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Current concepts in diagnosis of pneumonia

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Usefulness of monocyte distribution width (MDW) as a sepsis biomarker

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ABSTRACT

Sepsis is one of the main causes of mortality in the emergency department (ED), due to the fact that signs and symptoms are common to other acute diseases, and this can result in delayed detection. This diagnostic complexity has a huge impact on an entity in which early recognition determined treatment, as wells as enhance the patient's prognosis. Therefore, it is crucial to improve early identification. Different analytical tools arise from this approach, such as biomarkers: procalcitonin, C-reactive protein or MR-proadrenomedullin. In this review we will focus on a newer biomarker, the monocyte distribution width. The main objectives are to evaluate the usefulness of monocyte distribution width (MDW) in sepsis identification in ED, its limitations, and to compare it with other biomarkers.

Keywords: Biomarkers, Emergency department, Sepsis, Monocyte distribution width

INFECTIOUS DISEASES IN THE EMERGENCY DEPARTMENTS

Infectious disease is one of the most frequent reasons for consultation in the Emergency Department (ED), reaching around 15% of the patients assessed [1]. The profile of the patients attended are increasingly older with accumulative comorbidity, who are more frequently under immunosuppressive treatments, and have a higher prevalence of risk factors for infections by multidrug resistance microorganisms [1].

Lower respiratory tract infections are the main infection diagnosed and treated in ED. The incidence of community-acquired pneumonia (CAP) ranges between 2-15 cases/1,000 inhabitants/year, being higher in male patients, smokers, ≥75 years, with comorbidities or immunocompromised. Noteworthy that it represents the leading cause of death due to infectious disease in Western countries (10-14%) [2]. In EDs, 51% of CAPs correspond to patients aged ≥70 years, a subgroup with an increased diagnosis difficulty, greater clinical severity and short- and long-term mortality [3]. That is one of the reasons why it is the cause of most sepsis and septic shock treated [4], as well as the first cause of admission to intensive care unit [5]. There are great differences in diagnostic-therapeutic assessment in CAP, which is one of the reasons that explains the differences in admission rates (22-61%), the achievement of microbiological diagnosis, the request for complementary studies, and the choice of the antimicrobial regimen or the intensity of care offered [6]. Risk stratification is crucial to CAP patient management in ED in order to select the most appropriate care setting, including outpatient treatment, admission to a hospital ward or admission to an intensive care unit. Thus, clinical studies are currently focusing on searching for the most appropriate prognostic factors and risk stratification tools in respiratory medicine.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [7]. Patients with suspected infections presenting to the ED can potentially develop life-threatening conditions, so early detection of sepsis is the key to starting specific treatment and improving outcome. Nevertheless, sepsis is a heterogeneous syndrome and the detection during the initial assessments not only depends on site of infection, etiology, onset time, but also on the patient's profile (age, comorbidity and previous treatments). Despite the attempt to standardize the diagnosis, many controversies still exist. For this reason, the increasing value of those tools that can help physician with an early diagnosis is very important. Multiple studies, reviews and meta-analyses demonstrate the usefulness of biomarkers in EDs, especially in CAP [8].

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Different biomarkers emerged as a useful instrument for the early identification of sepsis, like C-reactive protein (CRP), procalcitonin (PCT) or MR-proadrenomodullin. According to this research line, a possible new biomarker emerges: monocyte distribution width (MDW). The aims of this review are: evaluate the utility of MDW in sepsis identification in ED, its limitations, and compare it with other biomarkers.

WHAT MONOCYTE DISTRIBUTION WIDTH IS?

MDW is a measure of the dispersion around the population mean, of the volume of monocytes in whole blood, obtained through the VCS (Volume, Conductivity, and Dispersion) technology [9]. It is a parameter calculated using an automated hematology analyzer that has enhanced cell counting capabilities through VCS technology. This improvement allows detection of morphological changes in immature and reactive cells, just as a microscopic evaluation of a peripheral blood smear would [10].

Sepsis is related to the balance of the pro-inflammatory and anti-inflammatory mechanism. Based on this knowledge, recent evidence supports that the monocyte could reflect early alterations in this inflammatory stage, since it undergoes morphological changes in inflammatory condition. Under this line of research, it is suggested that if these changes can be identified through VCS technology, it could be used as an early sepsis identification [9].

MONOCYTE DISTRIBUTION WIDTH COMPARE WITH CLINICAL SCORES

The perfect biomarker would be the one available at the admission in the emergency department. Due to the lack of this type of implement, different scores are used in daily medical practice. As reported in the Third International Consensus Definition for Sepsis and Septic shock (Sepsis-3), the recommended score were SOFA (Sequential Organ Failure Assessment) and qSOFA (Quick Sequential Organ Failure Assessment) outside the intensive Care Units. Furthermore, qSOFA score is accessible at the initial ED encounter. It is based on three criteria: tachypnea, altered mental status, and hypotension [7]. Despite the fact that it is easy to assess the compounding parameters, it is also common to find them in others acute illnesses. That is the reason why and accurate and reliable biomarker is needed to enhance sepsis suspicion.

Crouser et al. [11] compared the contribution of qSOFA score, and also SIRS (Systemic Inflammatory Response Syndrome) criteria, by their own in the early diagnose of sepsis, and also in contrast with the contribution of MDW alone. They also checked the improvement in the prompt detection of this entity using these scores along with MDW. The study supports that MDW improves the early recognition of sepsis as well as it is a complementary implement of timely detection of sepsis besides qSOFA and SIRS.

MONOCYTE DISTRIBUTION WIDTH COMPARE WITH OTHER BIOMARKERS

As aforementioned, sepsis disease is often not suspected on initial encounter. Therefore, until the laboratory parameters are obtained this entity it is sometimes not considered, which delays the diagnosis. Overall, in order to settle this suspicion an ordinary complete blood count is not enough, since it is confirmed by increase in sepsis biomarkers like procalcitonin, lactate, CRP.

Considering that MDW is a parameter obtained through a routine blood draw, whose result is obtained faster than other biomarkers, different studies arise to compare the reliability of this parameter in sepsis identification, in contrast to the biomarkers already used.

Agnello et al. [9] investigated the role of MDW as indicator of sepsis in the ED. An observational study was conducted, including consecutive adult patients divided into 4 groups: controls, non-infection SIRS, non-sepsis infection, and sepsis. Through an analyzed blood sample, the following parameters were determined: white blood cells (WBC); levels of CRP, and MDW. Regarding the results, MDW levels were higher in septic patients than in the others groups. In addition, it also revealed that there was significant statistic correlation between MDW and CRP. This correlation was higher than the one between MDW and WBC, or CRP and WBC. Furthermore, it was observed through receiver operating characteristic (ROC) curve analyzing sepsis prediction, that the area under the curve (AUC) was significantly higher for MDW, than CRP, showing an optimal diagnose accuracy of MDW.

Crouser et al. [12] developed a blinded prospective cohort study with two different ED population categorized as sepsis and non-sepsis infected patients. From blood collection, different parameters were obtained: mean neutrophil volume (MNV), neutrophil distribution width (NDW), mean monocyte volume (MMV), and MDW, as well as routine complete blood count (CBC). After establishing cut-off values for each one, MDW was the best discriminator of sepsis, based on AUC (0.79; confidence interval 95% 0.73 to 0.84). Additionally, the results provided showed a statistically significant added value for the association of MDW and WBC count (AUC 0.89) versus WBC alone (AUC 0.81). These results support the hypothesis that MDW could be used as a tool to improve early detection of sepsis on its own, as well as in conjunction with WBC count.

Subsequently, Crouser et al. [13] carried out a widespread study with a population of three EDs. It was also a blinded, prospective, cohort study, enrolling 2,158 subjects who were classified according to the Sepsis-2 criteria (control, SIRS, infection, and sepsis) and the Sepsis-3 criteria (control, infection, and sepsis). Through the examination of blood sample, the CBC and MDW values were obtained, analyzing these values according to the categorization carried out (Sepsis 2 and Sepsis 3 conditions). As it turned out before, it also concluded that MDW alone was sufficiently effective for early sepsis recognition, regardless of the sepsis criteria used. Moreover, in tandem with WBC increases the early identification of sepsis.

Regarding procalcitonin (PCT), Piva et al. [10] conducted a prospective observational study of adult patients admitted to an intensive care unit who were divided into 3 groups: non-septic, sepsis, and septic shock. As part of the clinical examination, not only CBC was analyzed, but CRP and PCT were also determined. Diagnostic performance in predicting sepsis was compared between PCT, CRP, and MDW, concluding that MDW was comparable to PCT, while it was better against CRP.

MONOCYTE DISTRIBUTION WIDTH CUT-OFF POINT

The different studies carried out to date differ regarding the best cut-off point for MDW as a predictor of sepsis: Crouser et al. [13] established that the best threshold to discriminate sepsis was 20, while Polilli et al. [14] determined that their best cut-off point was 21.9, and for Agnelle et al. [9] it was 23.5. Some of the reasons that could justify these variations would be the difference profile of the patients included in the studies developed in different setting as ED, infectious disease unit or in the intensive care unit are. On the other hand, it could also be related to the anticoagulant used in the sample (k3-EDTA; K2-EDTA). The discrepancy among different studies underline that more studies should be carried out to unify a reliable cut-off point.

MONOCYTE DISTRIBUTION WIDTH: FUTURE OPPORTUNITIES

Sepsis is a heterogeneous syndrome and the performance of biomarkers may be different depending on the patient's profile. In the ED, the patients who presents the greatest difficulty in terms of risk stratification and, therefore, whose diagnosis of sepsis may remain unnoticed, are those who are elderly, immunosuppressed, or undergoing biological therapies [15,16]. This patient condition is poorly represented in the studies carried out to date, which opens up an important line of research to assess the usefulness of MDW in these circumstances. Nevertheless, Lee AJ et al. [17] studied the utility of MDW in elderly patients concluding that MDW may be a promising hematological parameter to distinguish sepsis in elderly and therefore it may help clinicians in the prompt identification.

In addition, we must know the usefulness of MDW for the different sites of infection, such as pneumonia. Evidence on infection patterns is usually not reported in published articles. Only the Polilli et al. study [14] showed information on the type of infection, being lower respiratory tract infection represented in around 1 out of 3 patients, both in septic and non-septic patients included.

Whereas others biomarkers, such as PCT, have been shown to be useful in differentiating bacterial from viral infections, and it can be used for making-decisions regarding the use of antibiotics. It would be interesting not only to know how the etiology of the infection could condition the results of MDW, but also if its usefulness is maintained regardless of whether the infection is caused by bacteria, viruses or fungi. The study published by Piva E et al. [10] showed information based on the etiology of the infection. In particular, it is very interesting to note that there are important differences in MDW values between non-septic and septic patients, regardless of the etiology of the infection: septic patients without definitive identification, Gram negatives, Gram positive, virus, SARS-CoV-2, and fungi. However, there were no differences between the levels of MDW for the different causes of infection, which can be interpreted negatively (it would not be useful for antibiotic stewardship) or positively (similar utility regardless of the etiology).

Finally, it is also important to point out that the prognostic information, bacteraemia prediction, and monitoring antibiotic treatment response offered by other biomarkers have not yet been studied with the MDW [18,19].

CONCLUSIONS

The data suggest that incorporating MDW within current routine WBC counts may be of remarkable use for detection of sepsis. Further research is needed, but all articles support the hypothesis that, along with other biomarkers and clinical scores, MDW improves early detection of sepsis. MDW has the potential to become a fast, low-cost and accessible tool with a simple blood draw at ED admission, which would have a huge impact on the prompt recognition of sepsis. Therefore, multicenter studies should be expanded, considering that the current results are encouraging, and clinical trials should be designed in order to evaluate the impact of MDW value in the making-decisions in EDs.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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