Supplemental Table 1. Search strategy.

Keyword search	(sepsis*:ab,ti OR 'septic shock':ab,ti) AND (cluster*:ti OR phenotyp*:ti OR subphenotyp*:ti) AND (mortality* OR survival*) AND [article]/lim AND [english]/lim AND ([embase]/lim OR [medline]/lim OR [pubmed-not-medline]/lim)
Subject heading search	('sepsis'/exp OR 'septic shock'/exp) AND ('clustering algorithm'/exp OR 'phenotype'/exp) AND 'survival rate'/exp

Supplemental Table 2. Extracted variables.

Title
Last name of first author
Study aim
Data source
Study design
Study funding
Conflicts of interest
Population description
Inclusion criteria
Exclusion criteria
Total participants
Relevant differences between discovery, validation, and test cohorts
Clustering algorithm
Clustering variable type
Data imputation method
Cluster number
Principle difference between clusters
Cluster outcome prediction
Cluster treatment response prediction
Was sensitivity analysis performed?
Was external validation performed?
Were race/ethnicity included as clustering variables?
If race/ethnicity were included as clustering variables, were they different between clusters?

10. Exposure measured over time	11. Objective measurement of dependent variables?	12. Blinded outcome assessment	13. < 20% Loss to follow up	14. Adjustment for confounders
No	Yes	No	NA	No
No	Yes	No	Yes	Yes
Yes	Yes	No	NA	Yes
Yes	Yes	No	NA	Yes
No	Yes	No	NA	No
No	Yes	No	NA	Yes
No	Yes	No	NA	Yes
No	Yes	No	NA	Yes
Yes	Yes	No	NA	No
No	Yes	No	Yes	Yes
Yes	Yes	No	Yes	Yes
No	Yes	No	Yes	Yes
Yes	Yes	No	NA	Yes
Yes	Yes	No	NA	No
Yes	Yes	No	NA	No
No	Yes	No	Yes	Yes
No	Yes	No	NA	Yes

4. Uniform inclusion criteria	5. Sample size justification	6. Exposure measured prior to outcomes	7. Sufficient timeframe	8. Exposure dose dependency	9. Objective measurement of independent variable
No	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes
Yes	No	Yes	Yes	NA	Yes
Yes	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes
Yes	No	Yes	Yes	NA	Yes
Yes	No	NA	Yes	NA	Yes
Yes	No	Yes	Yes	NA	Yes
Yes	No	Yes	Yes	NA	Yes
Yes	No	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes
No	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes
No	No	Yes	Yes	NA	Yes

Supplemental Table 3. Study risk of bias

Author	1. Clearly stated question	2. Clearly stated study population	3. >= 50% participation rate
Geri 2019(12)	Yes	Yes	Yes
Seymour 2019(13)	Yes	Yes	Yes
Bhavani 2020(15)	Yes	Yes	NA
Ding 2021(16)	Yes	Yes	Yes
Gärdlund 2018(17)	Yes	Yes	NA
Han 2021(18)	Yes	Yes	Yes
Kudo 2021(19)	Yes	Yes	Yes
Scicluna 2017(20)	Yes	Yes	Yes
Sharafoddini 2021(21)	Yes	Yes	Yes
Antcliffe 2019 (22)	Yes	Yes	No
Bhavani 2019(23)	Yes	Yes	Yes
Davenport 2016(24)	Yes	Yes	Yes
Liu 2020(25)	Yes	Yes	NA
Mayhew 2018 (26)	Yes	Yes	NA
Nowak 2016 (27)	Yes	Yes	Yes
Sweeney 2018 (28)	Yes	Yes	Yes
Zhang 2020 (29)	Yes	Yes	No

Supplemental Table 4. Characteristics of study cohort selection and methodology.

Author	Data source	Possible conflicts of interest	Population description	Inclusion criteria	Exclusion criteria
Geri 2019 (12)	Two published prospective databases from 12 different ICUs including echocardiographic monitoring performed by a transesophageal route at the initial phase of septic shock were merged for post hoc analysis.	AVB received a grant from GSK for conducting clinical research and is member of the scientific advisory board.	Patients with septic shock in sinus rhythm undergoing critical care echocardiography or transpulmonary thermodilution from 2011-2013 in the Hemosepsis study; Patients with septic shock from any origin 2012-2014 collectively in the Hemopred study	Suspected infection responsible for sustained hypotension despite adequate fluid loading that required vasopressors, with associated clinical signs of tissue hypoperfusion	Chronic heart failure
Seymour 2019 (13)	12 community and academic hospitals in the University of Pittsburgh Medical Center, Genetic and Inflammatory Markers of Sepsis study, A Controlled Comparison of Eritoran in Severe Sepsis, Activated Protein C Worldwide Evaluation in Severe Sepsis Protocol-Based Care for Early Septic Shock	Dr Seymour reported receiving personal fees from Edwards Inc and Beckman Coulter Inc. Dr Gomez reported receiving grants from TES Pharma. Dr Huang reported receiving nonfinancial support (procalcitonin assays) from Biomerieux and grants from Thermofisher for microbiome research. Dr Vodovotz reported being the cofounder and a stakeholder in Immunetrics Inc and having a provisional patent application pending. Dr Yende reported receiving personal fees from Atox Bio and grants from Bristol-Myers Squibb. Dr Angus reported receiving personal fees from and serving as a consultant to Ferring Pharmaceuticals, Bristol-Myers Squibb, Bayer AG, and Beckman Coulter Inc; owning stock in Alung Technologies; and having patent applications pending for selepressin (compounds, compositions, and methods for treating sepsis) and proteomic biomarkers of sepsis in elderly patients. No other disclosures were reported.	Adults (aged >18 years) who met sepsis criteria within the first 6 hours of presentation at the 12 hospitals during 2010 to 2012 and during 2013 to 2014. The third cohort was the Genetic and Inflammatory Mark-ers of Sepsis (GenIMS) study. Data was also taken from 3 randomized clinical trials (ProCESS, PROWESS, and ACCESS).	Sepsis-3 criteria within the first 6hours of hospital presentation. Evidence of a suspected infection was defined as the combination of administration of antibiotics and a body fluid culture specimen obtained, the first of which was required within the first 6 hours of hospital presentation. In the GenIMS cohort, the Sepsis-2 definition was used because it was available at the time. All patients in the 3 RCTs met variationsof the Sepsis-2 criteria, and were therefore eligible for the cur-rent study	NA
Bhavani 2020 (15)	University of Chicago Medicine between 2013 and 2019	Dr. Carey disclosed work for hire. Dr. Churpek received funding from EarlySense, a medical device company, and has a patent for risk stratification algorithms.	Cohort 1) Adults with septic shock under sepsis-3 criteria in the ICU between 2017 and 2019 enrolled within 24 hours of onset of shock requiring vasopressors Cohort 2) Adults patients with at least one positive blood culture for Staph aureus in hospital wards and ICU between 2013 and 2014.	Adults with either 1) septic shock or 2) one positive Staph aureus blood culture	Death within 72 hour temperature measurement period
Ding 2021 (16)	MIMIC-III	None.	Patients from the Beth Israel Deaconess Medical Center ICU between 2001 and 2012	Patients whose sepsis onset was within 24 hours of ICU	Patients with values outside of measurable ranges

				admission using sepsis-3 criteria	
Gårdlund 2018 (17)	PROWESS shock clinical trial	Eli Lilly & Co sponsored the original clinical trial but had no role in the present study design, analysis, interpretation or reporting of results.	The study protocol, statistical plan, and results of the PROWESS shock trial (ClinicalTrials.gov number, NCT00604214) have been published previously. Briefly, 1696 adult patients with septic shock were enrolled into the trial between 2008 and 2011 in 208 sites around the world.	Continuous requirement for vasopressor support of at least 5 ug/min of norepinephrine equivalent for 4 hours despite fluid resuscitation Two or more of SIRS criteria Evidence of hypoperfusion Evidence of infection Administration of IV antibiotic therapy	Vasopressor support for more than 24 hours, sepsis for more 36 hours, patients not expected to survive for at least 28 days because of other severe underlying conditions, patients not committed to full intensive care, platelet count of less than 30,000. Conditions related to bleeding risk
Han 2021 (18)	Two tertiary care medical centers and 4 community hospitals	Dr. Kashiouris received funding from Xelia Pharmaceuticals.	Adult patients admitted through the ED to 6 Illinois hospitals: University of Chicago (2008-2018), Loyola University Medical Center (2006-2017), and 4 hospitals from the NorthShore University Health System (2008-2017).	Patients with blood culture orders, 4 consecutive days of antibiotics (or until discharge, if < 4 days), IV antibiotics within 24 hours of admission, and initiation of antibiotics within 48 hours of blood culture order within 24 hours of admission. IV antibiotics identified by SEP-1 guidelines	Those who did not meet the clinical criteria for infection.
Kudo 2021 (19)	Japan Septic Disseminated Intravascular Coagulation study, Tohoku Sepsis Registry, Focused Outcomes Research in Emergency Care for Acute Respiratory Distress Syndrome, Sepsis, and Trauma sepsis study	D.K., M.H., and S.K. received personal fees from Asahi Kasei Pharma Corpora-tion. The other authors have no conflicts of interest to declare.	Patients at least 16 years admitted to ICUs with severe sepsis or septic shock according to Sepsis-2 (1 registry) or Sepsis-1 (1 registry) criteria across two multicenter registries in Japan in 2011-2013 and 2015	Patients with severe sepsis or septic shock as defined by sepsis-1 or sepsis-2 criteria	Patients without 28-day mortality data
Scicluna 2017 (20)	Two ICUs in the Netherlands between 1/1/2011 and 7/20/2012, patients admitted with sepsis from community-acquired pneumonia to 29 ICUs, a nursing home in the Netherlands, USA ICUs	BPS and TvdP report a patent pending for a molecular biomarker for prognosis of sepsis patients (ref: 2016-054EP PR). All other authors declare no competing interests.	All patients older than 18 years admitted to the two ICUs between Jan 1, 2011, and July 20, 2012. Patients admitted to hospital in Amsterdam were used as the discovery cohort and those admitted to hospital in Utrecht were the first validation cohort	Expected length of stay above 24 hours Probable or definite infection using the CDC and International Sepsis Forum definitions One positive variable from Sepsis-1 criteria	Opt out Poor stability and quality of endotype

Sharafoddini 2021 (21)	MIMIC-III	None	Adult patients admitted to ICUs in the Beth Israel Deaconess Medical Center from 2008-2012	For patients with multiple admissions, only the first was included Adult patient Septic patient based on Sepsis-3 criteria	Pediatric patients Admissions other than the first for each patient Patients admitted to cardiothoracic surgical services Patients without charted data Patients without vital signs in the first 24 hours at the start of clinical concern
Antcliffe 2019 (22)	VANISH (Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock) Trial	Clustering method used was discovered and published by the present authors in a prior article. Dr. Gordon received non-funding support from Orion Pharma, personal fees from Amomed Pharma, Ferring Pharma, Tenax Therapeutics, Bristol-Myers Squibb, GSK, and HCA International.	Adults (>16 years) with septic shock within 6 hours' onset and who required vasopressors despite adequate fluid management at 18 ICUs in the UK allocated to receive either vasopressin or norepinephrine.	Adults (>16 years) with septic shock (2 of 4 SIRS criteria) within 6 hours' onset and who required vasopressors despite adequate fluid management.	Continuous infusion of vasopressors, an ongoing requirement for systemic steroid treatment, end-stage kidney failure, known mesenteric ischemia, Raynaud phenomenon, systemic sclerosis or other vasospastic disease, a medical team that was not committed to full active treatment, known pregnancy, enrollment in another interventional trial
Bhavani 2019 (23)	Adult inpatients admitted to University of Chicago Medicine from November 2008 to January 2016.All patients admitted to Loyola University Medical Center between 2006 and 2017 and between 2006 and 2017.	M.M.C. has a patent pending for risk stratification algorithms for hospitalized patients.	Patients with infection admitted to the center ED from November 2008 to January 2016	Patients as a blood culture order, at least 4 consecutive days of antibiotics, and antibiotics received within the first 24 hours of the first procured vital sign, with the first day of antibiotics required to be given within 48 hours before or after the blood culture order.	In a sensitivity analysis to assess for informative dropout in the development cohort, patients who died or were discharged before Hour 72 were excluded, and a new trajectory model was tested.
Davenport 2016 (24)	265 adult patients admitted to UK intensive care units	ACG reports research support and speaker fees from Orion Pharmaceuticals, grants and speaker fees from Tenax Therapeutics, consulting fees from Ferring Pharmaceuticals, advisory board fees from Baxter Healthcare, and grants from HCA International. CJH reports grants from the Wellcome Trust, the UK Intensive Care Society, and SIRIUS Genomics. All other authors declare no competing interests.	Patients with sepsis due to community-acquired pneumonia who were prospectively recruited to GAinS (UK Genomic Advances in Sepsis) from 29 participating ICUs between Feb 1, 2006, and Feb 20, 2014	Sepsis-2 criteria. Community acquired pneumonia as defined as a febrile illness associated with cough, sputum production, breathlessness, leukocytosis and radiological features of pneumonia acquired in the community or within less than 2 days of hospital admission.	Patient <18 years of age; pregnancy; admission for palliative care only; or immune-compromise.

Liu 2020 (25)	The eICU database	None	200,859 patients admitted to 208 US ICUs from 2014-2015 were present in the entire database	Suspicion of infection, as indicated by the presence of an ICD-9 code related to infection SOFA score of at least 2	NA
Mayhew 2018 (26)	large EMR dataset composed of more than 53,000 emergency department (ED) hospitalization episodes from Kaiser Permanente Northern California (KPNC)	None	Patients admitted to 21 Kaiser Permanente medical centers with suspected or confirmed infection and sepsis between 2009-2013	Hospitalization admission by the ED Hospitalization length of stay of at least 12 hours All vital signs were taken three or more times during the first three hours of hospitalization	NA
Nowak 2016 (27)	PREMIUM International Registry	The authors' previous work was funded by BMEYE, the company which manufactured the device used in the present work.	Adult sepsis patients in the ED with clinically suspected acute heart failure, sepsis, stroke in 4 large urban academic medical centers	Patients with suspected sepsis symptoms of acute onset (<3 days), blood culture or lactate orders and confirmed by initial and final diagnosis (at discharge) as sepsis Monitoring using the Nexfin device prior to administration of therapy, except supplemental oxygen and IV fluids at <50 ml/h	Could not be enrolled within 4 hours of ED arrival, had end-stage renal disease, were pregnant, had ST-segment elevation acute myocardial infarction, were unavailable for 30-day follow-up, had aortic valvular disease, were transferred from another facility,were excessively agitated, had a left ventricular assist device, or currently enrolled in any therapeutic investigational study.
Sweeney 2018 (28)	14 public GEO and ArrayExpress databases reporting sepsis with internal healthy controls	Discovered gene set has been submitted for possible patent protection. TES and PK are co-founders of Inflammatrix, Inc., which is interested in septic diagnostics.	Adult and pediatric patients admitted to hospitals, ICUs, and EDs with bacterial sepsis as assessed according to various criteria from 14 datasets	Study of whole blood gene expression at hospital or ICU admission (i.e. primary admission for sepsis) Bacterial sepsis	Viral sepsis unless a microbiologically confirmed bacterial co-infection present Patients sampled more than 48 hours after sepsis diagnosis
Zhang 2020 (29)	12 GEO and ArrayExpress databases of adult sepsis patients	None	The Gene Expression Omnibus (GEO) and ArrayExpress databases were searched from inception to April 2020 to identify relevant transcriptomic profiling datasets among adult patients with sepsis	GEO and ArrayExpress databases until April 2020 containing whole blood transcriptomic profiling of adult sepsis	Pediatric patients, were invitro experiments, not assaying whole blood samples, not measuring mRNA, focusing on diseases caused by special pathogens. Lack of mortality outcome, or did not contain complete expression data

Supplemental Table 5. Study prognostics and race and ethnicity information

Last name of lead author	Are clusters predictive of treatment response?	Are clusters predictive of clinical outcomes?	Was sensitivity analysis performed?	Was external validation performed?	Were race/ethnicity included as a clustering variable?	Was race different between clusters?
Geri, 2019 (12)	Yes	Yes	No	No	No	No
Seymour, 2019 (13)	Yes	Yes	Yes	Yes	No	No
Bhavani, 2020 (15)	No	Yes	No	Clusters discovered previously	No	Yes
Ding, 2021 (16)	No	Yes	Yes	No	No	No
Gärdlund, 2018 (17)	No	Yes	No	No	No	No
Han, 2021 (18)	Yes	Yes	Yes	No	Yes	No
Kudo, 2021 (19)	Yes	Yes	Yes	Yes	No	No
Scicluna, 2017 (20)	No	Yes	Yes	Yes	No	No
Sharafoddini 2021 (21)	No	Yes	No	No	Yes	Other: N/A
Antcliffe, 2018 (22)	Yes	Yes	Yes	Clusters discovered previously	No	Other: N/A
Bhavani, 2019 (23)	No	Yes	Yes	Yes	No	Other: NA
Davenport, 2016 (24)	No	Yes	Yes	Yes	No	No
Liu, 2020 (25)	Yes	Yes	Yes	No	No	No
Mayhew, 2018 (26)	No	Yes	No	No	No	No
Nowak, 2016 (27)	No	Yes	No	No	No	No
Sweeney 2018 (28)	No	Yes	Yes	Yes	No	No
Zhang 2020 (29)	Yes	Yes	Yes	Yes	No	No