination
    B. Any two of the following four:
        •   Central venous pressure measurement
        •   Central venous oxygen measurement
        •   Bedside cardiovascular ultrasound
        •   Passive leg raise or fluid challenge

e-Table 2: ICD-10-CM Codes for Severe Sepsis and Septic Shock

Code	Description
A021	Salmonella sepsis
A227	Anthrax sepsis
A267	Erysipelothrix sepsis
A327	Listerial sepsis
A400	Sepsis due to Streptococcus, group A
A401	Sepsis due to Streptococcus, group B
A403	Sepsis due to Streptococcus pneumoniae
A408	Other Streptococcal sepsis
A409	Streptococcal sepsis, unspecified
A4101	Sepsis due to Methicillin susceptible Staphylococcus aureus
A4102	Sepsis due to Methicillin resistant Staphylococcus aureus
A411	Sepsis due to other specified staphylococcus
A412	Sepsis due to unspecified Staphylococcus
A413	Sepsis due to Hemophilus influenzae
A414	Sepsis due to anaerobes
A4150	Gram-negative sepsis, unspecified
A4151	Sepsis due to Escherichia coli [E. coli]
A4152	Sepsis due to Pseudomonas
A4153	Sepsis due to Serratia
A4159	Other Gram-negative sepsis
A4181	Sepsis due to Enterococcus
A4189	Other specified sepsis
A419	Sepsis, unspecified organism
A427	Actinomycotic sepsis
A5486	Gonococcal sepsis
R6520	Severe sepsis without septic shock
R6521	Severe sepsis with septic shock

e-Table 3: Summary of Centers for Medicare & Medicaid Services criteria for severe sepsis and septic shock*

Definition	Criteria
Severe sepsis	1. Documentation by physician, advanced practice nurse (APN) or physician assistant (PA) of severe sepsis OR
	2. Severe sepsis clinical criteria are met when A, B and C are documented within six hours of each other (the last qualifying element of A, B and C is time zero).

    A. Documentation of suspected source of clinical infection and

    B. Two Systemic Inflammatory Response Syndrome criteria (not attributed to a documented chronic condition). Qualifying time is the later of the two SIRS within three hours of each other:
- Temperature >38.3°C, <36°C
- Heart Rate >90 beats/min
- Respiratory Rate >20 beats/min
- White Blood Cell Count >12,000 cells/µL, <4,000 cells/µL, >10% bands

    C. One organ dysfunction criterion
- Hypotension (SBP <90 mm Hg or MAP <65 mm Hg)
- Lactate >2 mmol/L
- Urine output (<0.5 mL/kg/h for >2 h)
- Creatinine >2 mg/dL
- Bilirubin >2 mg/dL
- Platelets <100,000 cells/µL
- Coagulopathy (INR >1.5 or aPTT >60 sec)
- Acute respiratory failure (mechanical ventilation)

Septic shock	1. Documentation by physician, APN or PA of septic shock OR
	2. Severe sepsis present (per above criteria) AND persistent hypotension in the hour after the abstraction verified completion of infusion of the target fluid volume and evidenced by two consecutive documented recordings of:

- Systolic blood pressure < 90 mmHg or
- MAP < 65 mmHg or
- A decrease in systolic blood pressure by > 40 mmHg from baseline. OR

3. Severe sepsis present (per above criteria) AND tissue hypoperfusion evidenced by initial lactate level > 4 mmol/L
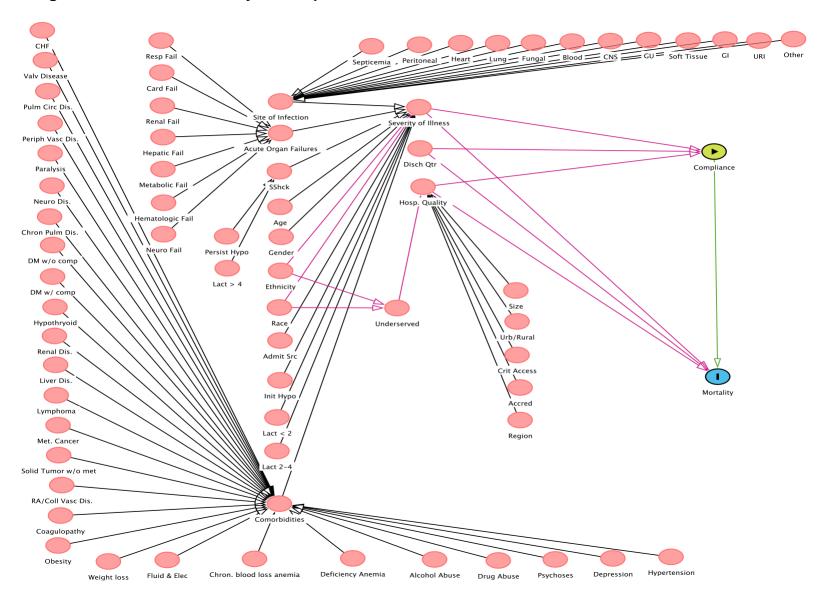
SBP = systolic blood pressure; MAP = mean arterial pressure;
INR = international normalized ratio; aPTT = activated partial thromboplastin time.
*e-Table 3 represents summary criteria. Full details about past and present quarterly algorithms are available at
https://www.qualitynet.org/inpatient/specifications-manuals.

e-Figure 1: SEP-1 Directed Acyclic Graph

e-Table 4: List of variables used in the hierarchical generalized linear models (HGLM) to generate the propensity for compliance with the SEP-1 measure and the risk-adjusted mortality model.

Covariate	Type	Comments
Patient level variables		
Age	Continuous	
Hispanic Ethnicity	Binary	
Race • White • American Indian/Alaska Native • Asian • Black/African American • Native Hawaiian/Pacific Islander • Unable to determine	Categorical	
Male	Binary	
Year – Quarter • 2015 Q4 • 2016 Q1 • 2016 Q2 • 2016 Q3 • 2016 Q4 • 2017 Q1	Categorical	
Persistent hypotension	Binary	As defined by requirements of SEP-1 algorithm logic typically requiring ongoing hypotension in the hour after abstraction verified completion of infusion of the target fluid volume and evidenced by two consecutive documented recordings of: systolic blood pressure < 90 mmHg, or MAP < 65 mmHg, or a decrease in systolic blood pressure by > 40 mmHg from baseline
Initial lactate level • Not collected • ≤ 2.0 mmol/L • > 2.0 and < 4.0 mmol/L • ≥ 4.0 mmol/L	Categorical	
Septic shock	Binary	As defined by requirements of SEP-1 algorithm logic
Comorbidities • Acquired immune deficiency syndrome • Alcohol abuse • Deficiency anemias • Rheumatoid arthritis/collagen vascular diseases • Chronic blood loss anemia • Congestive heart failure • Chronic pulmonary disease • Coagulopathy • Depression	All Binary	Comorbid conditions patients are thought to have derived from primary/secondary diagnosis codes provided in the SEP-1 dataset

Covariate	Type	Comments
• Diabetes without chronic complications • Diabetes with chronic complications • Drug abuse • Hypertension • Hypothyroidism • Liver disease • Lymphoma • Fluid and electrolyte disorders • Metastatic cancer • Other neurological disorders • Obesity • Paralysis • Peripheral vascular disease • Psychoses • Pulmonary circulation disease • Renal failure • Solid tumor without metastasis • Peptic ulcer disease excluding bleeding • Valvular disease • Weight loss		
Site of infection • Bacteremia • Central nervous system • Fungal • Gastrointestinal • Genitourinary • Heart • Lung • Missing • Other • Peritoneal • Septicemia • Soft tissue • Upper respiratory tract	All Binary	Source of infection derived from primary/secondary diagnosis codes provided in the SEP-1 dataset assigned based on hierarchal association with 30-day mortality
Organ failure • Cardiovascular • Hematologic • Metabolic • Neurologic • Renal • Respiratory	All Binary	Organs suffering acute dysfunction associated with sepsis derived from primary/secondary diagnosis codes provided in the SEP-1 dataset
Hospital level variables		
Hospital rural/urban indicator	Binary	
Hospital accreditation • AOA/HFAP • CIHQ	Categorical	

Covariate	Type	Comments
• DNV • NONE • TJC		
Critical Access Hospital vs. Short-term	Binary	
Hospital total certified beds Values between 2 and 2,449	Continuous	

e-Appendix 1: Hierarchical infection categories covariate derivation and assignment

Each patient was assigned an infection source modeled as hierarchical infection categories based upon unadjusted mortality in the manner of Darby.[1] This method was adapted from the extensively validated Angus sepsis definition,[2] and we cross-walked the Angus ICD-9-CM codes to ICD-10-CM using the relevant Diagnosis Code Set General Equivalence Mappings (GEMs) (e-Table 5).

In determining patients' infection sources nearly all patients (98.7%) had an explicit code for sepsis. Therefore, patients were first assigned infection sources other than septicemia by magnitude of the infection's parameter estimate (e-Table 7). For patients that had more than one code for infection source, we assigned the single source associated with the highest unadjusted mortality. Patients without another infection source were assigned to "septicemia alone." Infection sources were bacteremia, septicemia, fungal, peritoneal, heart, upper respiratory, lung, central nervous system, gastrointestinal, skin and other infections.

Following Darby, the final infection categories were modelled as a series of mutually exclusive indicator covariates with upper respiratory infection as the reference category (based on lowest parameter estimate).[1] See e-Table 9 and e-Table 12 for final matched outputs.

References:

1. Darby JL, Davis BS, Barbash IJ, Kahn JM. An administrative model for benchmarking hospitals on their 30-day sepsis mortality. *BMC Health Serv Res*. 2019;19(1):221. Published 2019 Apr 11.

2. Iwashyna TJ, Odden A, Rohde J, et al. Identifying patients with severe sepsis using administrative claims: patient-level validation of the angus implementation of the international consensus conference definition of severe sepsis. *Med Care*. 2014;52(6):e39-e43.

e-Table 5: Crosswalk of Elias ICD-9-CM classification of type of organ failure and code description to ICD-10-CM by General Equivalence Mappings

ICD-9-CM	ICD-10-CM
Respiratory Failure	**Respiratory Failure**

518.81 Acute respiratory failure
518.82 Acute respiratory distress syndrome
518.85 Acute respiratory distress syndrome after shock
            or trauma
786.09 Respiratory insufficiency
799.1   Respiratory arrest
96.7x   Ventilator management
	J96.01 Acute respiratory failure with hypoxia
	J96.02 Acute respiratory failure with hypercapnia
	J96.91 Respiratory failure, unspecified with hypoxia
	J96.92 Respiratory failure, unspecified with hypercapnia
	J96.00 Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
	J96.90 Respiratory failure, unspecified, unspecified whether with hypoxia or
	               hypercapnia
	J80 Acute respiratory distress syndrome
	R06.03 Acute respiratory distress
	R06.00 Dyspnea, unspecified
	R06.09 Other forms of dyspnea
	R06.3 Periodic breathing
	R06.83 Snoring
	R06.89 Other abnormalities of breathing
	R09.2 Respiratory arrest

Cardiovascular Failure	**Cardiovascular Failure**
458.0 Hypotension, postural 785.5 Shock 785.51 Shock, cardiogenic 785.59 Shock, circulatory or septic 458.0 Hypotension, postural 458.8 Hypotension, specified type, not elsewhere classified 458.9 Hypotension, arterial, constitutional 796.3 Hypotension, transient	I95.1 Orthostatic hypotension R57.9 Shock, unspecified R57.0 Cardiogenic shock R57.1 Hypovolemic shock R57.8 Other shock I95.89 Other hypotension I95.9 Hypotension, unspecified R03.1 Nonspecific low blood-pressure reading
Renal Failure	**Renal Failure**
584 Acute renal failure	N17.0 Acute kidney failure with tubular necrosis

580 Acute glomerulonephritis 584.5 Acute renal failure with lesion of tubular necrosis 584.6 Acute renal failure with lesion of renal cortical necrosis 584.7 Acute renal failure with lesion of renal medullary necrosis 584.8 Acute renal failure with other specified pathological lesion in kidney 584.9 Acute renal failure, unspecified	N17.1 Acute kidney failure with acute cortical necrosis N17.2 Acute kidney failure with medullary necrosis N17.8 Other acute kidney failure N17.9 Acute kidney failure, unspecified
Hepatic Failure	**Hepatic Failure**
570 Acute hepatic failure or necrosis 572.2 Hepatic encephalopathy 573.3 Hepatitis, septic or unspecified	K72.01 Acute and subacute hepatic failure with coma K72.00 Acute and subacute hepatic failure without coma K76.2 Central hemorrhagic necrosis of liver K70.41 Alcoholic hepatic failure with coma K71.11 Toxic liver disease with hepatic necrosis, with coma K72.90 Hepatic failure, unspecified without coma K72.91 Hepatic failure, unspecified with coma K716 Toxic Liver Disease with Hepatitis, not elsewhere classified K759 Inflammatory liver disease, unspecified
Hematologic Failure	**Hematologic Failure**
286.2 Disseminated intravascular coagulation 286.6 Purpura fulminans 286.9 Coagulopathy 287.3-5 Thrombocytopenia, primary, secondary, or unspecified	D65 Disseminated intravascular coagulation [defibrination syndrome] D68.8 Other specified coagulation defects D68.9 Coagulation defect, unspecified D69.49 Other primary thrombocytopenia D69.6 Thrombocytopenia, unspecified
Metabolic Failure	**Metabolic Failure**
276.2 Acidosis, metabolic or lactic	E87.2 Acidosis
Neurologic Failure	**Neurologic Failure**
293 Transient organic psychosis 348.1 Anoxic brain injury 348.3 Encephalopathy, acute 780.01 Coma 780.09 Altered consciousness, unspecified	F05 Delirium due to known physiological condition G93.1 Anoxic brain damage, not elsewhere classified G93.40 Encephalopathy, unspecified R40.20 Unspecified coma R40.0 Somnolence R40.1 Stupor

e-Table 6. Hierarchical infection category codes as mapped from ICD-9-CM to ICD-10-CM by General Equivalence Mappings

Category	ICD-9-CM codes	ICD-10-codes
Septicemia	038, 78552, 99592	A409, A412, A4101, A4102, A411, A403, A414, A4150, A413, A4151, A4152, A4153, A4159, A4189, A419, R6521, R6520
Heart infection	420, 421	I32, I309, I300, I308, I330, I39, I339
Peritoneal infection	00845, 567, 56983	A0471, A0472, K67, K658, K650, K651, K652, K650, K6812, K6819, K689, K653, K654, K658, K631
Lung infection	010, 011, 012, 0310, 481, 482, 485, 486	A157, A156, A155, A154, A158, A310, A311, A312, A318, A319, J13, J181, J150, J151, J14, J154, J153, J1520, J15211, J15212, J1529, J158, J155, J156, A481, J180, J189
Fungal infection	1120, 1124, 1125, 114, 115, 116, 117, 118	B370, B3783, B371, B377, B380, B383, B384, B3889, B381, B382, B389, B394, G02, H32, B392, B393, B395, J17, B399, B409, B410, B419, B480, B481, B420, B421, B427, B429, B439, B449, B470, B450, B457, B459, B482, B469, B488, B49
Bacteremia	018, 0312, 7907	A192, A198, A199, R7881
Central nervous system infection	013, 036, 094, 320, 322, 325, 3240, 3241, 3249	A170, A171, A1781, A1782, A1789, A179, A390, A3981, A5211, A5213, A5214, A5219, A523, G000, G001, G002, G003, G01, G008, G009, G042, G030, G038, G031, G039, G08, G060, G061, G062
Other infection	001, 002, 0045, 005, 008 (except 00845), 009, 020, 021, 022, 023, 024, 025, 026, 027, 0318, 0319, 032, 033, 034, 037, 039, 040, 041, 090, 091, 092, 093, 095, 096, 097, 100, 101, 102, 103, 104, 49121, 494,	A000, A001, A009, A0100, A011, A012, A013, A014, A030, A031, A032, A033, A038, A039, A050, A051, A052, A058, A053, A055, A054, A059, A044, A040, A041, A042, A043, A048, A045, A046, A049, A080, A082, A0811, A0819, A0831, A0832, A0839, A088, A09, A200, A201, A207, A202, A208, A209, A210, A213, A212, A211, A217, A218, A219, A220, A221, A222, A227, A228, A229, A230, A231, A232, A233, A238, A239, A240, A243, A249, A250, A251, A259, A3211, A3212, A327, A3281, A3289, A329, A267, A268, A269, A280, A288, A289, A360, A361, A3689, A362, A3686, A3681, A3685, A363, A3682, A3683, A3684, A369, A3700, A3710, A3780, A3790, L081, A420, A421, A422, B479, A4281, A4282, A4289, A438, A429, A439, B471, A480, A488, K9081, A4851, A4852, M60009, A483, B955, B950, B951, B954, B952, B958, B9561, B9562, B957, B953, B961, B9621, B9622, B9623, B9620, B9629,

Category	ICD-9-CM codes	ICD-10-codes
	510, 513, 730, 9966, 9985, 9993	B963, B964, B965, A493, B960, B966, B967, B9689, B9681, A5009, A501, A502, A5031, A5040, A5045, A5042, A5041, A5049, A5052, A5057, A5059, A506, A507, A509, A510, A511, A512, A5131, A5139, A5149, A5143, A5146, A5145, A5141, A5132, A515, A5201, A5202, A5203, A5206, A5209, A5200, A5271, A5272, A5274, A5275, A5277, A5278, A5273, A5276, A5279, A528, A529, A530, A539, A270, A2781, A2789, A279, A690, A691, A660, A661, A662, A663, A664, A665, A666, A667, A668, A669, A670, A671, A672, A673, A679, A65, A698, A699, J441, J479, J471, J860, J869, J850, J851, J852, J853, T8579XA, T826XXA, T827XXA, T85730A, T85731A, T85732A, T85733A, T85734A, T85735A, T85738A, T83510A, T83511A, T83512A, T83518A, T83590A, T83591A, T83592A, T83593A, T83598A, T8361XA, T8362XA, T8369XA, T8450XA, T8460XA, T847XXA, T8571XA, T814XXA, K6811, T80219A, T80211A, T80212A, T8022XA, T8029XA, T880XXA
Genitourinary infection	016, 098, 590, 597, 5990, 601, 614, 615, 616	A1811, A1810, A1812, A1813, A1815, A1814, A1817, A1816, A1818, A5400, A5429, A5401, A5422, A5423, A5403, A5424, A5421, A5442, N110, N151, N340, N341, N342, N343, N390, N410, N411, N412, N413, N51, N414, N418, N419, N7001, N7002, N7003, N7011, N7012, N7013, N7091, N7092, N7093, N730, N731, N732, N733, N736, N734, N738, N739, N710, N711, N719, N72, N760, N761, N762, N763, N771, N750, N751, N764, N766, N770, N7681, N759, N765, N7689
Soft tissue infection	015, 017, 0311, 035, 451, 110, 111, 1123, 681, 682, 683, 686, 7110, 730	A1801, A1802, A1803, A5431, A5432, A5439, A5433, A5449, A5441, A5440, A545, A46, I8000, I8010, I80209, I803, I80219, I808, I809, B350, B351, B352, B356, B353, B354, B355, B358, B359, B360, B361, B362, B363, B368, B369, B372, L03019, L03029, L03039, L03049, K122, L03211, L03212, L03213, L03221, L03222, L03319, L03329, L03129, L03119, L03317, L03811, L03818, L03891, L03898, L0390, L0391, L049, L080, L88, L0889, L980, L089, M0000, M0010, M0020, M0080, M009, M00019, M00219, M00819, M00029, M00129, M00229, M00829, M00039, M00139, M00239, M00839, M00049, M00149, M00249, M00849, M00059, M00159, M00259, M00859, M00069, M00169, M00269, M00869, M00079, M00179, M00279, M00879, M0008, M0018, M0028, M0088, M0009, M0019, M0029, M0089, M8610, M8620, M86119, M86219, M86129, M86229, M86139, M86239, M86149, M86249, M86159, M86259, M86169, M86269, M86179, M86279, M8618, M8628, M8619, M8629, M8660, M86619, M86629, M86639, M86642, M86659, M86669, M86679, M8668, M8669, M869, M4620, M8960, M89619, M89629, M89639, M89649, M89659, M89669, M89679, M8968,

Category	ICD-9-CM codes	ICD-10-codes
		M8969, M9080, M90819, M90829, M90839, M90849, M90859, M90869, M90879, M9088, M9089, M4630
Gastrointestinal infection	003, 014, 540, 541, 542, 56201, 56203, 56211, 56213, 566, 5695, 5720, 5721, 5750	A020, A0220, A0229, A028, A029, A1831, A1832, A1839, K352, K353, K3580, K3589, K37, K36, K5712, K5713, K5732, K5733, K610, K611, K613, K630, K750, K751, K810
Upper respiratory infection	461, 462, 463, 464, 465	J0100, J0110, J0120, J0130, J0140, J0190, J029, J0390, J040, J050, J0410, J0411, J042, J0510, J0511, J0430, J0431, J060, J069, Other infection, A000, A001, A009, A0100, A011, A012, A013, A014, A030, A031, A032, A033, A038, A039, A050, A051, A052, A058, A053, A055, A054, A059, A044, A040, A041, A042, A043, A048, A045, A046, A049, A080, A082, A0811, A0819, A0831, A0832, A0839, A088, A09, A200, A201, A207, A202, A208, A209, A210, A213, A212, A211, A217, A218, A219, A220, A221, A222, A227, A228, A229, A230, A231, A232, A233, A238, A239, A240, A243, A249, A250, A251, A259, A3211, A3212, A327, A3281, A3289, A329, A267, A268, A269, A280, A288, A289, A360, A361, A3689, A362, A3686, A3681, A3685, A363, A3682, A3683, A3684, A369, A3700, A3710, A3780, A3790, L081, A420, A421, A422, B479, A4281, A4282, A4289, A438, A429, A439, B471, A480, A488, K9081, A4851, A4852, M60009, A483, B955, B950, B951, B954, B952, B958, B9561, B9562, B957, B953, B961, B9621, B9622, B9623, B9620, B9629, B963, B964, B965, A493, B960, B966, B967, B9689, B9681, A5009, A501, A502, A5031, A5040, A5045, A5042, A5041, A5049, A5052, A5057, A5059, A506, A507, A509, A510, A511, A512, A5131, A5139, A5149, A5143, A5146, A5145, A5141, A5132, A515, A5201, A5202, A5203, A5206, A5209, A5200, A5271, A5272, A5274, A5275, A5277, A5278, A5273, A5276, A5279, A528, A529, A530, A539, A270, A2781, A2789, A279, A690, A691, A660, A661, A662, A663, A664, A665, A666, A667, A668, A669, A670, A671, A672, A673, A679, A65, A698, A699, J441, J479, J471, J860, J869, J850, J851, J852, J853, T8579XA, T826XXA, T827XXA, T85730A, T85731A, T85732A, T85733A, T85734A, T85735A, T85738A, T83510A, T83511A, T83512A, T83518A, T83590A, T83591A, T83592A, T83593A, T83598A, T8361XA, T8362XA, T8369XA, T8450XA, T8460XA, T847XXA, T8571XA, T814XXA, K6811, T80219A, T80211A, T80212A, T8022XA, T8029XA, T880XXA

*ICD-10-CM crosswalk from ICD-9-CM based upon Diagnosis Code Set General Equivalence Mappings (GEMs) available at:
https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs

e-Table 7: Order of assignment to infection source based upon magnitude of parameter estimate

Infection	Parameter Estimate	p-value	Odds Ratio	OR 95% CI	
Peritoneal	0.788	< 0.001	2.198	2.092	2.310
Heart	0.650	< 0.001	1.915	1.766	2.076
Lung	0.324	< 0.001	1.383	1.361	1.406
Fungal	0.216	< 0.001	1.242	1.185	1.301
Central Nervous System	0.072	0.257	1.075	0.948	1.216
Genitourinary	0.026	0.002	1.027	1.009	1.044
Bacteremia	-0.183	0.090	0.833	0.671	1.025
Skin	-0.257	< 0.001	0.773	0.740	0.808
Gastrointestinal	-0.317	< 0.001	0.729	0.685	0.774
Other	-0.423	< 0.001	0.655	0.644	0.666
Upper respiratory	-0.838	< 0.001	0.432	0.385	0.484

e-Table 8: Compliance Model Parameter Estimates

Compliance model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
Intercept	-0.823	0.108	-1.035	-0.610	< 0.001
Initial lactate level					
• Not collected	-5.583	0.271	-6.114	-5.053	< 0.001
• ≤ 2.0 mmol/L	1.956	0.034	1.888	2.023	< 0.001
• > 2.0 and < 4.0 mmol/L	1.761	0.033	1.697	1.825	< 0.001
• ≥ 4.0 mmol/L (referent)	0.000				
Persistent hypotension	-0.418	0.158	-0.727	-0.108	0.008
Year - Quarter					
• 2015Q4	0.104	0.050	0.006	0.203	0.038
• 2016Q1	0.594	0.048	0.500	0.688	< 0.001
• 2016Q2	0.800	0.048	0.705	0.895	< 0.001
• 2016Q3	-0.429	0.047	-0.521	-0.338	< 0.001
• 2016Q4	-0.308	0.046	-0.398	-0.219	< 0.001
• 2017Q1 (referent)	0.000				
Septic shock	0.566	0.038	0.492	0.640	< 0.001
Acquired immune deficiency syndrome	0.119	0.080	-0.039	0.276	0.139
Alcohol abuse	-0.056	0.026	-0.107	-0.005	0.032
Deficiency anemias	0.014	0.010	-0.005	0.033	0.140
Rheumatoid arthritis/collagen vascular diseases	0.035	0.021	-0.005	0.075	0.085
Chronic blood loss anemia	-0.112	0.041	-0.193	-0.032	0.006
Congestive heart failure	-0.259	0.022	-0.302	-0.216	< 0.001
Chronic pulmonary disease	0.018	0.010	0.000	0.037	0.055
Coagulopathy	0.018	0.013	-0.007	0.043	0.154
Depression	0.021	0.013	-0.004	0.046	0.096
Diabetes without chronic complications	0.004	0.012	-0.019	0.027	0.714
Diabetes with chronic complications	0.003	0.012	-0.020	0.026	0.818
Drug abuse	0.011	0.030	-0.048	0.071	0.708
Hypertension	0.035	0.010	0.015	0.055	0.001
Hypothyroidism	-0.002	0.011	-0.024	0.021	0.888
Liver disease	-0.027	0.020	-0.067	0.012	0.180
Lymphoma	0.045	0.033	-0.019	0.109	0.169
Fluid and electrolyte disorders	-0.008	0.010	-0.028	0.013	0.453
Metastatic cancer	-0.045	0.021	-0.087	-0.003	0.036
Other neurological disorders	0.066	0.011	0.044	0.087	< 0.001
Obesity	-0.137	0.013	-0.162	-0.112	< 0.001

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Compliance model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
Paralysis	0.002	0.015	-0.028	0.032	0.894
Peripheral vascular disease	-0.048	0.014	-0.076	-0.020	0.001
Psychoses	0.102	0.021	0.062	0.142	< 0.001
Pulmonary circulation disease	-0.087	0.032	-0.150	-0.024	0.007
Renal failure	-0.501	0.056	-0.612	-0.390	< 0.001
Solid tumor without metastasis	-0.006	0.022	-0.049	0.036	0.776
Peptic ulcer disease excluding bleeding	-0.091	0.037	-0.164	-0.019	0.014
Valvular disease	-0.056	0.015	-0.086	-0.026	0.000
Weight loss	-0.063	0.012	-0.088	-0.039	< 0.001
Critical access hospital	-0.177	0.079	-0.332	-0.021	0.026
Hospital accreditation					
• AOA/HFAP	-0.196	0.086	-0.365	-0.026	0.023
• CIHQ	0.226	0.216	-0.198	0.650	0.297
• DNV	-0.190	0.058	-0.303	-0.076	0.001
• NONE	-0.437	0.069	-0.572	-0.302	< 0.001
• TJC (referent)	0.000				
Square root of hospital certified bed count	-0.012	0.003	-0.018	-0.006	< 0.001
Urban hospital location	0.168	0.040	0.089	0.247	< 0.001
Site of infection					
• Bacteremia	-0.343	0.220	-0.774	0.087	0.118
• Central nervous system	-0.148	0.122	-0.387	0.090	0.222
• Fungal	-0.107	0.094	-0.290	0.077	0.255
• Gastrointestinal	-0.279	0.096	-0.467	-0.091	0.004
• Genitourinary	-0.019	0.087	-0.190	0.151	0.823
• Heart	0.013	0.100	-0.183	0.209	0.900
• Lung	0.024	0.087	-0.146	0.194	0.784
• Missing	-0.127	0.110	-0.343	0.088	0.247
• Other	-0.076	0.088	-0.248	0.096	0.387
• Peritoneal	-0.555	0.093	-0.737	-0.373	< 0.001
• Septicemia	-0.122	0.087	-0.293	0.048	0.159
• Soft tissue	-0.119	0.092	-0.299	0.061	0.196
• Upper respiratory tract (referent)	0.000				
Cardiovascular organ failure	-0.253	0.015	-0.283	-0.224	< 0.001
Hematologic organ failure	-0.255	0.033	-0.319	-0.191	< 0.001
Metabolic organ failure	0.079	0.011	0.057	0.102	< 0.001
Neurologic organ failure	-0.042	0.015	-0.072	-0.013	0.005
Renal organ failure	-0.136	0.012	-0.160	-0.113	< 0.001
Respiratory organ failure	-0.114	0.010	-0.134	-0.094	< 0.001
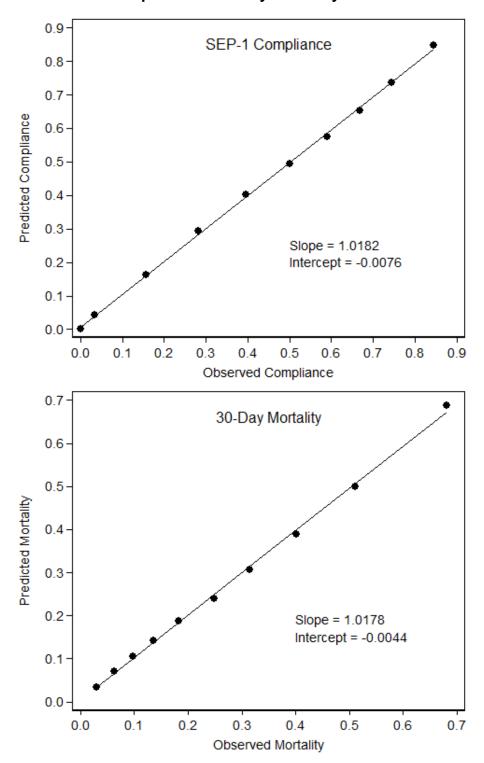
Compliance model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
Patient age	-0.001	0.000	-0.002	0.000	0.003
Patient Hispanic ethnicity (Yes)	0.072	0.023	0.027	0.117	0.002
Patient sex (Male)	0.068	0.009	0.050	0.085	< 0.001
Patient race					
• American Indian/Alaska Native	0.070	0.061	-0.050	0.189	0.253
• Asian	0.074	0.034	0.007	0.141	0.029
• Black/African American	-0.049	0.016	-0.080	-0.019	0.002
• Native Hawaiian/Pacific Islander	0.220	0.088	0.047	0.393	0.013
• Unable to Determine	-0.026	0.027	-0.079	0.026	0.320
• White (referent)	0.000				
Septic shock vs. Discharge quarter					
• 2015Q4 vs. Septic Shock	-2.306	0.049	-2.403	-2.210	< 0.001
• 2016Q1 vs. Septic Shock	-2.423	0.048	-2.518	-2.328	< 0.001
• 2016Q2 vs. Septic Shock	-2.407	0.048	-2.501	-2.313	< 0.001
• 2016Q3 vs. Septic Shock	-0.118	0.052	-0.220	-0.015	0.024
• 2016Q4 vs. Septic Shock	-0.084	0.051	-0.184	0.017	0.103
• 2017Q1 (referent) vs. Septic Shock	0.000				
Initial lactate level vs. Discharge quarter					
• 2015Q4 vs. Not collected	-0.268	0.540	-1.326	0.791	0.620
• 2016Q1 vs. Not collected	-0.699	0.543	-1.764	0.365	0.198
• 2016Q2 vs. Not collected	-0.902	0.562	-2.003	0.199	0.108
• 2016Q3 vs. Not collected	0.315	0.396	-0.461	1.090	0.426
• 2016Q4 vs. Not collected	0.209	0.397	-0.569	0.988	0.598
• 2017Q1 (referent) vs. Not collected	0.000				
• 2015Q4 vs. ≤ 2.0 mmol/L	-0.479	0.053	-0.582	-0.376	< 0.001
• 2016Q1 vs. ≤ 2.0 mmol/L	-0.775	0.051	-0.874	-0.675	< 0.001
• 2016Q2 vs. ≤ 2.0 mmol/L	-0.874	0.051	-0.974	-0.774	< 0.001
• 2016Q3 vs. ≤ 2.0 mmol/L	0.234	0.051	0.135	0.334	< 0.001
• 2016Q4 vs. ≤ 2.0 mmol/L	0.196	0.050	0.098	0.293	< 0.001
• 2017Q1 (referent) vs. ≤ 2.0 mmol/L	0.000				
• 2015Q4 vs. > 2.0 and < 4.0 mmol/L	-1.301	0.052	-1.404	-1.199	< 0.001
• 2016Q1 vs. > 2.0 and < 4.0 mmol/L	-1.347	0.050	-1.444	-1.249	< 0.001
• 2016Q2 vs. > 2.0 and < 4.0 mmol/L	-1.190	0.050	-1.288	-1.093	< 0.001
• 2016Q3 vs. > 2.0 and < 4.0 mmol/L	0.059	0.049	-0.036	0.155	0.223
• 2016Q4 vs. > 2.0 and < 4.0 mmol/L	0.163	0.048	0.070	0.256	0.001
• 2017Q1 (referent) vs. > 2.0 and < 4.0 mmol/L	0.000				
• 2015Q4 vs. ≥ 4.0 mmol/L (referent)	0.000				
• 2016Q1 vs. ≥ 4.0 mmol/L (referent)	0.000				

Compliance model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
• 2016Q2 vs. ≥ 4.0 mmol/L (referent)	0.000				
• 2016Q3 vs. ≥ 4.0 mmol/L (referent)	0.000				
• 2016Q4 vs. ≥ 4.0 mmol/L (referent)	0.000				
• 2017Q1 (referent) vs. ≥ 4.0 mmol/L (referent)	0.000				
Persistent hypotension vs. Discharge quarter					
• 2015Q4 vs. Persistent hypotension	1.174	0.079	1.019	1.330	< 0.001
• 2016Q1 vs. Persistent hypotension	1.221	0.077	1.071	1.371	< 0.001
• 2016Q2 vs. Persistent hypotension	1.169	0.076	1.021	1.318	< 0.001
• 2016Q3 vs. Persistent hypotension	0.037	0.078	-0.116	0.191	0.634
• 2016Q4 vs. Persistent hypotension	-0.006	0.076	-0.156	0.144	0.939
• 2017Q1 (referent) vs. Persistent hypotension	0.000				
Congestive heart failure vs. Discharge quarter					
• 2015Q4 vs. Congestive heart failure	0.221	0.032	0.158	0.285	< 0.001
• 2016Q1 vs. Congestive heart failure	0.185	0.031	0.124	0.246	< 0.001
• 2016Q2 vs. Congestive heart failure	0.238	0.031	0.176	0.299	< 0.001
• 2016Q3 vs. Congestive heart failure	-0.024	0.032	-0.088	0.039	0.458
• 2016Q4 vs. Congestive heart failure	-0.035	0.031	-0.097	0.026	0.260
• 2017Q1 (referent) vs. Congestive heart failure	0.000				
Septic shock vs. Renal organ failure	0.274	0.023	0.229	0.318	< 0.001
Septic shock vs. Hematologic organ failure	0.461	0.051	0.362	0.561	< 0.001
Persistent hypotension vs. Septic shock	-0.990	0.152	-1.288	-0.692	< 0.001
Persistent hypotension vs. Respiratory organ failure	0.599	0.041	0.519	0.679	< 0.001
Renal failure vs. Renal organ failure	0.190	0.020	0.152	0.229	< 0.001
Renal failure vs. Patient age	0.004	0.001	0.002	0.005	< 0.001

e-Figure 2: Calibration plots for observed vs. predicted compliance with the SEP-1 bundle and observed vs. predicted 30-day mortality

e-Table 9: Thirty-day mortality hierarchical generalized linear model (HGLM) parameter estimates

Mortality model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
Intercept	-6.602	0.200	-6.993	-6.210	< 0.001
Septic shock	-0.030	0.022	-0.073	0.012	0.156
Initial lactate level					
• Not collected	-0.272	0.025	-0.321	-0.223	< 0.001
• ≤ 2.0 mmol/L	-0.545	0.023	-0.591	-0.500	< 0.001
• > 2.0 and < 4.0 mmol/L	-0.593	0.022	-0.637	-0.550	< 0.001
• ≥ 4.0 mmol/L (referent)	0.000				
Persistent hypotension	0.134	0.021	0.093	0.176	< 0.001
Discharge quarter					
• 2015Q4	-0.007	0.016	-0.037	0.024	0.662
• 2016Q1	0.068	0.015	0.038	0.097	< 0.001
• 2016Q2	-0.024	0.015	-0.054	0.006	0.118
• 2016Q3	-0.087	0.015	-0.117	-0.058	< 0.001
• 2016Q4	-0.023	0.015	-0.052	0.006	0.114
• 2017Q1 (referent)	0.000				
Compliance	-0.188	0.011	-0.208	-0.167	< 0.001
Deficiency anemias	-0.089	0.010	-0.108	-0.069	< 0.001
Congestive heart failure	0.408	0.020	0.368	0.448	< 0.001
Coagulopathy	0.884	0.075	0.738	1.031	< 0.001
Depression	-0.090	0.014	-0.117	-0.063	< 0.001
Diabetes without chronic complications	-0.047	0.012	-0.071	-0.023	< 0.001
Diabetes with chronic complications	-0.093	0.012	-0.117	-0.070	< 0.001
Drug abuse	-0.301	0.037	-0.373	-0.229	< 0.001
Hypertension	-0.280	0.012	-0.303	-0.256	< 0.001
Hypothyroidism	-0.069	0.012	-0.092	-0.046	< 0.001
Liver disease	0.311	0.020	0.273	0.349	< 0.001
Lymphoma	0.433	0.031	0.372	0.494	< 0.001
Fluid and electrolyte disorders	0.172	0.011	0.150	0.194	< 0.001
Metastatic cancer	3.549	0.141	3.272	3.827	< 0.001
Other neurological disorders	0.174	0.011	0.152	0.196	< 0.001
Obesity	-0.304	0.014	-0.332	-0.276	< 0.001
Paralysis	0.199	0.016	0.168	0.230	< 0.001
Peripheral vascular disease	0.193	0.014	0.165	0.220	< 0.001
Psychoses	-0.061	0.023	-0.106	-0.015	0.009
Pulmonary circulation disease	0.450	0.030	0.391	0.508	< 0.001

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Mortality model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
Renal failure	1.327	0.064	1.202	1.452	< 0.001
Solid tumor without metastasis	2.086	0.158	1.777	2.395	< 0.001
Peptic ulcer disease excluding bleeding	-0.130	0.036	-0.200	-0.060	< 0.001
Weight loss	0.879	0.317	0.259	1.500	0.006
Urban hospital location	-0.118	0.017	-0.151	-0.085	< 0.001
Hospital accreditation					
• AOA/HFAP	0.059	0.038	-0.016	0.134	0.121
• CIHQ	0.030	0.097	-0.161	0.220	0.761
• DNV	-0.050	0.025	-0.100	0.000	0.050
• NONE	0.168	0.035	0.099	0.237	< 0.001
• TJC (referent)	0.000				
Hospital region					
• New England	0.121	0.052	0.019	0.223	0.020
• Northeast	0.421	0.045	0.333	0.509	< 0.001
• Mideast	0.205	0.043	0.121	0.289	< 0.001
• Southeast	0.377	0.040	0.298	0.456	< 0.001
• Great Lakes	0.085	0.041	0.004	0.165	0.041
• South	0.257	0.042	0.175	0.340	< 0.001
• Midwest	0.060	0.049	-0.036	0.155	0.220
• Mountain West	-0.113	0.055	-0.220	-0.005	0.040
• Southwest	0.089	0.043	0.005	0.173	0.038
• Northwest (referent)	0.000				
Site of infection					
• Bacteremia	0.127	0.413	-0.682	0.935	0.759
• Central nervous system	1.256	0.228	0.810	1.702	< 0.001
• Fungal	1.099	0.196	0.714	1.484	< 0.001
• Gastrointestinal	0.642	0.200	0.251	1.034	0.001
• Genitourinary	0.860	0.190	0.488	1.231	< 0.001
• Heart	1.659	0.200	1.267	2.052	< 0.001
• Lung	1.357	0.189	0.986	1.728	< 0.001
• Missing	0.051	0.233	-0.407	0.508	0.829
• Other	0.839	0.190	0.466	1.213	< 0.001
• Peritoneal	1.794	0.194	1.414	2.175	< 0.001
• Septicemia	1.197	0.190	0.826	1.569	< 0.001
• Soft tissue	0.906	0.196	0.522	1.290	< 0.001
• Upper respiratory tract (referent)	0.000				
Cardiovascular organ failure	0.243	0.014	0.215	0.271	< 0.001
Hematologic organ failure	1.469	0.127	1.220	1.718	< 0.001

Mortality model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
Metabolic organ failure	0.096	0.020	0.056	0.136	< 0.001
Neurologic organ failure	1.526	0.085	1.361	1.692	< 0.001
Renal organ failure	0.431	0.011	0.409	0.454	< 0.001
Respiratory organ failure	1.570	0.260	1.061	2.080	< 0.001
Patient sex (Male)	-0.054	0.009	-0.072	-0.036	< 0.001
Patient race					
• American Indian/Alaska Native	-0.069	0.063	-0.192	0.054	0.269
• Asian	-0.105	0.034	-0.171	-0.038	0.002
• Black/African American	0.026	0.015	-0.004	0.056	0.088
• Native Hawaiian/Pacific Islander	-0.043	0.092	-0.223	0.136	0.636
• Unable to Determine	0.011	0.026	-0.040	0.061	0.679
• White (referent)	0.000				
Patient age	0.048	0.001	0.047	0.050	< 0.001
Congestive heart failure vs. Hypertension	0.070	0.021	0.028	0.112	0.001
Congestive heart failure vs. Respiratory organ failure	-0.445	0.019	-0.481	-0.408	< 0.001
Weight loss vs. Respiratory organ failure	-0.378	0.022	-0.421	-0.334	< 0.001
Renal failure vs. Renal organ failure	-0.422	0.019	-0.460	-0.384	< 0.001
Weight loss vs. Hematologic organ failure	-0.476	0.049	-0.573	-0.380	< 0.001
Metastatic cancer vs. Renal failure	-0.261	0.045	-0.348	-0.173	< 0.001
Respiratory organ failure vs. Site of infection					
• Respiratory organ failure vs. Bacteremia	0.069	0.591	-1.090	1.228	0.907
• Respiratory organ failure vs. Central nervous system	-0.450	0.314	-1.065	0.166	0.152
• Respiratory organ failure vs. Fungal	-0.481	0.270	-1.009	0.048	0.075
• Respiratory organ failure vs. Gastrointestinal	-0.295	0.278	-0.840	0.251	0.290
• Respiratory organ failure vs. Genitourinary	-0.128	0.261	-0.639	0.383	0.623
• Respiratory organ failure vs. Heart	-0.256	0.276	-0.797	0.285	0.354
• Respiratory organ failure vs. Lung	-0.630	0.260	-1.140	-0.120	0.016
• Respiratory organ failure vs. Missing	-0.020	0.359	-0.724	0.685	0.956
• Respiratory organ failure vs. Other	-0.330	0.262	-0.844	0.183	0.207
• Respiratory organ failure vs. Peritoneal	-0.560	0.266	-1.080	-0.039	0.035
• Respiratory organ failure vs. Septicemia	-0.180	0.260	-0.690	0.330	0.489
• Respiratory organ failure vs. Soft tissue	-0.219	0.272	-0.752	0.315	0.422
• Respiratory organ failure vs. Upper respiratory tract (referent)	0.000				
Weight loss vs. Site of infection					
• Weight loss vs. Bacteremia	-0.067	0.687	-1.414	1.279	0.922
• Weight loss vs. Central nervous system	-0.413	0.383	-1.164	0.339	0.282

Mortality model fixed-effect parameters	Estimate	Standard Error	95% CI		p-value
• Weight loss vs. Fungal	-0.383	0.324	-1.018	0.253	0.238
• Weight loss vs. Gastrointestinal	-0.376	0.336	-1.033	0.282	0.263
• Weight loss vs. Genitourinary	-0.368	0.316	-0.988	0.252	0.245
• Weight loss vs. Heart	-0.521	0.335	-1.178	0.135	0.120
• Weight loss vs. Lung	-0.356	0.316	-0.975	0.264	0.261
• Weight loss vs. Missing	0.610	0.411	-0.196	1.416	0.138
• Weight loss vs. Other	-0.296	0.318	-0.920	0.327	0.352
• Weight loss vs. Peritoneal	-0.990	0.321	-1.619	-0.361	0.002
• Weight loss vs. Septicemia	-0.479	0.316	-1.099	0.141	0.130
• Weight loss vs. Soft tissue	-0.152	0.327	-0.793	0.489	0.642
• Weight loss vs. Upper respiratory tract (referent)	0.000				
Weight loss vs. Initial lactate level					
• Weight loss vs. Not collected	0.158	0.037	0.086	0.230	< 0.001
• Weight loss vs. ≤ 2.0 mmol/L	0.284	0.032	0.222	0.346	< 0.001
• Weight loss vs. > 2.0 and < 4.0 mmol/L	0.395	0.030	0.335	0.455	< 0.001
• Weight loss vs. ≥ 4.0 mmol/L (referent)	0.000				
Septic shock vs. Initial lactate level					
• Septic shock vs. Not collected	0.211	0.127	-0.038	0.460	0.097
• Septic shock vs. ≤ 2.0 mmol/L	0.157	0.030	0.098	0.217	< 0.001
• Septic shock vs. > 2.0 and < 4.0 mmol/L	0.358	0.029	0.301	0.415	< 0.001
• Septic shock vs. ≥ 4.0 mmol/L (referent)	0.000				
Metabolic organ failure vs. Initial lactate level					
• Metabolic organ failure vs. Not collected	0.208	0.032	0.146	0.270	< 0.001
• Metabolic organ failure vs. ≤ 2.0 mmol/L	0.227	0.029	0.171	0.283	< 0.001
• Metabolic organ failure vs. > 2.0 and < 4.0 mmol/L	0.029	0.025	-0.020	0.079	0.242
• Metabolic organ failure vs. ≥ 4.0 mmol/L (referent)	0.000				
Hematologic organ failure vs. Patient age	-0.006	0.002	-0.010	-0.003	< 0.001
Metastatic cancer vs. Patient age	-0.028	0.002	-0.031	-0.024	< 0.001
Neurologic organ failure vs. Patient age	-0.013	0.001	-0.015	-0.011	< 0.001
Renal failure vs. Patient age	-0.010	0.001	-0.012	-0.009	< 0.001
Coagulopathy vs. Patient age	-0.009	0.001	-0.011	-0.007	< 0.001
Solid tumor without metastasis vs. Patient age	-0.020	0.002	-0.024	-0.016	< 0.001

e-Table 10: Standard-match SEP-1 matched distributions where the matching is based on a greedy nearest neighbor with a caliper of 0.40 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.25

Variables	All Cases (N = 245,740)	Compliant (N = 122,870)	Non-Compliant (N = 122,870)
Percentage of cases	100.0	50.0	50.0
Hospital certified bed count			
• Mean	302.7	293.3	312.1
• Median	238	231	242
• Standard Deviation	265.9	258.7	272.5
• Interquartile Range	133 - 385	130 - 375	140 - 397
Hospital accreditation - N (%)			
• AOA/HFAP	10,201 (4.2)	4,910 (4.0)	5,291 (4.3)
• CIHQ	1,668 (0.7)	941 (0.8)	727 (0.6)
• DNV	23,183 (9.4)	11,034 (9.0)	12,149 (9.9)
• NONE	6,667 (2.7)	3,070 (2.5)	3,597 (2.9)
• TJC	204,021 (83.0)	102,915 (83.8)	101,106 (82.3)
Critical access hospital - N (%)	3,856 (1.6)	1,923 (1.6)	1,933 (1.6)
Urban hospital location - N (%)	186,117 (75.7)	92,831 (75.6)	93,286 (75.9)
Hospital region - N (%)			
• New England	8,773 (3.6)	4,310 (3.5)	4,463 (3.6)
• Northeast	20,038 (8.2)	9,754 (7.9)	10,284 (8.4)
• Mideast	34,472 (14.0)	17,579 (14.3)	16,893 (13.7)
• Southeast	54,877 (22.3)	27,822 (22.6)	27,055 (22.0)
• Great Lakes	42,047 (17.1)	19,777 (16.1)	22,270 (18.1)
• South	28,433 (11.6)	14,336 (11.7)	14,097 (11.5)
• Midwest	11,655 (4.7)	5,956 (4.8)	5,699 (4.6)
• Mountain West	7,028 (2.9)	3,474 (2.8)	3,554 (2.9)
• Southwest	30,257 (12.3)	15,902 (12.9)	14,355 (11.7)
• Northwest	8,160 (3.3)	3,960 (3.2)	4,200 (3.4)
Discharge quarter - N (%)			
• 2015Q4	38,784 (15.8)	16,165 (13.2)	22,619 (18.4)
• 2016Q1	42,300 (17.2)	19,402 (15.8)	22,898 (18.6)
• 2016Q2	41,548 (16.9)	20,633 (16.8)	20,915 (17.0)
• 2016Q3	36,986 (15.1)	18,967 (15.4)	18,019 (14.7)
• 2016Q4	40,945 (16.7)	22,102 (18.0)	18,843 (15.3)
• 2017Q1	45,177 (18.4)	25,601 (20.8)	19,576 (15.9)

Variables	All Cases (N = 245,740)	Compliant (N = 122,870)	Non-Compliant (N = 122,870)
Patient Hispanic ethnicity (Yes) - N (%)	13,385 (5.4)	6,638 (5.4)	6,747 (5.5)
Patient sex (Male) - N (%)	125,812 (51.2)	63,113 (51.4)	62,699 (51.0)
Patient race - N (%)			
• American Indian/Alaska Native	1,568 (0.6)	748 (0.6)	820 (0.7)
• Asian	5,471 (2.2)	3,079 (2.5)	2,392 (1.9)
• Black/African American	26,649 (10.8)	12,726 (10.4)	13,923 (11.3)
• Native Hawaiian/Pacific Islander	724 (0.3)	406 (0.3)	318 (0.3)
• Unable to Determine	8,504 (3.5)	4,305 (3.5)	4,199 (3.4)
• White	202,824 (82.5)	101,606 (82.7)	101,218 (82.4)
Patient age at admission (Years)			
• Mean	73.6	73.6	73.6
• Median	75	75	74
• Standard Deviation	13.0	13.0	13.0
• Interquartile Range	66 - 83	66 - 83	66 - 83
Persistent hypotension (=Yes) - N (%)	12,964 (5.3)	4,634 (3.8)	8,330 (6.8)
Initial lactate level - N (%)			
• Not collected	0 (0.0)	0 (0.0)	0 (0.0)
• ≤ 2.0 mmol/L	90,784 (36.9)	50,285 (40.9)	40,499 (33.0)
• > 2.0 and < 4.0 mmol/L	122,179 (49.7)	61,093 (49.7)	61,086 (49.7)
• ≥ 4.0 mmol/L	32,777 (13.3)	11,492 (9.4)	21,285 (17.3)
Severe sepsis - N (%)	196,455 (79.9)	104,264 (84.9)	92,191 (75.0)
Septic shock - N (%)	49,285 (20.1)	18,606 (15.1)	30,679 (25.0)
Site of infection - N (%)			
• Bacteremia	110 (0.0)	49 (0.0)	61 (0.0)
• Central nervous system	607 (0.2)	293 (0.2)	314 (0.3)
• Fungal	3,391 (1.4)	1,634 (1.3)	1,757 (1.4)
• Gastrointestinal	2,542 (1.0)	1,148 (0.9)	1,394 (1.1)
• Genitourinary	60,938 (24.8)	30,975 (25.2)	29,963 (24.4)
• Heart	1,807 (0.7)	871 (0.7)	936 (0.8)
• Lung	86,578 (35.2)	44,450 (36.2)	42,128 (34.3)
• Missing	941 (0.4)	464 (0.4)	477 (0.4)
• Other	21,777 (8.9)	10,985 (8.9)	10,792 (8.8)
• Peritoneal	4,001 (1.6)	1,576 (1.3)	2,425 (2.0)
• Septicemia only	57,895 (23.6)	27,884 (22.7)	30,011 (24.4)
• Soft tissue	4,536 (1.8)	2,222 (1.8)	2,314 (1.9)
• Upper respiratory tract	617 (0.3)	319 (0.3)	298 (0.2)
Organ failures - N (%)			

Variables	All Cases (N = 245,740)	Compliant (N = 122,870)	Non-Compliant (N = 122,870)
• Cardiovascular	22,641 (9.2)	10,188 (8.3)	12,453 (10.1)
• Hematologic	7,750 (3.2)	3,138 (2.6)	4,612 (3.8)
• Metabolic	63,996 (26.0)	30,139 (24.5)	33,857 (27.6)
• Neurologic	22,923 (9.3)	10,990 (8.9)	11,933 (9.7)
• Renal	114,529 (46.6)	54,655 (44.5)	59,874 (48.7)
• Respiratory	73,062 (29.7)	34,501 (28.1)	38,561 (31.4)
Comorbidities - N (%)			
• Acquired immune deficiency syndrome	728 (0.3)	367 (0.3)	361 (0.3)
• Alcohol abuse	7,219 (2.9)	3,430 (2.8)	3,789 (3.1)
• Chronic blood loss anemia	2,712 (1.1)	1,260 (1.0)	1,452 (1.2)
• Chronic pulmonary disease	84,689 (34.5)	43,136 (35.1)	41,553 (33.8)
• Coagulopathy	34,832 (14.2)	16,578 (13.5)	18,254 (14.9)
• Congestive heart failure	73,502 (29.9)	34,880 (28.4)	38,622 (31.4)
• Deficiency anemias	79,407 (32.3)	39,408 (32.1)	39,999 (32.6)
• Depression	34,277 (13.9)	17,372 (14.1)	16,905 (13.8)
• Diabetes with chronic complications	52,262 (21.3)	25,870 (21.1)	26,392 (21.5)
• Diabetes without chronic complications	45,924 (18.7)	22,711 (18.5)	23,213 (18.9)
• Drug abuse	5,332 (2.2)	2,699 (2.2)	2,633 (2.1)
• Fluid and electrolyte disorders	157,657 (64.2)	77,335 (62.9)	80,322 (65.4)
• Hypertension	174,578 (71.0)	87,597 (71.3)	86,981 (70.8)
• Hypothyroidism	45,796 (18.6)	22,990 (18.7)	22,806 (18.6)
• Liver disease	13,063 (5.3)	6,065 (4.9)	6,998 (5.7)
• Lymphoma	4,412 (1.8)	2,217 (1.8)	2,195 (1.8)
• Metastatic cancer	10,517 (4.3)	5,089 (4.1)	5,428 (4.4)
• Obesity	37,616 (15.3)	18,119 (14.7)	19,497 (15.9)
• Other neurological disorders	50,340 (20.5)	25,693 (20.9)	24,647 (20.1)
• Paralysis	23,378 (9.5)	11,770 (9.6)	11,608 (9.4)
• Peptic ulcer disease excluding bleeding	3,341 (1.4)	1,535 (1.2)	1,806 (1.5)
• Peripheral vascular disease	25,526 (10.4)	12,346 (10.0)	13,180 (10.7)
• Psychoses	12,031 (4.9)	6,327 (5.1)	5,704 (4.6)
• Pulmonary circulation disease	4,435 (1.8)	2,073 (1.7)	2,362 (1.9)
• Renal failure	73,577 (29.9)	35,466 (28.9)	38,111 (31.0)
• Rheumatoid arthritis/collagen vascular diseases	11,496 (4.7)	5,782 (4.7)	5,714 (4.7)
• Solid tumor without metastasis	10,056 (4.1)	4,999 (4.1)	5,057 (4.1)
• Valvular disease	22,509 (9.2)	10,836 (8.8)	11,673 (9.5)
• Weight loss	39,436 (16.0)	18,974 (15.4)	20,462 (16.7)

e-Table 11: Standard-match SEP-1 standardized mean differences where the matching is based on a greedy nearest neighbor with a caliper of 0.40 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.25

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
Square root of hospital certified bed count	-0.684	6.485	-0.105	0.891	-0.478	-0.074	30.2%	0.920
Hospital accreditation								
• AOA	-0.001	0.197	-0.007	0.966	-0.003	-0.016	0.0%	0.931
• CIHQ	0.002	0.079	0.031	1.482	0.002	0.022	28.8%	1.292
• DNV	-0.007	0.291	-0.024	0.936	-0.009	-0.031	0.0%	0.917
• NONE	-0.006	0.166	-0.038	0.806	-0.004	-0.026	32.0%	0.857
• TJC	0.012	0.374	0.033	0.944	0.015	0.039	0.0%	0.933
Critical access hospital	0.001	0.124	0.009	1.070	0.000	-0.001	92.3%	0.995
Urban hospital location	-0.008	0.428	-0.019	1.023	-0.004	-0.009	54.1%	1.010
Discharge quarter								
• 2015Q4	-0.045	0.358	-0.125	0.783	-0.053	-0.147	0.0%	0.761
• 2016Q1	-0.012	0.370	-0.031	0.945	-0.028	-0.077	0.0%	0.877
• 2016Q2	0.018	0.367	0.048	1.094	-0.002	-0.006	87.1%	0.989
• 2016Q3	-0.012	0.367	-0.032	0.943	0.008	0.021	33.3%	1.043
• 2016Q4	0.012	0.380	0.033	1.058	0.027	0.070	0.0%	1.136
• 2017Q1	0.038	0.391	0.097	1.166	0.049	0.125	0.0%	1.232
Patient Hispanic ethnicity (Yes)	-0.005	0.230	-0.020	0.927	-0.001	-0.004	80.4%	0.985
Patient sex (Male)	0.009	0.500	0.018	0.999	0.003	0.007	63.1%	1.000
Patient race								

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
• American Indian/Alaska Native	-0.001	0.081	-0.010	0.884	-0.001	-0.007	28.1%	0.913
• Asian	0.006	0.145	0.039	1.296	0.006	0.039	0.6%	1.280
• Black/African American	-0.020	0.317	-0.062	0.859	-0.010	-0.031	50.4%	0.924
• Native Hawaiian/Pacific Islander	0.001	0.054	0.013	1.271	0.001	0.013	0.0%	1.276
• Unable to Determine	0.000	0.184	-0.001	0.997	0.001	0.005	0.0%	1.024
• White	0.014	0.383	0.037	0.940	0.003	0.008	77.9%	0.986
Patient age	0.218	13.009	0.017	1.001	0.027	0.002	87.8%	1.006
Persistent hypotension	-0.025	0.213	-0.116	0.606	-0.030	-0.141	0.0%	0.574
Initial lactate level								
• Not collected	-0.232	0.298	-0.777	0.000	0.000	0.000	100.0%	
• ≤ 2.0 mmol/L	0.198	0.453	0.437	1.442	0.080	0.176	59.8%	1.094
• > 2.0 and < 4.0 mmol/L	0.174	0.485	0.359	1.136	0.000	0.000	100.0%	1.000
• ≥ 4.0 mmol/L	-0.140	0.357	-0.392	0.453	-0.080	-0.223	43.1%	0.592
Septic shock	-0.119	0.397	-0.299	0.634	-0.098	-0.247	17.2%	0.686
Site of infection	--	--	--	--	--	--	--	--
• Bacteremia	0.000	0.022	-0.007	0.721	0.000	-0.005	35.7%	0.803
• Central nervous system	0.000	0.050	-0.006	0.879	0.000	-0.003	47.3%	0.933
• Fungal	-0.002	0.119	-0.014	0.888	-0.001	-0.008	41.6%	0.931
• Gastrointestinal	-0.003	0.104	-0.031	0.746	-0.002	-0.019	37.5%	0.825
• Genitourinary	0.016	0.430	0.037	1.045	0.008	0.019	48.0%	1.023
• Heart	-0.001	0.086	-0.013	0.866	-0.001	-0.006	51.5%	0.931
• Lung	0.033	0.475	0.070	1.047	0.019	0.040	43.6%	1.025
• Missing	0.000	0.061	0.003	1.047	0.000	-0.002	37.9%	0.973

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
• Other	0.002	0.284	0.006	1.018	0.002	0.006	9.5%	1.016
• Peritoneal	-0.014	0.137	-0.101	0.477	-0.007	-0.050	50.1%	0.655
• Septicemia	-0.031	0.428	-0.072	0.917	-0.017	-0.040	44.0%	0.950
• Soft tissue	0.000	0.134	-0.003	0.978	-0.001	-0.006	0.0%	0.961
• Upper respiratory tract	0.000	0.049	0.009	1.190	0.000	0.003	59.1%	1.070
Cardiovascular organ failure	-0.030	0.296	-0.101	0.758	-0.018	-0.062	38.5%	0.835
Hematologic organ failure	-0.022	0.185	-0.117	0.546	-0.012	-0.065	44.3%	0.689
Metabolic organ failure	-0.053	0.443	-0.119	0.883	-0.030	-0.068	42.8%	0.927
Neurologic organ failure	-0.015	0.295	-0.051	0.869	-0.008	-0.026	49.0%	0.929
Renal organ failure	-0.063	0.498	-0.126	0.987	-0.042	-0.085	32.5%	0.989
Respiratory organ failure	-0.057	0.461	-0.125	0.901	-0.033	-0.072	42.5%	0.938
Acquired immune deficiency syndrome	0.000	0.055	0.002	1.030	0.000	0.001	44.4%	1.017
Alcohol abuse	-0.006	0.173	-0.035	0.826	-0.003	-0.017	51.9%	0.908
Deficiency anemias	-0.006	0.468	-0.013	0.990	-0.005	-0.010	21.2%	0.992
Rheumatoid arthritis/collagen vascular diseases	0.002	0.210	0.008	1.033	0.001	0.003	65.5%	1.011
Chronic blood loss anemia	-0.003	0.106	-0.025	0.797	-0.002	-0.015	39.8%	0.869
Congestive heart failure	-0.038	0.459	-0.083	0.931	-0.030	-0.066	20.1%	0.943
Chronic pulmonary disease	0.022	0.474	0.045	1.031	0.013	0.027	40.2%	1.018
Coagulopathy	-0.027	0.354	-0.078	0.856	-0.014	-0.039	50.4%	0.923
Depression	0.008	0.344	0.024	1.052	0.004	0.011	53.9%	1.023
Diabetes without chronic complications	0.000	0.388	0.000	0.999	-0.004	-0.011	0.0%	0.983
Diabetes with chronic complications	-0.010	0.411	-0.025	0.966	-0.004	-0.010	58.6%	0.986
Drug abuse	0.000	0.146	0.002	1.011	0.001	0.004	0.0%	1.025

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Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
Hypertension	0.006	0.454	0.014	0.987	0.005	0.011	22.5%	0.990
Hypothyroidism	0.003	0.388	0.008	1.013	0.002	0.004	52.2%	1.006
Liver disease	-0.014	0.230	-0.061	0.790	-0.008	-0.033	45.8%	0.874
Lymphoma	0.001	0.132	0.005	1.035	0.000	0.001	71.0%	1.010
Fluid and electrolyte disorders	-0.045	0.476	-0.094	1.061	-0.024	-0.051	45.6%	1.030
Metastatic cancer	-0.005	0.205	-0.024	0.899	-0.003	-0.013	43.6%	0.940
Other neurological disorders	0.013	0.402	0.032	1.048	0.009	0.021	33.0%	1.031
Obesity	-0.013	0.360	-0.035	0.934	-0.011	-0.031	11.9%	0.942
Paralysis	0.004	0.292	0.012	1.035	0.001	0.005	63.4%	1.013
Peripheral vascular disease	-0.010	0.307	-0.033	0.918	-0.007	-0.022	33.7%	0.944
Psychoses	0.006	0.214	0.029	1.131	0.005	0.024	18.6%	1.103
Pulmonary circulation disease	-0.004	0.136	-0.026	0.830	-0.002	-0.017	34.0%	0.880
Renal failure	-0.031	0.460	-0.068	0.944	-0.022	-0.047	31.0%	0.960
Solid tumor without metastasis	-0.001	0.199	-0.005	0.979	0.000	-0.002	48.5%	0.989
Peptic ulcer disease excluding bleeding	-0.004	0.119	-0.033	0.764	-0.002	-0.019	43.7%	0.852
Valvular disease	-0.006	0.289	-0.021	0.942	-0.007	-0.024	0.0%	0.935
Weight loss	-0.023	0.371	-0.061	0.896	-0.012	-0.033	46.2%	0.941

e-Table 12: Standard-match SEP-1 unmatched distributions where the matching is based on a greedy nearest neighbor with a caliper of 0.40 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.25

Variables	All Cases (N = 88,030)	Compliant (N = 17,634)	Non-Compliant (N = 70,396)
Percentage of cases	100.0	20.0	80.0
Hospital certified bed count			
• Mean	326.3	292.9	334.6
• Median	254	231	263
• Standard Deviation	292.8	264.8	298.8
• Interquartile Range	146 - 407	129 - 370	149 - 416
Hospital accreditation - N (%)			
• AOA/HFAP	3,379 (3.8)	688 (3.9)	2,691 (3.8)
• CIHQ	358 (0.4)	111 (0.6)	247 (0.4)
• DNV	8,122 (9.2)	1,586 (9.0)	6,536 (9.3)
• NONE	2,994 (3.4)	484 (2.7)	2,510 (3.6)
• TJC	73,177 (83.1)	14,765 (83.7)	58,412 (83.0)
Critical access hospital - N (%)	1,296 (1.5)	332 (1.9)	964 (1.4)
Urban hospital location - N (%)	67,341 (76.5)	13,208 (74.9)	54,133 (76.9)
Hospital region - N (%)			
• New England	3,034 (3.4)	677 (3.8)	2,357 (3.3)
• Northeast	7,687 (8.7)	1,496 (8.5)	6,191 (8.8)
• Mideast	12,919 (14.7)	2,572 (14.6)	10,347 (14.7)
• Southeast	21,074 (23.9)	4,080 (23.1)	16,994 (24.1)
• Great Lakes	15,016 (17.1)	2,920 (16.6)	12,096 (17.2)
• South	10,460 (11.9)	1,924 (10.9)	8,536 (12.1)
• Midwest	4,295 (4.9)	797 (4.5)	3,498 (5.0)
• Mountain West	2,068 (2.3)	528 (3.0)	1,540 (2.2)
• Southwest	8,585 (9.8)	2,071 (11.7)	6,514 (9.3)
• Northwest	2,892 (3.3)	569 (3.2)	2,323 (3.3)
Discharge quarter - N (%)			
• 2015Q4	13,001 (14.8)	1,993 (11.3)	11,008 (15.6)
• 2016Q1	12,558 (14.3)	2,752 (15.6)	9,806 (13.9)
• 2016Q2	11,455 (13.0)	3,121 (17.7)	8,334 (11.8)
• 2016Q3	16,950 (19.3)	2,797 (15.9)	14,153 (20.1)
• 2016Q4	17,008 (19.3)	3,300 (18.7)	13,708 (19.5)
• 2017Q1	17,058 (19.4)	3,671 (20.8)	13,387 (19.0)

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Variables	All Cases (N = 88,030)	Compliant (N = 17,634)	Non-Compliant (N = 70,396)
Patient Hispanic ethnicity (Yes) - N (%)	5,371 (6.1)	889 (5.0)	4,482 (6.4)
Patient sex (Male) - N (%)	43,992 (50.0)	9,111 (51.7)	34,881 (49.5)
Patient race - N (%)			
• American Indian/Alaska Native	642 (0.7)	116 (0.7)	526 (0.7)
• Asian	1,512 (1.7)	318 (1.8)	1,194 (1.7)
• Black/African American	11,664 (13.3)	1,803 (10.2)	9,861 (14.0)
• Native Hawaiian/Pacific Islander	217 (0.2)	46 (0.3)	171 (0.2)
• Unable to Determine	3,202 (3.6)	615 (3.5)	2,587 (3.7)
• White	70,793 (80.4)	14,736 (83.6)	56,057 (79.6)
Patient age at admission (Years)			
• Mean	73.2	73.6	73.1
• Median	74	74	74
• Standard Deviation	13.0	13.0	13.0
• Interquartile Range	66 - 83	66 - 83	66 - 83
Persistent hypotension (=Yes) - N (%)	3,702 (4.2)	374 (2.1)	3,328 (4.7)
Initial lactate level - N (%)			
• Not collected	44,838 (50.9)	0 (0.0)	44,838 (63.7)
• ≤ 2.0 mmol/L	8,337 (9.5)	7,548 (42.8)	789 (1.1)
• > 2.0 and < 4.0 mmol/L	11,480 (13.0)	9,333 (52.9)	2,147 (3.0)
• ≥ 4.0 mmol/L	23,375 (26.6)	753 (4.3)	22,622 (32.1)
Severe sepsis - N (%)	66,783 (75.9)	16,203 (91.9)	50,580 (71.9)
Septic shock - N (%)	21,247 (24.1)	1,431 (8.1)	19,816 (28.1)
Site of infection - N (%)			
• Bacteremia	50 (0.1)	6 (0.0)	44 (0.1)
• Central nervous system	242 (0.3)	38 (0.2)	204 (0.3)
• Fungal	1,423 (1.6)	253 (1.4)	1,170 (1.7)
• Gastrointestinal	1,170 (1.3)	154 (0.9)	1,016 (1.4)
• Genitourinary	20,151 (22.9)	4,450 (25.2)	15,701 (22.3)
• Heart	732 (0.8)	109 (0.6)	623 (0.9)
• Lung	27,813 (31.6)	6,428 (36.5)	21,385 (30.4)
• Missing	297 (0.3)	71 (0.4)	226 (0.3)
• Other	7,819 (8.9)	1,615 (9.2)	6,204 (8.8)
• Peritoneal	2,777 (3.2)	150 (0.9)	2,627 (3.7)
• Septicemia only	23,787 (27.0)	3,987 (22.6)	19,800 (28.1)
• Soft tissue	1,595 (1.8)	325 (1.8)	1,270 (1.8)
• Upper respiratory tract	174 (0.2)	48 (0.3)	126 (0.2)
Organ failures - N (%)			

Variables	All Cases (N = 88,030)	Compliant (N = 17,634)	Non-Compliant (N = 70,396)
• Cardiovascular	10,656 (12.1)	1,392 (7.9)	9,264 (13.2)
• Hematologic	4,660 (5.3)	333 (1.9)	4,327 (6.1)
• Metabolic	27,402 (31.1)	4,034 (22.9)	23,368 (33.2)
• Neurologic	9,578 (10.9)	1,467 (8.3)	8,111 (11.5)
• Renal	45,417 (51.6)	7,560 (42.9)	37,857 (53.8)
• Respiratory	31,234 (35.5)	4,729 (26.8)	26,505 (37.7)
Comorbidities - N (%)			
• Acquired immune deficiency syndrome	267 (0.3)	59 (0.3)	208 (0.3)
• Alcohol abuse	3,221 (3.7)	471 (2.7)	2,750 (3.9)
• Chronic blood loss anemia	1,139 (1.3)	150 (0.9)	989 (1.4)
• Chronic pulmonary disease	28,398 (32.3)	6,221 (35.3)	22,177 (31.5)
• Coagulopathy	14,965 (17.0)	2,148 (12.2)	12,817 (18.2)
• Congestive heart failure	28,624 (32.5)	5,010 (28.4)	23,614 (33.5)
• Deficiency anemias	28,730 (32.6)	5,617 (31.9)	23,113 (32.8)
• Depression	11,388 (12.9)	2,522 (14.3)	8,866 (12.6)
• Diabetes with chronic complications	19,914 (22.6)	3,678 (20.9)	16,236 (23.1)
• Diabetes without chronic complications	15,623 (17.7)	3,185 (18.1)	12,438 (17.7)
• Drug abuse	1,891 (2.1)	361 (2.0)	1,530 (2.2)
• Fluid and electrolyte disorders	60,522 (68.8)	10,875 (61.7)	49,647 (70.5)
• Hypertension	61,980 (70.4)	12,511 (70.9)	49,469 (70.3)
• Hypothyroidism	15,896 (18.1)	3,235 (18.3)	12,661 (18.0)
• Liver disease	6,036 (6.9)	836 (4.7)	5,200 (7.4)
• Lymphoma	1,500 (1.7)	322 (1.8)	1,178 (1.7)
• Metastatic cancer	4,258 (4.8)	733 (4.2)	3,525 (5.0)
• Obesity	13,889 (15.8)	2,527 (14.3)	11,362 (16.1)
• Other neurological disorders	16,854 (19.1)	3,626 (20.6)	13,228 (18.8)
• Paralysis	7,829 (8.9)	1,660 (9.4)	6,169 (8.8)
• Peptic ulcer disease excluding bleeding	1,573 (1.8)	215 (1.2)	1,358 (1.9)
• Peripheral vascular disease	9,867 (11.2)	1,720 (9.8)	8,147 (11.6)
• Psychoses	3,885 (4.4)	880 (5.0)	3,005 (4.3)
• Pulmonary circulation disease	1,926 (2.2)	315 (1.8)	1,611 (2.3)
• Renal failure	28,670 (32.6)	5,037 (28.6)	23,633 (33.6)
• Rheumatoid arthritis/collagen vascular diseases	3,960 (4.5)	855 (4.8)	3,105 (4.4)
• Solid tumor without metastasis	3,797 (4.3)	758 (4.3)	3,039 (4.3)
• Valvular disease	8,236 (9.4)	1,615 (9.2)	6,621 (9.4)
• Weight loss	16,126 (18.3)	2,584 (14.7)	13,542 (19.2)
Mortality - N (%)	28,429 (32.3)	3,641 (20.6)	24,788 (35.2)

Variables	All Cases (N = 88,030)	Compliant (N = 17,634)	Non-Compliant (N = 70,396)
• Severe Sepsis	19,902 (29.8)	3,182 (19.6)	16,720 (33.1)
• Septic Shock	8,527 (40.1)	459 (32.1)	8,068 (40.7)

e-Table 13: Stringent-match SEP-1 matched distributions where the matching is based on a greedy nearest neighbor with a caliper of 0.22 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.10

Variables	All Cases (N = 214,032)	Compliant (N = 107,016)	Non-Compliant (N = 107,016)
Percentage of cases	100.0	50.0	50.0
Hospital certified bed count			
• Mean	305.8	300.9	310.7
• Median	240	237	241
• Standard Deviation	269.1	265.9	272.2
• Interquartile Range	135 - 389	133 - 381	139 - 397
Hospital accreditation - N (%)			
• AOA/HFAP	8,914 (4.2)	4,334 (4.0)	4,580 (4.3)
• CIHQ	1,367 (0.6)	718 (0.7)	649 (0.6)
• DNV	20,427 (9.5)	9,901 (9.3)	10,526 (9.8)
• NONE	5,925 (2.8)	2,807 (2.6)	3,118 (2.9)
• TJC	177,399 (82.9)	89,256 (83.4)	88,143 (82.4)
Critical access hospital - N (%)	3,355 (1.6)	1,652 (1.5)	1,703 (1.6)
Urban hospital location - N (%)	162,038 (75.7)	80,961 (75.7)	81,077 (75.8)
Hospital region - N (%)			
• New England	7,823 (3.7)	3,892 (3.6)	3,931 (3.7)
• Northeast	17,642 (8.2)	8,755 (8.2)	8,887 (8.3)
• Mideast	29,774 (13.9)	15,027 (14.0)	14,747 (13.8)
• Southeast	47,675 (22.3)	24,238 (22.6)	23,437 (21.9)
• Great Lakes	37,320 (17.4)	17,931 (16.8)	19,389 (18.1)
• South	24,362 (11.4)	12,139 (11.3)	12,223 (11.4)
• Midwest	10,139 (4.7)	5,102 (4.8)	5,037 (4.7)
• Mountain West	6,259 (2.9)	3,119 (2.9)	3,140 (2.9)
• Southwest	25,791 (12.1)	13,288 (12.4)	12,503 (11.7)
• Northwest	7,247 (3.4)	3,525 (3.3)	3,722 (3.5)
Discharge quarter - N (%)			
• 2015Q4	33,706 (15.7)	15,171 (14.2)	18,535 (17.3)
• 2016Q1	36,967 (17.3)	17,711 (16.5)	19,256 (18.0)
• 2016Q2	35,969 (16.8)	18,071 (16.9)	17,898 (16.7)
• 2016Q3	32,886 (15.4)	16,604 (15.5)	16,282 (15.2)
• 2016Q4	35,666 (16.7)	18,605 (17.4)	17,061 (15.9)
• 2017Q1	38,838 (18.1)	20,854 (19.5)	17,984 (16.8)

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Variables	All Cases (N = 214,032)	Compliant (N = 107,016)	Non-Compliant (N = 107,016)
Patient Hispanic ethnicity (Yes) - N (%)	11,474 (5.4)	5,701 (5.3)	5,773 (5.4)
Patient sex (Male) - N (%)	109,454 (51.1)	54,824 (51.2)	54,630 (51.0)
Patient race - N (%)			
• American Indian/Alaska Native	1,380 (0.6)	680 (0.6)	700 (0.7)
• Asian	4,472 (2.1)	2,372 (2.2)	2,100 (2.0)
• Black/African American	23,347 (10.9)	11,358 (10.6)	11,989 (11.2)
• Native Hawaiian/Pacific Islander	582 (0.3)	303 (0.3)	279 (0.3)
• Unable to Determine	7,360 (3.4)	3,757 (3.5)	3,603 (3.4)
• White	176,891 (82.6)	88,546 (82.7)	88,345 (82.6)
Patient age at admission (Years)			
• Mean	73.6	73.6	73.6
• Median	74	74	74
• Standard Deviation	13.0	13.0	13.0
• Interquartile Range	66 - 83	66 - 83	66 - 83
Persistent hypotension (=Yes) - N (%)	10,719 (5.0)	4,496 (4.2)	6,223 (5.8)
Initial lactate level - N (%)			
• Not collected	0 (0.0)	0 (0.0)	0 (0.0)
• ≤ 2.0 mmol/L	80,222 (37.5)	41,995 (39.2)	38,227 (35.7)
• > 2.0 and < 4.0 mmol/L	108,896 (50.9)	53,505 (50.0)	55,391 (51.8)
• ≥ 4.0 mmol/L	24,914 (11.6)	11,516 (10.8)	13,398 (12.5)
Severe sepsis - N (%)	176,534 (82.5)	90,182 (84.3)	86,352 (80.7)
Septic shock - N (%)	37,498 (17.5)	16,834 (15.7)	20,664 (19.3)
Site of infection - N (%)			
• Bacteremia	97 (0.0)	45 (0.0)	52 (0.0)
• Central nervous system	546 (0.3)	271 (0.3)	275 (0.3)
• Fungal	3,008 (1.4)	1,455 (1.4)	1,553 (1.5)
• Gastrointestinal	2,244 (1.0)	1,042 (1.0)	1,202 (1.1)
• Genitourinary	52,885 (24.7)	26,721 (25.0)	26,164 (24.4)
• Heart	1,586 (0.7)	761 (0.7)	825 (0.8)
• Lung	75,126 (35.1)	38,163 (35.7)	36,963 (34.5)
• Missing	859 (0.4)	410 (0.4)	449 (0.4)
• Other	19,089 (8.9)	9,576 (8.9)	9,513 (8.9)
• Peritoneal	3,513 (1.6)	1,537 (1.4)	1,976 (1.8)
• Septicemia only	50,509 (23.6)	24,793 (23.2)	25,716 (24.0)
• Soft tissue	4,028 (1.9)	1,970 (1.8)	2,058 (1.9)
• Upper respiratory tract	542 (0.3)	272 (0.3)	270 (0.3)
Organ failures - N (%)			

Variables	All Cases (N = 214,032)	Compliant (N = 107,016)	Non-Compliant (N = 107,016)
• Cardiovascular	19,919 (9.3)	9,378 (8.8)	10,541 (9.8)
• Hematologic	6,472 (3.0)	2,951 (2.8)	3,521 (3.3)
• Metabolic	54,775 (25.6)	26,832 (25.1)	27,943 (26.1)
• Neurologic	19,837 (9.3)	9,661 (9.0)	10,176 (9.5)
• Renal	99,595 (46.5)	48,686 (45.5)	50,909 (47.6)
• Respiratory	63,267 (29.6)	30,865 (28.8)	32,402 (30.3)
Comorbidities - N (%)			
• Acquired immune deficiency syndrome	617 (0.3)	307 (0.3)	310 (0.3)
• Alcohol abuse	6,262 (2.9)	3,073 (2.9)	3,189 (3.0)
• Chronic blood loss anemia	2,368 (1.1)	1,122 (1.0)	1,246 (1.2)
• Chronic pulmonary disease	73,983 (34.6)	37,403 (35.0)	36,580 (34.2)
• Coagulopathy	29,998 (14.0)	14,704 (13.7)	15,294 (14.3)
• Congestive heart failure	65,080 (30.4)	31,569 (29.5)	33,511 (31.3)
• Deficiency anemias	69,149 (32.3)	34,380 (32.1)	34,769 (32.5)
• Depression	29,923 (14.0)	15,049 (14.1)	14,874 (13.9)
• Diabetes with chronic complications	45,845 (21.4)	22,745 (21.3)	23,100 (21.6)
• Diabetes without chronic complications	39,975 (18.7)	19,882 (18.6)	20,093 (18.8)
• Drug abuse	4,606 (2.2)	2,324 (2.2)	2,282 (2.1)
• Fluid and electrolyte disorders	136,948 (64.0)	67,979 (63.5)	68,969 (64.4)
• Hypertension	152,113 (71.1)	76,093 (71.1)	76,020 (71.0)
• Hypothyroidism	39,737 (18.6)	19,853 (18.6)	19,884 (18.6)
• Liver disease	11,343 (5.3)	5,480 (5.1)	5,863 (5.5)
• Lymphoma	3,817 (1.8)	1,923 (1.8)	1,894 (1.8)
• Metastatic cancer	9,154 (4.3)	4,517 (4.2)	4,637 (4.3)
• Obesity	33,359 (15.6)	16,330 (15.3)	17,029 (15.9)
• Other neurological disorders	43,449 (20.3)	21,991 (20.5)	21,458 (20.1)
• Paralysis	20,232 (9.5)	10,154 (9.5)	10,078 (9.4)
• Peptic ulcer disease excluding bleeding	2,916 (1.4)	1,377 (1.3)	1,539 (1.4)
• Peripheral vascular disease	22,377 (10.5)	10,967 (10.2)	11,410 (10.7)
• Psychoses	10,364 (4.8)	5,333 (5.0)	5,031 (4.7)
• Pulmonary circulation disease	3,894 (1.8)	1,882 (1.8)	2,012 (1.9)
• Renal failure	64,705 (30.2)	31,678 (29.6)	33,027 (30.9)
• Rheumatoid arthritis/collagen vascular diseases	10,093 (4.7)	5,081 (4.7)	5,012 (4.7)
• Solid tumor without metastasis	8,769 (4.1)	4,343 (4.1)	4,426 (4.1)
• Valvular disease	19,727 (9.2)	9,644 (9.0)	10,083 (9.4)
• Weight loss	34,248 (16.0)	16,704 (15.6)	17,544 (16.4)

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e-Table 14: Stringent-match SEP-1 standardized mean differences where the matching is based on a greedy nearest neighbor with a caliper of 0.22 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.10

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
Square root of hospital certified bed count	-0.684	6.485	-0.105	0.891	-0.243	-0.037	64.5%	0.956
Hospital accreditation								
• AOA	-0.001	0.197	-0.007	0.966	-0.002	-0.012	0.0%	0.949
• CIHQ	0.002	0.079	0.031	1.482	0.001	0.008	73.7%	1.106
• DNV	-0.007	0.291	-0.024	0.936	-0.006	-0.020	14.9%	0.947
• NONE	-0.006	0.166	-0.038	0.806	-0.003	-0.017	53.9%	0.903
• TJC	0.012	0.374	0.033	0.944	0.010	0.028	14.6%	0.953
Critical access hospital	0.001	0.124	0.009	1.070	0.000	-0.004	55.0%	0.971
Urban hospital location	-0.008	0.428	-0.019	1.023	-0.001	-0.003	86.6%	1.003
Discharge quarter								
• 2015Q4	-0.045	0.358	-0.125	0.783	-0.031	-0.088	29.8%	0.850
• 2016Q1	-0.012	0.370	-0.031	0.945	-0.014	-0.039	0.0%	0.936
• 2016Q2	0.018	0.367	0.048	1.094	0.002	0.004	90.9%	1.008
• 2016Q3	-0.012	0.367	-0.032	0.943	0.003	0.008	74.0%	1.016
• 2016Q4	0.012	0.380	0.033	1.058	0.014	0.038	0.0%	1.072
• 2017Q1	0.038	0.391	0.097	1.166	0.027	0.069	29.0%	1.122
Patient Hispanic ethnicity (Yes)	-0.005	0.230	-0.020	0.927	-0.001	-0.003	85.2%	0.988
Patient sex (Male)	0.009	0.500	0.018	0.999	0.002	0.004	80.2%	1.000

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
Patient race								
• American Indian/Alaska Native	-0.001	0.081	-0.010	0.884	0.000	-0.002	77.1%	0.972
• Asian	0.006	0.145	0.039	1.296	0.003	0.018	54.8%	1.127
• Black/African American	-0.020	0.317	-0.062	0.859	-0.006	-0.019	70.0%	0.954
• Native Hawaiian/Pacific Islander	0.001	0.054	0.013	1.271	0.000	0.004	67.4%	1.086
• Unable to Determine	0.000	0.184	-0.001	0.997	0.001	0.008	0.0%	1.041
• White	0.014	0.383	0.037	0.940	0.002	0.005	86.8%	0.992
Patient age	0.218	13.009	0.017	1.001	0.005	0.000	97.9%	0.992
Persistent hypotension	-0.025	0.213	-0.116	0.606	-0.016	-0.076	34.6%	0.735
Initial lactate level								
• Not collected	-0.232	0.298	-0.777	0.000	0.000	0.000	100.0%	
• ≤ 2.0 mmol/L	0.198	0.453	0.437	1.442	0.035	0.078	82.2%	1.038
• > 2.0 and < 4.0 mmol/L	0.174	0.485	0.359	1.136	-0.018	-0.036	89.9%	1.001
• ≥ 4.0 mmol/L	-0.140	0.357	-0.392	0.453	-0.018	-0.049	87.4%	0.877
Septic shock	-0.119	0.397	-0.299	0.634	-0.036	-0.090	69.8%	0.851
Site of infection	--	--	--	--	--	--	--	--
• Bacteremia	0.000	0.022	-0.007	0.721	0.000	-0.003	56.9%	0.865
• Central nervous system	0.000	0.050	-0.006	0.879	0.000	-0.001	88.5%	0.986
• Fungal	-0.002	0.119	-0.014	0.888	-0.001	-0.008	46.6%	0.938
• Gastrointestinal	-0.003	0.104	-0.031	0.746	-0.002	-0.014	53.3%	0.868
• Genitourinary	0.016	0.430	0.037	1.045	0.005	0.012	67.2%	1.014
• Heart	-0.001	0.086	-0.013	0.866	-0.001	-0.007	45.2%	0.923
• Lung	0.033	0.475	0.070	1.047	0.011	0.024	66.5%	1.015
• Missing	0.000	0.061	0.003	1.047	0.000	-0.006	0.0%	0.914

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
• Other	0.002	0.284	0.006	1.018	0.001	0.002	66.1%	1.006
• Peritoneal	-0.014	0.137	-0.101	0.477	-0.004	-0.030	70.4%	0.781
• Septicemia	-0.031	0.428	-0.072	0.917	-0.009	-0.020	72.1%	0.975
• Soft tissue	0.000	0.134	-0.003	0.978	-0.001	-0.006	0.0%	0.958
• Upper respiratory tract	0.000	0.049	0.009	1.190	0.000	0.000	95.5%	1.007
Cardiovascular organ failure	-0.030	0.296	-0.101	0.758	-0.011	-0.037	63.7%	0.900
Hematologic organ failure	-0.022	0.185	-0.117	0.546	-0.005	-0.029	75.3%	0.843
Metabolic organ failure	-0.053	0.443	-0.119	0.883	-0.010	-0.023	80.4%	0.974
Neurologic organ failure	-0.015	0.295	-0.051	0.869	-0.005	-0.016	68.0%	0.954
Renal organ failure	-0.063	0.498	-0.126	0.987	-0.021	-0.042	67.0%	0.994
Respiratory organ failure	-0.057	0.461	-0.125	0.901	-0.014	-0.031	75.0%	0.972
Acquired immune deficiency syndrome	0.000	0.055	0.002	1.030	0.000	-0.001	68.1%	0.990
Alcohol abuse	-0.006	0.173	-0.035	0.826	-0.001	-0.006	82.1%	0.965
Deficiency anemias	-0.006	0.468	-0.013	0.990	-0.004	-0.008	40.4%	0.994
Rheumatoid arthritis/collagen vascular diseases	0.002	0.210	0.008	1.033	0.001	0.003	59.8%	1.013
Chronic blood loss anemia	-0.003	0.106	-0.025	0.797	-0.001	-0.011	55.4%	0.902
Congestive heart failure	-0.038	0.459	-0.083	0.931	-0.018	-0.040	52.4%	0.967
Chronic pulmonary disease	0.022	0.474	0.045	1.031	0.008	0.016	64.3%	1.011
Coagulopathy	-0.027	0.354	-0.078	0.856	-0.006	-0.016	80.0%	0.968
Depression	0.008	0.344	0.024	1.052	0.002	0.005	80.2%	1.010
Diabetes without chronic complications	0.000	0.388	0.000	0.999	-0.002	-0.005	0.0%	0.992
Diabetes with chronic complications	-0.010	0.411	-0.025	0.966	-0.003	-0.008	67.7%	0.989
Drug abuse	0.000	0.146	0.002	1.011	0.000	0.003	0.0%	1.018

Variables	All Observations				Matched Observations			
	Mean Difference	Standard Deviation	Standardized Mean Difference	Variance Ratio	Mean Difference	Standardized Mean Difference	Percent Reduction	Variance Ratio
Hypertension	0.006	0.454	0.014	0.987	0.001	0.002	89.5%	0.999
Hypothyroidism	0.003	0.388	0.008	1.013	0.000	-0.001	90.8%	0.999
Liver disease	-0.014	0.230	-0.061	0.790	-0.004	-0.016	74.4%	0.938
Lymphoma	0.001	0.132	0.005	1.035	0.000	0.002	56.2%	1.015
Fluid and electrolyte disorders	-0.045	0.476	-0.094	1.061	-0.009	-0.019	79.3%	1.011
Metastatic cancer	-0.005	0.205	-0.024	0.899	-0.001	-0.005	77.1%	0.975
Other neurological disorders	0.013	0.402	0.032	1.048	0.005	0.012	60.8%	1.019
Obesity	-0.013	0.360	-0.035	0.934	-0.007	-0.018	48.7%	0.966
Paralysis	0.004	0.292	0.012	1.035	0.001	0.002	80.3%	1.007
Peripheral vascular disease	-0.010	0.307	-0.033	0.918	-0.004	-0.013	59.6%	0.966
Psychoses	0.006	0.214	0.029	1.131	0.003	0.013	54.7%	1.057
Pulmonary circulation disease	-0.004	0.136	-0.026	0.830	-0.001	-0.009	65.9%	0.937
Renal failure	-0.031	0.460	-0.068	0.944	-0.013	-0.027	59.6%	0.977
Solid tumor without metastasis	-0.001	0.199	-0.005	0.979	-0.001	-0.004	15.4%	0.982
Peptic ulcer disease excluding bleeding	-0.004	0.119	-0.033	0.764	-0.002	-0.013	61.3%	0.896
Valvular disease	-0.006	0.289	-0.021	0.942	-0.004	-0.014	32.1%	0.961
Weight loss	-0.023	0.371	-0.061	0.896	-0.008	-0.021	65.1%	0.961

e-Table 15: Stringent-match SEP-1 unmatched distributions where the matching is based on a greedy nearest neighbor with a caliper of 0.22 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.10

Variables	All Cases (N = 119,738)	Compliant (N = 33,488)	Non-Compliant (N = 86,250)
Percentage of cases	100.0	28.0	72.0
Hospital certified bed count			
• Mean	314.5	268.7	332.3
• Median	242	217	261
• Standard Deviation	280.9	236.2	294.6
• Interquartile Range	140 - 395	121 - 346	148 - 415
Hospital accreditation - N (%)			
• AOA/HFAP	4,666 (3.9)	1,264 (3.8)	3,402 (3.9)
• CIHQ	659 (0.6)	334 (1.0)	325 (0.4)
• DNV	10,878 (9.1)	2,719 (8.1)	8,159 (9.5)
• NONE	3,736 (3.1)	747 (2.2)	2,989 (3.5)
• TJC	99,799 (83.3)	28,424 (84.9)	71,375 (82.8)
Critical access hospital - N (%)	1,797 (1.5)	603 (1.8)	1,194 (1.4)
Urban hospital location - N (%)	91,420 (76.4)	25,078 (74.9)	66,342 (76.9)
Hospital region - N (%)			
• New England	3,984 (3.3)	1,095 (3.3)	2,889 (3.3)
• Northeast	10,083 (8.4)	2,495 (7.5)	7,588 (8.8)
• Mideast	17,617 (14.7)	5,124 (15.3)	12,493 (14.5)
• Southeast	28,276 (23.6)	7,664 (22.9)	20,612 (23.9)
• Great Lakes	19,743 (16.5)	4,766 (14.2)	14,977 (17.4)
• South	14,531 (12.1)	4,121 (12.3)	10,410 (12.1)
• Midwest	5,811 (4.9)	1,651 (4.9)	4,160 (4.8)
• Mountain West	2,837 (2.4)	883 (2.6)	1,954 (2.3)
• Southwest	13,051 (10.9)	4,685 (14.0)	8,366 (9.7)
• Northwest	3,805 (3.2)	1,004 (3.0)	2,801 (3.2)
Discharge quarter - N (%)			
• 2015Q4	18,079 (15.1)	2,987 (8.9)	15,092 (17.5)
• 2016Q1	17,891 (14.9)	4,443 (13.3)	13,448 (15.6)
• 2016Q2	17,034 (14.2)	5,683 (17.0)	11,351 (13.2)
• 2016Q3	21,050 (17.6)	5,160 (15.4)	15,890 (18.4)
• 2016Q4	22,287 (18.6)	6,797 (20.3)	15,490 (18.0)
• 2017Q1	23,397 (19.5)	8,418 (25.1)	14,979 (17.4)

Variables	All Cases (N = 119,738)	Compliant (N = 33,488)	Non-Compliant (N = 86,250)
Patient Hispanic ethnicity (Yes) - N (%)	7,282 (6.1)	1,826 (5.5)	5,456 (6.3)
Patient sex (Male) - N (%)	60,350 (50.4)	17,400 (52.0)	42,950 (49.8)
Patient race - N (%)			
• American Indian/Alaska Native	830 (0.7)	184 (0.5)	646 (0.7)
• Asian	2,511 (2.1)	1,025 (3.1)	1,486 (1.7)
• Black/African American	14,966 (12.5)	3,171 (9.5)	11,795 (13.7)
• Native Hawaiian/Pacific Islander	359 (0.3)	149 (0.4)	210 (0.2)
• Unable to Determine	4,346 (3.6)	1,163 (3.5)	3,183 (3.7)
• White	96,726 (80.8)	27,796 (83.0)	68,930 (79.9)
Patient age at admission (Years)			
• Mean	73.3	73.7	73.2
• Median	74	75	74
• Standard Deviation	13.1	13.2	13.0
• Interquartile Range	66 - 83	67 - 83	66 - 83
Persistent hypotension (=Yes) - N (%)	5,947 (5.0)	512 (1.5)	5,435 (6.3)
Initial lactate level - N (%)			
• Not collected	44,838 (37.4)	0 (0.0)	44,838 (52.0)
• ≤ 2.0 mmol/L	18,899 (15.8)	15,838 (47.3)	3,061 (3.5)
• > 2.0 and < 4.0 mmol/L	24,763 (20.7)	16,921 (50.5)	7,842 (9.1)
• ≥ 4.0 mmol/L	31,238 (26.1)	729 (2.2)	30,509 (35.4)
Severe sepsis - N (%)	86,704 (72.4)	30,285 (90.4)	56,419 (65.4)
Septic shock - N (%)	33,034 (27.6)	3,203 (9.6)	29,831 (34.6)
Site of infection - N (%)			
• Bacteremia	63 (0.1)	10 (0.0)	53 (0.1)
• Central nervous system	303 (0.3)	60 (0.2)	243 (0.3)
• Fungal	1,806 (1.5)	432 (1.3)	1,374 (1.6)
• Gastrointestinal	1,468 (1.2)	260 (0.8)	1,208 (1.4)
• Genitourinary	28,204 (23.6)	8,704 (26.0)	19,500 (22.6)
• Heart	953 (0.8)	219 (0.7)	734 (0.9)
• Lung	39,265 (32.8)	12,715 (38.0)	26,550 (30.8)
• Missing	379 (0.3)	125 (0.4)	254 (0.3)
• Other	10,507 (8.8)	3,024 (9.0)	7,483 (8.7)
• Peritoneal	3,265 (2.7)	189 (0.6)	3,076 (3.6)
• Septicemia only	31,173 (26.0)	7,078 (21.1)	24,095 (27.9)
• Soft tissue	2,103 (1.8)	577 (1.7)	1,526 (1.8)
• Upper respiratory tract	249 (0.2)	95 (0.3)	154 (0.2)
Organ failures - N (%)			

Variables	All Cases (N = 119,738)	Compliant (N = 33,488)	Non-Compliant (N = 86,250)
• Cardiovascular	13,378 (11.2)	2,202 (6.6)	11,176 (13.0)
• Hematologic	5,938 (5.0)	520 (1.6)	5,418 (6.3)
• Metabolic	36,623 (30.6)	7,341 (21.9)	29,282 (34.0)
• Neurologic	12,664 (10.6)	2,796 (8.3)	9,868 (11.4)
• Renal	60,351 (50.4)	13,529 (40.4)	46,822 (54.3)
• Respiratory	41,029 (34.3)	8,365 (25.0)	32,664 (37.9)
Comorbidities - N (%)			
• Acquired immune deficiency syndrome	378 (0.3)	119 (0.4)	259 (0.3)
• Alcohol abuse	4,178 (3.5)	828 (2.5)	3,350 (3.9)
• Chronic blood loss anemia	1,483 (1.2)	288 (0.9)	1,195 (1.4)
• Chronic pulmonary disease	39,104 (32.7)	11,954 (35.7)	27,150 (31.5)
• Coagulopathy	19,799 (16.5)	4,022 (12.0)	15,777 (18.3)
• Congestive heart failure	37,046 (30.9)	8,321 (24.8)	28,725 (33.3)
• Deficiency anemias	38,988 (32.6)	10,645 (31.8)	28,343 (32.9)
• Depression	15,742 (13.1)	4,845 (14.5)	10,897 (12.6)
• Diabetes with chronic complications	26,331 (22.0)	6,803 (20.3)	19,528 (22.6)
• Diabetes without chronic complications	21,572 (18.0)	6,014 (18.0)	15,558 (18.0)
• Drug abuse	2,617 (2.2)	736 (2.2)	1,881 (2.2)
• Fluid and electrolyte disorders	81,231 (67.8)	20,231 (60.4)	61,000 (70.7)
• Hypertension	84,445 (70.5)	24,015 (71.7)	60,430 (70.1)
• Hypothyroidism	21,955 (18.3)	6,372 (19.0)	15,583 (18.1)
• Liver disease	7,756 (6.5)	1,421 (4.2)	6,335 (7.3)
• Lymphoma	2,095 (1.7)	616 (1.8)	1,479 (1.7)
• Metastatic cancer	5,621 (4.7)	1,305 (3.9)	4,316 (5.0)
• Obesity	18,146 (15.2)	4,316 (12.9)	13,830 (16.0)
• Other neurological disorders	23,745 (19.8)	7,328 (21.9)	16,417 (19.0)
• Paralysis	10,975 (9.2)	3,276 (9.8)	7,699 (8.9)
• Peptic ulcer disease excluding bleeding	1,998 (1.7)	373 (1.1)	1,625 (1.9)
• Peripheral vascular disease	13,016 (10.9)	3,099 (9.3)	9,917 (11.5)
• Psychoses	5,552 (4.6)	1,874 (5.6)	3,678 (4.3)
• Pulmonary circulation disease	2,467 (2.1)	506 (1.5)	1,961 (2.3)
• Renal failure	37,542 (31.4)	8,825 (26.4)	28,717 (33.3)
• Rheumatoid arthritis/collagen vascular diseases	5,363 (4.5)	1,556 (4.6)	3,807 (4.4)
• Solid tumor without metastasis	5,084 (4.2)	1,414 (4.2)	3,670 (4.3)
• Valvular disease	11,018 (9.2)	2,807 (8.4)	8,211 (9.5)
• Weight loss	21,314 (17.8)	4,854 (14.5)	16,460 (19.1)
Mortality - N (%)	37,092 (31.0)	6,661 (19.9)	30,431 (35.3)

Variables	All Cases (N = 119,738)	Compliant (N = 33,488)	Non-Compliant (N = 86,250)
• Severe Sepsis	24,414 (28.2)	5,712 (18.9)	18,702 (33.2)
• Septic Shock	12,678 (38.4)	949 (29.6)	11,729 (39.3)

e-Table 16: Standard-match variable distribution by deciles of compliance propensity deciles where the matching is based on a greedy nearest neighbor with a caliper of 0.40 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.25

Variables	All (1.4-98.5)	Decile 1 (1.4-24.3)	Decile 2 (24.3-32.9)	Decile 3 (32.9-40.2)	Decile 4 (40.2-46.8)	Decile 5 (46.8-52.8)	Decile 6 (52.8-58.6)	Decile 7 (58.6-64.4)	Decile 8 (64.4-70.5)	Decile 9 (70.5-77.8)	Decile 10 (77.8-98.5)
Observations - N (%)	245,740 (100.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)	24,574 (10.0)
Hospital cert bed count											
• Mean	302.7	330.6	321.7	318.1	320.4	313.7	305.2	294.9	288.5	277.7	256.2
• Median	238	263	254	250	243	242	240	232	229	222	211
• Standard Deviation	265.9	277.1	272.3	269.6	285.7	285.0	279.3	262.3	257.9	240.2	211.0
• Interquartile Range	133 - 385	149 - 425	145 - 413	144 - 407	139 - 408	141 - 397	132 - 385	129 - 376	124 - 371	122 - 362	122 - 334
Hospital accreditation - N (%)											
• AOA/HFAP	10,201 (4.2)	1,150 (4.7)	1,064 (4.3)	1,159 (4.7)	1,088 (4.4)	1,053 (4.3)	1,013 (4.1)	960 (3.9)	885 (3.6)	791 (3.2)	1,038 (4.2)
• CIHQ	1,668 (0.7)	118 (0.5)	127 (0.5)	123 (0.5)	133 (0.5)	128 (0.5)	132 (0.5)	150 (0.6)	182 (0.7)	290 (1.2)	285 (1.2)
• DNV	23,183 (9.4)	2,577 (10.5)	2,574 (10.5)	2,541 (10.3)	2,536 (10.3)	2,488 (10.1)	2,218 (9.0)	2,212 (9.0)	2,207 (9.0)	2,045 (8.3)	1,785 (7.3)
• NONE	6,667 (2.7)	687 (2.8)	803 (3.3)	830 (3.4)	778 (3.2)	707 (2.9)	699 (2.8)	641 (2.6)	570 (2.3)	525 (2.1)	427 (1.7)
• TJC	204,021 (83.0)	20,042 (81.6)	20,006 (81.4)	19,921 (81.1)	20,039 (81.5)	20,198 (82.2)	20,512 (83.5)	20,611 (83.9)	20,730 (84.4)	20,923 (85.1)	21,039 (85.6)
Critical access hospital - N (%)	3,856 (1.6)	326 (1.3)	373 (1.5)	385 (1.6)	415 (1.7)	439 (1.8)	413 (1.7)	416 (1.7)	389 (1.6)	369 (1.5)	331 (1.3)
Urban hospital location - N (%)	186,117 (75.7)	19,184 (78.1)	18,824 (76.6)	18,631 (75.8)	18,438 (75.0)	18,583 (75.6)	18,496 (75.3)	18,390 (74.8)	18,366 (74.7)	18,466 (75.1)	18,739 (76.3)
Hospital region - N (%)											
• New England	8,773 (3.6)	883 (3.6)	764 (3.1)	894 (3.6)	918 (3.7)	947 (3.9)	959 (3.9)	961 (3.9)	897 (3.7)	824 (3.4)	726 (3.0)
• Northeast	20,038 (8.2)	2,076 (8.4)	2,019 (8.2)	2,109 (8.6)	2,100 (8.5)	2,122 (8.6)	2,023 (8.2)	2,020 (8.2)	1,986 (8.1)	1,927 (7.8)	1,656 (6.7)

Variables	All (1.4-98.5)	Decile 1 (1.4-24.3)	Decile 2 (24.3-32.9)	Decile 3 (32.9-40.2)	Decile 4 (40.2-46.8)	Decile 5 (46.8-52.8)	Decile 6 (52.8-58.6)	Decile 7 (58.6-64.4)	Decile 8 (64.4-70.5)	Decile 9 (70.5-77.8)	Decile 10 (77.8-98.5)
• Mideast	34,472 (14.0)	3,311 (13.5)	3,437 (14.0)	3,303 (13.4)	3,402 (13.8)	3,358 (13.7)	3,348 (13.6)	3,425 (13.9)	3,460 (14.1)	3,420 (13.9)	4,008 (16.3)
• Southeast	54,877 (22.3)	5,314 (21.6)	5,392 (21.9)	5,249 (21.4)	5,306 (21.6)	5,486 (22.3)	5,541 (22.5)	5,574 (22.7)	5,697 (23.2)	5,754 (23.4)	5,564 (22.6)
• Great Lakes	42,047 (17.1)	4,604 (18.7)	4,758 (19.4)	4,775 (19.4)	4,615 (18.8)	4,339 (17.7)	4,264 (17.4)	4,139 (16.8)	4,042 (16.4)	3,537 (14.4)	2,974 (12.1)
• South	28,433 (11.6)	2,947 (12.0)	2,901 (11.8)	2,781 (11.3)	2,786 (11.3)	2,762 (11.2)	2,734 (11.1)	2,600 (10.6)	2,771 (11.3)	2,966 (12.1)	3,185 (13.0)
• Midwest	11,655 (4.7)	1,066 (4.3)	1,032 (4.2)	1,16 (4.7)	1,237 (5.0)	1,205 (4.9)	1,119 (4.6)	1,162 (4.7)	1,147 (4.7)	1,200 (4.9)	1,324 (5.4)
• Mountain • West	7,028 (2.9)	683 (2.8)	681 (2.8)	648 (2.6)	732 (3.0)	721 (2.9)	746 (3.0)	783 (3.2)	784 (3.2)	729 (3.0)	521 (2.1)
• Southwest	30,257 (12.3)	2,881 (11.7)	2,792 (11.4)	2,787 (11.3)	2,646 (10.8)	2,765 (11.3)	2,995 (12.2)	3,009 (12.2)	2,920 (11.9)	3,417 (13.9)	4,045 (16.5)
• Northwest	8,160 (3.3)	809 (3.3)	798 (3.2)	865 (3.5)	83 (3.4)	869 (3.5)	845 (3.4)	901 (3.7)	870 (3.5)	800 (3.3)	571 (2.3)
Discharge quarter - N (%)											
• 2015Q4	38,784 (15.8)	6,971 (28.4)	5,705 (23.2)	4,928 (20.1)	4,429 (18.0)	3,815 (15.5)	3,267 (13.3)	2,914 (11.9)	2,578 (10.5)	2,278 (9.3)	1,899 (7.7)
• 2016Q1	42,300 (17.2)	5,929 (24.1)	5,165 (21.0)	4,604 (18.7)	4,425 (18.0)	4,283 (17.4)	4,068 (16.6)	3,824 (15.6)	3,688 (15.0)	3,298 (13.4)	3,016 (12.3)
• 2016Q2	41,548 (16.9)	4,698 (19.1)	4,137 (16.8)	3,921 (16.0)	3,915 (15.9)	4,054 (16.5)	4,259 (17.3)	4,142 (16.9)	4,204 (17.1)	4,177 (17.0)	4,041 (16.4)
• 2016Q3	36,986 (15.1)	2,526 (10.3)	3,426 (13.9)	3,866 (15.7)	3,899 (15.9)	3,934 (16.0)	3,997 (16.3)	4,121 (16.8)	3,829 (15.6)	3,759 (15.3)	3,629 (14.8)
• 2016Q4	40,945 (16.7)	2,403 (9.8)	3,119 (12.7)	3,810 (15.5)	3,943 (16.0)	4,076 (16.6)	4,305 (17.5)	4,583 (18.6)	4,725 (19.2)	4,971 (20.2)	5,010 (20.4)
• 2017Q1	45,177 (18.4)	2,047 (8.3)	3,022 (12.3)	3,445 (14.0)	3,963 (16.1)	4,412 (18.0)	4,678 (19.0)	4,990 (20.3)	5,550 (22.6)	6,091 (24.8)	6,979 (28.4)
Patient Hispanic ethnicity (Yes) - N (%)	13,385 (5.4)	1,489 (6.1)	1,362 (5.5)	1,329 (5.4)	1,292 (5.3)	1,327 (5.4)	1,379 (5.6)	1,283 (5.2)	1,268 (5.2)	1,349 (5.5)	1,307 (5.3)
Patient sex (Male) - N (%)	125,812 (51.2)	12,486 (50.8)	12,423 (50.6)	12,457 (50.7)	12,432 (50.6)	12,537 (51.0)	12,633 (51.4)	12,553 (51.1)	12,662 (51.5)	12,758 (51.9)	12,871 (52.4)
Patient race - N (%)											
• American Indian/Alaska Native	1,568 (0.6)	199 (0.8)	155 (0.6)	196 (0.8)	176 (0.7)	143 (0.6)	146 (0.6)	172 (0.7)	140 (0.6)	136 (0.6)	105 (0.4)

Variables	All (1.4-98.5)	Decile 1 (1.4-24.3)	Decile 2 (24.3-32.9)	Decile 3 (32.9-40.2)	Decile 4 (40.2-46.8)	Decile 5 (46.8-52.8)	Decile 6 (52.8-58.6)	Decile 7 (58.6-64.4)	Decile 8 (64.4-70.5)	Decile 9 (70.5-77.8)	Decile 10 (77.8-98.5)
• Asian	5,471 (2.2)	508 (2.1)	440 (1.8)	456 (1.9)	452 (1.8)	413 (1.7)	503 (2.0)	534 (2.2)	519 (2.1)	671 (2.7)	975 (4.0)
• Black/African American	26,649 (10.8)	3,099 (12.6)	3,080 (12.5)	2,904 (11.8)	2,827 (11.5)	2,711 (11.0)	2,544 (10.4)	2,529 (10.3)	2,426 (9.9)	2,275 (9.3)	2,254 (9.2)
• Native Hawaiian/Pacific Islander	724 (0.3)	45 (0.2)	47 (0.2)	53 (0.2)	52 (0.2)	52 (0.2)	63 (0.3)	58 (0.2)	73 (0.3)	96 (0.4)	185 (0.8)
• Unable to Determine	8,504 (3.5)	898 (3.7)	844 (3.4)	816 (3.3)	825 (3.4)	851 (3.5)	873 (3.6)	805 (3.3)	816 (3.3)	891 (3.6)	885 (3.6)
• White	202,824 (82.5)	19,825 (80.7)	20,008 (81.4)	20,149 (82.0)	20,242 (82.4)	20,404 (83.0)	20,445 (83.2)	20,476 (83.3)	20,600 (83.8)	20,505 (83.4)	20,170 (82.1)
Patient age at admission (Years)											
• Mean	73.6	73.3	73.6	73.7	73.8	73.7	73.6	73.7	73.5	73.5	73.6
• Median	75	74	74	75	75	75	75	75	74	75	75
• Standard Deviation	13.0	12.7	12.8	12.8	12.9	13.1	13.1	13.2	13.0	13.3	13.2
• Interquartile Range	66 - 83	66 - 83	66 - 83	67 - 83	67 - 83	67 - 83	66 - 83	67 - 83	66 - 83	66 - 83	66 - 83
Length of stay (Days)											
• Mean	7.5	8.4	8.0	7.8	7.6	7.4	7.5	7.3	7.2	7.2	7.2
• Median	6	6	6	6	6	6	6	5	5	5	5
• Standard Deviation	7.1	7.8	7.4	7.3	7.1	6.8	7.0	6.8	6.7	6.8	6.8
• Interquartile Range	3 - 9	4 - 10	4 - 10	4 - 10	3 - 9	3 - 9	3 - 9	3 - 9	3 - 9	3 - 9	3 - 9
Persistent hypotension (=Yes) - N (%)	12,964 (5.3)	4,045 (16.5)	2,199 (8.9)	1,392 (5.7)	1,153 (4.7)	973 (4.0)	797 (3.2)	707 (2.9)	631 (2.6)	564 (2.3)	503 (2.0)
Initial lactate level - N (%)											
• ≤ 2.0 mmol/L	90,784 (36.9)	4,589 (18.7)	6,301 (25.6)	7,017 (28.6)	8,233 (33.5)	8,857 (36.0)	9,507 (38.7)	10,124 (41.2)	11,034 (44.9)	11,924 (48.5)	13,198 (53.7)
• > 2.0 and < 4.0 mmol/L	122,179 (49.7)	9,207 (37.5)	10,857 (44.2)	12,437 (50.6)	12,977 (52.8)	13,570 (55.2)	13,492 (54.9)	13,422 (54.6)	12,859 (52.3)	12,229 (49.8)	11,129 (45.3)
• ≥ 4.0 mmol/L	32,777 (13.3)	10,778 (43.9)	7,416 (30.2)	5,120 (20.8)	3,364 (13.7)	2,147 (8.7)	1,57 (6.4)	1,028 (4.2)	681 (2.8)	421 (1.7)	247 (1.0)
• Severe sepsis - N (%)	196,455 (79.9)	8,979 (36.5)	15,815 (64.4)	18,860 (76.7)	20,433 (83.1)	21,452 (87.3)	22,108 (90.0)	22,396 (91.1)	22,514 (91.6)	22,335 (90.9)	21,563 (87.7)
Septic shock - N (%)	49,285	15,595	8,759	5,714	4,141	3,122	2,466	2,178	2,060	2,239	3,011

Variables	All (1.4-98.5)	Decile 1 (1.4-24.3)	Decile 2 (24.3-32.9)	Decile 3 (32.9-40.2)	Decile 4 (40.2-46.8)	Decile 5 (46.8-52.8)	Decile 6 (52.8-58.6)	Decile 7 (58.6-64.4)	Decile 8 (64.4-70.5)	Decile 9 (70.5-77.8)	Decile 10 (77.8-98.5)
	(20.1)	(63.5)	(35.6)	(23.3)	(16.9)	(12.7)	(10.0)	(8.9)	(8.4)	(9.1)	(12.3)
Mortality - N (%)	60,569 (24.6)	8,278 (33.7)	7,255 (29.5)	6,556 (26.7)	6,141 (25.0)	5,753 (23.4)	5,594 (22.8)	5,411 (22.0)	5,174 (21.1)	5,223 (21.3)	5,184 (21.1)
Severe Sepsis	43,608 (22.2)	2,681 (32.4)	4,107 (56.6)	4,554 (69.5)	4,686 (76.3)	4,695 (81.6)	4,801 (85.8)	4,737 (87.5)	4,534 (87.6)	4,546 (87.0)	4,267 (82.3)
Septic Shock	16,961 (34.4)	5,597 (67.6)	3,148 (43.4)	2,002 (30.5)	1,455 (23.7)	1,058 (18.4)	793 (14.2)	674 (12.5)	640 (12.4)	677 (13.0)	917 (17.7)
Site of infection - N (%)											
Bacteremia	110 (0.0)	13 (0.1)	11 (0.0)	12 (0.0)	14 (0.1)	8 (0.0)	14 (0.1)	17 (0.1)	6 (0.0)	5 (0.0)	10 (0.0)
• Central nervous system	607 (0.2)	59 (0.2)	73 (0.3)	81 (0.3)	66 (0.3)	59 (0.2)	61 (0.2)	52 (0.2)	61 (0.2)	46 (0.2)	49 (0.2)
• Fungal	3,391 (1.4)	377 (1.5)	363 (1.5)	355 (1.4)	344 (1.4)	350 (1.4)	343 (1.4)	310 (1.3)	320 (1.3)	329 (1.3)	300 (1.2)
• Gastrointestinal	2,542 (1.0)	348 (1.4)	289 (1.2)	287 (1.2)	309 (1.3)	265 (1.1)	247 (1.0)	247 (1.0)	209 (0.9)	183 (0.7)	158 (0.6)
• Genitourinary	60,938 (24.8)	5,766 (23.5)	5,823 (23.7)	5,861 (23.9)	5,939 (24.2)	6,079 (24.7)	6,018 (24.5)	6,245 (25.4)	6,309 (25.7)	6,379 (26.0)	6,519 (26.5)
• Heart	1,807 (0.7)	195 (0.8)	210 (0.9)	204 (0.8)	189 (0.8)	179 (0.7)	178 (0.7)	170 (0.7)	175 (0.7)	153 (0.6)	154 (0.6)
• Lung	86,578 (35.2)	7,770 (31.6)	8,149 (33.2)	8,210 (33.4)	8,392 (34.1)	8,614 (35.1)	8,834 (35.9)	8,904 (36.2)	8,937 (36.4)	9,226 (37.5)	9,542 (38.8)
• Missing	941 (0.4)	66 (0.3)	100 (0.4)	101 (0.4)	97 (0.4)	121 (0.5)	106 (0.4)	108 (0.4)	83 (0.3)	93 (0.4)	66 (0.3)
• Other	21,777 (8.9)	2,000 (8.1)	2,046 (8.3)	2,145 (8.7)	2,221 (9.0)	2,186 (8.9)	2,236 (9.1)	2,235 (9.1)	2,245 (9.1)	2,259 (9.2)	2,204 (9.0)
• Peritoneal	4,001 (1.6)	859 (3.5)	648 (2.6)	540 (2.2)	465 (1.9)	378 (1.5)	280 (1.1)	254 (1.0)	256 (1.0)	178 (0.7)	143 (0.6)
• Septicemia only	57,895 (23.6)	6,660 (27.1)	6,349 (25.8)	6,250 (25.4)	5,998 (24.4)	5,743 (23.4)	5,712 (23.2)	5,545 (22.6)	5,438 (22.1)	5,235 (21.3)	4,965 (20.2)
• Soft tissue	4,53 (1.8)	417 (1.7)	464 (1.9)	473 (1.9)	486 (2.0)	517 (2.1)	485 (2.0)	429 (1.7)	461 (1.9)	420 (1.7)	384 (1.6)
• Upper respiratory tract	617 (0.3)	44 (0.2)	49 (0.2)	55 (0.2)	54 (0.2)	75 (0.3)	60 (0.2)	58 (0.2)	74 (0.3)	68 (0.3)	80 (0.3)
• Organ failures - N (%)											
Cardiovascular	22,641	3,241	2,900	2,714	2,438	2,283	2,159	1,981	1,735	1,693	1,497

Variables	All (1.4-98.5)	Decile 1 (1.4-24.3)	Decile 2 (24.3-32.9)	Decile 3 (32.9-40.2)	Decile 4 (40.2-46.8)	Decile 5 (46.8-52.8)	Decile 6 (52.8-58.6)	Decile 7 (58.6-64.4)	Decile 8 (64.4-70.5)	Decile 9 (70.5-77.8)	Decile 10 (77.8-98.5)
	(9.2)	(13.2)	(11.8)	(11.0)	(9.9)	(9.3)	(8.8)	(8.1)	(7.1)	(6.9)	(6.1)
• Hematologic	7,750 (3.2)	1,653 (6.7)	1,338 (5.4)	1,034 (4.2)	810 (3.3)	690 (2.8)	556 (2.3)	502 (2.0)	419 (1.7)	382 (1.6)	366 (1.5)
• Metabolic	63,996 (26.0)	9,005 (36.6)	7,673 (31.2)	6,939 (28.2)	6,298 (25.6)	6,084 (24.8)	5,831 (23.7)	5,670 (23.1)	5,527 (22.5)	5,493 (22.4)	5,476 (22.3)
• Neurologic	22,923 (9.3)	2,967 (12.1)	2,559 (10.4)	2,361 (9.6)	2,334 (9.5)	2,242 (9.1)	2,108 (8.6)	2,145 (8.7)	2,093 (8.5)	2,049 (8.3)	2,065 (8.4)
• Renal	114,529 (46.6)	14,054 (57.2)	13,204 (53.7)	12,488 (50.8)	11,808 (48.1)	11,259 (45.8)	10,855 (44.2)	10,520 (42.8)	10,362 (42.2)	9,949 (40.5)	10,030 (40.8)
• Respiratory	73,062 (29.7)	9,715 (39.5)	8,597 (35.0)	8,123 (33.1)	7,398 (30.1)	7,000 (28.5)	6,877 (28.0)	6,589 (26.8)	6,410 (26.1)	6,260 (25.5)	6,093 (24.8)
• Comorbidities - N (%)											
Acquired immune deficiency syndrome	728 (0.3)	68 (0.3)	77 (0.3)	75 (0.3)	60 (0.2)	63 (0.3)	78 (0.3)	78 (0.3)	61 (0.2)	76 (0.3)	92 (0.4)
• Alcohol abuse	7,219 (2.9)	946 (3.8)	878 (3.6)	731 (3.0)	702 (2.9)	706 (2.9)	721 (2.9)	649 (2.6)	653 (2.7)	638 (2.6)	595 (2.4)
• Chronic blood loss anemia	2,712 (1.1)	348 (1.4)	353 (1.4)	298 (1.2)	286 (1.2)	289 (1.2)	260 (1.1)	222 (0.9)	227 (0.9)	236 (1.0)	193 (0.8)
• Chronic pulmonary disease	84,689 (34.5)	7,780 (31.7)	8,015 (32.6)	8,160 (33.2)	8,319 (33.9)	8,517 (34.7)	8,576 (34.9)	8,631 (35.1)	8,819 (35.9)	8,881 (36.1)	8,991 (36.6)
• Coagulopathy	34,832 (14.2)	4,717 (19.2)	4,056 (16.5)	3,672 (14.9)	3,457 (14.1)	3,295 (13.4)	3,237 (13.2)	3,197 (13.0)	3,121 (12.7)	3,047 (12.4)	3,033 (12.3)
• Congestive heart failure	73,502 (29.9)	8,179 (33.3)	8,425 (34.3)	8,377 (34.1)	8,049 (32.8)	7,610 (31.0)	7,295 (29.7)	7,086 (28.8)	6,587 (26.8)	6,192 (25.2)	5,702 (23.2)
• Deficiency anemias	79,407 (32.3)	8,283 (33.7)	8,047 (32.7)	8,031 (32.7)	7,936 (32.3)	7,826 (31.8)	7,797 (31.7)	7,905 (32.2)	7,826 (31.8)	7,815 (31.8)	7,941 (32.3)
• Depression	34,277 (13.9)	3,188 (13.0)	3,225 (13.1)	3,299 (13.4)	3,347 (13.6)	3,371 (13.7)	3,526 (14.3)	3,609 (14.7)	3,582 (14.6)	3,584 (14.6)	3,546 (14.4)
• Diabetes with chronic complications	52,262 (21.3)	5,016 (20.4)	5,441 (22.1)	5,513 (22.4)	5,487 (22.3)	5,424 (22.1)	5,242 (21.3)	5,149 (21.0)	5,112 (20.8)	4,968 (20.2)	4,910 (20.0)
• Diabetes without chronic complications	45,924 (18.7)	4,904 (20.0)	4,693 (19.1)	4,670 (19.0)	4,706 (19.2)	4,570 (18.6)	4,540 (18.5)	4,551 (18.5)	4,499 (18.3)	4,407 (17.9)	4,384 (17.8)
• Drug abuse	5,332 (2.2)	583 (2.4)	534 (2.2)	474 (1.9)	475 (1.9)	530 (2.2)	551 (2.2)	547 (2.2)	515 (2.1)	571 (2.3)	552 (2.2)
• Fluid and electrolyte disorders	157,657 (64.2)	17,763 (72.3)	16,829 (68.5)	16,216 (66.0)	15,783 (64.2)	15,534 (63.2)	15,269 (62.1)	15,121 (61.5)	15,029 (61.2)	15,067 (61.3)	15,046 (61.2)

Variables	All (1.4-98.5)	Decile 1 (1.4-24.3)	Decile 2 (24.3-32.9)	Decile 3 (32.9-40.2)	Decile 4 (40.2-46.8)	Decile 5 (46.8-52.8)	Decile 6 (52.8-58.6)	Decile 7 (58.6-64.4)	Decile 8 (64.4-70.5)	Decile 9 (70.5-77.8)	Decile 10 (77.8-98.5)
• Hypertension	174,578 (71.0)	16,766 (68.2)	17,363 (70.7)	17,462 (71.1)	17,670 (71.9)	17,656 (71.8)	17,634 (71.8)	17,542 (71.4)	17,542 (71.4)	17,375 (70.7)	17,568 (71.5)
• Hypothyroidism	45,796 (18.6)	4,572 (18.6)	4,484 (18.2)	4,562 (18.6)	4,510 (18.4)	4,594 (18.7)	4,672 (19.0)	4,584 (18.7)	4,641 (18.9)	4,575 (18.6)	4,602 (18.7)
• Liver disease	13,063 (5.3)	1,741 (7.1)	1,631 (6.6)	1,523 (6.2)	1,377 (5.6)	1,268 (5.2)	1,260 (5.1)	1,134 (4.6)	1,025 (4.2)	1,096 (4.5)	1,008 (4.1)
• Lymphoma	4,412 (1.8)	447 (1.8)	424 (1.7)	438 (1.8)	436 (1.8)	449 (1.8)	415 (1.7)	425 (1.7)	438 (1.8)	448 (1.8)	492 (2.0)
• Metastatic cancer	10,517 (4.3)	1,229 (5.0)	1,146 (4.7)	1,087 (4.4)	1,036 (4.2)	1,064 (4.3)	1,034 (4.2)	1,000 (4.1)	1,016 (4.1)	1,002 (4.1)	903 (3.7)
• Obesity	37,616 (15.3)	3,944 (16.0)	4,189 (17.0)	4,172 (17.0)	4,058 (16.5)	3,941 (16.0)	3,803 (15.5)	3,671 (14.9)	3,523 (14.3)	3,305 (13.4)	3,010 (12.2)
• Other neurological disorders	50,340 (20.5)	4,822 (19.6)	4,877 (19.8)	4,843 (19.7)	4,678 (19.0)	4,919 (20.0)	4,963 (20.2)	5,068 (20.6)	5,318 (21.6)	5,316 (21.6)	5,536 (22.5)
• Paralysis	23,378 (9.5)	2,354 (9.6)	2,274 (9.3)	2,300 (9.4)	2,301 (9.4)	2,289 (9.3)	2,326 (9.5)	2,331 (9.5)	2,381 (9.7)	2,370 (9.6)	2,452 (10.0)
• Peptic ulcer disease excluding bleeding	3,341 (1.4)	463 (1.9)	437 (1.8)	376 (1.5)	341 (1.4)	323 (1.3)	316 (1.3)	274 (1.1)	280 (1.1)	281 (1.1)	250 (1.0)
• Peripheral vascular disease	25,526 (10.4)	2,848 (11.6)	2,773 (11.3)	2,794 (11.4)	2,662 (10.8)	2,565 (10.4)	2,526 (10.3)	2,467 (10.0)	2,352 (9.6)	2,270 (9.2)	2,269 (9.2)
• Psychoses	12,031 (4.9)	1,060 (4.3)	1,058 (4.3)	1,120 (4.6)	1,084 (4.4)	1,099 (4.5)	1,146 (4.7)	1,257 (5.1)	1,328 (5.4)	1,349 (5.5)	1,530 (6.2)
• Pulmonary circulation disease	4,435 (1.8)	540 (2.2)	510 (2.1)	535 (2.2)	451 (1.8)	454 (1.8)	452 (1.8)	374 (1.5)	386 (1.6)	396 (1.6)	337 (1.4)
• Renal failure	73,577 (29.9)	7,819 (31.8)	8,238 (33.5)	8,055 (32.8)	7,935 (32.3)	7,505 (30.5)	7,297 (29.7)	7,128 (29.0)	6,821 (27.8)	6,611 (26.9)	6,168 (25.1)
• Rheumatoid arthritis/collagen vascular diseases	11,496 (4.7)	1,134 (4.6)	1,110 (4.5)	1,106 (4.5)	1,147 (4.7)	1,151 (4.7)	1,171 (4.8)	1,170 (4.8)	1,196 (4.9)	1,182 (4.8)	1,129 (4.6)
• Solid tumor without metastasis	10,056 (4.1)	1,042 (4.2)	1,037 (4.2)	976 (4.0)	1,021 (4.2)	970 (3.9)	1,005 (4.1)	1,009 (4.1)	964 (3.9)	1,028 (4.2)	1,004 (4.1)
• Valvular disease	22,509 (9.2)	2,465 (10.0)	2,484 (10.1)	2,397 (9.8)	2,349 (9.6)	2,306 (9.4)	2,247 (9.1)	2,229 (9.1)	2,101 (8.5)	2,013 (8.2)	1,918 (7.8)
• Weight loss	39,436 (16.0)	4,744 (19.3)	4,504 (18.3)	4,177 (17.0)	3,998 (16.3)	3,760 (15.3)	3,920 (16.0)	3,557 (14.5)	3,620 (14.7)	3,481 (14.2)	3,675 (15.0)

e-Table 17: Stringent-match variable distribution by deciles of compliance propensity deciles where the matching is based on a greedy nearest neighbor with a caliper of 0.22 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.10

Variables	All (1.4-98.3)	Decile 1 (1.4-27.0)	Decile 2 (27.0-35.0)	Decile 3 (35.0-41.3)	Decile 4 (41.3-46.4)	Decile 5 (46.7-52.0)	Decile 6 (52.0-57.3)	Decile 7 (57.3-62.7)	Decile 8 (62.7-68.8)	Decile 9 (68.8-76.2)	Decile 10 (76.2-98.3)
Observations - N (%)	214,032 (100.0)	21,404 (10.0)	21,402 (10.0)	21,404 (10.0)	21,404 (10.0)	21,402 (10.0)	21,404 (10.0)	21,404 (10.0)	21,402 (10.0)	21,404 (10.0)	21,402 (10.0)
Hospital cert bed count											
• Mean	305.8	329.5	324.6	318.4	314.7	316.3	313.7	304.2	296.8	279.1	260.5
• Median	240	266	255	245	244	244	241	237	233	223	215
• Standard Deviation	269.1	275.5	273.8	276.5	271.1	279.4	286.3	281.3	276.8	241.1	212.5
• Interquartile Range	135 - 389	149 - 425	145 - 418	142 - 407	145 - 398	144 - 399	138 - 395	131 - 382	128 - 380	123 - 362	122 - 340
Hospital accreditation - N (%)											
• AOA/HFAP	8,914 (4.2)	975 (4.6)	997 (4.7)	961 (4.5)	1,006 (4.7)	966 (4.5)	953 (4.5)	878 (4.1)	743 (3.5)	641 (3.0)	794 (3.7)
• CIHQ	1,367 (0.6)	109 (0.5)	96 (0.4)	119 (0.6)	104 (0.5)	97 (0.5)	115 (0.5)	136 (0.6)	135 (0.6)	185 (0.9)	271 (1.3)
• DNV	20,427 (9.5)	2,232 (10.4)	2,240 (10.5)	2,309 (10.8)	2,265 (10.6)	2,149 (10.0)	2,022 (9.4)	1,880 (8.8)	1,861 (8.7)	1,818 (8.5)	1,651 (7.7)
• NONE	5,925 (2.8)	635 (3.0)	732 (3.4)	703 (3.3)	672 (3.1)	656 (3.1)	617 (2.9)	543 (2.5)	522 (2.4)	451 (2.1)	394 (1.8)
• TJC	177,399 (82.9)	17,453 (81.5)	17,337 (81.0)	17,312 (80.9)	17,357 (81.1)	17,534 (81.9)	17,697 (82.7)	17,967 (83.9)	18,141 (84.8)	18,309 (85.5)	18,292 (85.5)
Critical access hospital - N (%)	3,355 (1.6)	306 (1.4)	317 (1.5)	350 (1.6)	381 (1.8)	343 (1.6)	362 (1.7)	354 (1.7)	367 (1.7)	312 (1.5)	263 (1.2)
Urban hospital location - N (%)	162,038 (75.7)	16,610 (77.6)	16,440 (76.8)	16,079 (75.1)	16,132 (75.4)	16,134 (75.4)	16,176 (75.6)	16,134 (75.4)	16,127 (75.4)	15,993 (74.7)	16,213 (75.8)
Hospital region - N (%)											
• New England	7,823 (3.7)	730 (3.4)	693 (3.2)	753 (3.5)	883 (4.1)	868 (4.1)	869 (4.1)	822 (3.8)	801 (3.7)	770 (3.6)	634 (3.0)
• Northeast	17,642 (8.2)	1,787 (8.3)	1,783 (8.3)	1,733 (8.1)	1,763 (8.2)	1,882 (8.8)	1,917 (9.0)	1,857 (8.7)	1,790 (8.4)	1,590 (7.4)	1,540 (7.2)
• Mideast	29,774 (13.9)	2,956 (13.8)	2,979 (13.9)	2,857 (13.3)	2,896 (13.5)	2,938 (13.7)	2,887 (13.5)	3,005 (14.0)	2,973 (13.9)	3,020 (14.1)	3,263 (15.2)

Variables	All (1.4-98.3)	Decile 1 (1.4-27.0)	Decile 2 (27.0-35.0)	Decile 3 (35.0-41.3)	Decile 4 (41.3-46.4)	Decile 5 (46.7-52.0)	Decile 6 (52.0-57.3)	Decile 7 (57.3-62.7)	Decile 8 (62.7-68.8)	Decile 9 (68.8-76.2)	Decile 10 (76.2-98.3)
• Southeast	47,675 (22.3)	4,582 (21.4)	4,541 (21.2)	4,577 (21.4)	4,500 (21.0)	4,624 (21.6)	4,723 (22.1)	5,014 (23.4)	5,144 (24.0)	5,102 (23.8)	4,868 (22.7)
• Great Lakes	37,320 (17.4)	4,111 (19.2)	4,269 (19.9)	4,160 (19.4)	4,067 (19.0)	3,915 (18.3)	3,752 (17.5)	3,551 (16.6)	3,416 (16.0)	3,291 (15.4)	2,788 (13.0)
• South	24,362 (11.4)	2,527 (11.8)	2,577 (12.0)	2,446 (11.4)	2,382 (11.1)	2,423 (11.3)	2,341 (10.9)	2,310 (10.8)	2,229 (10.4)	2,387 (11.2)	2,740 (12.8)
• Midwest	10,139 (4.7)	937 (4.4)	914 (4.3)	1,033 (4.8)	1,080 (5.0)	1,010 (4.7)	1,108 (5.2)	995 (4.6)	995 (4.6)	970 (4.5)	1,097 (5.1)
• Mountain West	6,259 (2.9)	618 (2.9)	558 (2.6)	620 (2.9)	609 (2.8)	618 (2.9)	639 (3.0)	651 (3.0)	723 (3.4)	731 (3.4)	492 (2.3)
• Southwest	25,791 (12.1)	2,427 (11.3)	2,367 (11.1)	2,496 (11.7)	2,452 (11.5)	2,360 (11.0)	2,418 (11.3)	2,402 (11.2)	2,613 (12.2)	2,856 (13.3)	3,400 (15.9)
• Northwest	7,247 (3.4)	729 (3.4)	721 (3.4)	729 (3.4)	772 (3.6)	764 (3.6)	750 (3.5)	797 (3.7)	718 (3.4)	687 (3.2)	580 (2.7)
Discharge quarter - N (%)											
• 2015Q4	33,706 (15.7)	5,806 (27.1)	5,102 (23.8)	4,285 (20.0)	3,821 (17.9)	3,201 (15.0)	2,910 (13.6)	2,551 (11.9)	2,288 (10.7)	2,057 (9.6)	1,685 (7.9)
• 2016Q1	36,967 (17.3)	4,924 (23.0)	4,324 (20.2)	4,107 (19.2)	3,972 (18.6)	3,671 (17.2)	3,588 (16.8)	3,575 (16.7)	3,175 (14.8)	2,965 (13.9)	2,666 (12.5)
• 2016Q2	35,969 (16.8)	3,940 (18.4)	3,395 (15.9)	3,319 (15.5)	3,287 (15.4)	3,693 (17.3)	3,601 (16.8)	3,652 (17.1)	3,785 (17.7)	3,711 (17.3)	3,586 (16.8)
• 2016Q3	32,886 (15.4)	2,467 (11.5)	3,091 (14.4)	3,408 (15.9)	3,474 (16.2)	3,535 (16.5)	3,590 (16.8)	3,469 (16.2)	3,393 (15.9)	3,283 (15.3)	3,176 (14.8)
• 2016Q4	35,666 (16.7)	2,354 (11.0)	2,851 (13.3)	3,159 (14.8)	3,415 (16.0)	3,529 (16.5)	3,742 (17.5)	3,930 (18.4)	4,073 (19.0)	4,234 (19.8)	4,379 (20.5)
• 2017Q1	38,838 (18.1)	1,913 (8.9)	2,639 (12.3)	3,126 (14.6)	3,435 (16.0)	3,773 (17.6)	3,973 (18.6)	4,227 (19.7)	4,688 (21.9)	5,154 (24.1)	5,910 (27.6)
Patient Hispanic ethnicity (Yes) - N (%)	11,474 (5.4)	1,251 (5.8)	1,198 (5.6)	1,092 (5.1)	1,163 (5.4)	1,096 (5.1)	1,136 (5.3)	1,129 (5.3)	1,125 (5.3)	1,118 (5.2)	1,166 (5.4)
Patient sex (Male) - N (%)	109,454 (51.1)	10,867 (50.8)	10,784 (50.4)	10,922 (51.0)	10,778 (50.4)	10,961 (51.2)	10,879 (50.8)	10,971 (51.3)	10,981 (51.3)	11,104 (51.9)	11,207 (52.4)
Patient race - N (%)											
• American Indian/Alaska Native	1,380 (0.6)	162 (0.8)	141 (0.7)	177 (0.8)	148 (0.7)	145 (0.7)	115 (0.5)	139 (0.6)	132 (0.6)	123 (0.6)	98 (0.5)
• Asian	4,472 (2.1)	444 (2.1)	405 (1.9)	366 (1.7)	379 (1.8)	391 (1.8)	400 (1.9)	408 (1.9)	425 (2.0)	481 (2.2)	773 (3.6)
• Black/African American	23,347 (10.9)	2,732 (12.8)	2,673 (12.5)	2,565 (12.0)	2,476 (11.6)	2,366 (11.1)	2,298 (10.7)	2,170 (10.1)	2,103 (9.8)	2,014 (9.4)	1,950 (9.1)
• Native Hawaiian/Pacific Islander	582 (0.3)	37 (0.2)	35 (0.2)	50 (0.2)	38 (0.2)	53 (0.2)	55 (0.3)	38 (0.2)	53 (0.2)	72 (0.3)	151 (0.7)

Online supplements are not copyedited prior to posting and the author(s) take full responsibility for the accuracy of all data.

Variables	All (1.4-98.3)	Decile 1 (1.4-27.0)	Decile 2 (27.0-35.0)	Decile 3 (35.0-41.3)	Decile 4 (41.3-46.4)	Decile 5 (46.7-52.0)	Decile 6 (52.0-57.3)	Decile 7 (57.3-62.7)	Decile 8 (62.7-68.8)	Decile 9 (68.8-76.2)	Decile 10 (76.2-98.3)
• Unable to Determine	7,360 (3.4)	760 (3.6)	738 (3.4)	707 (3.3)	688 (3.2)	714 (3.3)	726 (3.4)	734 (3.4)	740 (3.5)	781 (3.6)	772 (3.6)
• White	176,891 (82.6)	17,269 (80.7)	17,410 (81.3)	17,539 (81.9)	17,675 (82.6)	17,733 (82.9)	17,810 (83.2)	17,915 (83.7)	17,949 (83.9)	17,933 (83.8)	17,658 (82.5)
Patient age at admission (Years)											
• Mean	73.6	73.4	73.5	73.7	73.7	73.7	73.6	73.6	73.5	73.4	73.6
• Median	74	74	74	74	75	75	75	74	74	74	75
• Standard Deviation	13.0	12.6	12.8	12.8	12.9	12.9	13.1	13.1	13.1	13.2	13.2
• Interquartile Range	66 - 83	66 - 83	66 - 83	67 - 83	67 - 83	67 - 83	66 - 83	66 - 83	66 - 83	66 - 83	66 - 83
Length of stay (Days)											
• Mean	7.6	8.3	8.0	7.7	7.6	7.6	7.4	7.4	7.3	7.1	7.2
• Median	6	6	6	6	6	6	6	5	5	5	5
• Standard Deviation	7.1	7.6	7.4	7.2	7.1	7.0	6.9	7.1	6.7	6.6	7.0
• Interquartile Range	3 - 9	4 - 10	4 - 10	4 - 10	3 - 9	3 - 9	3 - 9	3 - 9	3 - 9	3 - 9	3 - 9
Persistent hypotension (=Yes) - N (%)	10,719 (5.0)	3,332 (15.6)	1,687 (7.9)	1,195 (5.6)	952 (4.4)	775 (3.6)	653 (3.1)	630 (2.9)	567 (2.6)	508 (2.4)	420 (2.0)
Initial lactate level - N (%)											
• ≤ 2.0 mmol/L	80,222 (37.5)	4,282 (20.0)	5,925 (27.7)	6,539 (30.6)	7,189 (33.6)	7,809 (36.5)	8,332 (38.9)	8,961 (41.9)	9,499 (44.4)	10,300 (48.1)	11,386 (53.2)
• > 2.0 and < 4.0 mmol/L	108,896 (50.9)	7,852 (36.7)	10,561 (49.3)	11,619 (54.3)	11,846 (55.3)	11,816 (55.2)	11,868 (55.4)	11,567 (54.0)	11,303 (52.8)	10,669 (49.8)	9,795 (45.8)
• ≥ 4.0 mmol/L	24,914 (11.6)	9,270 (43.3)	4,916 (23.0)	3,246 (15.2)	2,369 (11.1)	1,777 (8.3)	1,204 (5.6)	876 (4.1)	600 (2.8)	435 (2.0)	221 (1.0)
Severe sepsis - N (%)	176,534 (82.5)	9,262 (43.3)	15,206 (71.0)	17,318 (80.9)	18,312 (85.6)	18,947 (88.5)	19,488 (91.0)	19,632 (91.7)	19,716 (92.1)	19,635 (91.7)	19,018 (88.9)
Septic shock - N (%)	37,498 (17.5)	12,142 (56.7)	6,196 (29.0)	4,086 (19.1)	3,092 (14.4)	2,455 (11.5)	1,916 (9.0)	1,772 (8.3)	1,686 (7.9)	1,769 (8.3)	2,384 (11.1)
Mortality - N (%)	51,906 (24.3)	7,044 (32.9)	5,975 (27.9)	5,554 (25.9)	5,259 (24.6)	5,104 (23.8)	4,761 (22.2)	4,697 (21.9)	4,577 (21.4)	4,463 (20.9)	4,472 (20.9)
Severe Sepsis	39,096 (22.2)	2,699 (38.3)	3,797 (63.5)	4,137 (74.5)	4,207 (80.0)	4,278 (83.8)	4,150 (87.2)	4,127 (87.9)	4,032 (88.1)	3,922 (87.9)	3,747 (83.8)
Septic Shock	12,810 (34.2)	4,345 (61.7)	2,178 (36.5)	1,417 (25.5)	1,052 (20.0)	826 (16.2)	611 (12.8)	570 (12.1)	545 (11.9)	541 (12.1)	725 (16.2)
Site of infection - N (%)											

Variables	All (1.4-98.3)	Decile 1 (1.4-27.0)	Decile 2 (27.0-35.0)	Decile 3 (35.0-41.3)	Decile 4 (41.3-46.4)	Decile 5 (46.7-52.0)	Decile 6 (52.0-57.3)	Decile 7 (57.3-62.7)	Decile 8 (62.7-68.8)	Decile 9 (68.8-76.2)	Decile 10 (76.2-98.3)
• Bacteremia	97 (0.0)	11 (0.1)	8 (0.0)	10 (0.0)	11 (0.1)	17 (0.1)	13 (0.1)	6 (0.0)	11 (0.1)	3 (0.0)	7 (0.0)
• Central nervous system	546 (0.3)	51 (0.2)	76 (0.4)	48 (0.2)	65 (0.3)	55 (0.3)	57 (0.3)	57 (0.3)	50 (0.2)	43 (0.2)	44 (0.2)
• Fungal	3,008 (1.4)	355 (1.7)	310 (1.4)	317 (1.5)	307 (1.4)	324 (1.5)	325 (1.5)	287 (1.3)	294 (1.4)	229 (1.1)	260 (1.2)
• Gastrointestinal	2,244 (1.0)	306 (1.4)	260 (1.2)	285 (1.3)	241 (1.1)	234 (1.1)	212 (1.0)	216 (1.0)	191 (0.9)	174 (0.8)	125 (0.6)
• Genitourinary	52,885 (24.7)	4,918 (23.0)	5,092 (23.8)	5,078 (23.7)	5,268 (24.6)	5,138 (24.0)	5,405 (25.3)	5,378 (25.1)	5,387 (25.2)	5,518 (25.8)	5,703 (26.6)
• Heart	1,586 (0.7)	182 (0.9)	178 (0.8)	186 (0.9)	163 (0.8)	166 (0.8)	149 (0.7)	166 (0.8)	134 (0.6)	137 (0.6)	125 (0.6)
• Lung	75,126 (35.1)	6,825 (31.9)	7,040 (32.9)	7,191 (33.6)	7,275 (34.0)	7,412 (34.6)	7,528 (35.2)	7,652 (35.8)	7,852 (36.7)	8,097 (37.8)	8,254 (38.6)
• Missing	859 (0.4)	75 (0.4)	88 (0.4)	100 (0.5)	112 (0.5)	91 (0.4)	89 (0.4)	78 (0.4)	85 (0.4)	83 (0.4)	58 (0.3)
• Other	19,089 (8.9)	1,671 (7.8)	1,820 (8.5)	1,936 (9.0)	1,952 (9.1)	2,008 (9.4)	1,935 (9.0)	1,949 (9.1)	1,954 (9.1)	1,964 (9.2)	1,900 (8.9)
• Peritoneal	3,513 (1.6)	781 (3.6)	574 (2.7)	452 (2.1)	393 (1.8)	318 (1.5)	242 (1.1)	248 (1.2)	213 (1.0)	168 (0.8)	124 (0.6)
• Septicemia only	50,509 (23.6)	5,815 (27.2)	5,490 (25.7)	5,303 (24.8)	5,135 (24.0)	5,157 (24.1)	4,959 (23.2)	4,911 (22.9)	4,792 (22.4)	4,539 (21.2)	4,408 (20.6)
• Soft tissue	4,028 (1.9)	372 (1.7)	430 (2.0)	440 (2.1)	424 (2.0)	430 (2.0)	440 (2.1)	405 (1.9)	380 (1.8)	380 (1.8)	327 (1.5)
• Upper respiratory tract	542 (0.3)	42 (0.2)	36 (0.2)	58 (0.3)	58 (0.3)	52 (0.2)	50 (0.2)	51 (0.2)	59 (0.3)	69 (0.3)	67 (0.3)
Organ failures - N (%)											
• Cardiovascular	19,919 (9.3)	2,816 (13.2)	2,558 (12.0)	2,309 (10.8)	2,169 (10.1)	2,073 (9.7)	1,877 (8.8)	1,783 (8.3)	1,559 (7.3)	1,421 (6.6)	1,354 (6.3)
• Hematologic	6,472 (3.0)	1,373 (6.4)	1,059 (4.9)	843 (3.9)	677 (3.2)	596 (2.8)	488 (2.3)	462 (2.2)	345 (1.6)	326 (1.5)	303 (1.4)
• Metabolic	54,775 (25.6)	7,649 (35.7)	6,273 (29.3)	5,717 (26.7)	5,493 (25.7)	5,337 (24.9)	5,014 (23.4)	4,915 (23.0)	4,879 (22.8)	4,738 (22.1)	4,760 (22.2)
• Neurologic	19,837 (9.3)	2,541 (11.9)	2,217 (10.4)	2,021 (9.4)	2,052 (9.6)	1,931 (9.0)	1,905 (8.9)	1,819 (8.5)	1,845 (8.6)	1,763 (8.2)	1,743 (8.1)
• Renal	99,595 (46.5)	12,190 (57.0)	11,322 (52.9)	10,776 (50.3)	10,133 (47.3)	10,041 (46.9)	9,483 (44.3)	9,163 (42.8)	9,042 (42.2)	8,737 (40.8)	8,708 (40.7)
• Respiratory	63,267 (29.6)	8,318 (38.9)	7,293 (34.1)	6,858 (32.0)	6,346 (29.6)	6,295 (29.4)	5,917 (27.6)	5,739 (26.8)	5,727 (26.8)	5,544 (25.9)	5,230 (24.4)
Comorbidities - N (%)											

Variables	All (1.4-98.3)	Decile 1 (1.4-27.0)	Decile 2 (27.0-35.0)	Decile 3 (35.0-41.3)	Decile 4 (41.3-46.4)	Decile 5 (46.7-52.0)	Decile 6 (52.0-57.3)	Decile 7 (57.3-62.7)	Decile 8 (62.7-68.8)	Decile 9 (68.8-76.2)	Decile 10 (76.2-98.3)
Acquired immune deficiency syndrome	617 (0.3)	63 (0.3)	74 (0.3)	59 (0.3)	42 (0.2)	61 (0.3)	63 (0.3)	58 (0.3)	52 (0.2)	64 (0.3)	81 (0.4)
Alcohol abuse	6,262 (2.9)	824 (3.8)	688 (3.2)	667 (3.1)	621 (2.9)	596 (2.8)	605 (2.8)	593 (2.8)	575 (2.7)	588 (2.7)	505 (2.4)
Chronic blood loss anemia	2,368 (1.1)	307 (1.4)	315 (1.5)	269 (1.3)	236 (1.1)	245 (1.1)	234 (1.1)	210 (1.0)	196 (0.9)	177 (0.8)	179 (0.8)
Chronic pulmonary disease	73,983 (34.6)	6,733 (31.5)	7,046 (32.9)	7,190 (33.6)	7,330 (34.2)	7,364 (34.4)	7,444 (34.8)	7,537 (35.2)	7,661 (35.8)	7,806 (36.5)	7,872 (36.8)
Coagulopathy	29,998 (14.0)	3,956 (18.5)	3,421 (16.0)	3,210 (15.0)	2,933 (13.7)	2,864 (13.4)	2,723 (12.7)	2,861 (13.4)	2,758 (12.9)	2,653 (12.4)	2,619 (12.2)
Congestive heart failure	65,080 (30.4)	7,183 (33.6)	7,529 (35.2)	7,339 (34.3)	7,022 (32.8)	6,787 (31.7)	6,542 (30.6)	6,167 (28.8)	5,944 (27.8)	5,572 (26.0)	4,995 (23.3)
Deficiency anemias	69,149 (32.3)	7,144 (33.4)	7,078 (33.1)	6,989 (32.7)	6,928 (32.4)	6,821 (31.9)	6,823 (31.9)	6,838 (31.9)	6,811 (31.8)	6,777 (31.7)	6,940 (32.4)
Depression	29,923 (14.0)	2,798 (13.1)	2,848 (13.3)	2,827 (13.2)	2,893 (13.5)	3,018 (14.1)	3,043 (14.2)	3,151 (14.7)	3,031 (14.2)	3,238 (15.1)	3,076 (14.4)
Diabetes with chronic complications	45,845 (21.4)	4,439 (20.7)	4,835 (22.6)	4,797 (22.4)	4,765 (22.3)	4,718 (22.0)	4,686 (21.9)	4,544 (21.2)	4,405 (20.6)	4,338 (20.3)	4,318 (20.2)
Diabetes without chronic complications	39,975 (18.7)	4,241 (19.8)	4,117 (19.2)	4,099 (19.2)	4,034 (18.8)	3,976 (18.6)	3,977 (18.6)	3,958 (18.5)	3,873 (18.1)	3,875 (18.1)	3,825 (17.9)
Drug abuse	4,606 (2.2)	485 (2.3)	436 (2.0)	438 (2.0)	435 (2.0)	433 (2.0)	497 (2.3)	480 (2.2)	445 (2.1)	476 (2.2)	481 (2.2)
Fluid and electrolyte disorders	136,948 (64.0)	15,304 (71.5)	14,503 (67.8)	13,932 (65.1)	13,686 (63.9)	13,594 (63.5)	13,341 (62.3)	13,259 (61.9)	13,121 (61.3)	13,069 (61.1)	13,139 (61.4)
Hypertension	152,113 (71.1)	14,664 (68.5)	15,231 (71.2)	15,256 (71.3)	15,262 (71.3)	15,385 (71.9)	15,286 (71.4)	15,311 (71.5)	15,221 (71.1)	15,295 (71.5)	15,202 (71.0)
Hypothyroidism	39,737 (18.6)	3,945 (18.4)	4,040 (18.9)	3,829 (17.9)	3,950 (18.5)	4,036 (18.9)	3,980 (18.6)	3,980 (18.6)	4,019 (18.8)	3,998 (18.7)	3,960 (18.5)
Liver disease	11,343 (5.3)	1,534 (7.2)	1,397 (6.5)	1,293 (6.0)	1,157 (5.4)	1,089 (5.1)	1,077 (5.0)	1,056 (4.9)	948 (4.4)	916 (4.3)	876 (4.1)
Lymphoma	3,817 (1.8)	375 (1.8)	372 (1.7)	371 (1.7)	360 (1.7)	404 (1.9)	384 (1.8)	353 (1.6)	395 (1.8)	371 (1.7)	432 (2.0)
Metastatic cancer	9,154 (4.3)	1,072 (5.0)	973 (4.5)	883 (4.1)	952 (4.4)	933 (4.4)	880 (4.1)	921 (4.3)	884 (4.1)	875 (4.1)	781 (3.6)
Obesity	33,359 (15.6)	3,419 (16.0)	3,807 (17.8)	3,629 (17.0)	3,580 (16.7)	3,533 (16.5)	3,359 (15.7)	3,290 (15.4)	3,054 (14.3)	2,982 (13.9)	2,706 (12.6)
Other neurological disorders	43,449 (20.3)	4,171 (19.5)	4,253 (19.9)	4,093 (19.1)	4,115 (19.2)	4,221 (19.7)	4,352 (20.3)	4,326 (20.2)	4,567 (21.3)	4,537 (21.2)	4,814 (22.5)
Paralysis	20,232 (9.5)	2,026 (9.5)	2,006 (9.4)	1,978 (9.2)	1,970 (9.2)	2,012 (9.4)	1,923 (9.0)	1,982 (9.3)	2,093 (9.8)	2,107 (9.8)	2,135 (10.0)

Variables	All (1.4-98.3)	Decile 1 (1.4-27.0)	Decile 2 (27.0-35.0)	Decile 3 (35.0-41.3)	Decile 4 (41.3-46.4)	Decile 5 (46.7-52.0)	Decile 6 (52.0-57.3)	Decile 7 (57.3-62.7)	Decile 8 (62.7-68.8)	Decile 9 (68.8-76.2)	Decile 10 (76.2-98.3)
• Peptic ulcer disease excluding bleeding	2,916 (1.4)	414 (1.9)	371 (1.7)	338 (1.6)	307 (1.4)	266 (1.2)	256 (1.2)	273 (1.3)	248 (1.2)	227 (1.1)	216 (1.0)
• Peripheral vascular disease	22,377 (10.5)	2,501 (11.7)	2,441 (11.4)	2,455 (11.5)	2,320 (10.8)	2,307 (10.8)	2,186 (10.2)	2,061 (9.6)	2,094 (9.8)	2,002 (9.4)	2,010 (9.4)
• Psychoses	10,364 (4.8)	918 (4.3)	961 (4.5)	918 (4.3)	915 (4.3)	979 (4.6)	991 (4.6)	1,052 (4.9)	1,132 (5.3)	1,203 (5.6)	1,295 (6.1)
• Pulmonary circulation disease	3,894 (1.8)	459 (2.1)	446 (2.1)	426 (2.0)	442 (2.1)	412 (1.9)	383 (1.8)	362 (1.7)	306 (1.4)	361 (1.7)	297 (1.4)
• Renal failure	64,705 (30.2)	6,849 (32.0)	7,221 (33.7)	7,086 (33.1)	6,796 (31.8)	6,724 (31.4)	6,489 (30.3)	6,285 (29.4)	5,981 (27.9)	5,793 (27.1)	5,481 (25.6)
• Rheumatoid arthritis/collagen vascular diseases	10,093 (4.7)	978 (4.6)	968 (4.5)	1,003 (4.7)	973 (4.5)	996 (4.7)	1,008 (4.7)	1,050 (4.9)	1,071 (5.0)	1,028 (4.8)	1,018 (4.8)
• Solid tumor without metastasis	8,769 (4.1)	953 (4.5)	872 (4.1)	908 (4.2)	810 (3.8)	863 (4.0)	865 (4.0)	894 (4.2)	874 (4.1)	867 (4.1)	863 (4.0)
• Valvular disease	19,727 (9.2)	2,084 (9.7)	2,169 (10.1)	2,130 (10.0)	2,028 (9.5)	2,083 (9.7)	2,035 (9.5)	1,915 (8.9)	1,855 (8.7)	1,788 (8.4)	1,640 (7.7)
• Weight loss	34,248 (16.0)	4,213 (19.7)	3,754 (17.5)	3,702 (17.3)	3,525 (16.5)	3,423 (16.0)	3,225 (15.1)	3,150 (14.7)	3,103 (14.5)	3,051 (14.3)	3,102 (14.5)

e-Table 18: SEP-1 algorithm as represented as four bundles of care with three- and six- hour elements of care for both severe sepsis and septic shock

SEP-1 Data Element	Severe Sepsis		Septic Shock	
	Three Hour Bundle	Six Hour Bundle	Three Hour Bundle	Six Hour Bundle
Initial Lactate Collection	Yes	Must be completed within three hours of Severe Sepsis Presentation		
Blood Culture Collection	Yes			
Initial Antibiotic Started	Yes			
Repeat Lactate Collection (if Initial Lactate is ≥ 2 mmol/L)	N/A	Yes	Must be completed within six hours of Severe Sepsis presentation	
30mL/kg Crystalloid Fluids Started (initial hypotension or lactate ≥ 4 mmol/L)	N/A	N/A	Yes	Must be completed within 3 hours of Septic Shock
Vasopressor Given (for persistent hypotension)	N/A	N/A	Must be completed within 6 hours of Septic Shock	Yes
Repeat Volume Status/ Tissue Perfusion Assessment	N/A	N/A		Yes

e-Appendix 2: Sensitivity analysis results

Sensitivity analyses using preferential within-cluster matching and Mahalanobis distance within propensity score calipers set at 0.55 and 0.21 SD of LPS to achieve absolute SMDs $\leq$ 0.25 and $\leq$ 0.10, respectively, showed an association that was similar to Standard-match (5.38% ARR versus 5.67% ARR) and Stringent-match (4.06% ARR each), respectively (e-Table 19).

Sensitivity analyses using propensity score distance matching at 0.36 and .21 SD of LPS without Mahalanobis distance to achieve absolute SMDs $\leq$ 0.25 and $\leq$ 0.10, respectively, showed an association that was similar to Standard-match (5.47% ARR versus 5.67% ARR) and Stringent-match (4.05% ARR versus 4.06% ARR), respectively (e-Table 19).

e-Table 19: Sensitivity Analysis Comparisons

Sensitivity Analysis	Matching Method	N	Percent Match	Mean Difference	Total Absolute STD Difference	Compliance Mortality	Non-compliance Mortality	Absolute Mortality Difference	Relative Risk	RR 95% CI*		Odds Ratio	RR 95% CI*	
Preferential Within Cluster Matching	Standard-match: GNN (0.40) - MAH	245,740	76.63%	0.175	2.724	21.81	27.48	5.67	0.794	0.783	0.805	0.736	0.723	0.750
	PWM GNN (0.55) - MAH	228,552	66.29%	0.117	2.552	21.94	27.32	5.38	0.803	0.792	0.815	0.748	0.734	0.762
	Stringent-match: GNN (0.22) - MAH	214,032	64.10%	0.095	1.391	22.22	26.28	4.06	0.846	0.833	0.858	0.802	0.786	0.818
	PWM GNN (0.21) - MAH	192,260	57.60%	0.051	1.710	22.08	26.14	4.06	0.845	0.831	0.858	0.801	0.784	0.817
Without Mahalanobis Distance	Standard-match: GNN (0.40) - MAH	245,740	76.63%	0.175	2.724	21.81	27.48	5.67	0.794	0.783	0.805	0.736	0.723	0.750
	GNN (0.36) - LPS	239,516	71.76%	0.157	2.447	21.92	27.39	5.47	0.800	0.789	0.812	0.744	0.731	0.758
	Stringent-match: GNN (0.22) - MAH	214,032	64.10%	0.095	1.391	22.22	26.28	4.06	0.846	0.833	0.858	0.802	0.786	0.818
	GNN (0.21) - LPS	211,996	63.52%	0.089	1.284	22.36	26.41	4.05	0.847	0.834	0.860	0.803	0.787	0.819

PWM - Preferential within-cluster matching
GNN – Greedy nearest neighbor matching where the caliber width is the number in the parentheses
MAH - Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L)
LPS – Distance between two matched logits of the propensity score
STD - Standardized
*Generalized estimating equation (GEE) methods were used to account for matched pairs and to calculate robust standard errors

e-Table 20: Standard-match quantitative bias analysis for unmeasured confounder using HGLM using adaptive Gaussian quadrature

Tests for location: Mu0 = 0			Standard-match based on a greedy nearest neighbor with a caliper of 0.40 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.25
Test	**Statistic**	**p-value**	
Student's t	t	77.6	< 0.001
Sign	M	10,686	< 0.001
Signed rank	S	920,330,000	< 0.001

Observation	Pairs	Signed rank	Mean0	Variance0	Gamma	Mean	Variance	t-test	p- value
1	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.00	2,863,132,818.0	1.0213E+14	91.1	< 0.001
2	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.10	2,999,472,476.0	1.019E+14	77.7	< 0.001
3	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.20	3,123,417,619.6	1.0129E+14	65.6	< 0.001
4	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.30	3,236,584,924.7	1.004E+14	54.6	< 0.001
5	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.40	3,340,321,621.0	9.9297E+13	44.5	< 0.001
6	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.50	3,435,759,381.6	9.8049E+13	35.1	< 0.001
7	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.60	3,523,855,776.0	9.6695E+13	26.4	< 0.001
8	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.70	3,605,426,511.6	9.5269E+13	18.2	< 0.001
9	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.80	3,681,170,766.0	9.3797E+13	10.6	< 0.001
10	107,016	3,783,463,650	5,726,265,636	4.0854E+14	1.90	3,751,691,278.8	9.2297E+13	3.3	< 0.001
11	107,016	3,783,463,650	5,726,265,636	4.0854E+14	2.00	3,817,510,424.0	9.0786E+13	-3.6	> 0.99

e-Table 21: Stringent-match quantitative bias analysis for unmeasured confounder using HGLM using adaptive Gaussian quadrature

Tests for location: Mu0 = 0			Stringent-match based on a greedy nearest neighbor with a caliper of 0.22 and using Mahalanobis distance constituted by the logit of the propensity score and three binary lactate variables (≤ 2.0, > 2.0 and < 4.0, ≥ 4.0 mmol/L) which keeps all standardized mean differences < 0.10
Test	**Statistic**	**p-value**	
Student's t	t	52.9	< 0.001	
Sign	M	7,126	< 0.001	
Signed rank	S	521,560,000	< 0.001	

Observation	Pairs	Signed rank	Mean0	Variance0	Gamma	Mean	Variance	t-test	p- value
1	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.00	2,863,132,818	1.0213E+14	51.609	< 0.001
2	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.05	2,932,965,326	1.0207E+14	44.712	< 0.001
3	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.10	2,999,472,476	1.019E+14	38.161	< 0.001
4	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.15	3,062,886,270	1.0164E+14	31.921	< 0.001
5	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.20	3,123,417,620	1.0129E+14	25.961	< 0.001
6	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.25	3,181,258,687	1.0087E+14	20.256	< 0.001
7	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.30	3,236,584,925	1.004E+14	14.782	< 0.001
8	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.35	3,289,556,855	9.9869E+13	9.520	< 0.001
9	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.40	3,340,321,621	9.9297E+13	4.453	< 0.001
10	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.45	3,389,014,356	9.8689E+13	-0.435	0.668
11	107,016	3,384,696,883	5,726,265,636	4.0854E+14	1.50	3,435,759,382	9.8049E+13	-5.157	> 0.99

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