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Short Communication

The role of Monocyte Distribution Width (MDW) in the prognosis and monitoring of COVID-19 patients

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ABSTRACT

The new parameter derived from the standard deviation of the monocyte distribution width (MDW) has shown a good diagnostic efficacy in COVID-19 patients. In this study, we propose MDW as a prognostic and monitoring parameter in patients with severe forms of COVID-19. Sixty SARS-CoV-2-positive patients admitted to the San Donato Hospital in Arezzo were enrolled. A blood sample taken to measure the complete blood count was used for the determination of MDW using a UniCel DxH 900 instrument (Beckman Coulter). For each patient, a mean of 6 ± 2 measurements of MDW were taken. The difference between the last and first MDW results was reported as the ΔMDW variable. The ΔMDW and age were significantly correlated to the outcome. In non-survivors patients, the difference in the mean of the MDW between the first and other points was not significant, while in survivors, the first point was higher than the other points ($p < 0.005$), with the exception of the mean of the second point (p-value = NS). The ΔMDW area under the curve (AUC) was 0.84, and with a cut-off lower than 0.00 the sensitivity and specificity were 88% and 81%, respectively. The most important result of this study is the ΔMDW calculated on the basis of the difference between the first and third measurement, after approximately the 5–7th day of hospitalisation. A ΔMDW less than one was indicative of an unfavourable prognosis. The data reported suggest that MDW could be used to support monitoring and surveillance, alongside other tests such as procalcitonin, in critically ill patients in the ICU.

1. Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) has spread rapidly around the world since December 2019, with the World Health Organization (WHO) declaring a global pandemic on 12 March 2020 [1,2]. At the start of the pandemic, Europe was the world's COVID-19 epicentre and Italy was the country with the highest number of reported cases and deaths, surpassing China for the most SARS-CoV-2-related victims [3]. SARS-CoV-2 primarily affects the respiratory tract, inducing a broad spectrum of clinical features, ranging from asymptomatic or paucisymptomatic forms to interstitial pneumonia or, in the case of progressive alveolar damage, to severe acute respiratory failure, which may require advanced respiratory support and intensive care [3]. The diagnostic strategies related to epidemiological investigations have been indicated differently by the WHO and the Italian Health Institute, but the molecular investigation of nasopharyngeal swabs using RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) still remains the gold standard for the diagnosis of COVID-19 [4]. Despite the validity of the molecular test, which is very accurate for diagnosis, its results to not contribute to the assessment of the clinical evolution of patients hospitalised with COVID-19. Furthermore, the role of some no-specific laboratory tests in COVID-19, especially those for the investigation of

Abbreviations: MDW, Monocyte distribution width; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; AUC, Area under the curve; WHO, World Health Organization; RT-PCR, Reverse transcriptase-polymerase chain reaction; ICU, Intensive care unit; EDTA-K2, Ethylenediaminetetraacetic acid-K2; LOS, Length of hospital stay; MGUS, Monoclonal Gammopathy of Undetermined Significance; AMI, Acute Myocardial Infarction; CRP, C-reactive protein; PCT, Procalcitonin; NIV, No-invasive ventilation; HFNC, High-flow nasal cannula; ROC, Receiver operating characteristic.

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coagulation, have been studied, with uncertain results [5]. Recently, a new parameter for the diagnosis of sepsis has emerged from numerous contributions in the literature [6,7]. This parameter, derived from the standard deviation of the monocyte distribution width (MDW), has shown a good diagnostic efficacy in COVID-19 patients compared to COVID-19-free subjects [8]. The MDW parameter can be easily obtained from the daily complete blood count (CBC) of hospitalised patients. Given the high mortality of patients with severe COVID-19, we have proposed to evaluate the contribution of daily monitoring of MDW to the assessment of the outcome of patients admitted to Infectious Diseases Unit, Pneumology Unit and ICU (intensive care unit). In particular, as the MDW has been evaluated as a prognostic tool in the follow-up of sepsis patients [7], we were interested in evaluating not only the variation in the parameter during the hospitalisation period, but also in analysing its trends, which may be able to guide the clinician towards a specific prognosis or patient outcome.

2. Materials and methods

Sixty patients suffering from severe COVID-19 with symptoms of severe respiratory failure admitted to the San Donato Hospital in Arezzo in the period between March and June 2020 were enrolled. All patients tested positive for SARS-CoV-2 by nasopharyngeal swab (RT-PCR) and had been hospitalised in the Infectious Diseases Units (n = 47), ICU (n = 4) or Pneumology Units (n = 9). All patients were treated with cortisone, hydrochloroquine and O_2 therapy. Upon admission to the hospital, a blood sample was taken in a tube with EDTA-K2 anticoagulant in order to perform the complete blood count. The same blood sample was used for the determination of MDW using a UniCel DxH 900 instrument (Beckman Coulter), within 2 h of collection. Measurements of MDW, for all patients' length of hospital stay (LOS), averaged 6 ± 2 repetitions every 2–3 days until patients were discharged or died. The overall LOS for survivors and non-survivors patients averaged 16 days (SD = 7.2) and 10 days (SD = 6.5), respectively. Patients who had < 3 MDW determinations (20 patients) with<4 days of hospitalisation were excluded from the study. The 40 enrolled patients had the following comorbidities: among the survivors, seven were suffering from diabetes, one from heart failure, one from MGUS (Monoclonal Gammopathy of Undetermined Significance), one from hypercholesterolemia and one from previous AMI (Acute Myocardial Infarction). Among the deceased, three patients presented diabetes, one renal insufficiency and one anaemia. Additionally, one surviving patient had a positive urine culture and one deceased patient had a previous infection. In addition to clinical information, results of routine laboratory tests including serum C-reactive protein (CRP) and procalcitonin (PCT), determined using a Cobas 8000 instrument (Roche Diagnostic), were collected. The study was approved by the local ethics committee. Excel (Microsoft Corporation) and SPSS 20.0 (IBM) software were used for statistical analysis.

3. Results

Of the 60 patients hospitalised for severe COVID-19, 20 were excluded from the study because they had<4 days of hospitalisation or less than three MDW determinations. Table 1 shows the main characteristics of the enrolled patients. The MDW, age and PCT were statistically different between deceased and discharged patients (P < 0.005); the mean age was 82.67 (SD = 11.55) and 65.82 (SD = 11.96) years, respectively. The difference between the last and first MDW results was reported as ΔMDW. ΔMDW (r = 0.53) and age (r = 0.51) were significantly correlated with outcome (Fig. 1), even after adjustment for therapy and sex. The change in MDW values during LOS is associated with patient outcome but not with age. There were no statistically significant correlations between the type of therapy administered NIV (No-Invasive Ventilation) or HFNC (High-Flow Nasal Cannula) and baseline MDW or ΔMDW, as well as with outcome, although all deceased patients were treated with HCNF. As shown in Fig. 1, the average MDW of the survivors is higher than that of the deceased. Fig. 2 shows single-point MDW values in survivors during hospitalisation. In the survivors, the trend of the MDW measurements decreases, while the ΔMDW increases from the third measurement in a statistically significant way. In the non-survivors patients, the means of MDW at the first point and the other points was not significantly different, while in the survivors, the mean of MDW at the first point was higher than that of the other points (p < 0.005), with the exception of the mean of the second point (p-value = NS). The receiver operation characteristic (ROC) curve shows an AUC of 0.84, both for those obtained from the difference between the first and third points (ΔMDW1–3; AUC 0.84, CI 95% 0.69–0.96) and for those obtained from the difference between the first and the last point (ΔMDW; AUC 0.84, CI 95% 0.66–1.00).

ΔMDW1–3 values below 0.00 (cut-off) are predictors of a fatal outcome, with a sensitivity and specificity of 88% of 81%, respectively; a positive predictive value (PPV) and negative predictive value (NPV) of 54% and 96%, respectively; and positive and negative likelihood ratios (LR) of 4.6 and 0.15, respectively.

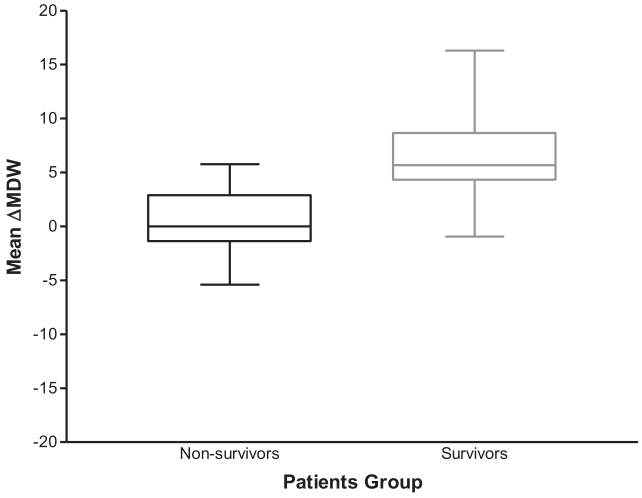

Fig. 1. The plot shows mean ΔMDW distribution in the survivors and non-survivors' patients p < 0.005.

Table 1
Characteristics of studied patients. Legend: Pneumology (P), Infection Diseases (ID), Intensive Care Unit (ICU), Procalcitonin (PCT), C-reactive protein (CRP).

Outcome	First MDW	ΔMDW mean [±SD]	Age (years) [mean ± SD]	Sex	Unit	NIV O_2 therapy	HCNF O_2 therapy	PCT (ng/mL) [mean ± SD]	PCR (mg/dL) [mean ± SD]
Non-survivors	24.8 [3.01]	0.50 [3.85]	82.67 [11.55]	5F	3 ID, 2P	0	5	2.14 [3.84] §	10.2 [6.99]
				3 M	2 ID, 1P	0	3	0.75 [1.17] §	6.12 [3.85]
Survivor	26.2 [3.39]	5.88 [3.98] §	65.82 [11.96] §	10F	8 ID, 1P, 1 ICU	6	4	0.10 [0.07] §	5.46 [5.48]
				22 M	15 ID, 4P, 3 ICU	16	6	0.23 [0.27] §	9.98 [8.65]

(§) P < 0,05.

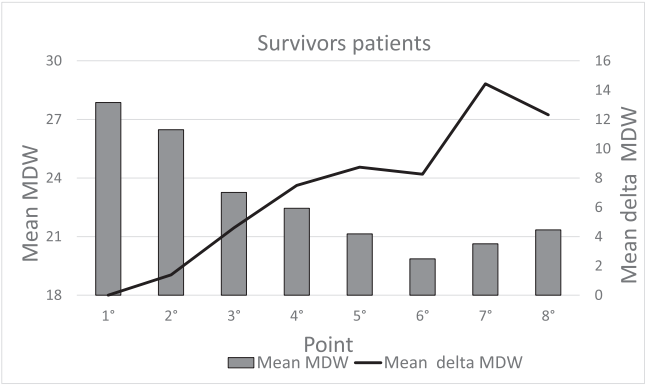

Fig. 2. Trends of mean MDW and ΔMDW during hospitalisation of survivors' patients.

4. Discussion and conclusion

The most important result of this study is the ΔMDW value calculated on the basis of the difference between the first and third determination of MDW, after about 5–7 days of hospitalisation in both survivors and non-survivors patients. The non-survivors patients had very low ΔMDW values between the first and third and/or last measurement (mean = 0.50 ± 3.85) compared to the survivors (mean = 5.88 ± 3.98). A ΔMDW value < 1 was indicative of an unfavourable prognosis. This data is independent of the initial value of the MDW and does not confirm the concept expressed by Riva et al. [9], where the initial value indicated patients with poor prognosis. The MDW parameter, in addition to being studied as an early biomarker of sepsis in its original definition [6], was recently for first time demonstrated to be elevated in COVID-19 patients, with significantly different values between mild and severe forms [8]. As is well-known [10], circulating mononuclear cells, such as monocytes and lymphocytes, play a key role in the surveillance and maintenance of immune homeostasis. They are among the first cells to respond to the invasion of intracellular pathogens such as SARS-CoV-2. Activation of immune cells leads to morphological changes that can be quantitatively determined and serve as potential viral biomarkers for detecting SARS-CoV-2 infection. Zeng et al. [10] demonstrated that both lymphatic index and MDW were significantly increased in COVID-19 patients, and Riva et al. [9] reported the proinflammatory status of monocytes/macrophages in patients with severe COVID-19, highlighting a significant correlation between MDW and inflammatory markers such as CRP, fibrinogen and ferritin with normal PCT values.

In our study, the differences between the mean PCT values in non-survivors and surviving patients are statistically significant in both genders; this can be explained by the fact that the deceased patients developed opportunistic bacterial infection during hospitalisation. The initial or single value of MDW during LOS cannot represent, in our opinion, a prognostic value. Even if the value contains information on the severity of the disease, it cannot give information on the course, which, as we know, is related to therapeutic and individual factors in COVID-19. Our contribution considers the values and variation of MDW during the LOS. The AUC of the ΔMDW obtained between the first and third point and that obtained between the first and last point of the MDW based on the outcome was found to be 0.84 for both. This may suggest that the prognostic value of the MDW index can help to define the outcome of COVID-19 patients as early as the third MDW measurement. It is essential to note that a progressive and statistically significant decrease in value during hospitalisation suggests progression towards positive outcomes. We have seen that a decrease in MDW (Δ < 1) compared to the initial value is strongly linked to an unfavourable outcome.

All subjects enrolled were suffering from severe COVID-19 and 34% of surviving patients had comorbidities (diabetes, heart failure, MGUS, hypercholesterolemia, previous myocardial infarction, renal failure or anaemia), compared to 63% in the deceased group. As described in the literature [11], patients with comorbidities were more susceptible to COVID-19 in its most severe form. Subjects with severe COVID-19 enrolled during the initial phase of the pandemic were treated uniformly, with oxygen, cortisone and hydrochloroquine therapy. This choice reduced bias, but also the number of subjects and therefore the statistical potential of the study, a factor that weakens the results. Further studies will be needed to confirm our findings, both for viral sepsis but also bacterial and fungal infections. Despite the small number of subjects enrolled, that represented the main limitation of the present study, the results are very suggestive that MDW is a test that could support monitoring and surveillance alongside other tests such as PCT for critically ill patients in intensive care. In particular, the ΔMDW can contribute to the prediction of the outcome and prognosis of patients with severe COVID-19, as shown by the results, starting from the third measurement of MDW during hospitalisation monitoring.

CRediT authorship contribution statement

Maria Lorubbio: Writing – review & editing, Conceptualization, Data curation, Project administration, Investigation. **Danilo Tacconi:** Investigation, Writing – review & editing. **Giovanni Iannelli:** Investigation, Writing – review & editing. **Marco Feri:** Investigation, Writing – review & editing. **Raffaele Scala:** Investigation, Writing – review & editing. **Sara Montemerani:** Data curation. **Massimo Mandò:** Investigation, Writing – review & editing. **Agostino Ognibene:** Writing – review & editing, Conceptualization.

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