Early Sepsis Indicator (ESID) – Monocyte Distribution Width(MDW)

於診斷 sepsis 之臨床應用

馬偕紀念醫院台北與淡水院區 感染管制中心張富傑感染管制醫檢師
馬偕紀念醫院台北與淡水院區 感染管制中心/感染科林志錚主治醫師
馬偕紀念醫院台北與淡水院區 感染管制中心/感染科劉昌邦主任
馬偕紀念醫院台北院區 檢驗科王敦仁主任

前言

敗血症(Sepsis)為一個嚴重的感染症狀，傳統上，病人會先經過局部感染(Localization infected)後，接著進入到全身性炎症反應徵候群(Systemic Inflammatory Response Syndrome, SIRS)，如果沒有妥善的處理，就會再進入菌血症(Bacteremia)，然後演變成敗血症(Sepsis)、嚴重敗血症(Sever sepsis)與敗血性休克(Septic shock)[1]。根據 JAMA Sepsis-3 的新版定義，定義敗血症為因感染的反應繼發危及生命的器官失能(Organ Dysfunction)，器官失能定義因感染導致 SOFA score ≥ 2 分之情形，Septic shock 則為因 Sepsis 導致循環或細胞層次的異常，進而造成死亡增加之情形，臨床定義需 Vasopressors 維持 MAP ≥ 65mm-Hg 加上 Serum lactate >2 mmol/L ，其死亡率 > 40%[2]。

臨床上診斷早期敗血症指標(Early Sepsis Indicator, ESID)的生物指標包含了 Lipopolysaccharide-Binding Protein[3]、secretory phospholipase A2(sPLA2-IIA)[4]、前降鈣素(Procalcitonin, PCT)[5]、IL-18、IL-12[6]、CD64[7]、Soluble CD14 subtype(sCD14-ST)[8]、Mid-Regional Pro-Adrenomedullin(MR-proADM)[9]，還有傳統上的發炎蛋白(C-Reactive protein, CRP)[10] 等等。臨床上，檢驗前降鈣素與發炎蛋白為最常見的檢驗項目，其餘檢驗項目因為價格或方法學限制，所以鮮少應用於臨床。大多數的檢驗項目，都屬於抗原抗體檢測，必須仰賴 ELISA、EIA、FIA 等等之檢驗方法，換句話說，其檢測的時間會比較長，且耗費較多成本。

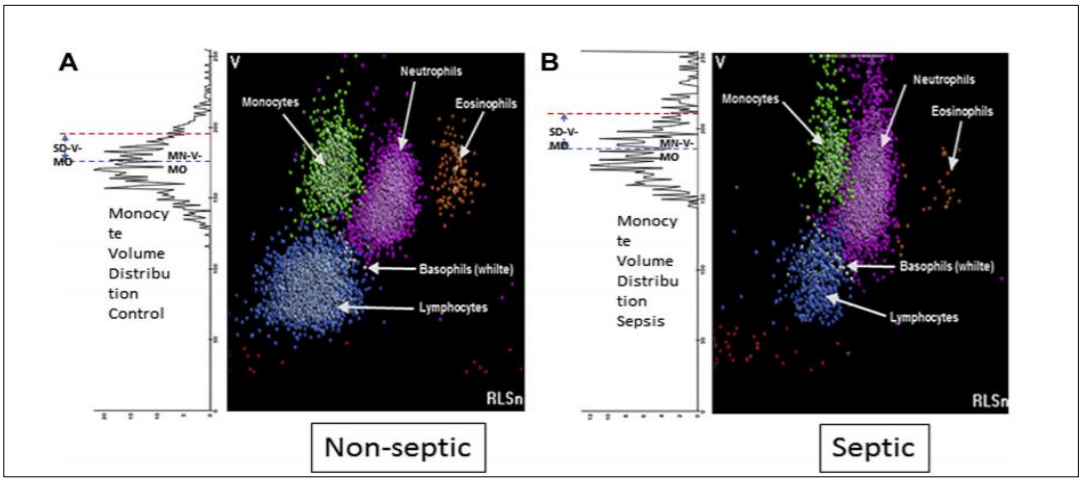
近幾年來，有些許的研究開始探討是否在敗血症前期，可檢驗血球的型態、血小板數量或是血球分布會有所改變，來評斷是否也可以做為診斷早期敗血症的指標。而在近年的研究中發現，檢驗單核球分佈寬度(Monocyte Distribution Width, MDW)可以做為一個診斷早期敗血症(Early Sepsis)的參考依據 [11]。且幸運的是，檢驗單核球分佈寬度可以直接透過機器的光學檢驗，就可以得知相關的檢驗結果。

單核球分佈寬度與菌血症之關係

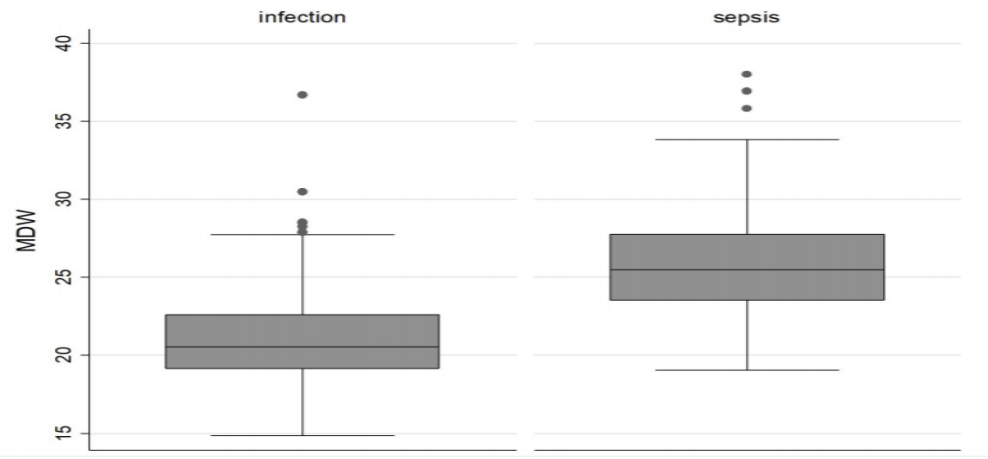
根據學理，人體被細菌感染後，會啟動免疫系統進行防衛，最常見的就是補體系統 [12,13]，其次就是白血球-嗜中性球(Neutrophil)，嗜中性球會因為無法辨識細菌的細胞壁，而啟動毒殺反應 [14,15]，接著單核球(Monocyte)也會因為無法辨識抗原，進行相關的胞吞作用 [16-18]。也因為此特點，當細菌跑到血液裡面後，正常情況下，嗜中性球會進行毒殺作用，針對細

菌進行攻擊，接著單核球會開始進行吞噬作用，針對細菌死掉後的屍體，進行胞吞作用，而吞噬了外來物之後，單核球數目也許不會再增加，但有趣的是，因為單核球進行胞吞作用，所以單核球的寬度就會變寬，也因為如此，文獻才會探討單核球分佈寬度是否可以作為診斷早期敗血症 [11,19,20]，並且透過及早的診斷，達到預防與治療的效果，當檢驗結果偏高的時候，建議病患留觀 4~8 小時後再次採檢，如果超過 Cut-off 值，則盡早使用注射型之抗生素藥物，便免造成後續的敗血症與敗血性休克 [21-23]。

根據過往的研究，單核球分佈寬度(Monocyte Distribution Width, MDW)正常應落在 < 20，但是在感染的病人中，MDW 因為 Monocyte 吞噬了細菌，所以會較一般 Monocyte 的還大，通常會大於 20(圖一)。根據之前的研究，單核球分佈寬度(Monocyte Distribution Width, MDW)的結果會因為感染而升高(圖二)，再 Sepsis 的病人身上，單核球分佈寬度會比只有感染的病人高。然而，如果單用一個單核球分佈寬度(Monocyte Distribution Width, MDW)來預測 Sepsis，則根據文獻的表示(表一)，沒有一個較好的 Cut-off 值可以做為單一評斷的標準 [24]。



圖一、Monocyte 因為吞噬了細菌，造成其較一般的 Monocyte 還要大，所以單核球分佈寬度(Monocyte Distribution Width, MDW)就會大於 20



圖二、單核球分佈寬度在一般感染與 Sepsis 病人的結果，可以明顯看到在 Sepsis 的病人身上，其檢驗結果較高

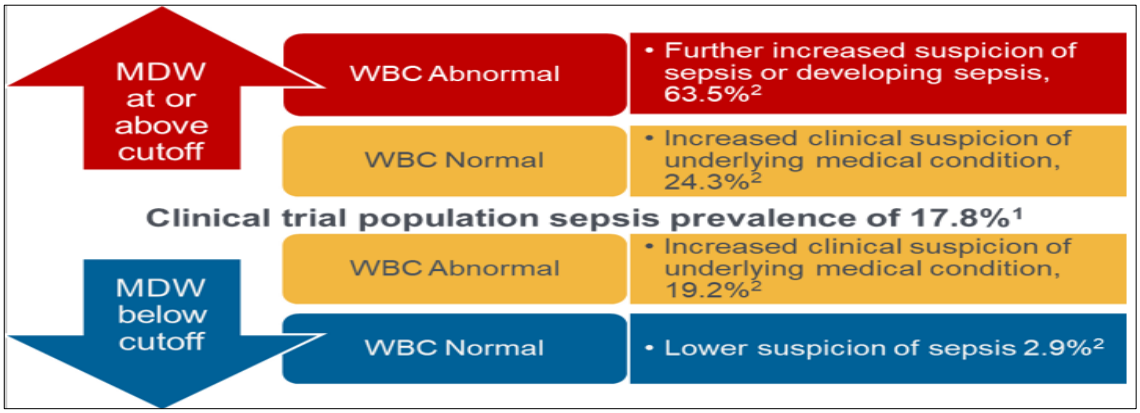
表一、根據過往文獻，單利用單核球分佈寬度作為預測 Sepsis 的結果，並沒有一個 Cut-off 值可以做診斷的依據

a)

Variable	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)
MDW>19	100 (96.5–100)	22.6 (16.3–30.3)	46.7 (40–53.4)	100 (90–100)
MDW>20	98.1 (93.3–99.8)	41.9 (34.1–50.1)	53.4 (46.1–60.6)	97.0 (89.6–99.6)
MDW>21	95.2 (82.2–98.4)	59.4 (51.2–67.2)	61.3 (53.4–68.9)	94.8 (88.4–98.3)
MDW>22	94.3 (88.0–97.9)	69.7 (61.8–76.8)	67.8 (59.6–75.3)	94.7 (88.9–98.0)
MDW>23	81.9 (73.2–88.7)	77.4 (70.0–83.7)	71.1 (62.1–79.0)	86.3 (79.5–91.6)
MDW>24	68.6 (58.8–77.3)	86.5 (80.0–91.4)	77.4 (67.6–85.4)	80.2 (73.4–86.0)
MDW>25	54.3 (44.3–64.0)	91.6 (86.1–95.5)	81.4 (70.3–89.7)	74.7 (67.9–80.7)
MDW>26	41.0 (31.5–51.0)	93.5 (88.5–96.9)	81.1 (68.0–90.6)	70.0 (63.3–76.2)
MDW>27	29.5 (21.0–39.2)	94.2 (89.3–97.3)	77.5 (61.5–89.2)	66.4 (59.7–72.6)
MDW>28	22.9 (15.2–32.1)	96.8 (92.6–98.9)	82.8 (64.2–94.2)	64.9 (58.4–71.1)
MDW>29	18.1 (11.3–26.8)	98.7 (95.4–99.8)	90.5 (69.6–98.8)	64.0 (57.6–70.1)
MDW>30	15.2 (9.0–23.6)	98.7 (95.4–99.8)	88.9(65.3–98.6)	63.2 (56.8–69.3)
MDW>31	13.3 (7.5–21.4)	99.4 (96.5–100)	93.3 (68.1–99.8)	62.9 (56.5–68.9)

臨床建議

根據上述所言，過往的研究(圖三)也建議加入 WBC 一起評估可以增加敗血症評估的準確性，透過檢驗 WBC 的結果，判斷是否符合全身性炎症反應徵候群(Systemic Inflammatory Response Syndrome, SIRS)的定義，如果 WBC 數值不是正常的情況下，在透過檢驗單核球分佈寬度，將 Cut-off 值定在 20，則 MDW ≤ 20：敗血症低風險但無法完全排除；MDW > 20：可能有較高的風險為敗血症 [25]。



圖三、根據過往文獻，先參考 WBC 的檢驗數值後，再參考單核球分佈寬度，可以及早診斷 Sepsis

參考文獻：

1. Rivers EP, Jaehne AK, Nguyen HB, Papamatheakis DG, Singer D, Yang JJ, Brown S, Klausner H. Early biomarker activity in severe sepsis and septic shock and a contemporary review of immunotherapy trials: not a time to give up, but to give it earlier. Shock 2013;39(2):127-137.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810.
3. Chen KF, Chaou CH, Jiang JY, Yu HW, Meng YH, Tang WC, Wu CC. Diagnostic Accuracy of Lipopolysaccharide-Binding Protein as Biomarker for Sepsis in Adult Patients: A Systematic Review and Meta-Analysis. PLoS One 2016;11(4):e0153188.
4. Tan TL, Goh YY. The role of group IIA secretory phospholipase A2 (sPLA2-IIA) as a

biomarker for the diagnosis of sepsis and bacterial infection in adults-A systematic review. PLoS One 2017;12(7):e0180554.

5. Reyna-Figueroa J, Lagunas-Martinez A, Martinez Matsumoto P, Madrid-Marina V. Procalcitonin as a diagnostic biomarker of sepsis in children with cancer, fever and neutropenia: literature review. Arch Argent Pediatr. 2015;113(1):46-52.
6. Emmanuilidis K, Weighardt H, Matevossian E, Heidecke CD, Ulm K, Bartels H, Siewert JR, Holzmann B. Differential regulation of systemic IL-18 and IL-12 release during postoperative sepsis: high serum IL-18 as an early predictive indicator of lethal outcome. Shock 2002;18(4):301-305.
7. Shang YX, Wang LR. Neutrophil CD64 Expression as A Biomarker in the Early Diagnosis of Sepsis in Malignant Hematologic Disease--Review. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2016;24(1):241-244.
8. van Maldeghem I, Nusman CM, Visser DH. Soluble CD14 subtype (sCD14-ST) as biomarker in neonatal early-onset sepsis and late-onset sepsis: a systematic review and meta-analysis. BMC Immunol. 2019;20:17.
9. Onal U, Valenzuela-Sanchez F, Vandana KE, Rello J. Mid-Regional Pro-Adrenomedullin (MR-proADM) as a Biomarker for Sepsis and Septic Shock: Narrative Review. Healthcare (Basel). 2018;6(3):110.
10. Neely AN, Smith WL, Warden GD. Efficacy of a rise in C-reactive protein serum levels as an early indicator of sepsis in burned children. J Burn Care Rehabil. 1998;19(2): 102-105.
11. Crouser ED, Parrillo JE, Seymour C, Angus DC, Bicking K, Tejidor L, Magari R, Careaga D, Williams J, Closser DR, et al. Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker. Chest. 2017;152(3):518-526.
12. Tsai CC, Nilsson UR, McArthur WP, Taichman NS. Activation of the complement system by some gram-positive oral bacteria. Arch Oral Biol. 1977;22:309-312.
13. Stiffel C, Biozzi G, Mouton D, Bouthillier Y, Decreusefond C. Studies on Phagocytosis of Bacteria by the Reticuloendothelial System in a Strain of Mice Lacking Hemolytic Complement. J Immunol. 1964;93:246-249.
14. Kochi C. Neutrophil granulocyte function in vitro. Evaluation of a fluid-phase leucocyte-bacteria reaction system. Acta Pathol Microbiol Scand B Microbiol Immunol. 1974;82:127-135.
15. Solberg CO. Protection of phagocytized bacteria against antibiotics. A new method for the evaluation of neutrophil granulocyte functions. Acta Med Scand. 1972;191(5):383-387.
16. Newman SL, Tucci MA. Regulation of human monocyte/macrophage function by extracellular matrix. Adherence of monocytes to collagen matrices enhances phagocytosis of opsonized bacteria by activation of complement receptors and enhancement of Fc receptor function. J Clin Invest. 1990;86(3):703-714.
17. Antonaci S, Jirillo E. Relationship between immune system and gram-negative bacteria: monocyte chemotaxis induced by supernatants from human peripheral blood OKT8+ lymphocytes stimulated with smooth and rough Salmonella strains. Cell Immunol. 1985;95:258-64.

18. Elberg SS, Fong J, Schneider P. Studies on tubercle bacillus-monocyte relationship. II. Induction of monocyte degeneration by bacteria and culture filtrate: specificity of serum and monocyte effects on resistance to degeneration. J Exp Med. 1957;105(1):25-37.
19. Crouser ED, Parrillo JE, Seymour CW, Angus DC, Bicking K, Esguerra VG, Peck-Palmer OM, Magari RT, Julian MW, Kleven JM, et al. Monocyte distribution width: a novel indicator of sepsis2 and sepsis-3 in high-risk emergency department patients. Crit Care Med. 2019;47:1018-1025.
20. Rezende SM, Lijfering WM, Rosendaal FR, Cannegieter SC. Hematologic variables and venous thrombosis: red cell distribution width and blood monocyte count are associated with an increased risk. Haematologica. 2014;99:194-200.
21. Tezol O, Bozlu G, Sagcan F, Tuncel Daloglu F, Citak C. Value of neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio and red blood cell distribution width in distinguishing between reactive lymphadenopathy and lymphoma in children. Bratisl Lek Listy. 2020; 121: 287-292.
22. Li X, Wu J, Mao W. Evaluation of the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and red cell distribution width for the prediction of prognosis of patients with hepatitis B virus-related decompensated cirrhosis. J Clin Lab Anal. 2020;e23478.
23. Crouser ED, Parrillo JE, Martin GS, Huang DT, Hausfater P, Grigorov I, Careaga D, Osborn T, Hasan M, Tejidor L. Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA. J Intensive Care. 2020;8:33.
24. Polilli E, Sozio F, Frattari A, Persichitti L, Sensi M, Posata R, Di Gregorio M, Sciacca A, Flacco ME, Manzoli L, et al. Comparison of Monocyte Distribution Width (MDW) and Procalcitonin for early recognition of sepsis. PLoS One 2020;15:e0227300.
25. Agnello L, Lo Sasso B, Giglio RV, Bivona G, Gambino CM, Cortegiani A, Ciaccio AM, Vidali M, Ciaccio M. EXPRESS: Monocyte distribution width as a biomarker of sepsis in the Intensive Care Unit: a pilot study. Ann Clin Biochem. 2020;4563220970447.