Table 1: Timeline of clinical scoring systems.

	Year	Acronym	Range	N	Aim	Features	Immune	Respiratory	Cardiovascular	Renal	Metabolic	Digestive	Neurological	Other
[1]	1974	GCS	3–15	3	Alertness	Eye, verbal, and motor responses							✓	
[2]	1974	TRISS	0–12	3	Trauma	GCS, RR, SBP		✓	✓				✓	
[3]	1978	APACHE II	0–71	14	Severity/Mortality	GCS, RR, FiO_2, HR, MAP, HCT, CRE, pH, Na, K, WBC, BT, age, acute renal failure	✓	✓	✓	✓	✓		✓	✓
[4]	1989	PBS	0–14	7	Severity/Mortality	CNS, RR, SBP, DBP, BT, mechanical ventilation, cardiac arrest		✓	✓				✓	✓
[5]	1991	APACHE III	0–299	17	Severity/Mortality	HR, MBP, BT, RR, PaO2, HCT, WBC, CRE, BUN, Na, ALB, BIL, Glucose, Age, Urine output, ...	✓	✓	✓	✓	✓	✓	✓	✓
[6]	1992	SIRS	0–4	5	Inflammation	HR, BT, RR, $PaCO_2$, WBC	✓	✓	✓					✓
[7]	1993	SAPS II	0–163	15	Mortality	Age, HR, SBP, BT, PaO2, FiO2, BUN, NA, K, BIL, WBC, Bicarbonate, urine output, chronic disease, type of admission	✓	✓	✓	✓	✓	✓		✓
[8]	1994	SOFA	0–24	8	Organ Dysfunction	GCS, PaO_2, FiO_2, MAP, PLT, BIL, CRE, MVENT		✓	✓	✓		✓	✓	
[9]	1995	MODS	0–21	9	Organ Dysfunction	GCS, PaO_2, FiO_2, MAP, PLT, BIL, CRE, CVP, HR		✓	✓	✓		✓	✓	
[10]	1998	MEWS	0–14	5	Severity	HR, RR, BT, SBP, AVPU		✓	✓				✓	✓
	1999	MEWS II		6	Severity	HR, RR, BT, SBP, CNS, Urine Output		✓	✓	✓			✓	
[11]	2003	IPS	0–26	12	BSI	BT, HR, RR, WBC, CRP, SOFA	✓	✓	✓	✓		✓	✓	✓
[12]	2003	MEDS	0–27		Mortality	tachypnea or hypoxia, septic shock, PLT, Bands, Age, CNS, lower respiratory infection, nursing home residence								
[13]	2005	SAPS III	0–217	33	Mortality	GCS, PaO_2, FiO_2, BT, HR, SBP, pH, WBC, PLT, BIL, CRE, age, LOS before ICU, comorbidities and others (see supplementary material)	✓	✓	✓	✓	✓	✓		✓
[14]	2006	APACHE IV	0–286	35	Severity/Mortality	GCS, FiO_2, PO_2, PCO_2, RR, MVENT, HR, MAP, HCT, pH, K, BIL, ALB, CRE, Urea, WBC, BT, age, urine output, comorbidities and others (see supplementary materia)	✓	✓	✓	✓	✓	✓	✓	✓
[15]	2008	Shapiro	0–16	11	Bacteremia	BT, SBP, WBC, PLT, CRE, Bands, age, chills, vomiting, suspected endocarditis, indwelling vascular catheter	✓		✓	✓				✓
[16]	2011	METTS	0–4	7	Severity	RR, HR, BT, SBP, PO_2, consciousness, airway		✓	✓				✓	✓
[17]	2015	NEWS	0–20	6	Severity	RR, HR, BT, SBP, O2SAT, oxygen therapy		✓	✓					✓
[18]	2016	PRESEP	0–11	7	Sepsis	RR, HR, BT, SBP, SaO_2, GCS, Glucose		✓	✓		✓		✓	✓
[19]	2016	qSOFA	0–3	3	Organ Dysfunction	GCS, RR, SBP		✓	✓				✓	

For detailed definitions of the clinical scoring systems, please refer to the supplementary material (SM1–Scores).
GCS: Glasgow Coma Score; **TRISS:** Trauma-Injury Severity Score; **APACHE:** Acute Physiology and Chronic Health Evaluation; **PBS:** Pitt Bacteraemia Score; **SIRS:** Systemic Inflammatory Response Syndrome; **SAPS:** Simplified Acute Physiology Score; **SOFA:** Sequential Organ Failure Assessment; **MODS:** Multiple Organ Dysfunction Syndrome; **MEWS:** Modified Early Warning Score; **IPS:** Infection Probability Score; **MEDS:** Mortality in Emergency Department for Sepsis; **METTS:** Rapid Emergency Triage and Treatment System; **N:** Number of features; **NEWS:** National Early Warning Score; **PRESEP:** Prehospital Early Sepsis; **CNS:** altered mental status; **CVP:** Central venous pressure; **MVENT:** Mechanical ventilation

Table 2: Timeline of clinical definitions for blood-related conditions.

	Year	Acronym	N	Definition	Immune	Respiratory	Cardiovascular	Renal	Metabolic	Digestive	Neurological	Other
		Bacteremia	1	Blood culture with significant pathogen (see WHO[?], CDC/NHSN[?], or CLSI[?])								✓
		BSI	1^{+}	Bacteremia + Signs of infection								✓
[19]	1991	SEPSIS-1	5	SIRS	✓	✓	✓					✓
[19]	2001	SEPSIS-2	6	Suspected Infection + SIRS	✓	✓	✓					✓
[19]	2016	SEPSIS-3	9	Suspected Infection + SOFA		✓	✓	✓		✓	✓	✓

BSI: Blood-stream infection; **N:** number of clinical variables; **WHO:** World Health Organization; **CDC/NHSN:** Centers for Disease Control and prevention / National Healthcare Safety Network; **CLSI:** Clinical and Laboratory Standards Institute; **SIRS:** Systemic Inflammatory Response Syndrome; **SOFA:** Sequential Organ Failure Assessment;

Table 3: Essential takeaways from the discussion, recommendations, and opportunities.

Datasets
Limited public, diverse, and linked datasets There is a scarcity of publicly available and well-curated healthcare datasets, making it difficult to replicate findings and develop effective models. Additionally, data often lacks diversity and continuity, hindering the use of sequential models.
Handle clinical codes carefully Clinical classification systems can be useful for modeling and research, but it is important to use them with caution as they can vary between regions and healthcare systems and they undergo regular updates as our understanding of diseases evolves.
Need for continuous data labelling Existing datasets often lack continuous labelling for time series data, making it challenging to use supervised learning techniques effectively. Information available varies across time points, making it difficult to track disease progression.
Feature selection
Oversight of clinical management pathway Studies often neglect the clinical management pathway to select the appropriate predictors. Including features aligned with the management pathway and available at each stage could improve model performance and feasibility of implementation in clinical practice.
Be realistic selecting predictors The selection of features for machine learning models is important, and factors such as relevance, accessibility, data quality, and frequency of updates should be considered. Feature selection should also be mindful of practicality and avoid biases towards unrealistic data availability.
Be careful with data leakage Numerous studies inadvertently leaked future information that was not available at the time of assessment (time leakage) or used clinical variables that were part of the label definition (target leakage).
Model validation
Embrace structured and thorough reporting Studies primarily rely on generic metrics like area under the ROC, sensitivity, and specificity which often provide insufficient insights. Aim for a structure and clear reporting, including inclusion criteria, label definitions, experimental setup, and performance metrics in diverse scenarios.
Describe model's behaviour Feature importance can be a valuable tool, but it is important to scrutinize the results and question them to ensure they are valid. Assess other aspects of model behavior, such as probability calibration and temporal decay.
Capturing dynamics boosts performance Conventional machine learning models adopting strategies to account for the temporal aspect of data tend to provide better performance indicating that temporal information is relevant.
Existing limitations with sequential models Research has gravitated to sequential models to take advantage of temporal information, but the drawbacks associated tend to outweigh their advantages. The performance gains are minimal, and in many cases worse when using external datasets. This is often because there is not enough good quality and granular data available to train these data-hungry models properly. Moreover, even if these models worked well, adapting them to existing healthcare systems presents a big obstacle.
Opportunities
Clinical information available varies across time points To truly capture the dynamic nature of the disease progression, it is necessary to account for the evolving information landscape and use flexible models that can adapt to this changing data ecosystem.
Clinical history matters Models often overlook patient history information effectively, especially that collected in primary care. This might prove important, particularly in early stages where symptoms are not evident or laboratory results are unavailable.
Need for new data collection methods New methods are needed to capture real-time data at different stages of the disease progression. Wearable devices and microneedles show promise for collecting granular, real-time data on vital signs and biochemical markers respectively.
Harness the potential of sequential models We need better data collection and integration into existing healthcare settings if we want to make better use of sequential models in areas like managing blood-related infections.
Need for research on early stages of disease Existing research mostly focuses on sepsis (the later stages of the disease) and is oriented towards the assessment of organ dysfunction rather than infection diagnosis. More efforts are needed in understanding the early stages to improve diagnosis and decision-making throughout the patient journey. Moreover, there is evidence of the significant clinical benefit of providing support at earlier stages of the disease.
Continual diagnostic beyond treatment Existing approaches are often useless after treatment is initiated. However, disease is a continuum and antimicrobial therapy is only the beginning of the diagnostic journey. Newly acquired information should be accumulated and used to confirm, refuse, or refine the previous hypothesis.

Table 4: Comparison of static machine learning models.

R	Model	LB	LA	FxT	ROC	PR	SENS	SPEC
Static								
[?]	**?**, **?** Positive culture[a], 540.871 (4.3%) daily profiles, 6 clinical variables, All							
	SVM	NA	0h	6x1	0.83	0.88	0.75	0.91
	RFC				0.82	0.88	0.73	0.91
	DTC				0.78	0.88	0.64	0.96
	GNB				0.81	0.87	0.73	0.90
	SVM prospective [?]				0.84	-	0.89	0.63
[?]	**?**, **?** Bacteremia, 518.805 (1%) daily profiles, 6 clinical variables, All							
	SVM	NA	0h	6x1	0.88	0.85	0.79	0.81
	RFC				0.85	0.85	0.54	0.92
	DTC				0.81	0.82	0.49	0.92
	GNB				0.80	0.79	0.47	0.89

LA: Look-ahead (h); **LB:** Look-back (h); **R:** Reference;
[a]Positive microbiology culture in any specimen type.

Table 5: Comparison of non-sequential machine learning models.

R	Model	LB	LA	FxT	ROC	PR	SENS	SPEC
Non-Sequential (temporal)								
?	**?, ?** Bacteremia, 17038 (7.4%) episodes, 18 clinical variables, All							
	GNB (A)	72h*	0h	20x1	0.70	-	-	-
	RFC				0.73	-	0.68	0.66
	SVM				0.70	-	0.69	0.55
	MLP128 (B)				0.73	-	0.81	0.59
	MLP256 (C)				0.73	-	0.81	0.53
	Ensemble (A+B+C)				0.73	-	0.79	0.57
?	**?, ?** BSI, 5030 (38%) episodes, 28 clinical variables, ICU							
	XGB	72h	24h	32x1	0.82	-	0.71	0.78
	SVM				0.70	-	0.57	0.76
	MLP				0.67	-	0.40	0.81
	LR				0.66	-	0.61	0.64
?	**?, ?** Sepsis-2, 1394 (11.4%) patients, 9 clinical variables, ICU							
	InSight	5h	3h	†	0.92	-	0.90	0.63
?	**?, ?** Sepsis-2, 90353 (1.3%) patients, 6 clinical variables, ICU							
	InSight	3h	0h	†	0.92	-	0.80	0.95
	SIRS			5	0.75	-	0.82	0.32
	SOFA			8	0.63	-	0.82	0.51
?	**?, ?** Sepsis-3, 19048 (9.7%) patients, 8 variables, ICU							
	InSight	2h	0h	†	0.88	0.60	0.80	0.80
	SIRS	2h	0h	5	0.61	0.16	0.72	0.44
	SOFA	2h	0h	8	0.77	0.28	0.80	0.48
	qSOFA	2h	0h	3	0.73	0.28	0.56	0.84
	InSight	2h	4h	†	0.77	0.28	0.80	0.52
?	**?, ?** Sepsis-2, 600 (50%) episodes, 3 variables, ICU							
	LR	8h	4h	4x1	0.85	-	0.92	0.82
	SVM				0.88	-	0.78	0.96
	ANN				0.85	-	0.75	0.94

LA: Look-ahead (h); **LB:** Look-back (h); **R:** Reference;
*Further in time allowed for some specific sporadic clinical variables.
† Unclear number of features due to complex feature engineering.

Table 6: Comparison of sequential machine learning models.

R	Model	LB	LA	FxT	ROC	PR	SENS	SPEC
Sequential (temporal)								
?	**?, ?** BSI, 20850 (7.3%) patients, 24 clinical variables, All							
	LSTM[c]	168h	0h	24x7	0.97	0.65	0.93	0.98
	LR	NA	0h	24x1	0.74	0.48	0.58	0.95
?	**?, ?** BSI, 6557 (13.4%), 33 clinical variables, ICU							
	GRU				0.84	0.48	-	-
	CNN	48h	0h	33x48	0.83	0.52	-	-
	FFN				0.77	0.45	-	-
?	**?, ?** Sepsis-2, 5803 (6.2%) episodes, 9 clinical variables, ICU							
	DFN	5h	3h	20x5	0.92	-	0.89	0.94
	LSTM				0.93	-	0.91	0.94
?	**?, ?** Sepsis-2, 51697 (21.4%) episodes, 77 clinical variables, ICU							
	MGP + RNN-MI	All	0h	†	0.90	0.74	-	-
	MGP + RNN		0h		0.81	0.51	-	-
	RNN		0h		0.77	0.50	-	-
	RFC + FE		0h		0.86	0.67	-	-
	MEWS		0h		0.73	0.48	-	-
	MGP + RNN-MI		12h		0.79	0.52	-	-
	MGP + RNN		12h		0.74	0.42	-	-
	RNN		12h		0.72	0.43	-	-
	RFC+FE		12h		0.70	0.42	-	-
	MEWS		12h		0.65	0.36	-	-
?	**?, ?** Sepsis-2, 33084 (4.56%) episodes, 10 clinical variables							
	RNN	20h	3h	10x20	0.81	-	0.90	0.47
	RNN		6h		0.79	-	0.90	0.45
	RNN		12h		0.76	-	0.90	0.39
	InSight		3h		0.72	-	0.90	0.31
	InSight		6h		0.71	-	0.90	0.29
	InSight		12h		0.68	-	0.90	0.24
?	**?, ?** Sepsis-3, 27278 (37%) patients, 63 clinical variables							
	SIRS	16h	6h	5	0.63	-	-	-
	SOFA			8	0.71	-	-	-
	LGBM			1269x1	0.75	-	-	-
	GRU			†	0.76	-	-	-
	ATTN			†	0.84	-	-	-
	ATTN-POOL			†	0.76	-	-	0.80

LA: Look-ahead (hours); **LB:** Look-back (hours); **R:** Reference; **MI:** Missing Indicator; **FE:** Feature Engineering; **LR:** Logistic Regression; **LSTM:** Long Short Term Memory; **GRU:** Gated Recurrent Unit; **CNN:** Convolutional Neural Network; **FFN:** Feed Forward Neural Network; **MGP:** Multi-Output Gaussian Process; **RFC:** Random Forest Classifier; **ATTN:** Attention Layer; **LGBM:** Light Gradient Boosting Machine; **FxT:** Features inputed to the model x Timesteps;
† Unclear number of features due to complex feature engineering.

Table 7: Overview of biochemical, physical, and surrogate markers grouped by organ system.

System	Component	Biochemical Marker	Physical Marker	Surrogate Marker
Immune	Lymphatic	Leukocytes (WBC), Erythrocytes (RBC), Thrombocytes (PLT), Monocytes (MONO), Eosinophils (EOS), Neutrophils (NEUT), Lymphocytes (LYMPH), Basophils (BASO)		Cancer Immunosupressed redness (rubor) swelling (tumour) joint pain/stiffness loss of function
	Inflammatory	C-Reactive Protein (CRP), Procalcitonin (PCT), IL-6		
Respiratory	Lungs	Fraction of inspired oxygen (FiO2) Endtidal carbon dioxide (EtCO2)	Respiratory Rate (RR)	Cough Chest pain Crackles Respiratory Distress Shortness of breath Ventilation support Minute-Ventilation Pleural Efussion Hypoxia COPD
	Blood	Oxygen saturation – arterial (SaO2, O2SAT) Oxygen saturation – venous (SvO2) Partial pressure of oxygen – ambient (PO2) Partial pressure of oxygen – arterial (PaO2) Partial pressure of oxygen – venous (PvO2) Partial pressure of carbon dioxide – ambient PCO2) Partial pressure of carbon dioxide – arterial (PaCO2) Partial pressure of carbon dioxide – venous (PvCO2)	Peripheral capillary oxygen saturation (SPO2)	
Cardiovascular	Heart	Troponin Test	Heart Rate (HR)	Palpitations Tachycardia Bradycardia Coronary heart disease Ischemic heart disease Use of vasopressors CVD, CHF Hypertension Hypotension Anemia
	Blood	Platelets (PLT), Haematocrits (HCT), Haemoglobin (HGB), Fibrinogen (FIB) International Normalized Ratio (INR)		
	Blood vessels	Bands, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), Activated Partial Thromboplastin Time (aPTT), Mean Corpuscular HGB Volume (MCV), Mean Corpuscular HGB Level (MCH), Mean Corpuscular HGB Concentration (MCHC), Red cell Distribution Width (RDW)	Systolic Blood Pressure (SBP) Diastolic Blood Pressure (DBP) Pulse Pressure (PP) Mean Arterial Pressure (MAP)	
Renal	Kidney	Urea Creatinine (CRE) Blood Urea Nitrogen (BUN)	Urine output	Foley Catheter Acute kidney injury Renal failure CKD
Metabolic	Name	Glucose, Cholesterol, Sodium (Na), Potassium (K), Magnesium (Mg), Calcium (Ca), Lactate (LAC), Lactate Dehydrogenase (LDA), Creatine Kinase (CK), Creatine Kinase MB (CKMB), Total Carbon Dioxide (TCO2), Low-density Lipoprotein (LDL), Blood gas pH (PH)		Obesity Diabetes Hyperglicemia
Digestive	Liver	Albumin (ALB)[c], Bilirubin (BIL), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT)		Jaundice, Cirrhosis Fatty liver disease Hepatitis A/B/C
	Pancreas		Pancreatic injury, Pancreatitis	
Digestive	GI		Diarrhoea, Abdominal pain, Nausea, Vomiting	
Neurological	Brain	Cholinesterase (ChEs)	Delirium, Fatigue, Agitation, Depression, PTSD, Ictus	
	Sensory organs		GCS, AVPU	
Other	Thermoregulatory		Body Temperature (BT)	Fever
	Demographics		Age, Gender, Ethnicity, Height, Weight, BMI	

Continued on next page

Table 7: Overview of biochemical, physical, and surrogate markers grouped by organ system. (Continued)

	Management		Ward, Length of stay (LOS), Blood culture (BC), X-Ray, Electrocardiogram (ECG), Computerized Tomography (CT), Ultrasound, Use of steroids, Use of antimicrobials, Central Venous Cathether (CVC)
	Scores		SOFA, SIRS

GI: Gastroinstetinal Tract; **PTSD:** Post-Traumatic Stress Disorder ; **CKD:** Chronic Kidney Disease; **CHF:** Congestive Heart Failure; **CVC:** Central Venous Catheter; **COPD:** Chronic Obstructive Pulmonary Disease; **ENDO:** Endotracheal Tube; **CVS:** Cardiovascular Disease; **GCS:** Glasgow Coma Score; **AVPU:** Alert, Voice, Pain, Unresponsive; **BMI:** Body Mass Index; **HD:** Heart Disease; **SOFA:** Sequential Organ Failure Assessment; **SIRS:** Systemic Inflammatory Response Syndrome; **CVD:** Cardiovascular Disease;

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