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Original Article

Is it Possible to Use Monocyte Distribution Width (MDW) as a Diagnostic Parameter for COVID-19 in the Emergency Department?

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ABSTRACT

Background: COVID-19 has been shown to cause an overactivation of monocytes. The Monocyte Distribution Width (MDW) parameter correlates with the cytomorphological changes that monocytes undergo after their massive activation. MDW is obtained from the blood count, and it could be established as a potential diagnostic biomarker for COVID-19. Therefore, the aim of this study is to deeply analyze the value of MDW in patients with SARS-CoV-2 infection. **Materials and Methods:** A total of 4,153 patients treated in the Emergency Department with suspicion of SARS-CoV-2 infection due to suggestive symptoms were recruited. A blood count and a nasopharyngeal swab for SARS-CoV-2 RNA detection were requested. **Results:** Significant differences (p<0.001) were observed between the MDW values in patients with COVID-19 (n =1285), with a mean and standard deviation of 23.69 ± 4.27 compared to patients without COVID-19 disease (n = 2870) whose mean and standard deviation is 19.17 ± 3.52. The Area Under the Curve (AUC) obtained was 0.822 and the cut-off point was MDW≥20.8, (77.7% sensitivity, 78.1% specificity). The combination of MDW with White Blood Count (WBC) through a regression model got the best AUC (AUC=0.855), with a sensitivity of 79.2% and a specificity of 83.7%. **Conclusion:** Patients with SARS-CoV-2 infection have been shown to have higher MDW values. The combination of MDW with WBC allowed to obtain the highest specificity from all the studies performed, so this combination could be helpful when classifying patients with possible COVID-19. Both markers are obtained very quickly and easily from a blood count sample.

Keywords: MDW, COVID-19, White blood cell, Diagnostic, Pandemic, Laboratory.

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), initially known as 2019-nCoV, was identified in late 2019 as cause of several cases of pneumonia in Wuhan, Hubei, China. In February 2020, the World Health Organization (WHO) named the disease caused by this coronavirus as COVID-19.[1-3] Since then, millions of cases of COVID-19 have been confirmed around the world, which translates into a high spread of the virus. Therefore, early detection of patients with COVID-19 is essential for the prevention and control of cases during the pandemic.[4]

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Currently, the gold-standard method for the diagnosis of COVID-19 is the detection of nucleic acids using the Polymerase Chain Reaction (PCR). Particularly, real-time Reverse Transcriptase-PCR (RT-PCR) from a nasopharyngeal swab is recognized as the most reliable technique, with high sensitivity and specificity.[5-7] This technique must be performed in specialized laboratories by qualified personnel. Although it is increasingly more accessible for all health centers to have this technique, it can still be a problem in many others that, due to the great care pressure of laboratories at certain times of the pandemic, can lead to a delay in results of these diagnostic tests. Such a situation makes the investigation of biomarkers really important, especially in the emergency department for an initial screening, because their application allows to identify possible SARS-CoV-2 infected patients with a certain sensitivity and specificity in a faster, easier and more affordable way.

Laboratory parameters are necessary to help in the diagnosis and prognosis in these patients. To date, it has been reported that some parameters of the hematological count are very useful, both in the diagnosis and in the prognosis of the COVID-19 disease.[8-12] Lymphocytes and monocytes populations are important in the immune response against viral infections, including SARS-CoV-2. COVID-19 causes a very diverse clinical picture, which is partly due to the overactivation of monocytes that trigger a large release of cytokines causing a general inflammatory state.[13] Several authors have observed a higher percentage of monocytes in patients with COVID-19 compared to healthy patients and even with respect to patients infected by other viruses such as influenza.[14,15] In addition, Zhang *et al*. identified a qualitative change in monocytes, both in their morphology and in their function, detected by flow cytometry, that also represented a subset of inflammatory monocytes not typically observed in healthy patients.[16] These morphological changes correlated by observed in monocyte cells by light microscopy through blood smears stained with Wright´s stain, as shown in Figure 1. For this reason, the in-depth study of the monocytic population is of great importance. Currently, there is an automated parameter known as Monocyte Distribution Width (MDW), obtained from the hemogram that measures anisocytosis or the different sizes of monocytes. It is a measure of dispersion of the mean of this cell population.

Until now, it has been studied as a marker of sepsis, the Food and Drug Administration (FDA) approved the use of MDW in the emergency department in 2019, as an adjunct for sepsis diagnosis in adult patients. The current study suggests that more widespread use of this readily available diagnostic marker may be warranted.[17]

MDW has reported very good results as early sepsis indicator (ESId test), with remarkable negative predictive values (NPV, 93–97%) and the area under the ROC Curve (AUC) between 0.73-0.87.[18,19] To date, a few authors have studied the relationship between the values of COVID-19 and MDW, with very good results. In this work, a greater number of patients is provided than in published studies.[20-25]

The aim of this study is to analyze MDW in patients with COVID-19 in order to establish it as a possible diagnostic biomarker.

MATERIALS AND METHODS

Type of Study

This retrospective observational study has been carried out at the Clinic Hospital San Carlos. Currently the San Carlos Clinic is a tertiary level hospital, the highest level, which provides medical care to an estimated population of 430,000 inhabitants with 861 beds, in Madrid, Spain.

This study was approved by the local Ethical Committee of the Clinic Hospital San Carlos, Madrid (Spain) (Code Protocol: 20/412-E_COVID).

Study population

A total of 4153 patients were enrolled, who were treated in the Emergency Department of the Hospital Clínic San Carlos, with suspicion of COVID-19 infection due to the suggestive symptoms (respiratory failure, fever, malaise, among others), in the period between May 2020 and January 2021. These patients were randomly selected and the inclusion criterion were: symptoms compatible with SARS-CoV-2 infection, to have requested a complete blood count and a nasopharyngeal swab for SARS-CoV-2 RNA detection. Demographic data (gender and age) and laboratory data including White Blood Cell (WBC), platelet count, and differential blood counts, as well as MDW were collected from all patients (Table 1).

Data collection

Whole blood venous samples for the hemogram were collected on K2 EDTA and analyzed on a UniCel DxH 900 Hematology Analyzer (Beckman Coulter, Inc), is an automatic and quantitative hematology analyzer for use *in vitro* diagnostics in the review of populations of patients from clinical laboratories.

This equipment uses VCS 360 technology that measures and quantifies three morphological characteristics of each cell: individual cell Volume (V), high frequency Conductivity (C) and 5 angles laser light Scattering (S). Monocytes are morphologically altered during infection and this alteration can be measured using the MDW, a parameter that measures the width of the size distribution of monocytes, which is calculated with a set of monocyte cell volume values as the Standard Deviation (SD).

The diagnosis of SARS-CoV-2 was performed by the Microbiology Laboratory employing different commercial kits according to their availability. All the techniques were carried out following the manufacturer's instructions. The commercial kits employed were Xpert Xpress SARS-CoV-2 Assay (Cepheid), Allplex™ SARS-COV-2 Assay (Seegene), FTD SARS-COV-2 Assay (Siemens) and COVID-19 Assay (Genómica), all of them Real time PCR. Hologic Aptima Panther (transcription-mediated amplification method) was also employed.

Statistical analysis

The association between patients infected or not infected by SARS-CoV-2 according to hematological parameters was analyzed with the student's test. Receiver Operating Characteristic (ROC) curve analysis was performed to obtain a measure of global accuracy through the area under the ROC Curve (AUC) and the 95% confidence interval, ROC curve was used to determine the optimal cutoff value (optimal decision threshold). The ROC curve is a fundamental tool for diagnostic test evaluation based on the notions of specificity and sensitivity. It´s a measure of how well a parameter can distinguish between the infected or not infected group. Sensitivity and specificity were calculated for the cut-off point with the highest Youden's index for continuous variables such as MDW to distinguish patients infected or not infected group. For all tests the level of significance is 0.05. Data analysis was performed by IBM SPSS © Statistics program.

RESULTS

A total of 4155 patients treated in the Emergency Department with symptoms compatible with SARS-CoV-2 infection were included: 1285 were positive for SARS-CoV-2 by RT-PCR and 2870 were negative. The mean and standard deviation of the MDW value is shown in Table 2, significant differences ($p<0.0001$) were observed between the MDW values in patients with COVID-19 compared to patients without COVID-19 disease. The AUC obtained is 0.822, 95% CI (0.808-0.836) and the cut-off point established by the Youden´s Index is MDW≥20.87, sensitivity of 77.7% and a specificity of 78.1%. Mean, standard deviation and AUC of all the parameters studied (MDW, WBC, neutrophils, lymphocytes, monocytes, eosinophils) as well as the results obtained when using them in combination with MDW, are also shown in Table 2. WBC is the parameter that in combination with MDW got the best AUC, 0.855 (0.842-0.855), with a sensitivity of 79.22% and a specificity of 83.72%, above that presented by the MDW (Figure 2A).

For the logistic regression model including the two mentioned parameters (MDW, WBC), a ROC curve was made to see their joint classificatory capacity (Figure 2B). The Youden´s index shows a cut-off point, for the probability predicted with the model, of 0.3173. Regression model is shown in Figure 3A. Patients with a predicted probability less than 0.3173 would be classified as COVID-19 negative and patients with a predicted probability greater or equal than 0.3173 would be classified as COVID-19 positive, with a sensibility of 79.2% and a specificity of 83.7%.

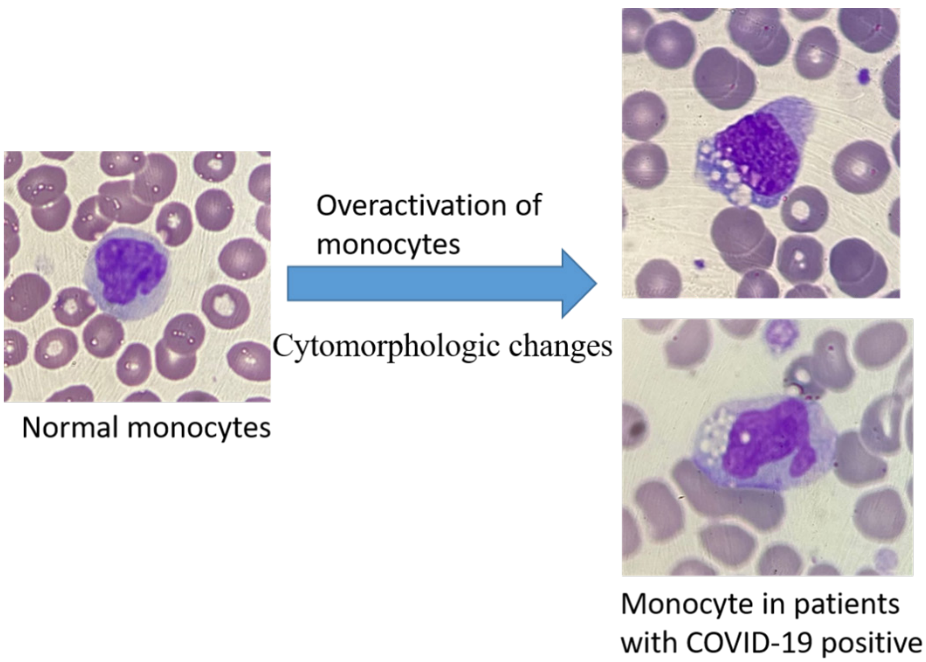

Figure 1: Microscopy image of peripheral blood representative morphologic changes in monocyte cells due to COVID-19 infection.

Table 1: Demographics information of study population.

	Gender	Mean Age ±SD (years)	Median Age (IQR) (years)	Age Range (years)
SARS-CoV-2 RT- PCR Negative (n= 2870)	MEN n=1406 WOMEN n=1464	61.85 ± 22.84	65.0 (46.0-79.0)	2-104
SARS-CoV-2 RT-PCR Positive (n=1285)	MEN n=643 WOMEN n=642	61.45 ± 20.02	61.0 (44.0-82.0)	8-104

Table 2: MDW and complete blood count parameters.

Parameter	SARS-CoV-2 RT- PCR Negative (*n*= 2870) Mean ± SD	SARS-CoV-2 RT-PCR Positive (*n*=1285) Mean ± SD	AUC (CI95%)	AUC Parameter + MDW (CI95%)	Sensitivity Specificity	*p* value
MDW Cut-off MDW>20.8	19.17 ± 3.52 95%CI:19.04-19.30	23.69 ± 4.27 95%CI:23.46-23.93	0.822 (0.808-0.836)		77.7% 78.1%	< 0.0001
WBC (x10⁹/L)	9.22 ± 4.37	6.80 ± 3.64	0.713 (0.663-0.731)	0.855 (0.842-0.855)	79.2% 83.7%	< 0.0001
Neutrophils (x10⁹/L)	6.67 ± 3.81	4.94 ± 3.15	0.664 (0.646-0.682)	0.8512 (0.838-0.865)	75.6% 86.3%	< 0.0001
Lymphocytes (x10⁹/L)	1.68 ± 1.74	1.23 ± 1.46	0.664 (0.647-0.681)	0.825 (0.81-0.826)	78.1% 78.6%	< 0.0001
Monocytes (x10⁹/L)	0.69 ± 0.37	0.57 ± 0.31	0,621 (0.602-0.639)	0.834 (0.820-0.847)	77.7% 79.7%	< 0.0001
Eosinophils (x10⁹/L)	0.12 ± 0.19	0.03 ± 0.09	0.711 (0.696-0.724)	0.830 (0.816-0.844)	80.2% 78.4%	< 0.0001

Data expressed as mean ±SD, AUC information of all the parameters studied, sensitivity and specificity. Abbreviations: WBC: White Blood Cell, CI: Confidence Interval.

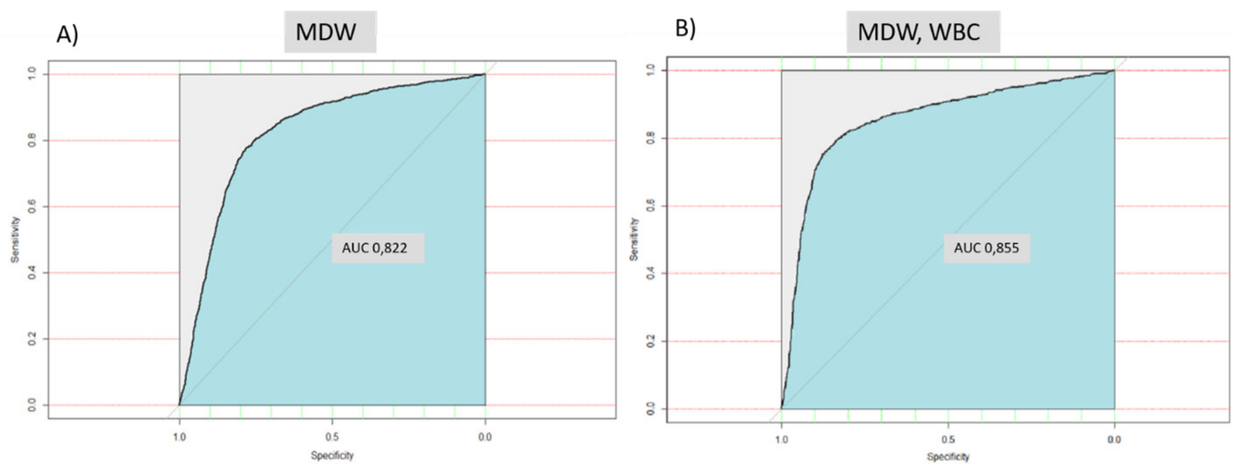

Figure 2: ROC curve for predicting COVID-19. A) ROC curve for predicting COVID-19 using MDW. AUC=0.822 (0.808-0.836); Cut-off MDW ≥ 20.87. Sensitivity=77.7% Specificity= 78.1%. B) ROC curve for predicting COVID-19 using MDW and WBC AUC=0.855 (0.842-0.855). Sensitivity=79.22%. Specificity= 83.72%.

DISCUSSION

The early diagnosis of COVID-19 has become one of the main tools for the control of the pandemic as well as the control of cases and their correct isolation.[4] Currently, the gold standard method in diagnosis is RT-PCR, with a very high sensitivity and specificity, but it requires time and many resources. For this reason, it is necessary to implement new markers that allow us to quickly screening the infection.

The symptoms caused by SARS-CoV-2 infection and their severity are very diverse and are given by numerous factors that continue to be studied, among them is the great release of cytokines suffered by patients with COVID-19, presenting high plasma concentrations of pro-inflammatory cytokines causing a general inflammatory state of the patient.[13,26,27] The producers of these cytokines, in particular monocytes, undergo transformation processes due to the immune activation produced by the SARS-CoV-2 infection, these transformations are both at the level of their functionality and their morphology.[28-30] Several authors have documented the qualitative changes in monocytes, some even relate it to the severity of the condition, trying to predict the patient's prognosis.[14,23] In addition, they found serological markers of activation of monocytes and macrophages significantly increased in patients with COVID-19,

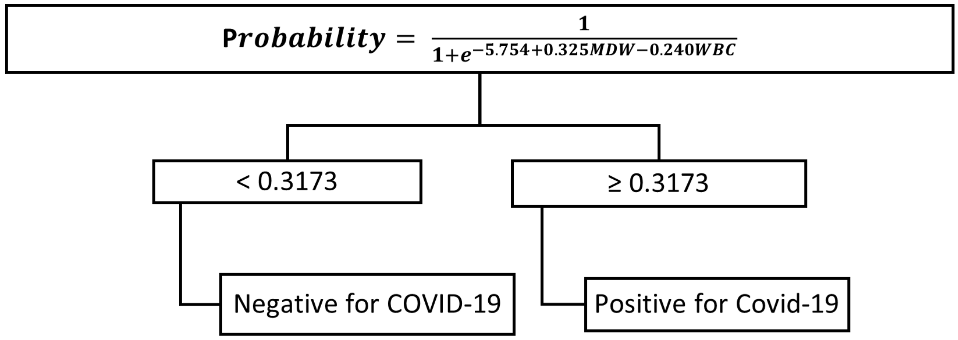

Figure 3: Algorithm for predicting COVID-19 (sensibility: 79.2%; specificity: 83.7%). Figure 3A: Regression model for predicting COVID-19.

thus correlating the activation of monocytes with the production of highly inflammatory cytokines and in turn with the severe infection caused by SARS-CoV-2.[14-16,23]

MDW is a parameter that undergoes modifications when the size of the monocyte's changes, so it could be a good biomarker in the diagnosis of COVID-19. MDW is currently used as early sepsis indicator, and its use is intended for adult patients aged ≥18 to ≤89 years at emergency department, helping to identify patients with sepsis or with increased risk of developing sepsis within the first 12 hr after admission to the hospital, with a high sensitivity, depending on the cut-off point used from 85% for cut-off MDW> 20 to 89% for MDW> 20.5.[17,18]

To date, few publications have studied MDW as a diagnostic marker for COVID-19, all of them, including the results here shown, show a significant increase in the value of MDW in patients infected with SARS-CoV-2.[20-22,24,25,30]

The value of AUC obtained was 0.82 (0.808-0.836), a similar value, although with a lower sensitivity (77.7%), to that obtained by Ognibene *et al*. (sensitivity of 98% and AUC 0.91 (0.842-0.855)), as by Zeng X *et al*. (sensibility of 82.26% and AUC 0.85 (0.795-0.9152)), both studies with sample sizes lower than ours.[20,21] On the other hand, our study shows remarkably higher specificity. The lowest AUC was obtained by the study by Lin H *et al*., who performed it exclusively in patients who required hospitalization, they did not describe the sensitivity and specificity obtained.[22] Finally, the review by Lippi *et al*. analyzes the data provided by the studies mentioned above, propose the mean and standard deviation unifying the results of the three previous studies, thus expanding the cohort studied. Thus, they suggest that MDW values at hospital admission are higher in subjects with active SARS-CoV-2 infection than in those without the infection,[30] hence the importance of defining the value of MDW as a possible diagnostic marker. The latest published articles, not included in the review by Lippi *et al*., also obtained higher MDW values in patients with COVID-19 compared to controls Table 3.[24,25]

In addition, several authors combined MDW with other blood count parameters in order to improve the AUC therefore

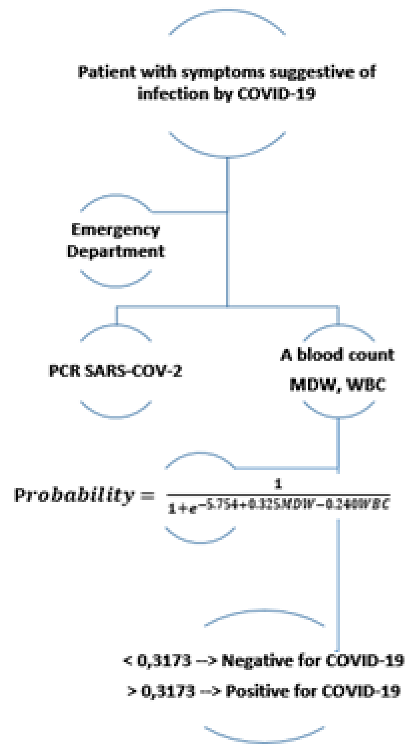

Figure 3B: Emergency Flowchart Classification.

obtaining better diagnostic power of the test Table 3. Zeng X *et al*. combined it with what they call the lymphatic index, and Lin H *et al*. combined MDW with the Neutrophil-Lymphocyte Ratio (NLR) in both studies obtained higher AUC values.[22] In our study, this combination was studied with different hematologic parameters but the parameter that considerably improved the AUC was the WBC, obtaining an AUC value of 0.855. Regarding to the sensitivity obtained, it was also increased (79.22%), but the most pronounced increase has been observed in the specificity (83.72%). We consider this fact important, since patients who come to the emergency department usually have increased acute phase reactant values, so a high specificity could be of great help when classifying patient as possible COVID-19. This regression model would be useful for prevalence's similar to the prevalence

Table 3: Main results of the previous studies, mentioned above.

Authors	N	SARS-CoV-2 positive	MDW CUT-OFF	SARS-CoV-2 positive MDW main ± SD	SARS-CoV-2 negative MDW main ± SD	AUC: MDW (CI95%)	AUC: MDW + *	Sensibility (%) MDW	Specificity (%) MDW
Ognibene *et al.*[20]	147	41	≥20	27.3 ± 4.9	20.3 ± 3.3	0.91 (0.842-0.855)	-	98	65
Zeng X *et al.*[21]	155	93	≥20	22.1 ± 2.3	18.9 ± 2	0.85 (0.795-0.915)	*0.89 (0.84-0.94)	82.26	72.58
Lin H *et al.*[22]	150	9	≥20	23.5 ± 2.1	21,8 ± 5.4	0.703 (0.665–0.741)	*0.840 (0.739–0.942)	-	-
Lippi *et al.*[30]	452	143		23.7 ± 3	20.7 ± 4			-	-
Piva *et al.*[24]	1783	243		26.2 ± 4.3	22.1 ± 3.3				
Cusinato *et al.*[25]	26	15		23.0 ± 4.3	16.0 ± 1.2				
In the current study	4153	1285	≥20.8	23.69±4.27	19.17±3.53	0.82 (0.808-0.836)	*0.85 (0.842-0.855) Sensitivity=79.2% Specificity=83.7%	77.7	78.1

Zeng X et al.20 : + Lymph index = LV LV-SD/LC (mean Lymphocyte Volume (LV). Lymphocyte distribution width (LV-SD). Lymphocyte Conductivity (LC) * (21) Lin H et al.: + NLR (Neutrophil-to-Lymphocyte Ratio) *Our study: +WBC.Abbreviations: n: sample size. SD: standard deviation. CI: Confidence Interval.

of the period of time studied, following the flowchart that we observed in Figure 3B.

CONCLUSION

The significant increase in MDW values in patients infected with SARS-CoV-2 is evident. The use of MDW, in conjunction with WBC as biomarkers of COVID-19, could be very useful to establish an initial screening of patients attended at the emergency room with compatible symptoms with SARS-CoV-2 infection, who are waiting for a confirmatory result (RT-PCR). Both markers have demonstrated high sensitivity and specificity, they are obtained very quickly and they are easy to interpret. Their use is affordable for most emergency services, since only a blood count would be needed and it would not entail any extra expense.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MDW: Monocyte Distribution Width; **WBC:** White Blood Cell; **N:** Sample Size; **ROC:** Receiver Operating Characteristic; **AUC:** ROC curve; **SD**: Standard Deviation; **CI**: Confidence Interval.

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