The 2026 Sepsis Guideline Era

Evolving Definitions and the Role of Biomarkers

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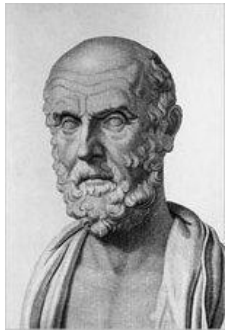
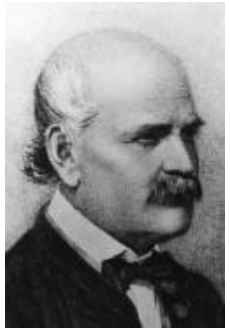
何謂 sepsis？

Hippocrates（西元前 460–西元前370 ）



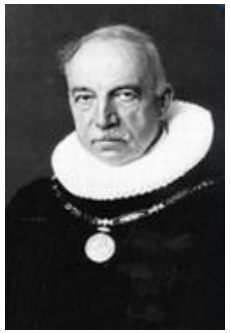
被譽為**「醫學之父」**的古希臘醫師，最早以 sepsis 一詞描述此病。字源為希臘文 **sipsi**（意為「使腐敗、腐化」）；該詞最早見於約 2700 年前 Homer 的史詩。

Ignaz Semmelweis (1818–1865)



首位發展出 sepsis **現代觀點（modern view）**的研究者，Vienna General Hospital 產科醫師。指出解剖室的 **cadaverous particles** 經醫師之手傳播，並以 **chlorine handwashing**（1847）大幅降低死亡率。

Hugo Schottmüller (1867–1936)



1914 年提出首個 sepsis **現代定義**：「體內形成病灶（**focus**），**pathogenic bacteria** 持續或間歇侵入血流（**blood stream**），造成主觀與客觀 **symptoms**。」首次確立「感染病灶」為 sepsis 的根本原因。

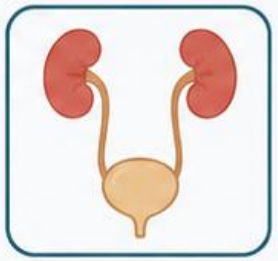
Schottmüller H. Verh Dtsch Ges Inn Med 1914;31:257–280. | Noakes TD, et al. Epidemiol Infect 2008;136:1–9. | Gyawali B, et al. SAGE Open Med 2019.

SEPSIS

INFECTION

Lung/chest infection

Bloodstream infection (bacteremia)

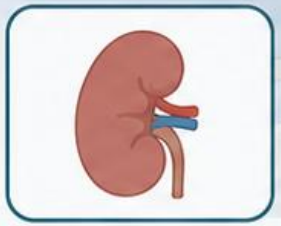


Urinary tract infection (UTI)

ORGAN INJURY

ARDS (lung injury)

Hypotension / Shock



AKI (kidney injury)

敗血症乃**因感染**而造成**宿主反應失衡**，產生危及生命的**器官失能**。

Sepsis: Life-threatening **organ dysfunction** caused by a **dysregulated host response to infection**.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801–810.

Global sepsis-related incidence, mortality, and case fatality rate in 1990, 2019, and 2021

	1990				2019				2021			
	Mortality		Incidence		Mortality		Incidence		Mortality		Incidence	
	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)
All ages	16 500 (15 700–17 300)	309·3 (294·3–325·1)	136 000 (113 000–161 000)	2543·2 (2112·5–3016·5)	14 100 (13 200–15 100)	182·2 (170·4–194·9)	128 000 (102 000–157 000)	1655·6 (1314·5–2024·4)	21 400 (20 300–22 500)	270·6 (257·4–284·6)	166 000 (135 000–201 000)	2111·0 (1708·2–2550·8)

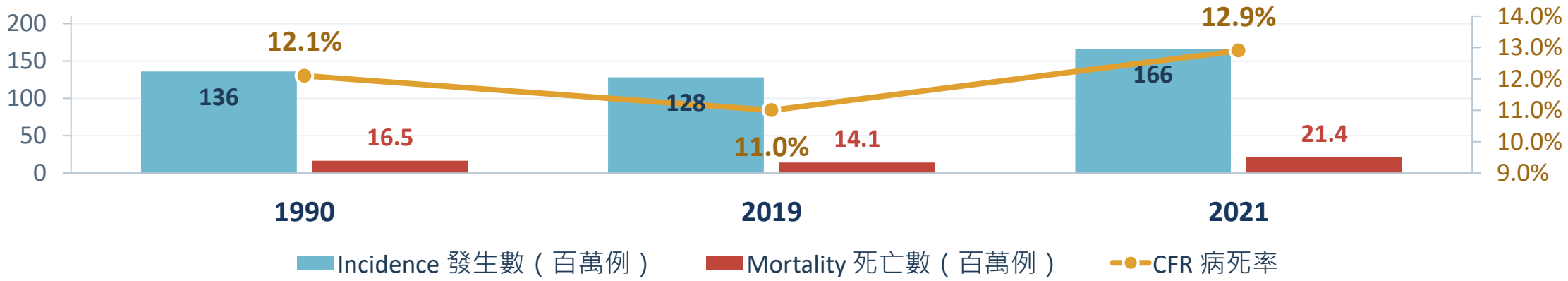
Lancet Glob Health. 2025 Dec;13(12):e2013-e2026.

CFR（case fatality rate，病死率）＝ 死亡數 ÷ 發生數 × 100%

1990 1,650 萬 ÷ 1.36 億
CFR ≈ 12.1%

2019 1,410 萬 ÷ 1.28 億
CFR ≈ 11.0%

2021 2,140 萬 ÷ 1.66 億
CFR ≈ 12.9%



Sepsis 沒有診斷的 gold standard

NEJM 2024 Review Article：Sepsis and Septic Shock（Meyer NJ & Prescott HC）— 爭議與不確定領域

臨床上**缺乏診斷 sepsis 的黃金標準（gold standard）**，也沒有精確的診斷測試；診斷仍仰賴臨床綜合判斷。

缺乏精確工具

仍缺乏能證實「**宿主反應失調**（dysregulated host response）」存在的精確定義與客觀診斷測試。

無法即時確認感染

難以在第一時間證實或描繪感染病原；回顧研究顯示高達 **1/3** 被診斷並治療為細菌性 sepsis 者，實為非感染性疾病。

新興技術仍在發展

已有數個 **protein-based** 或 **transcriptome-based** 預測工具獲美、歐核准，但臨床工作流中的成效與能否改善預後仍待驗證。

臨床意涵：sepsis 仍是**症候群式診斷（syndromic diagnosis）**——需結合感染證據與器官功能變化綜合判斷，並隨病程**反覆重新評估**；診斷準則的**用途在於警示與分流**，而非取代臨床判斷。

Meyer NJ, Prescott HC. Sepsis and Septic Shock. N Engl J Med 2024;391:2133–2146.

SEPSIS 1.0（1991）

ACCP（American College of Chest Physicians）+ SCCM（Society of Critical Care Medicine）共識會議

1 / 8

加護病房中合併感染與急性器官衰竭的病人，每 8 位就有 1 位**不符合 2 項 SIRS 準則**。

Kaukonen KM, et al. NEJM 2015

專家指出的問題：**過度聚焦發炎反應**、誤把 sepsis 當成 SIRS → severe sepsis → shock 的**連續過程**

Bone RC, et al. Chest 1992;101:1644–1655. | Singer M, et al. JAMA 2016;315:801–810. | Raith EP, et al. JAMA 2017;317:290–300.

SIRS（ Systemic Inflammatory Response Syndrome ）

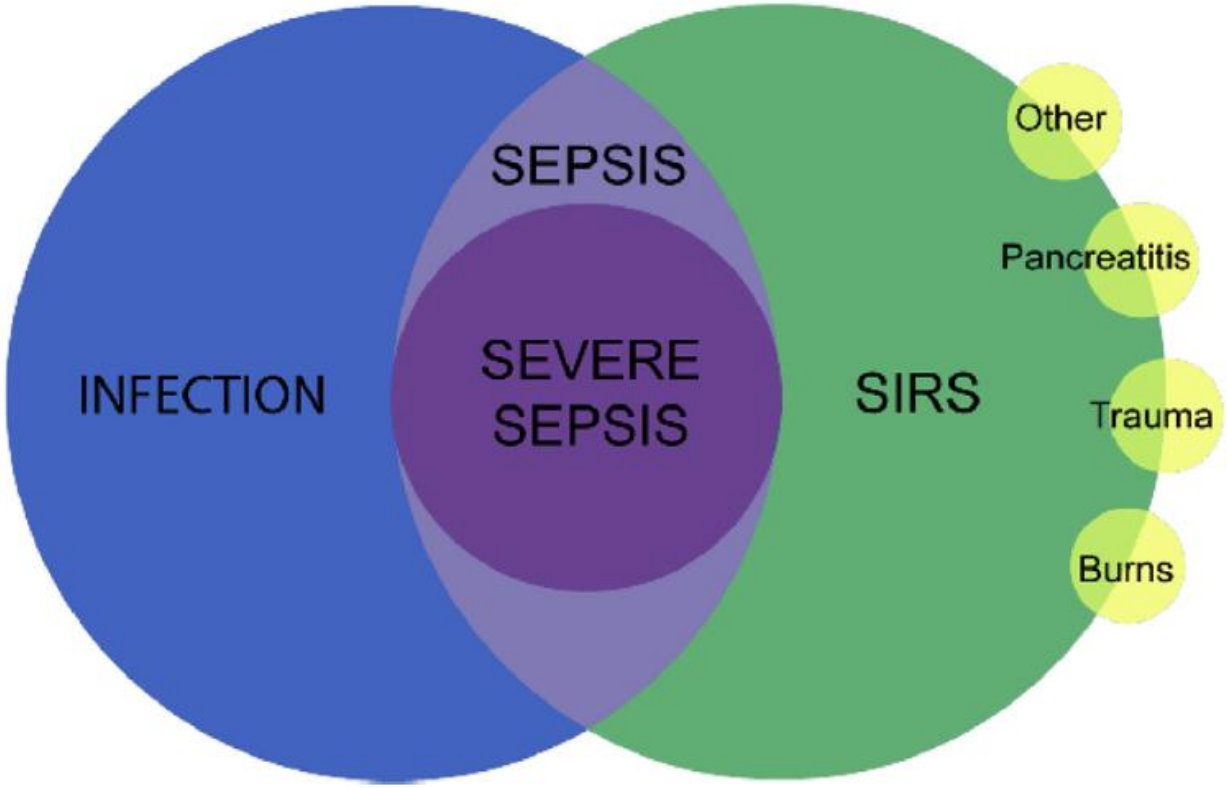


Fig. 1. Spectrum of infection, SIRS, sepsis, and severe sepsis. (*Data from* Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.)

≥ 2 項

符合即定義為 SIRS。

非感染專屬：外傷、手術後、胰臟炎、燒傷等也會出現。

ICU 新發燒的非感染性原因

Noninfectious Causes of New Fever in ICU Patients

來源指引 (Guideline source)

Society of Critical Care Medicine (SCCM) and Infectious Diseases Society of America (IDSA) Guidelines for Evaluating New Fever in Adult Patients in the ICU
Adapted from Table 1

1. 心血管／血栓栓塞 Cardiovascular / Thromboembolic

- Acute myocardial infarction
- Dressler syndrome (pericardial injury syndrome)
- Pulmonary infarction
- Venous thrombosis
- Fat emboli

2. 呼吸系統 Respiratory

- Atelectasis
- Fibroproliferative phase of acute respiratory distress syndrome
- Pneumonitis without infection

3. 神經／內分泌／代謝 Neurologic / Endocrine / Metabolic

- Adrenal insufficiency
- Intracranial bleed
- Nonconvulsive status epilepticus
- Stroke
- Thyroid storm
- Malignant hyperthermia
- Tumor lysis syndrome

4. 藥物／撤藥／醫療相關 Drug / Withdrawal / Iatrogenic

- Drug fever
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Withdrawal from certain substances including alcohol, opiates, barbiturates, benzodiazepines
- Blood product transfusion

5. 免疫／發炎相關 Immune / Inflammatory

- Cytokine release syndrome
- Immune reconstitution inflammatory syndrome
- Jarisch-Herxheimer reaction
- Transplant rejection

6. 腹部／其他發炎 Abdominal / Other Inflammatory

- Acalculous cholecystitis
- Pancreatitis
- Gout
- Heterotopic ossification

重點：ICU 新發燒的鑑別診斷不只感染，非感染性原因也應納入評估。

Noninfectious etiologies should remain in the differential diagnosis of new fever in ICU patients.

Reference: O'Grady NP, Alexander E, Alhazzani W, et al. Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU. Critical Care Medicine. 2023;51(11):1570–1586.

SEPSIS 2.0（2001）

SCCM / ESICM / ACCP / ATS / SIS International Sepsis Definitions Conference

Infection[a]

Documented or suspected *and* some of the following[b]:

General parameters

Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C
Heart rate >90 bpm or >2 SD above the normal value for age
Tachypnea: >30 bpm
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes

Inflammatory parameters

Leukocytosis (white blood cell count >12,000/μl)
Leukopenia (white blood cell count <4,000/μl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value

Hemodynamic parameters

Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation >70%[b]
Cardiac index >3.5 l min^{-1} m^{-2}[c,d]
Organ dysfunction parameters
Arterial hypoxemia ($PaO_2/FIO2$ <300)
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/μl)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

Tissue perfusion parameters

Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

“some of the following”

原文**未規定需符合幾項**，並非「≥ 2 項」；僅提供擴充徵象清單，且只採計無法用其他原因解釋者。

會議認為 SIRS 太敏感、特異度不足：3,708 位住院病人中 **68% 曾符合 SIRS**，病房病人約 **50%**。

Levy MM, et al. Crit Care Med 2003;31:1250–1256.
Rangel-Frausto MS, et al. JAMA 1995;273:117–123. | Churpek MM, et al. AJRCCM 2015;192:958–964.

SEPSIS 3.0（2016）

The Third International Consensus Definitions for Sepsis and Septic Shock

JAMA, February 23, 2016; Vol 315, No. 8

發表方式

於 **SCCM 2016** 年會會場演講公告，**同步刊登於 JAMA**。

2016/02/23，Vol 315, No. 8，pp. 801–810。

同期並刊出 **SOFA / qSOFA** 臨床準則驗證研究（315:762–774、775–787）。

SCCM 2016 Critical Care Congress, Orlando, USA

Singer M, et al. JAMA 2016;315(8):801–810.

Sepsis 3.0：為了更準確辨識高死亡風險的感染病人

以較佳的 **predictive validity** 取代舊有 **SIRS** 導向概念

為何需要 Sepsis-3？

舊有 SIRS 為基礎的判準，
對不良預後（特別是 in-hospital mortality）
的 predictive validity 有限。

Sepsis-3 強調：選擇能更準確預測不良預後的 clinical criteria

ED / 普通病房

suspected or confirmed infection + **qSOFA ≥ 2**

呼吸速率
≥ 22 /min

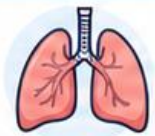
意識改變

收縮壓
≤ 100 mmHg

qSOFA：床邊快速警示工具（prompt / screening clue），**不是 sepsis 定義**

ICU

suspected or confirmed infection + **acute SOFA increase ≥ 2**



PaO_2/FiO_2 ↓

platelets ↓

bilirubin ↑

MAP ↓ / vasopressor

Glasgow Coma Scale ↓

creatinine ↑ / oliguria

SOFA：較完整反映器官功能障礙，為 sepsis operational definition 的核心

核心觀念：Sepsis-3 不是單純換名詞，而是用更能預測死亡與器官衰竭風險的標準來定義 sepsis

Reference: Singer M, et al. JAMA. 2016;315:801-810. Seymour CW, et al. JAMA. 2016;315:762-774.

Sepsis-3 時代：qSOFA 與 SOFA 在 non-ICU 與 ICU 預測 hospital mortality 的差異

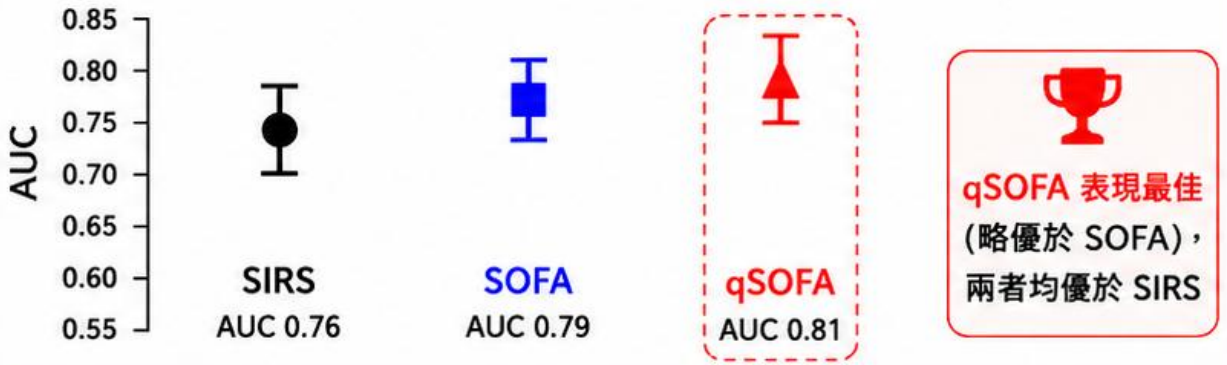
原始資料來源：多中心真實世界隊列

KCEMS	UPMC	KPNC	VA	ALERTS
(社區醫療) King County Emergency Medical Services	University of Pittsburgh Medical Center	Kaiser Permanente Northern California	Veterans Administration	(院內感染) Jena University Hospital

納入 suspected infection encounters
148,907 筆納入 primary cohort analysis

Non-ICU encounters（非加護病房） n = 66,522

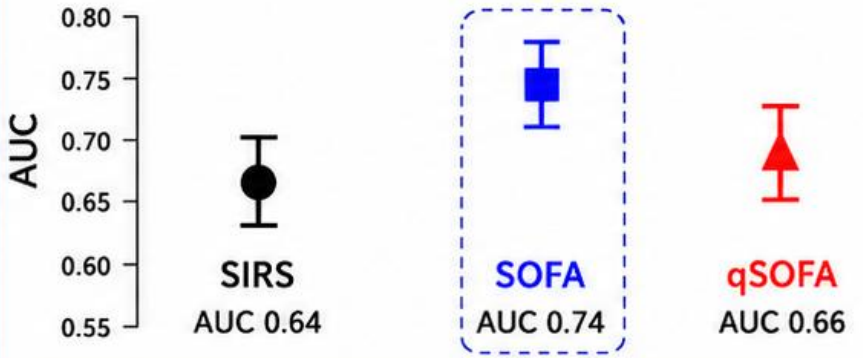
以 AUC 比較預測 hospital mortality 的能力（越高越好）



qSOFA 表現最佳（略優於 SOFA），兩者均優於 SIRS

ICU encounters（加護病房） n = 7,932

以 AUC 比較預測 hospital mortality 的能力（越高越好）



SOFA 表現最佳，明顯優於 qSOFA 與 SIRS

重點結論

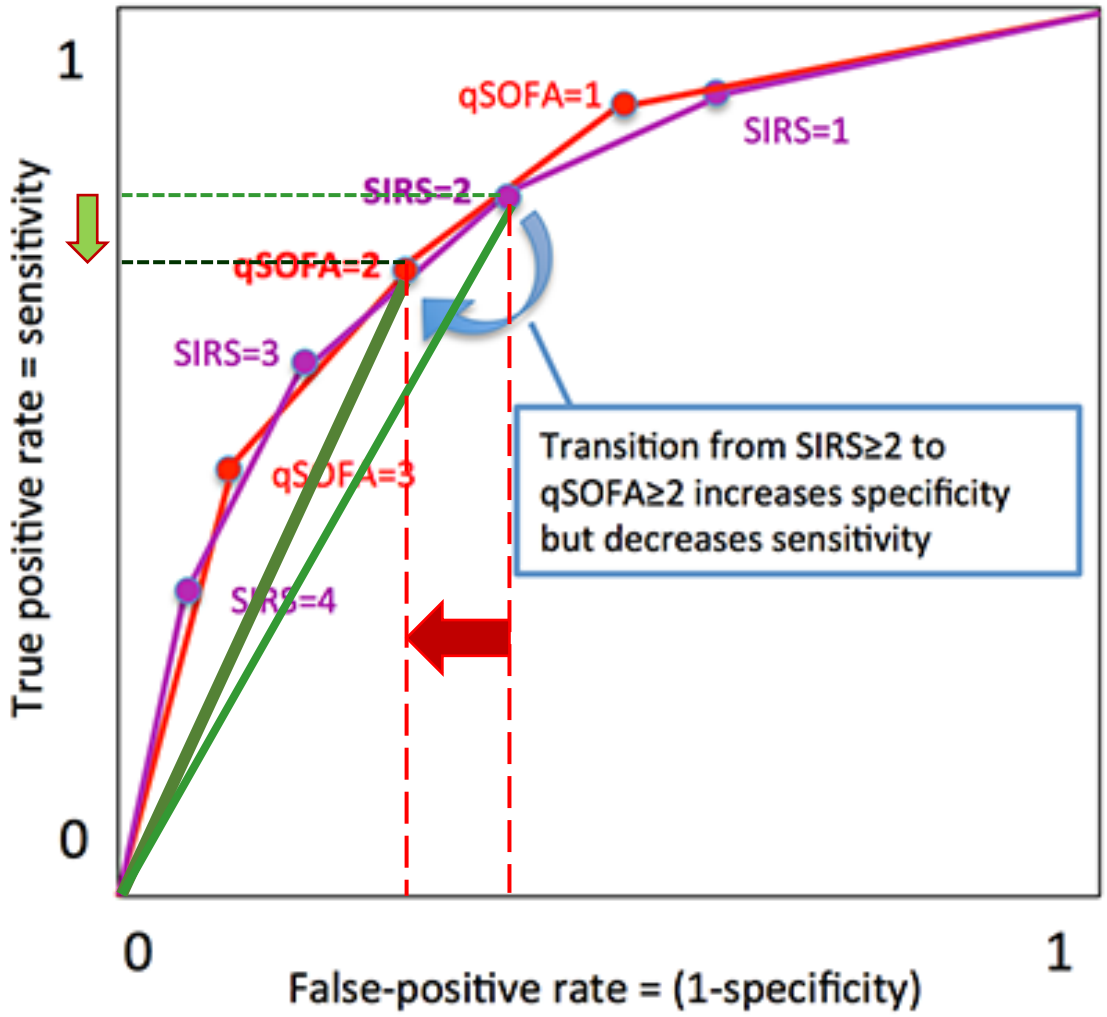
- non-ICU：qSOFA 對 hospital mortality 的辨識能力略優於 SOFA。
- ICU：SOFA 對 hospital mortality 的辨識能力明顯優於 qSOFA。
- qSOFA 適合 bedside risk stratification；SOFA 適合較完整的器官功能與嚴重度評估。

Reference: Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis. JAMA. 2016;315(8):762-774.

用 Likelihood Ratio 闡述 qSOFA

Likelihood ratio（LR）= 概似比：LR+ 越大越能確診，LR– 越小越能排除

Imagined ROC curves for SIRS vs. qSOFA for mortality prediction



SIRS ≥2 → qSOFA ≥2

特異度 ↑、敏感度 ↓

LR(+) 上升：陽性時更能確診（rule in）

LR(–) 上升：陰性時較難排除（rule out 變差）

➔ qSOFA 真的適合當篩檢工具嗎?

LR(+) = sensitivity/(1-specificity)

LR(-) = (1-sensitivity)/specificity

Farkas J. PulmCrit — Top ten problems with the new sepsis definition. EMCrit Blog, April 11, 2016.

SSC 的演進

Surviving Sepsis Campaign (SSC) guidelines：2004 → 2008 → 2012 → 2016 → 2021

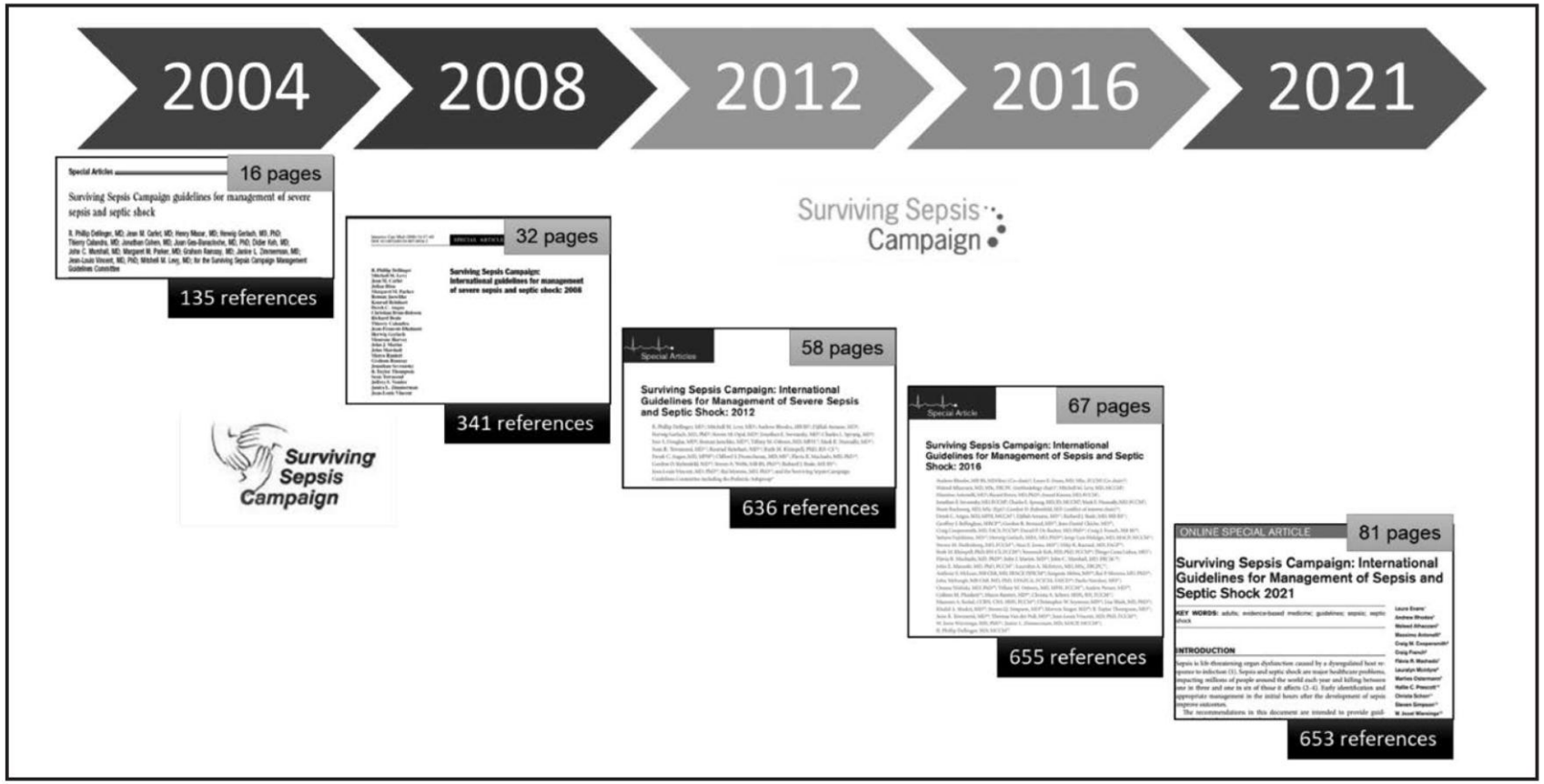


Figure 1. Surviving Sepsis Campaign (SSC) guidelines publication timeline and metrics. Guideline mastheads are displayed from original 2004 publication through the 2021 revision. The timeline displays and contrasts page numbers and numbers of references. To the left is the original SSC logo (2004 and 2008 editions) and the revised logo (2012 and forward).

SSC 2021：qSOFA

不建議將 qSOFA 單獨作為 sepsis / septic shock 的篩檢工具（相較 SIRS、NEWS、MEWS）。

強建議（strong recommendation）/ 中等品質證據（moderate-quality evidence）

理由：qSOFA 較**特異**但**敏感度低**；原始研究中僅 24% 感染者 qSOFA ≥2，卻占 70% 不良結果。

Evans L, et al. Crit Care Med 2021;49(11):e1063–e1143. | Crit Care Med 2023;51(4):431–444.

MEWS、NEWS、NEWS2 的組成項目

Components of Modified Early Warning Score (MEWS), National Early Warning Score (NEWS), and National Early Warning Score 2 (NEWS2)

Variable	NEWS — Points	NEWS2 — Points	MEWS — Points
AVPU	Alert — 0 VPU — 3	Alert — 0 CVPU* — 3	Alert — 0 React to voice (V) — 1 React to pain (P) — 2 Unresponsive (U) — 3
HR (beats/min)	51–90 — 0 91–110 or 41–50 — 1 111–130 — 2 ≤40 or ≥131 — 3	51–90 — 0 91–110 or 41–50 — 1 111–130 — 2 ≤40 or ≥131 — 3	51–100 — 0 41–50 or 101–110 — 1 <40 or 111–129 — 2 ≥130 — 3
O_2Sat (%)	≥96 — 0 94–95 — 1 92–93 — 2 ≤91 — 3	≥96† — 0 94–95 — 1 92–93 — 2 ≤91 — 3	—
Oxygen supp.	No — 0 Yes — 2	No — 0 Yes — 2	—
RR (breaths/min)	12–20 — 0 9–11 — 1 21–24 — 2 ≤8 or ≥25 — 3	12–20 — 0 9–11 — 1 21–24 — 2 ≤8 or ≥25 — 3	9–14 — 0 15–20 — 1 <9 or 21–29 — 2 ≥30 — 3
SBP (mm Hg)	111–219 — 0 101–110 — 1 91–100 — 2 ≤90 or ≥220 — 3	111–219 — 0 101–110 — 1 91–100 — 2 ≤90 or ≥220 — 3	101–199 — 0 81–100 — 1 71–80 or ≥200 — 2 ≤70 — 3
Temperature (°C)	36.1–38.0 — 0 35.1–36.0 or 38.1–39.0 — 1 ≥39.1 — 2 ≤35.0 — 3	36.1–38.0 — 0 35.1–36.0 or 38.1–39.0 — 1 ≥39.1 — 2 ≤35.0 — 3	35.0–38.4 — 0 <35.0 or ≥38.5 — 2
Maximum score:	**NEWS 20**	**NEWS2 20**	**MEWS 14**

AVPU: Alert, verbal, pain, or unresponsive; HR: Heart rate; O_2Sat: Oxygen saturation; RR: Respiratory rate; SBP: Systolic blood pressure.

* NEWS2 includes new confusion, so AVPU becomes ACVPU, where C = new confusion.

† NEWS2 has a dedicated SpO2 Scale 2 for patients with hypercapnic respiratory failure who have a recommended oxygen saturation target of 88–92%.

Reference: Algarni AM, Alfaifi MS, Al Bshabshe AA, et al. Prognostic accuracy of qSOFA score, SIRS criteria, and EWSs for in-hospital mortality among adult patients presenting with suspected infection to the emergency department (PASSEM): Multicenter prospective external validation cohort study protocol. PLoS ONE. 2024;19(1):e0281208. doi:10.1371/journal.pone.0281208

Early warning scores for sepsis identification and prediction of in-hospital mortality in adults with sepsis

A systematic review and meta-analysis

TABLE 2 Summary estimates of sensitivity, specificity, diagnostic odd ratios and likelihood ratios for the primary analysis and sensitivity analyses.

Group/subgroup	No. of dataset (No. of patients)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odd ratio (95% CI)
(a) Sepsis diagnosis						
All studies (EWS)	15 (40,525)	65 [55, 75]	77 [64, 86]	2.89 [2.00, 4.18]	0.45 [0.36, 0.55]	6.49 [4.47, 9.44]
NEWS/NEWS2 only	9 (27,785)	58 [47, 68]	84 [69, 93]	3.65 [2.02, 6.59]	0.50 [0.42, 0.59]	7.33 [4.04, 13.30]
NEWS/NEWS2 ≥5 only	5 (27,092)	65 [56, 72]	77 [59, 88]	2.76 [1.49, 5.08]	0.46 [0.36, 0.61]	5.94 [2.60, 13.54]
NEWS/NEWS2 ≥5 in ED only	3 (26,823)	58 [53, 63]	82 [59, 94]	3.25 [1.19, 8.88]	0.51 [0.39, 0.68]	6.33 [1.78, 22.45]
NEWS/NEWS2 ≥7 only	3 (3076)	52 [28, 75]	87 [55, 97]	4.00 [1.45, 11.00]	0.55 [0.40, 0.77]	7.23 [3.33, 15.70]
MEWS ≥4 only	4 (13,379)	67 [46, 83]	73 [60, 83]	2.49 [1.93, 3.22]	0.45 [0.29, 0.71]	5.51 [3.38, 9.00]
qSOFA	7 (40,202)	37 [20, 59]	94 [86, 98]	6.06 [3.72, 9.88]	0.67 [0.50, 0.89]	9.07 [5.56, 14.80]
SIRS	5 (16,135)	70 [49, 85]	62 [41, 80]	1.85 [1.29, 2.67]	0.49 [0.32, 0.72]	3.82 [2.19, 6.67]
(b) In-hospital mortality						
All studies (EWS)	7 (12,358)	94 [83, 98]	21 [12, 35]	1.18 [1.08, 1.29]	0.31 [0.17, 0.57]	3.86 [2.12, 7.00]
NEWS/NEWS2 only	5 (12,358)	96 [80, 99]	18 [9, 31]	1.16 [1.07, 1.25]	0.26 [0.09, 0.76]	4.47 [1.55, 12.87]
NEWS/NEWS2 ≥5 only	3 (10,769)	90 [85, 94]	20 [14, 27]	1.12 [1.07, 1.18]	0.50 [0.39, 0.65]	2.25 [1.69, 2.99]
qSOFA	3 (12,358)	65 [48, 75]	59 [48, 69]	1.58 [1.29, 1.92]	0.59 [0.41, 0.85]	2.66 [1.59, 4.46]
SIRS	3 (10,769)	92 [86, 96]	12 [7, 19]	1.04 [1.02, 1.07]	0.69 [0.56, 0.84]	1.52 [1.23, 1.87]

Abbreviations: EWS, early warning score; MEWS, modified early warning score; NEWS, national early warning score; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.

記憶法

SpPin：高特異度檢查**陽性** → **rule in**

SnNout：高敏感度檢查**陰性** → **rule out**

篩檢為何要高敏感度？

漏掉一位 sepsis 的代價是**延遲抗生素與死亡**；偽陽性雖多做評估，但代價可接受。故篩檢先求**不漏診**，確診再靠高特異度工具。

為何 qSOFA 不適合當 screening？敏感度僅 **37%**、特異度 94%：**LR+ 6.06** 適合 rule in，但 **LR− 0.67**陰性無法排除。

J Clin Nurs. 2024 Jun;33(6):2005–2018.

SSC 2026：sepsis 篩檢建議（第 3、4 點）

Surviving Sepsis Campaign International Guidelines 2026

3	✓ ⊕○○○	In acutely ill adults en route to hospital by ambulance or flight, we **suggest** using a standard sepsis screening tool over not using a screening tool.
4	✓✓ ⊕⊕⊕○	For acutely ill patients in hospital, we **recommend** using NEWS, NEWS2, MEWS, or SIRS over qSOFA as a single tool to screen for sepsis.

3. 到院前篩檢（NEW）

救護車 / 空中轉送的急性病成人，**建議使用標準化 sepsis 篩檢工具**，優於不篩檢。

條件式建議 / 極低確定性證據

- 約半數 sepsis 病人由救護車送醫，到院前是**提早辨識與預先通報**的關鍵時機。
- 221,429 筆到院前紀錄：**NEWS2 最佳**（Se 73.1%、AUC 0.77、Sp 81.6%）；**qSOFA Se 僅 23.1%**。
- 因偽陽性高（PPV 6.5%）與現場操作困難，**未指定單一工具**。
- 到院前通報可縮短抗生素時間，但僅一項研究顯示死亡率下降。

4. 院內篩檢（Revisited）

住院之急性病人，**建議用 NEWS、NEWS2、MEWS 或 SIRS** 作為單一篩檢工具，**優於 qSOFA**。

強建議 / 中等確定性證據

- 延續 2021 SSC「不建議單用 qSOFA」，此次以新證據重新檢視。
- **四篇系統性回顧與統合分析**一致顯示 EWS 診斷 sepsis 的敏感度優於 qSOFA，LMIC 亦然。
- 沒有兼具高敏感度與特異度的理想工具；**篩檢應以高敏感度為先**，以減少偽陰性。
- qSOFA 陽性仍應**立即警覺 sepsis**，只是不宜用來篩檢。

Prescott HC, et al. Crit Care Med 2026;54(4):725–812.（同步刊登於 Intensive Care Med）

Infection indicators?

Sepsis I-II: ▶ **Sepsis =** **Suspected infection** (Infection indicator) + **[SIRS]**

Sepsis-III: ▶ **Sepsis =** **Suspected infection** (Infection indicator) + **[qSOFA]** + **[SOFA]**

SIRS = Systemic Inflammatory Response Syndrome; qSOFA = quick SOFA; SOFA = Sequential Organ Failure Assessment

SSC 2026 第 5、6 點：sepsis 的診斷與新型檢驗

Biomarkers and Rapid Diagnostic Tests for Sepsis

第 5 點：sepsis 是臨床診斷

「sepsis 為**臨床診斷**，不應以**單一生物標記或單一檢驗**來 rule in 或 rule out。」

good practice statement（NEW）

- 感染明確、器官功能異常可歸因時診斷不難；**感染未證實**或有其他病因時最困難。
- 新型檢驗**不給陽性 / 陰性**，只給 low → very high 的風險分級。
- 任何檢驗都**不具決定性**，必須與完整臨床評估合併判讀。

第 6 點：新型宿主反應檢驗

對於**novel rapid host response diagnostics**，**證據不足**，無法做出建議。

insufficient evidence（NEW）

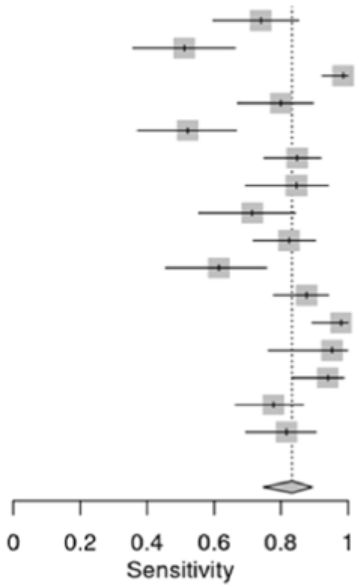
- 已核准者：**MDW**、**IntelliSep**（白血球特性）；**SeptiCyte Rapid**、**TriVerity**（mRNA 轉錄體）；Sepsis ImmunoScore（AI）。
- 各檢驗 **post-test LR 不一致**；尚**無研究**證明能改善臨床結果或資源使用，成本亦高。
- 故**不推薦任何特定工具**，但可行時使用屬合理，並列為研究優先。

臨床落地：檢驗結果只改變**事前機率 → 事後機率**。臨床已高度懷疑（>90%）時加做幾乎無附加價值；**MDW 例外**——隨 CBC 自動產生，可提示非典型病人重新評估。資源有限地區多數尚無法取得。

Prescott HC, et al. Crit Care Med 2026;54(4):725–812.

C-reactive protein in adult sepsis：systematic review and meta-analysis

Study	TP	Total (TP+FN)	Sensitivity	95% CI
Chuang CL 2025	37	50	0.74	[0.60; 0.85]
Zhu Q 2024	23	45	0.51	[0.36; 0.66]
Juneja D 2023	69	70	0.99	[0.92; 1.00]
Arbutina DD 2022	44	55	0.80	[0.67; 0.90]
Sui YD 2020	25	48	0.52	[0.37; 0.67]
Pradhan S 2016	67	79	0.85	[0.75; 0.92]
Nargis W 2014	33	39	0.85	[0.69; 0.94]
Meidani M 2013	30	42	0.71	[0.55; 0.84]
Tsalik EL 2012	61	74	0.82	[0.72; 0.90]
Castelli GP 2006	27	44	0.61	[0.45; 0.76]
Wang L 2021	64	73	0.88	[0.78; 0.94]
Juroš GF 2019	49	50	0.98	[0.89; 1.00]
Menon MS 2015	20	21	0.95	[0.76; 1.00]
Farag NA 2013	47	50	0.94	[0.83; 0.99]
Zhang H 2017	56	72	0.78	[0.66; 0.87]
Chen M 2017	49	60	0.82	[0.70; 0.90]
Random effects model			**0.83**	**[0.75; 0.89]**



Study	TN	Total (TN+FP)	Specificity	95% CI
Chuang CL 2025	34	50	0.68	[0.53; 0.80]
Zhu Q 2024	46	55	0.84	[0.71; 0.92]
Juneja D 2023	1	30	0.03	[0.00; 0.17]
Arbutina DD 2022	27	45	0.60	[0.44; 0.74]
Sui YD 2020	32	52	0.62	[0.47; 0.75]
Pradhan S 2016	11	21	0.52	[0.30; 0.74]
Nargis W 2014	20	61	0.33	[0.21; 0.46]
Meidani M 2013	24	58	0.41	[0.29; 0.55]
Tsalik EL 2012	10	26	0.38	[0.20; 0.59]
Castelli GP 2006	49	56	0.88	[0.76; 0.95]
Wang L 2021	16	27	0.59	[0.39; 0.78]
Juroš GF 2019	7	50	0.14	[0.06; 0.27]
Menon MS 2015	50	79	0.63	[0.52; 0.74]
Farag NA 2013	40	50	0.80	[0.66; 0.90]
Zhang H 2017	21	28	0.75	[0.55; 0.89]
Chen M 2017	27	40	0.68	[0.51; 0.81]
Random effects model			**0.56**	**[0.41; 0.69]**

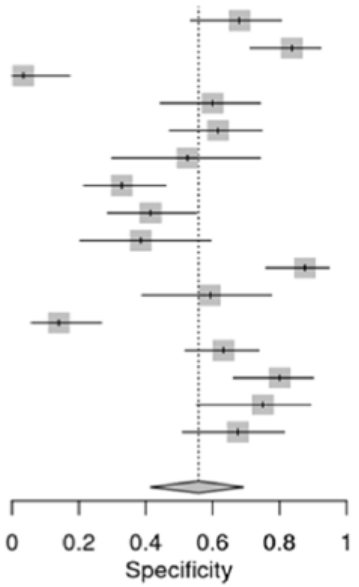


Fig. 2. CPR diagnostic sensitivity and specificity.

彙總 **Se 0.83**、**Sp 0.56**

LR(+) = Se ÷ (1−Sp) = 0.83 ÷ 0.44 ≈ **1.9**

LR(−) = (1−Se) ÷ Sp

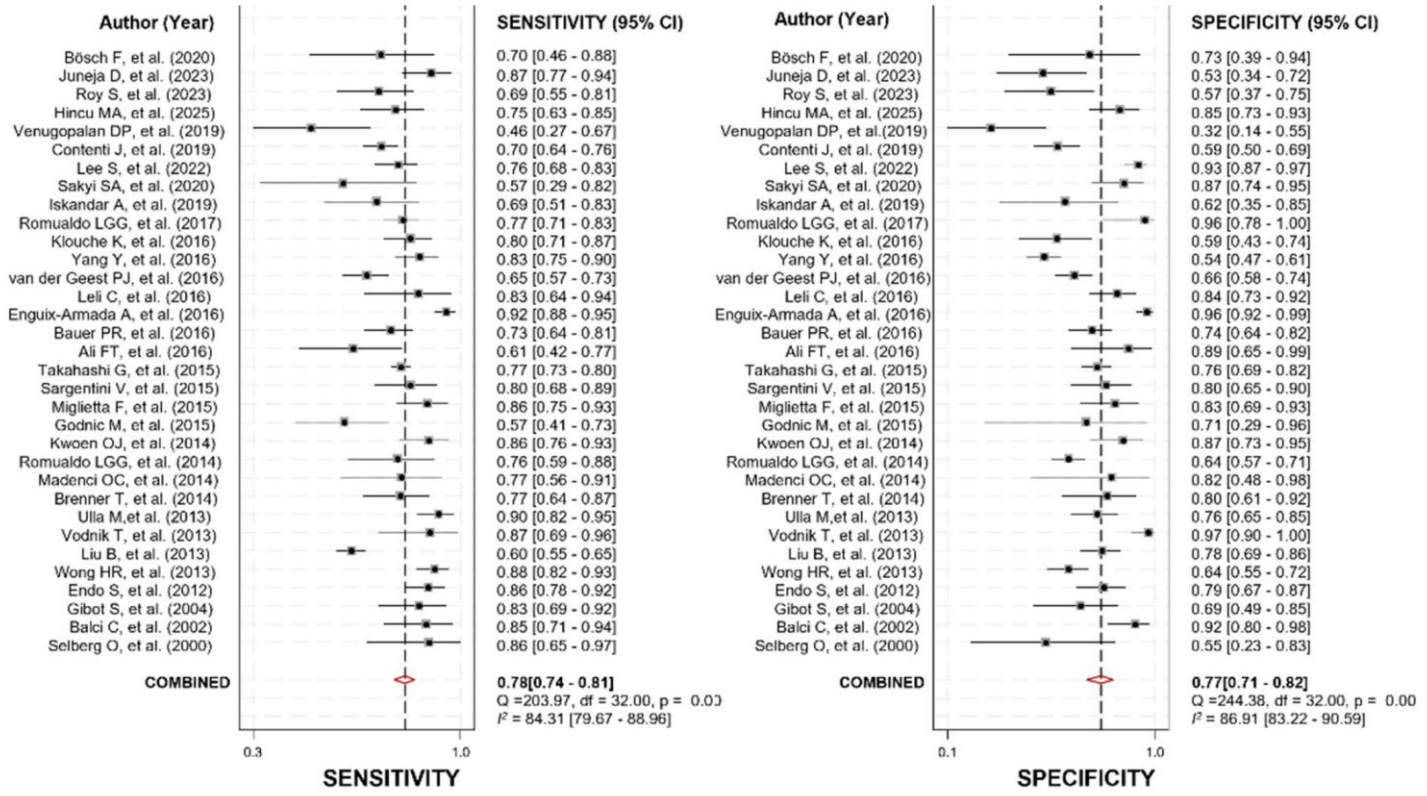
= 0.17 ÷ 0.56 ≈ **0.30**

判讀：LR+ 1.9 **幾乎不改變機率**（rule in 弱）；

LR− 0.30 可**中度下修機率**，CRP 陰性較有排除價值。

Clinics. 2025 Dec 20;81:100848.

Diagnostic performance of procalcitonin in sepsis: a systematic review and meta-analysis



彙總 **Se 0.78**、**Sp 0.77**

LR(+) = Se ÷ (1−Sp) = 0.78 ÷ 0.23 ≈ **3.4**

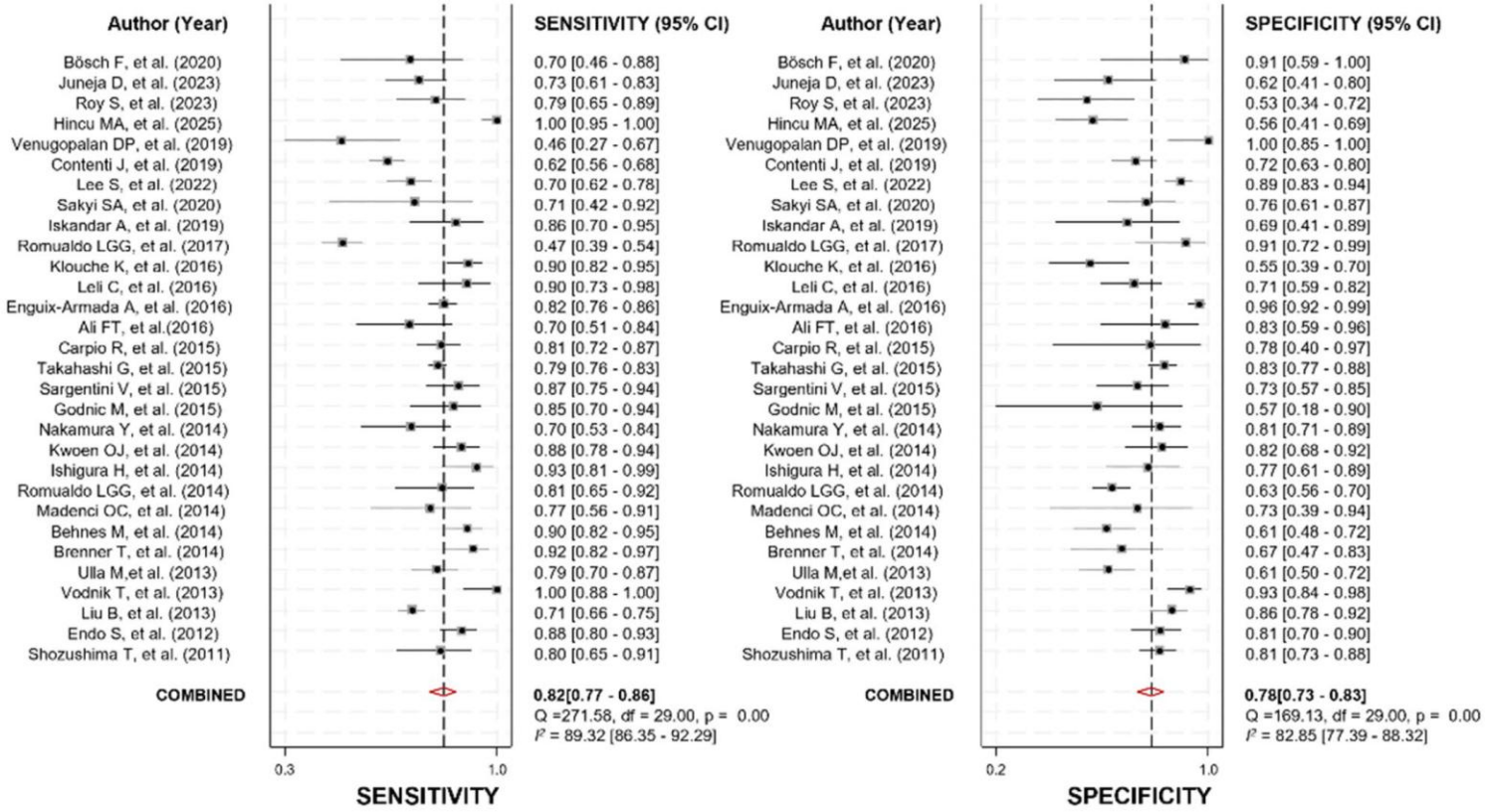
LR(−) = (1−Se) ÷ Sp

= 0.22 ÷ 0.77 ≈ **0.29**

判讀：LR+ 3.4 屬 **中度上修**、LR− 0.29 屬 **中度下修**，procalcitonin 比 CRP 均衡；但仍**非決定性**，須結合臨床。

BMC Emerg Med. 2025 Dec 4;26(1):9.

Diagnostic performance of presepsin in sepsis: a systematic review and meta-analysis



彙總 **Se 0.82**、**Sp 0.78**

LR(+) = 0.82 ÷ 0.22 ≈ **3.7**

LR(−) = (1−Se) ÷ Sp

= 0.18 ÷ 0.78 ≈ **0.23**

判讀：LR+ 3.7、LR− 0.23 皆屬 **中度**；表現略優於 PCT，但仍**不足以單獨確診或排除**。

BMC Emerg Med. 2025 Dec 4;26(1):9.

C-reactive protein (CRP)

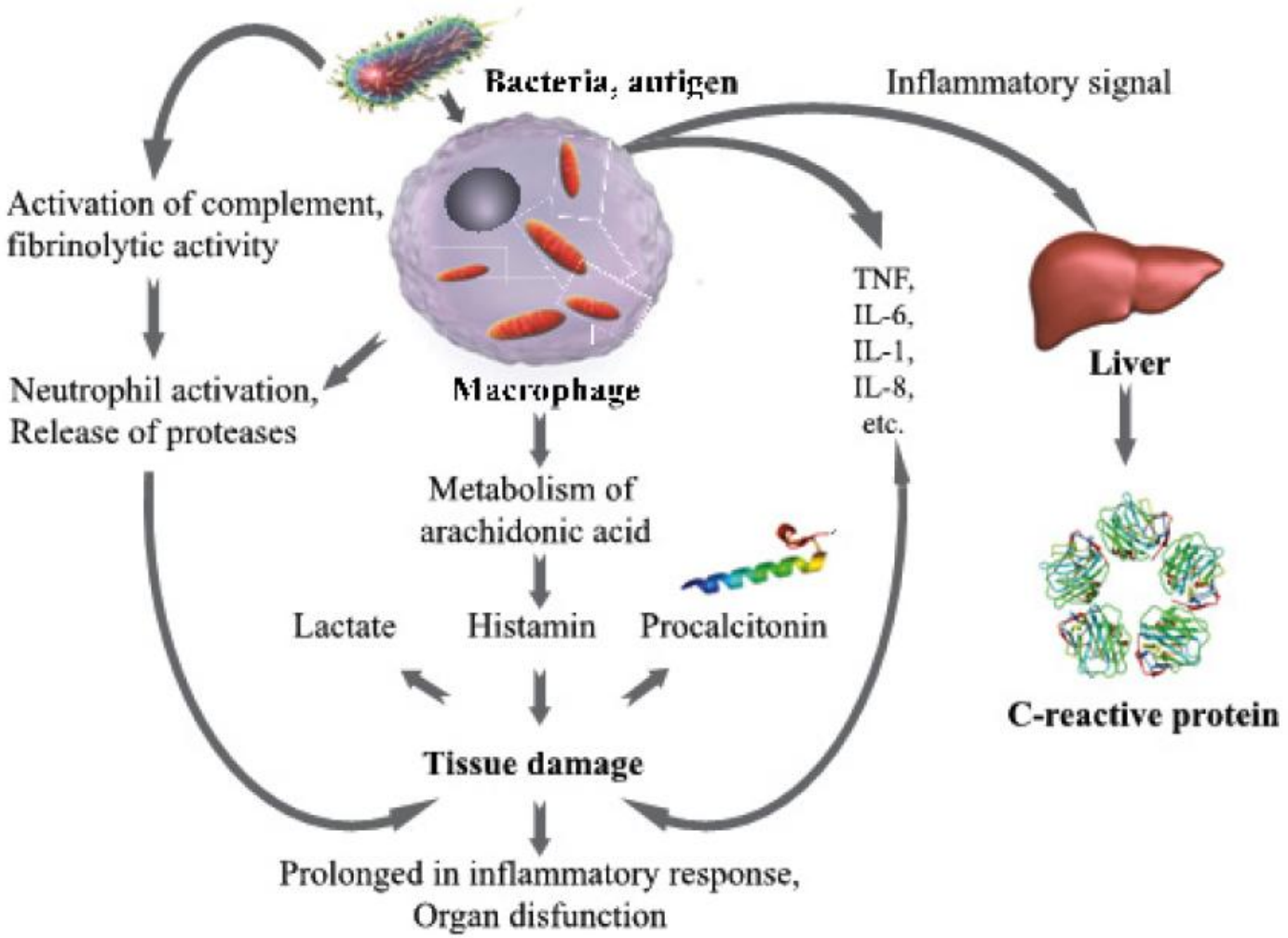
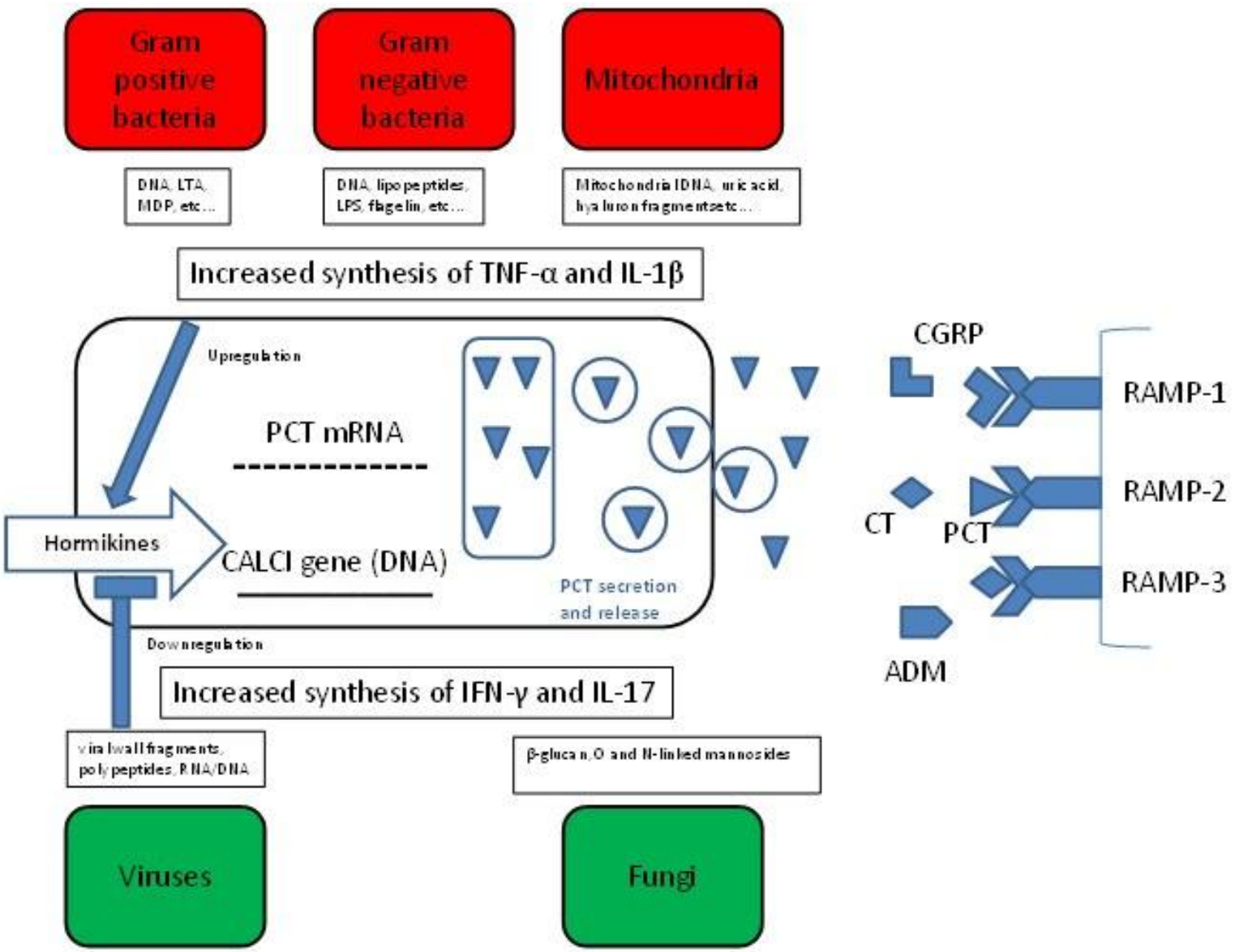


Fig. 2. Mechanisms of sepsis, release of procalcitonin and C-reactive protein, on [41] with modifications

Biomed Pharmacol J. 2020;13(3):1075-1093.

Procalcitonin (PCT)



J Hum Virol Retrovirol. 2016;3(2):119–122.

Presepsin (soluble CD14 subtype, sCD14-ST)

- 由單核球 / 巨噬細胞表面 **CD14** 受 **LPS**（lipopolysaccharide，脂多醣）經 **TLR4**（Toll-like receptor 4）活化後酵素切割產生的 **13 kDa** 片段
- 受腎功能影響：**eGFR**（estimated glomerular filtration rate，估算腎絲球過濾率）下降時 presepsin 上升，呈**強烈負相關**，判讀需校正腎功能

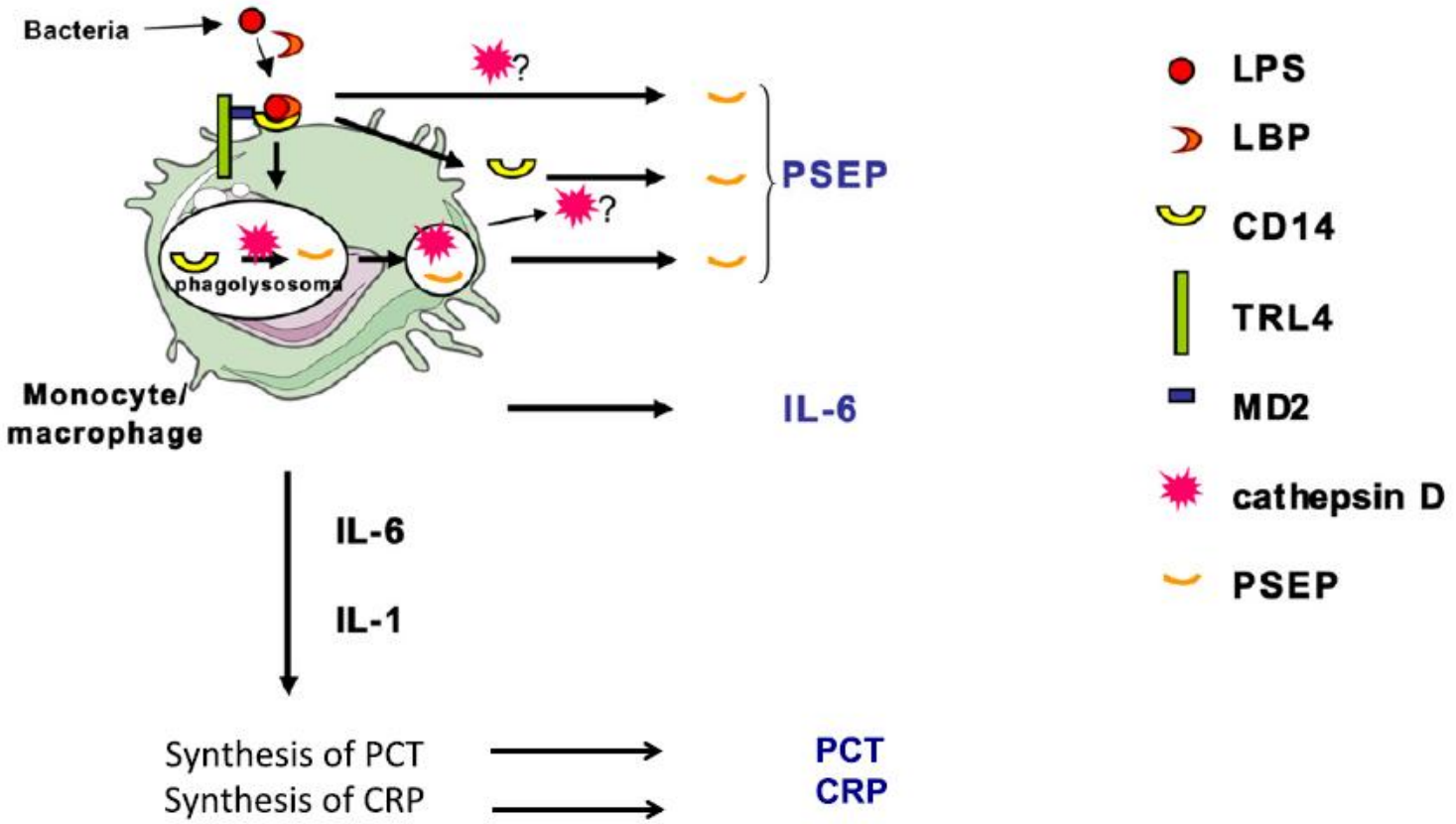


Fig. 1. Schematic production of presepsin. TLR: Toll-like-receptor; LPS: lipopolysaccharides; LBP: LPS-binding protein; MD2: molecular dynamic-2; PSEP: presepsin.

Clin Chim Acta. 2015 Oct 23;450:97-103.

Sepsis 生物標記比較：CRP、PCT、Presepsin

Table comparison for clinical interpretation

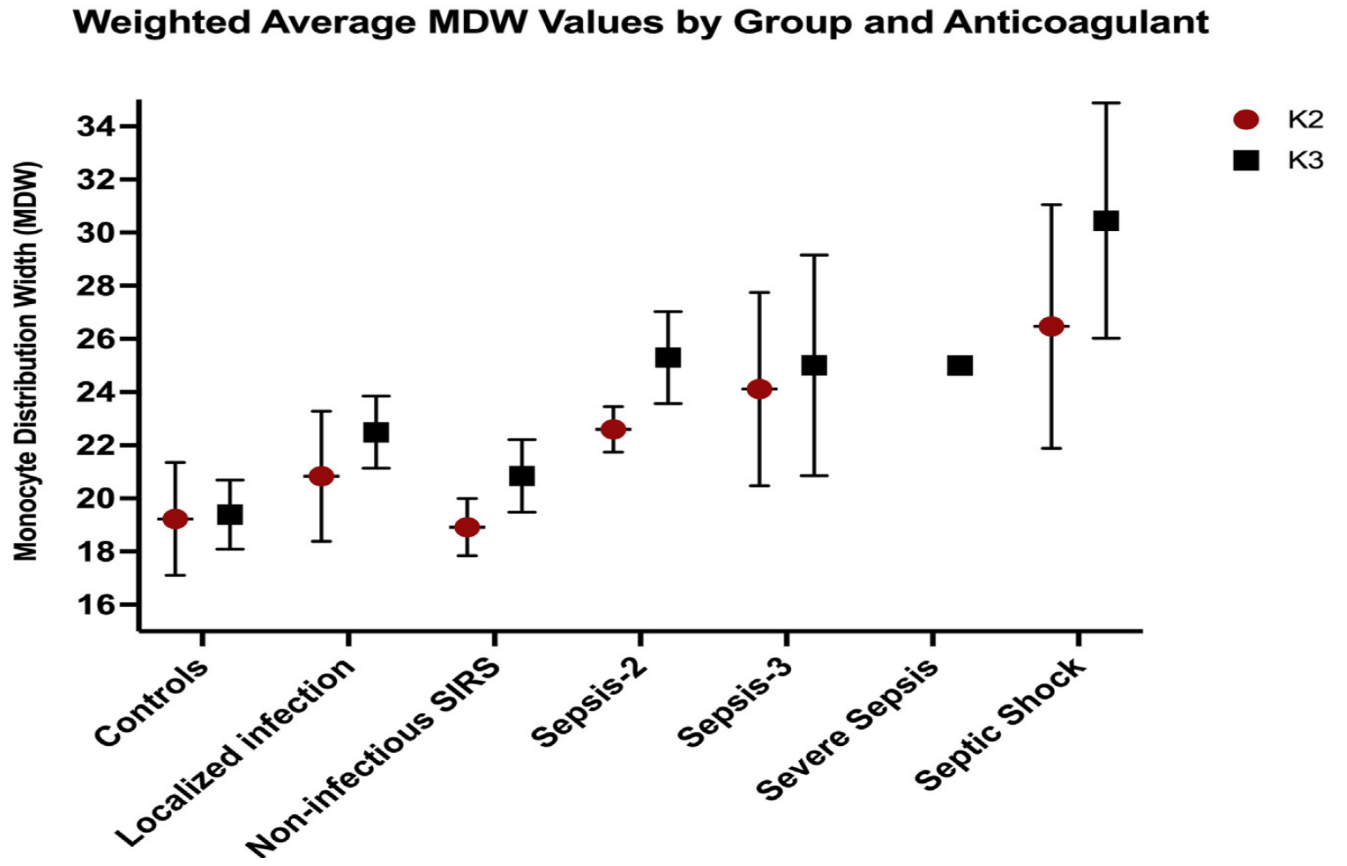
項目	CRP	PCT	Presepsin
全名 / 本質	C-reactive protein 急性期蛋白（pentraxin）	Procalcitonin calcitonin 前驅物	soluble CD14 subtype (sCD14-ST) 13 kDa peptide fragment
生產處 (production site)	主要由 liver / hepatocytes 產生 少量可見於 adipocytes	平時由 thyroid、lung、pancreas 的 neuroendocrine cells 表現 sepsis 時主要由 liver 與多種 parenchymal organs 產生	不是典型「分泌合成」蛋白 由 CD14 經 proteolytic cleavage 形成； 來源與 monocytes / macrophages / neutrophils 相關
Trigger molecules	IL-6、IL-1、TNF-α 發炎、感染、組織損傷皆可誘發	bacterial endotoxin / LPS、peptidoglycan 以及 inflammatory cytokines	LPS–LBP complex 經 CD14 / TLR pathway 細菌吞噬與 innate immune activation
Onset time	約 6–12 小時開始上升 臨床上常約 12 小時可偵測	約 2–4 小時	最快約 1 小時 多數資料約 1–2 小時
Peak time	約 20–72 小時	約 12–24 小時	約 3 小時
Duration / half-life	half-life 約 19 小時 下降較慢，常可持續數天	half-life 約 20–24 小時 控制感染後會逐日下降	half-life 約 4–5 小時 變化快，適合早期追蹤
優點	便宜、普及、可追蹤發炎趨勢	對 bacterial sepsis 較具特異性 可協助 antibiotic stewardship	上升最快 可協助早期 sepsis recognition 與 prognostic assessment
限制	特異性差 手術、創傷、惡性腫瘤、 非感染性發炎也會升高	並非完美；部分 trauma / surgery / renal dysfunction 也可能影響	受 renal function 影響明顯 目前證據仍較少，未明顯優於 PCT

* *Kinetic values are approximate and may vary by clinical context.*

References:

Rogić D, et al. eJIFCC. 2017;28(2):114-121. Meisner M. Ann Lab Med. 2014;34(4):263-273. Gabay C, Kushner I. N Engl J Med. 1999;340:448-454.
Pizzolato E, et al. Clin Chem Lab Med. 2018;56(10):1395-1405.

Diagnostic performance of monocyte distribution width (MDW) for the detection of sepsis: a systematic review and meta-analysis

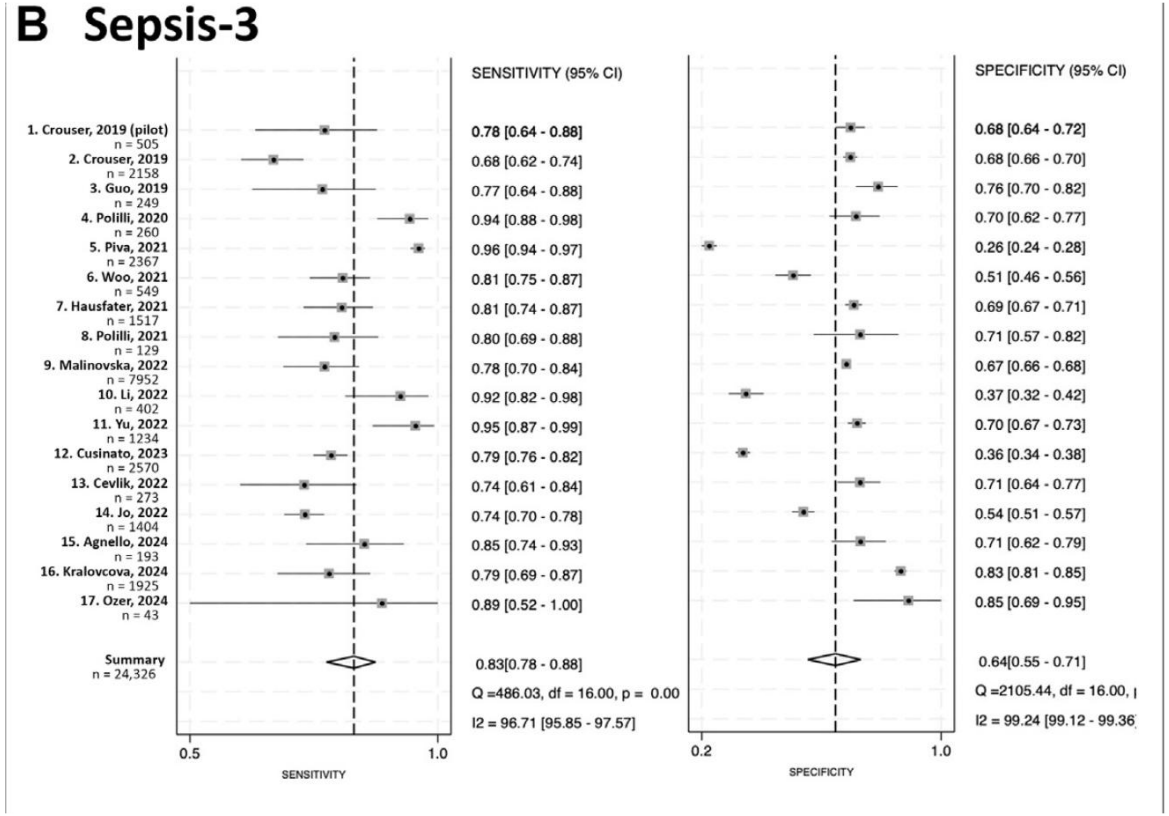


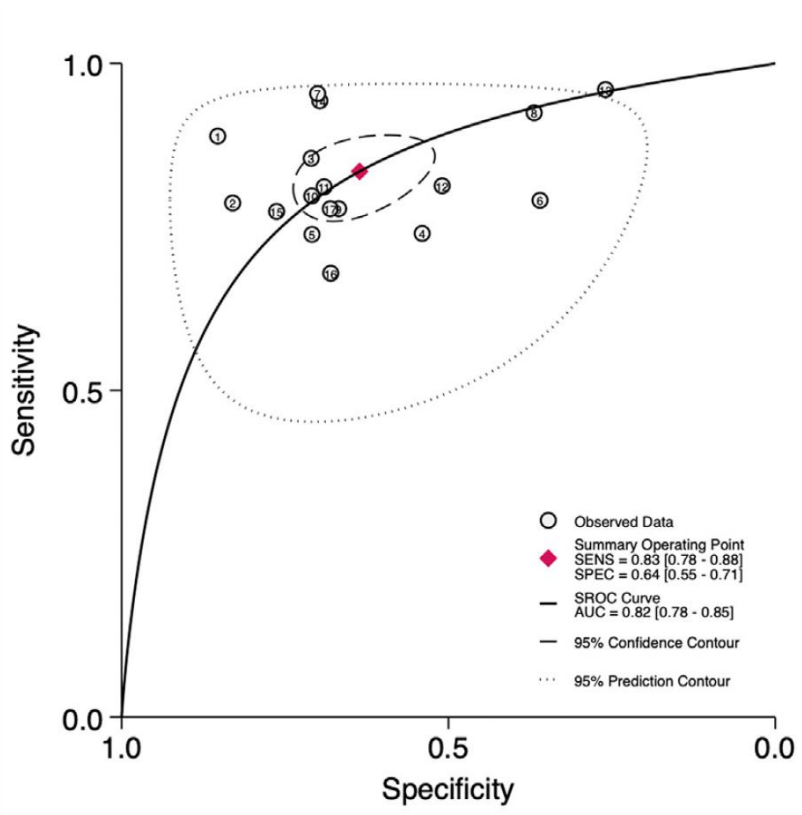
各族群之加權平均 **單核球分布寬度（monocyte distribution width, MDW）**隨疾病嚴重度上升

K2 = EDTA 二鉀管；K3 = EDTA 三鉀管；SIRS = 全身性發炎反應症候群（systemic inflammatory response syndrome）

J Am Coll Emerg Physicians Open. 2025 Feb 21;6(2):100073.

Diagnostic performance of monocyte distribution width (MDW) for the detection of sepsis: a systematic review and meta-analysis





彙總 **Se 0.83**、**Sp 0.64**

LR(+) = 0.83 ÷ 0.36 ≈ **2.3**

LR(−) = (1−Se) ÷ Sp

= 0.17 ÷ 0.64 ≈ **0.27**

判讀：高敏感度、低特異度，AUC 0.82；適合**排除**而非**確診**，須合併臨床評估。

J Am Coll Emerg Physicians Open. 2025 Feb 21;6(2):100073.

Monocyte distribution width (MDW) 的判讀限制

病毒感染
SARS-CoV-2、流感本身即可提升 MDW（COVID-19 中位數 **23.0**、流感 **24.1**），無法特異區分細菌性 sepsis

自體發炎 / 免疫疾病
成人史迪爾氏病（Adult-onset Still's disease）活動期 MDW 中位數 **28.3**，易被誤判為感染性 sepsis

非感染性重症
在**非感染性發炎狀態、細胞激素風暴、大手術及重大創傷後**皆可能上升，這反映其偵測的是單核球活化與大小異質性（anisocytosis）增加：預測感染特異性僅 **82%**、預測 sepsis 僅 **83%**

免疫抑制 / 單核球反應遲鈍
嗜中性球低下、化療後骨髓抑制者，MDW 反映單核球型態變化的能力可能不足（直接證據有限）

極早期採血
型態改變尚未發生，數值可能仍正常；與 PCT、CRP 同屬**時間依賴性**標記

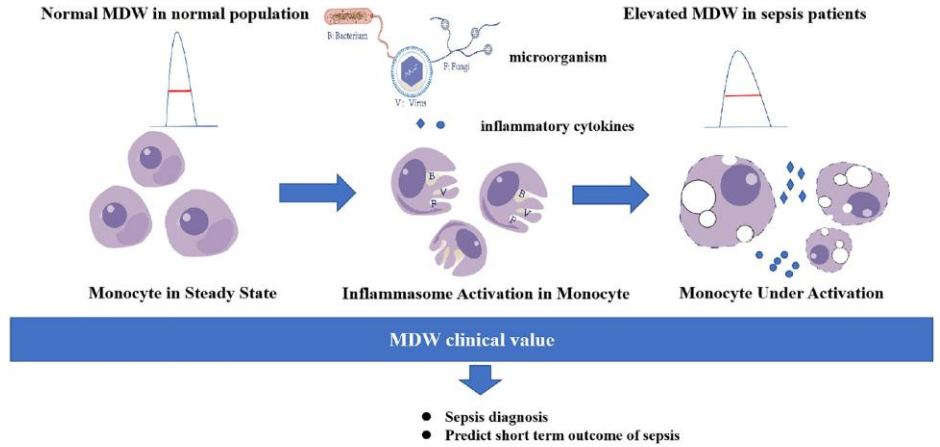
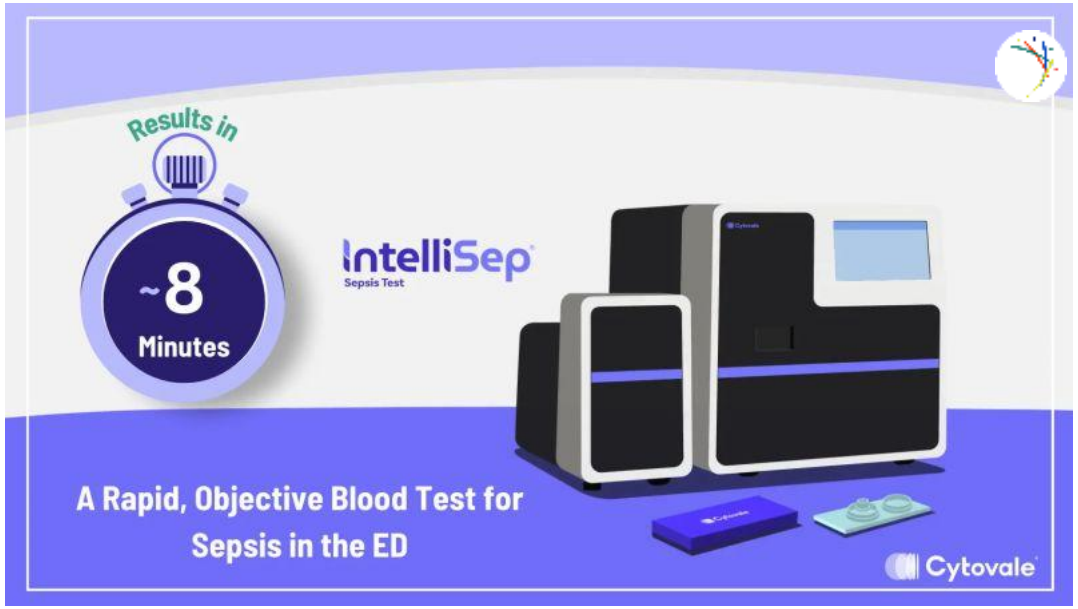


FIGURE 1 Demonstration of monocyte distribution width in normal population and sepsis patients.

臨床要點
MDW 上升代表**單核球活化**，並非細菌感染專屬；須與病史、影像及其他標記/檢驗合併判讀。

IntelliSep（Cytovale）：微流體形變式細胞儀



IntelliSep（Cytovale）以**微流體形變式細胞儀（microfluidic deformability cytometry）**評估白血球（單核球與嗜中性球）的生物物理特性變化，反映宿主免疫活化程度，用於輔助診斷敗血症（sepsis），並已獲美國 FDA 許可作為 sepsis 生物標記檢測。

原理

- 血液通過微流道時白血球受機械應力而變形，儀器測量其**外觀比（aspect ratio）與黏彈性慣性反應（visco-elastic inertial response）**，較細胞大小或計數更能反映免疫細胞在感染 / 發炎下的結構改變（如細胞骨架重組）。
- 僅需**單次抽血**，不需病人或實驗室其他資訊，運轉時間短，適合急診快速判讀。

判讀方式：IntelliSep Index（ISI）

- 分數範圍**0.1（最低風險）~ 10（最高風險）**，分為三個判讀區間：
  - **Band 1（Green）**：低風險
  - **Band 2（Yellow）**：中度風險
  - **Band 3（Red）**：高風險，對應較高疾病嚴重度

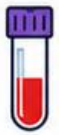
Cellular host response sepsis test for ED risk stratification

Pooled analysis of 5 adult cohorts from 7 U.S. emergency departments

1 Study design

Adults with signs/suspicion of infection

High-confidence adjudicated cohort: n = 1002



IntelliSep test from 100-µL whole blood

Turnaround time: <10 min

Output: IntelliSep Index (ISI) with 3 interpretation bands

2 Risk bands

Low risk	Intermediate	High risk
n = 521 (53.8%)	n = 243 (24.8%)	n = 238 (20.7%)

LOWER RISK → HIGHER RISK

Higher band = higher probability of sepsis

3 Diagnostic performance

Sensitivity (Band 1 cutoff): **93.2%**

Specificity (Band 3 cutoff): **87.0%**

PPV in Band 3: **55.9%**

NPV in Band 1: **97.5%**

0% sepsis-associated 30-day mortality in Band 1

Comparable or better high-risk detection; superior low-risk identification versus common sepsis indicators

4 Severity and resource use

30-day in-hospital mortality: 2.9% (Band 1) → 12.6% (Band 3)

Hospital admission:

Band 1	Band 2	Band 3
57.6%	72.0%	86.6%

ICU admission:

Band 1	Band 2	Band 3
11.3%	16.5%	26.1%

Higher ISI bands were associated with longer hospital stay and greater resource utilization

Clinical message

A rapid cellular host response test can help ED clinicians identify low- and high-risk patients with suspected sepsis and support earlier, more appropriate care.

Reference: O'Neal HR Jr, Sheybani R, Kraus CK, et al. Cellular host response sepsis test for risk stratification of patients in the emergency department: A pooled analysis. *Academic Emergency Medicine*. 2024;31:883-893. doi:10.1111/acem.14923

SeptiCyte RAPID vs TriVerity

Host-response molecular tests for suspected sepsis / acute infection

> ⚠ 2026 SSC: insufficient evidence to recommend routine use; always integrate with clinical assessment

Item	SeptiCyte RAPID	TriVerity
Regulatory status	FDA-cleared (510(k)) Initial clearance: 2021 EDTA whole-blood update: 2024	FDA-cleared (510(k)) Cleared: Jan 10, 2025 K241676
Clinical role	Helps differentiate sepsis from non-infectious systemic inflammation Main use: hospitalized / ICU day 1	Classifies bacterial infection, viral infection, or non-infectious illness Also predicts need for critical-care interventions within 7 days
Principle	qRT-PCR host-response assay 2 mRNAs: PLAC8 + PLA2G7 Output: SeptiScore, 4 bands	RT-LAMP + machine learning 29 host mRNAs on the Myrna instrument Outputs: Bacterial, Viral, Severity scores; 5 bands each
Turnaround time	Sample-to-answer: ~1 hour	Testing time: ~30 min Hands-on time: <1 min
Accuracy	Sepsis vs non-infectious inflammation AUROC ~0.82–0.85 in adult validation Spanish Sepsis-3 study: AUROC 0.84	SEPSIS-SHIELD Bacterial AUROC 0.83 Viral AUROC 0.91 Severity AUROC 0.78 Rule-in specificity >92%; rule-out sensitivity >95%
Key limitations / message	Probability-based test; not binary yes/no Must be interpreted with the full clinical picture	Probability-based multi-score test; not binary yes/no No proof yet that routine use improves hard clinical outcomes

Bottom line

Both are FDA-cleared host-response diagnostics. SeptiCyte RAPID is a focused sepsis-vs-noninfection inflammation tool, whereas TriVerity provides broader bacterial / viral / non-infectious classification plus short-term severity prediction. Neither should be used alone to rule in or rule out sepsis.

References

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4. Liesenfeld O, et al. Nat Med. 2025;31:4044-4054.
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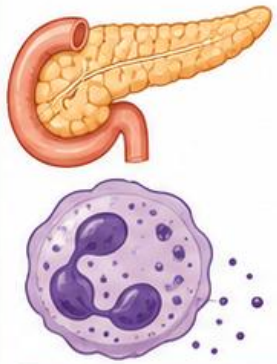
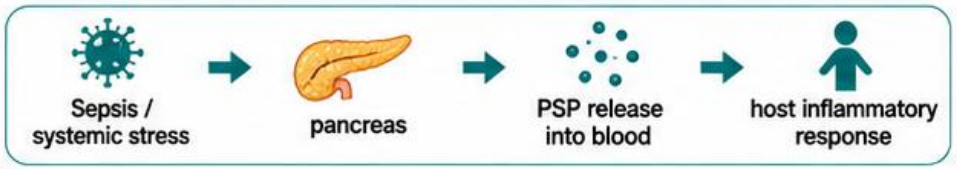
Pancreatic Stone Protein (PSP) for Sepsis Diagnosis

Molecular mechanism, FDA status, timeliness, and meta-analytic accuracy

1. Molecular mechanism



- **PSP = REG1B / lithostatin**; a C-type lectin protein
- **Main source**: pancreatic acinar cells (major source; much higher than other organs)
- Acts as an acute-phase protein during systemic stress / sepsis
- Animal models: pancreatic PSP synthesis increases after remote injury and septic stimulation
- **Pathophysiology**: can activate neutrophils and may contribute to sepsis-related MODS
- But in sepsis-associated pancreatic injury, PSP/Reg may also reduce pyroptosis by downregulating NLRP3, caspase-1 p20, and GSDMD-N



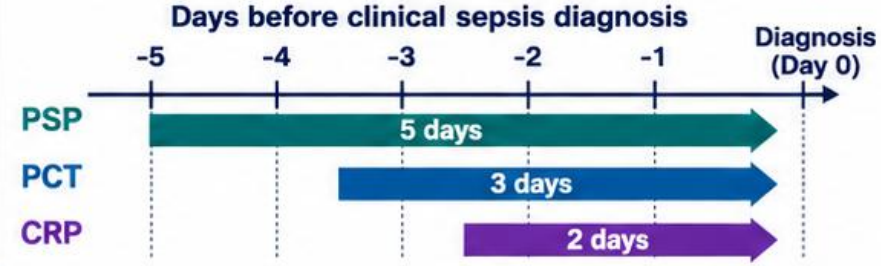
2. FDA status

Currently no FDA clearance

- No FDA-cleared / FDA-approved PSP diagnostic assay identified in current literature
- Most studies used research-use or CE-marked immunoassay platforms
- Examples: abioSCOPE point-of-care assay, AlphaLISA laboratory assay

3. Measurement & timeliness

- Protein immunoassay measured in serum, plasma, or whole blood
- abioSCOPE point-of-care: sample-to-result within about **1 hour**
- AlphaLISA assay: about **5 minutes**
- Serial ICU study: PSP began rising about **5 days** before clinical sepsis diagnosis
- Earlier than PCT (**~3 days**) and CRP (**~2 days**)



4. Meta-analytic diagnostic accuracy

A. Individual patient-level meta-analysis (Prazak et al., 2021)

- 5 studies, n = 631
- Cutoff: 44.18 ng/mL
- AUC **0.81** (95% CI 0.78–0.85)
- Sensitivity 0.66
- Specificity 0.83
- PPV 0.85, NPV 0.63
- PSP + CRP improved AUC to **0.90**; adding PCT gave no further gain

B. Systematic review & meta-analysis (Mai et al., 2024)

- Pooled sensitivity 0.88 (0.77–0.94)
- Pooled specificity 0.78 (0.65–0.87)
- PLR 4.1, NLR 0.16, DOR 26
- SROC AUC **0.90** (0.87–0.92)
- Neonatal subgroup: sensitivity 0.91, specificity 0.66

5. Clinical interpretation

- PSP is a promising early sepsis biomarker
- Diagnostic performance is generally good (AUC about 0.81–0.90)
- Cutoffs and study populations are heterogeneous
- No FDA-cleared assay yet
- Clinical utility for guiding antibiotics still needs stronger prospective validation

Bottom line: PSP is biologically plausible and diagnostically promising, but it is not yet an FDA-cleared routine sepsis test.

References Hu P et al. Front Med. 2023; Liu P et al. Front Med. 2025; Reding T et al. Oncotarget. 2017; Shorr AF et al. Crit Care Med. 2026; Michailides C et al. Infect Dis (Lond). 2026; Xiang Z et al. Clin Chim Acta. 2022; Pugin J et al. Crit Care. 2021; Prazak J et al. Crit Care. 2021; Mai B et al. BMC Infect Dis. 2024.

Sepsis ImmunoScore：AI 整合生物標記與臨床資料的風險評分

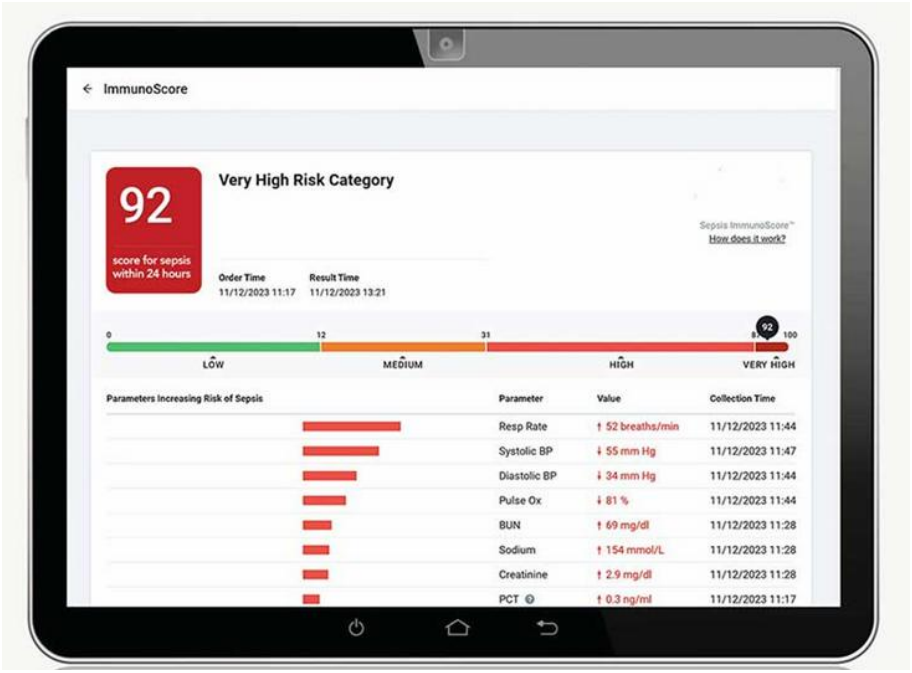
News

FDA authorises Prenosis' AI-based tool for sepsis diagnosis

It is said to be the first-ever FDA approval for an AI software as a medical device for diagnosis and prediction of sepsis.

April 4, 2024

Share



- **Sepsis ImmunoScore** 以 AI 整合生物標記與臨床資料，評估病人在**評估後 24 小時內**出現或惡化為敗血症（sepsis）的風險，適用急診與住院病人。
- 納入 **22 項參數**，綜合評估生理狀態，輸出一個風險分數與**四個風險級別**（Low / Medium / High / Very high）。
- 資料基礎：與美國 10 家夥伴醫院合作十年，建立含 **超過 100,000 份血液樣本、超過 25,000 名病人** 的生物樣本庫（Immunix）。
- Prenosis 以自有實驗室檢驗產生生物數據，再與夥伴醫院**電子病歷（electronic medical record, EMR）**的臨床資料整合。

臨床意義

把多項生物標記與臨床資料整合為**單一風險分數與分層**，價值在急診的早期辨識與分流，仍須前瞻性驗證與流程整合。

Prenosis, Inc.；全球首個獲美國 FDA 許可用於 sepsis 診斷與預測的 AI 軟體醫療器材（2024 年 4 月）

FDA 授權的 sepsis AI 預測工具：開發與驗證

NEJM AI 2024;1(12)　DOI: 10.1056/AIoa2400867

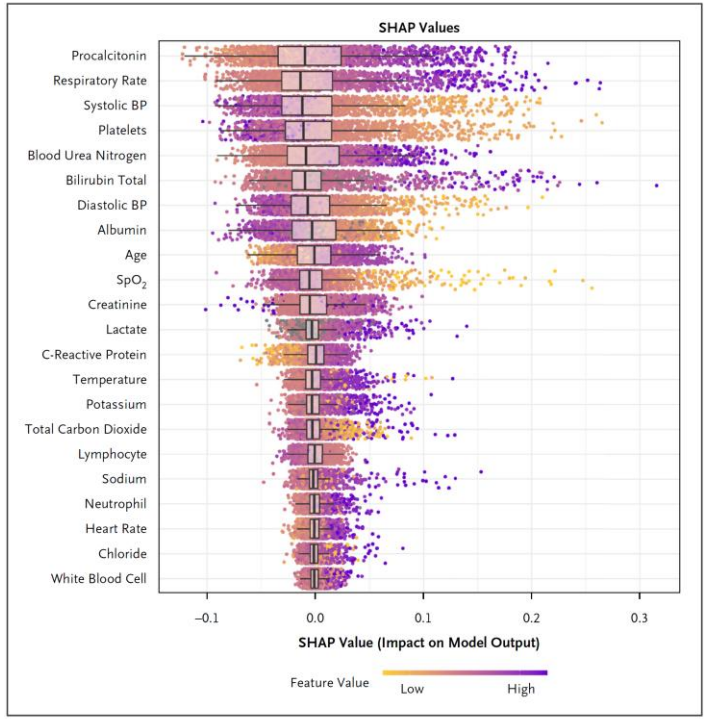


Figure 1. Sepsis ImmunoScore Feature Importance.

SHAP = SHapley Additive exPlanations，各變項對模型輸出的貢獻度

- **分層特異性概似比（stratum-specific likelihood ratio, SSLR）**
- =（該層病例數 / 總病例數）÷（該層非病例數 / 總非病例數）

Table 1. Baseline Data and Adverse Outcomes for the Derivation, Internal Validation, and External Validation Cohorts.*

Characteristic	Patient Encounters, No. (%)		
	Derivation Cohort (n=2366)	Internal Validation Cohort (n=393)	External Validation Cohort (n=698)

Table 3. External Validation Sepsis ImmunoScore Risk Stratification for Sepsis-3 within 24 Hours.*

Cohort ImmunoScore Risk Category	Patients (no.)	Patients with Sepsis (no.)	Sepsis PV (% [95% CI])	Sepsis Likelihood Ratio [95% CI]	Cochran–Armitage Test (P Value)
External validation (n=698)					
Low	232	7	3.0% [1.2%, 6.1%]	0.1 [0.1, 0.2]	<0.001
Medium	157	20	12.7% [7.96%, 19.0%]	0.5 [0.3, 0.8]	
High	276	101	36.6% [30.1%, 42.6%]	2.1 [1.8, 2.5]	
Very high	33	23	69.7% [51.3%, 84.4%]	8.3 [4.1, 17.1]	

*CI denotes confidence interval, and PV, predictive value.

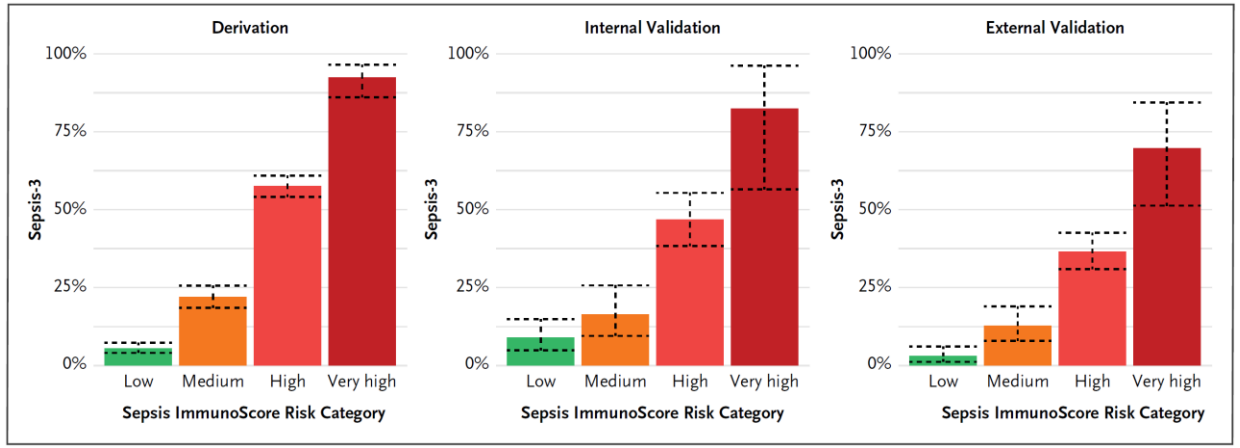
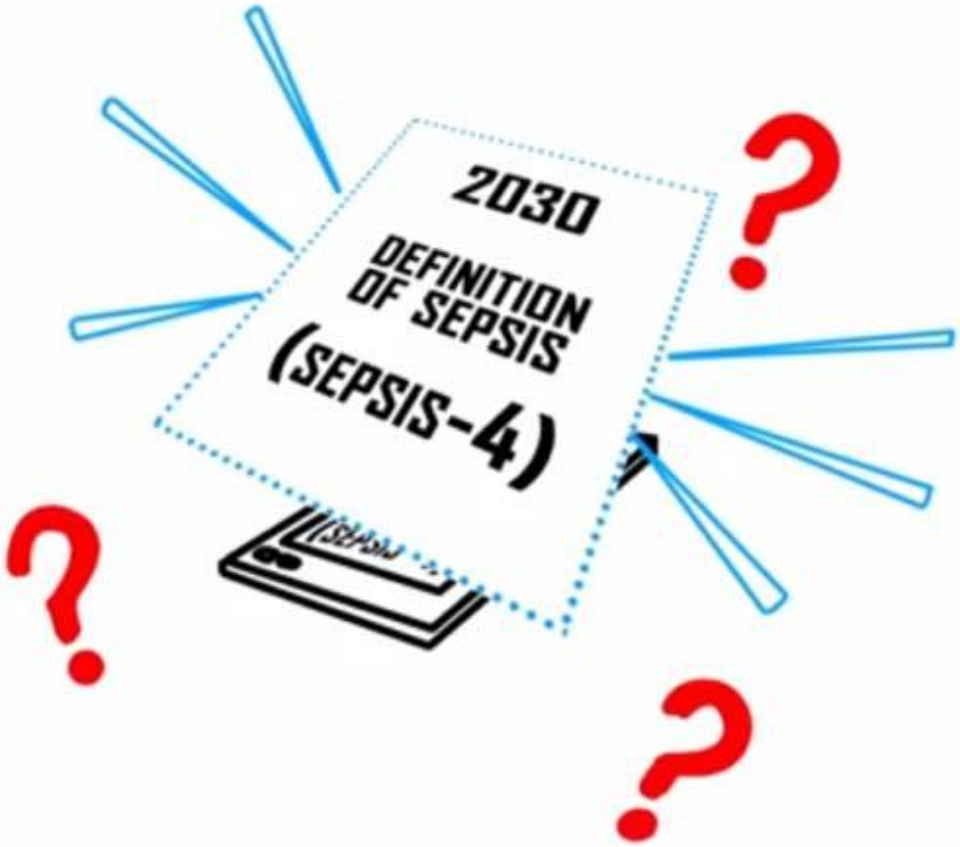


Figure 2. Sepsis ImmunoScore Stratification for Sepsis-3 in All Cohorts.

下一個~~男人~~ 也許會更好...

Sepsis-4？定義與診斷工具理當會繼續演進



Take Home Message

定義仍在演進，且沒有診斷金標準

Sepsis 從 **SIRS（systemic inflammatory response syndrome）**（1991）走到 **Sepsis-3**（2016）：核心是感染引起的失調宿主反應造成器官功能失常。至今仍無 gold standard，任何工具都只能輔助臨床判斷。

篩檢：要用工具，但不能只靠單一工具

SSC 2026 建議對高風險病人常規進行 sepsis 篩檢；**qSOFA 單獨使用敏感度不足**（LR– 不夠低、無法用來排除），應搭配 NEWS / MEWS 等 early warning score 與臨床評估。

生物標記各有極限，重點在「輔助」而非「確診」

CRP（C-reactive protein）、PCT（procalcitonin）、presepsin、MDW（monocyte distribution width）都無法單獨確診 sepsis；適合用於風險分層、鑑別診斷與抗生素療程決策的參考。

新型檢驗與 AI：從「診斷」走向「早期風險預測」

IntelliSep（ISI 0.1 ~ 10，Band 1–3）與 FDA 授權的 **Sepsis ImmunoScore** 等 AI / ML 工具整合多項生物標記與臨床資料，價值在於早期辨識與分層，仍須前瞻性驗證與流程整合。

關鍵不變：早期辨識、及早抗生素與復甦；檢驗與 AI 是加速決策的輔助，不是取代臨床判斷。