



# Interest of the cellular population data analysis as an aid in the early diagnosis of SARS-CoV-2 infection

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## Abstract

**Introduction:** Coronavirus disease 2019 (COVID-19) is characterized by a high contagiousness requiring isolation measures. At this time, diagnosis is based on the positivity of specific RT-PCR and/or chest computed tomography scan, which are time-consuming and may delay diagnosis. Complete blood count (CBC) can potentially contribute to the diagnosis of COVID-19. We studied whether the analysis of cellular population data (CPD), provided as part of CBC-Diff analysis by the DxH 800 analyzers (Beckman Coulter), can help to identify SARS-CoV-2 infection.

**Methods:** Cellular population data of the different leukocyte subpopulations were analyzed in 137 controls, 322 patients with proven COVID-19 (COVID+), and 285 patients for whom investigations were negative for SARS-CoV-2 infection (COVID-). When CPD of COVID+ were different from controls and COVID- patients, we used receiver operating characteristic analysis to test the discriminating capacity of the individual parameters. Using a random forest classifier, we developed the algorithm based on the combination of 4 monocyte CPD to discriminate COVID+ from COVID- patients. This algorithm was tested prospectively in a series of 222 patients referred to the emergency unit.

**Results:** Among the 222 patients, 86 were diagnosed as COVID-19 and 60.5% were correctly identified using the discriminating protocol. Among the 136 COVID- patients, 10.3% were misclassified (specificity 89.7%, sensitivity 60.5%). False negatives were observed mainly in patients with a low inflammatory state whereas false positives were mainly seen in patients with sepsis.

**Conclusion:** Consideration of CPD could constitute a first step and potentially aid in the early diagnosis of COVID-19.

## KEYWORDS

cellular population data, DxH800 analyzer, SARS-CoV-2 diagnosis

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, first reported in Wuhan, China, has rapidly spread into other countries

leading to a current worldwide pandemic.<sup>1</sup> Symptoms can range from mild, common cold-like, to life-threatening with intensive care unit admission and extensive mechanical ventilation.<sup>2</sup> The subsequent exponential increase in prevalence has resulted in overcrowding of

emergency units (EmU) and has led to a shortage of isolation rooms. For correct triaging of patients, diagnostic testing is of key importance. The leading standard test for detecting SARS-CoV-2 is a RT-PCR of nasopharyngeal swab material.<sup>3,4</sup> However, RT-PCR testing is time-consuming, and the shortage of testing materials and capacity imposes a serious threat. Chest computed tomography scan (CT scan) has also been proposed for the diagnosis of COVID-19, but its availability can be problematic, and it can be inconclusive in the early phase of the disease.<sup>4</sup> Several biological abnormalities were also described, such as leukopenia and lymphopenia. Therefore, CBC and differential (Diff) can potentially contribute to the diagnosis of COVID-19.<sup>5</sup>

The white blood cell (WBC) differential analysis performed on Beckman Coulter hematology analyzers is based on "VCS technology." Briefly, WBC is characterized and identified by their volume "V" (measured by direct impedance), their conductivity "C" (analyzed by conductivity in radio frequency current), and their scatter "S" of a laser beam. Several reports indicated that VCS parameters, called CPD, are modified in case of infectious diseases.<sup>6-9</sup> Therefore, we tested whether CPD are affected in cases of infection with SARS-CoV-2 and whether these variations could constitute an element for helping for the diagnosis of COVID-19. Currently, these morphometric parameters are research use only; their clinical utility has not been established.

## 2 | PATIENTS AND METHODS

### 2.1 | Study populations

The work was divided into two parts. In a first part (March 11 to April 5, 2020), the CPD of 322 consecutive patients from the EmU with positive RT-PCR (Allplex 2019 nCoV Assay; Eurobio) were collected. The CPD of these patients were compared to those of 285 consecutive patients for whom COVID-19 was suspected by clinical examination, but who had a negative RT-PCR and for whom CT scan was not suggestive of COVID-19 infection. The CPD patient groups were analyzed in reference to a control group, composed of 137 subjects with a normal CBC and differential, referred to our institution from January 21, to February 9, 2020, without evidence of infectious diseases and when prevalence of SARS-CoV-2 was very low in France.<sup>10</sup> The main demographic and hematological parameters of this patient

cohort are presented in Table 1. The second part of the study was prospective: from April 6, to April 13, 2020, 400 patients came to the emergency unit and their initial evaluation included a CBC and Diff. Among them, COVID-19 was suspected in 222 cases, and a RT-PCR was performed. It was positive for 77 cases. We also included as COVID-19-positive cases, 7 patients with characteristic clinical signs and a typical CT scan whereas RT-PCR was negative and 2 cases with a characteristic CT scan in the absence of RT-PCR. Therefore, a total of 86 patients were considered COVID-19 positive, whereas 136 (out of 222, tested by RT-PCR) were considered negative for SARS-CoV-2 infection. The performance of the developed classification algorithm (decision tree) for the detection of SARS-CoV-2 was tested in this population of 222 patients with suspicion of COVID-19 and in a series of 392 CBC-Diff results of the patients who came to the EmU from September 30, to October 7, 2019, when COVID-19 had not yet been described, in order to detect false positives. The study was performed in agreement with the French ethical laws (the patients and their family are informed that their biological data used for routine care may be used in an anonymous manner, unless they express their opposition).

### 2.2 | WBC count and differential

Blood was collected in 3 mL S-Monovettes (Sarstedt) containing 4.8 mg EDTA-K3. Analyses were performed within 6 hours after collection on DxH 800(Beckman Coulter, Inc.). The instrument characteristics and performances have been previously reported.<sup>9</sup>

### 2.3 | C-reactive protein measurement

C-reactive protein (CRP) was quantified using Alinity CRP Vario Reagent on Alinity analyzers (Abbott Diagnostics France).

### 2.4 | Cellular population data

White blood cell differential analysis performed by the Coulter DxH 800 is based on the measurement of seven distinct parameters for each cellular event: In addition to the volume (V) and conductivity (C),

**TABLE 1** Main demographic and CBC results of the populations enrolled for cellular population data analysis

	n	F/M (n/n)	Age (years)	WBC ( $\times 10^9/L$ )	Haemoglobin (g/dL)	Platelets ( $\times 10^9/L$ )
Controls	137	79/58	58 [17-97]	7.3 [4.2-11]	13.9 [12-16.3]	232 [152-386]
Confirmed COVID	322	112/210*	64*** [22-98]	6.2*** [1.3-22.4]	13.6* [7.7-18.3]	207* [42-619]
Investigations negative for SARS-CoV-2 infection	285	147/138	60 [16-102]	8.3 [1.2-29.7]	13.4* [5.5-18.2]	235 [14-766]

Note: Values are expressed as median and [range].

Abbreviations: F, females; M, males.

\* $P < .001$  vs controls;

\*\* $P < .01$ ,

\*\*\* $P < .001$  vs "negative for SARS-CoV-2 infection" (Mann-Whiney test).

there are different measurements of the scatter:median angle light scatter (MALS), lower median angle light scatter (LMALS), low angle light scatter (LALS), and upper median angle light scatter (UMALS) which inform about granularity of the cytoplasm, nucleus lobularity and membrane surface and the axial light loss (AL2) measurement, which analyses cellular transparency.<sup>11</sup> Therefore, for each leukocyte subpopulation, mean (MN) and standard deviation (SD) of the mean are calculated for these seven parameters, providing additional 14 cellular morphometric parameters for each WBC subpopulation (neutrophils [NE], lymphocytes [LY], monocytes [MO], eosinophils [EO], and basophils). Currently, these morphometric parameters are research use only; their clinical utility has not been established.

## 2.5 | Statistical analysis

At the first stage of the analysis, we used MEDCALC software, version 19.2 (MedCalc Software Ltd.). To test the difference for each parameter (in total 58 parameters including 42 CPD parameters for NE, LY, and MO and 16 commonly used hematological parameters) between groups of patients (322 COVID-19 positive vs 285 COVID-19 negative), we used the Mann-Whitney test. Only parameters which demonstrated statistically significant difference between groups ( $P$ -value  $<.05$ ) were used for further analysis.

To evaluate the performance of individual parameters to discriminate COVID-19 positive and COVID-19-negative patients, we used receiver operating characteristic (ROC) analysis to obtain the area under the curve (AUC), which demonstrates the discriminative ability of each individual parameter.

At the second stage, our goal was to establish a decision tree using 35 parameters (selected with  $P$ -value  $<.05$ ) and 521 samples selected after outliers were excluded. The exclusion of outliers helps increase the robustness in selection-specific parameters and cutoff values. As our goal was to assess performance of the model on the whole data set, all outliers were included in the final analysis of the model's performance. To implement the decision tree in the hematology analyzer, it should have a maximum of 4 levels. We also aimed to generate minimum false-positive results. At this stage, we implemented random forest algorithm (RF) (R package, randomForest 4.6-14).

First, 30% of samples were randomly selected for validation set and others were used as a test set for computation. RF was used to estimate the ability of a given set of parameters to deliver the desired tree classifier. The RF algorithm was applied several times to produce between 100 and 500 classification trees. This allows to estimate the best possible prediction power for the validation set. This technique delivers a robust estimation for all critical parameters of the decision tree construction process to provide classification accuracy for the test set and for a given set of parameters, prediction power on validation set, and relative importance of parameters for tree construction. Unfortunately, the result of RF could not be described explicitly and, therefore, be directly implemented for prediction. The result of RF is a big set of trees, not a particular tree.

Secondly, using this information, we tried to compute the decision tree in Excel, which delivered similar results as the RF algorithm for the test set and validation set, respectively.

Finally, we adjusted thresholds at each node to minimize the number of false-positive samples for the initial database, which includes all samples: test set, validation set, and outliers.

## 3 | RESULTS

### 3.1 | Comparisons of CPD in controls, patients with proven COVID-19 and patients in nonconfirmed SARS-CoV-2 infection—application for a discriminating protocol

Cellular population data of polymorphonuclear cells, lymphocytes, and monocytes were recorded. The vast majority of CPD was different among the 3 groups, and CPD of patients (with or without COVID-19) were significantly different from CPD of controls, except for MN-C-NE, MN-V-NE, and MN-LALS-LY (data not shown). As the goal of our study was to discriminate patients with COVID-19 from patients without COVID-19, we focused on CPD which were different between both groups and by ROC analysis, selected only parameters for which the AUC was above 0.6. Four, six, and nine CPD fulfilled these criteria, for NE, LY, and MO, respectively, (Table 2). Therefore, monocytes CPD were clearly the most affected by SARS-CoV-2 infection.

The best discriminative CPD, SD-V-Mo, if used alone, demonstrated AUC 0.819 to separate COVID-19-positive patients vs COVID-19-negative patients, with sensitivity of 91.6%, specificity of 63% at the cutoff of 21.71. If we would like to achieve higher specificity for practical purposes of early detection, patients with strong suspicion of COVID-19, then at a cutoff of 25.51, the specificity would be 89.79%, but sensitivity would drop to 36.76%.

As none of these CPD values alone had enough discriminating capacity, we tested several combinations of these parameters. Our goal was to achieve the best possible specificity to minimize the number of false-positive results. The best result was obtained with a combination of four MO-CPD (SD-V-MO, MN-C-MO, SD-LALS-MO, and SD-UMALS-MO) as presented in Figure 1. We applied the proposed classification tree on the cohort of patients referred to our EmU from September 30, to October 7, 2019, when COVID-19 was not yet described, and only 16 among 392 patients (4.1%) were flagged as "possible SARS-CoV-2 infection." The main CBC parameters and the final diagnosis of these false positives are reported in Table 3. Most of the cases were sepsis or infections.

### 3.2 | Evaluation of the discriminating protocol in real life

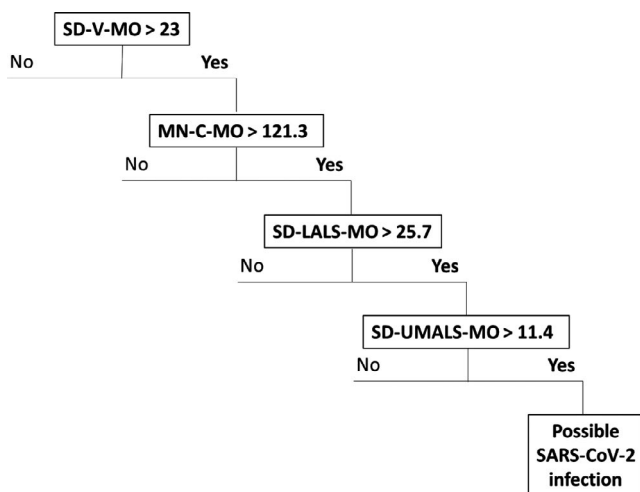
Second, we analyzed the accuracy of the discriminating protocol in real life, analyzing a series of 400 consecutive patients who came

**TABLE 2** Comparison of the results of differential parameters and lymphocyte cellular population data in 137 controls, 322 patients with proven COVID infection, and 285 patients for whom investigations were negative for SARS-CoV-2 infection (COVID-)

	Controls	COVID +	COVID-	Optimal cutoff	AUC [95% CI]
NE ( $\times 10^9/L$ )	4.9 [1.7-7.3]	4.6 [0.6-17.3]	5.6 [0-27.18]	$\leq 4.4$	0.594 [0.555-0.633]
EO ( $\times 10^9/L$ )	0.1 [0-0.5]	0 [0-0.9]	0.1 [0-1]	$\leq 0$	0.716 [0.678-0.752]
LY ( $\times 10^9/L$ )	1.9 [1-3.9]	0.9 [0.1-12.4]	1.3 [0.1-17.1]	$\leq 1.1$	0.688 [0.650-0.725]
MO ( $\times 10^9/L$ )	0.5 [0.2-1]	0.5 [0.1-7]	0.6 [0-11.5]	$\leq 0.4$	0.626 [0.587-0.665]
SD-MALS-NE	10.4 [8.3-16.7]	10.2 [8.7-17.3]	10.8 [8.6-43.5]	$\leq 10.43$	0.622 [0.582-0.661]
MN-UMALS-NE	139 [124-152]	143 [116-158]	141 [118-155]	$> 139$	0.62 [0.58-0.659]
SD-LMALS-NE	13.2 [10.4-25.5]	12.7 [10.3-24.6]	13.6 [10.5-40.7]	$\leq 12.68$	0.609 [0.569-0.648]
SD-LALS-NE	32.1 [25.6-53.1]	30.5 [23.4-57.8]	32.2 [25.1-57.5]	$\leq 31.46$	0.604 [0.564-0.643]
SD-V-LY	14 [11.3-24.3]	16.5 [11.6-36.5]	14.6 [9.7-31.2]	$> 15.07$	0.689 [0.651-0.726]
SD-C-LY	7.5 [5.4-10.9]	8.9 [5.7-26.8]	8 [4.6-28.9]	$> 8.15$	0.612 [0.572-0.651]
SD-MALS-LY	16.3 [13-23]	17.7 [13.5-35.4]	16.3 [12.8-39]	$> 16.36$	0.664 [0.625-0.702]
SD-UMALS-LY	20 [16.2-26.6]	21.6 [15.4-37.1]	20 [14.6-40.7]	$> 21.18$	0.658 [0.618-0.695]
SD-LMALS-LY	18.3 [14.6-24.4]	19 [15.5-33.6]	18.2 [15-40.1]	$> 18.61$	0.63 [0.59-0.669]
SD-AL2-LY	12.6 [11.1-14.5]	13.8 [11.4-18.9]	13.2 [10.8-24.9]	$> 13.35$	0.661 [0.622-0.699]
MN-V-MO	175 [153-214]	187 [166-228]	177 [152-229]	$> 180$	0.742 [0.705-0.777]
SD-V-MO	19.1 [15.6-35.1]	24.8 [16.8-33.6]	20.3 [14.5-41.6]	$> 21.71$	0.819 [0.786-0.849]
MN-C-MO	122 [110-129]	124 [115-133]	123 [111-132]	$> 123$	0.613 [0.573-0.652]
SD-MALS-MO	10.8 [8.8-13.7]	11.4 [8.8-18.2]	10.9 [8-25.6]	$> 11.31$	0.611 [0.571-0.650]
SD-UMALS-MO	12.3 [9.2-27.9]	13.9 [9.2-27.7]	12.4 [8.8-31.3]	$> 12.85$	0.65 [0.611-0.688]
SD-LMALS-MO	14 [11.6-18.6]	15 [10.5-20.5]	14.4 [10.1-26.1]	$> 14.08$	0.611 [0.571-0.65]
SD-LALS-MO	27.8 [17.1-39.9]	29.3 [21-43.3]	27.5 [15.9-47]	$> 24.71$	0.62 [0.58-0.659]
MN-AL2-MO	106 [87-147]	141 [93-162]	137 [3-161]	$> 145$	0.611 [0.571-0.65]
SD-AL2-MO	17.1 [6-26.2]	19.7 [11.8-30]	17.4 [10.9-38.5]	$> 17.51$	0.722 [0.684-0.757]

Note: Results are expressed as the median and [range]. CPD are expressed as arbitrary units. For all the parameters presented in this table,  $P$  between COVID+ and COVID- patients were  $< .0001$  (Mann-Whitney test).

Abbreviations: AUC, area under the curve; CI, confidence interval.



**FIGURE 1** Discriminating protocol based on monocyte (MO) cellular population data to identify patients with SARS-CoV-2 infection. C, Conductivity; LALS, low angle light scatter; MN, mean; SD, standard deviation; UMALS, upper median angle light scatter; V, volume

to the EmU from April 6, to April 13, 2020. A COVID-19 infection was clinically suspected for 222 patients, and a RT-PCR and/or a CT scan was performed: 86 patients were diagnosed as COVID-19, 52 of them (60.5%) were correctly identified using the discriminating protocol. Among the 136 patients without SARS-CoV-2 infection, 14 (10.3%) were classified as "possible SARS-CoV-2 infection." Therefore, the specificity was 89.7% and the sensitivity was 60.5%. If we analyze the differences between the different groups (Table 4), false negatives were inpatients with a lower inflammatory state, as shown by the CRP levels ( $P = .0003$ ). False positives were mainly patients with sepsis in a context of cancer (6 cases), 2 cases of severe infection of urinary tract, 1 case of myelodysplastic syndrome, and 1 case of severe dehydration in a context of uncontrolled diabetes. For the 4 last cases, patients referred to the EmU for bronchopulmonary disorders compatible with COVID-19, but RT-PCR and/or CT scan were negative. False positive is characterized by a significant higher WBC count ( $P < .001$ ), because of an increase of neutrophils ( $P < .001$ ) than patients with COVID-19. A ROC curve analysis indicated that NE

**TABLE 3** Differential and diagnosis of the false-positive patients (CBC performed from September 30, to October 7, 2019) identified by the discriminating protocol

Patient	WBC ( $\times 10^9/L$ )	NE ( $\times 10^9/L$ )	LY ( $\times 10^9/L$ )	MO ( $\times 10^9/L$ )	Final diagnosis
1	4.8	1.9	2.5	0.3	Dyspnea due to severe anemia (Hb = 5.4 g/dL)
2	11.9	9.2	1	1.6	Urinary tract infection
3	16.4	15.2	0.5	0.4	Digestive infection
4	17.6	12.4	1.9	3.2	Microbial peri-anal infection
5	14.7	12.8	1.1	0.7	Pyelonephritis
6	32.9	30.6	0.3	1	Severe sepsis (advanced hepato-carcinoma)
7	6.9	5.4	0.9	0.3	Sepsis (digestive carcinoma)
8	12.5	10	1.3	1.1	Pneumopathy of unknown origin
9	4.9	4.3	0.3	0.3	Pyelonephritis (advanced ovarian cancer)
10	15.1	12.6	1.3	1.1	Sepsis in a diabetic patient
11	10.2	8.2	0.9	1	Pneumopathy of unknown origin
12	15	13.8	0.6	0.5	Sepsis in a cirrhotic patient
13	4.9	2.5	0.2	1.7	Pneumopathy of unknown origin
14	22.8	21.2	0.5	1	Sepsis in a patient with lymphoma
15	13.1	12.2	0.6	0.3	Peritonitis
16	9.8	8.1	0.8	0.8	Sepsis in a renal transplanted

Abbreviations: LY, lymphocytes; MO, monocytes; NE, neutrophils; WBC, white blood cells.

**TABLE 4** Comparison of biological data from patients correctly or misclassified using the proposed discriminating protocol (prospective study)

	n	Age (years)	WBC ( $\times 10^9/L$ )	NE ( $\times 10^9/L$ )	LY ( $\times 10^9/L$ )	MO ( $\times 10^9/L$ )	CRP (mg/L)
True positives	52	66 [20-97]	7.3 [7.1-39.1]	5.2 [1.1-28.5]	1.0 [0.1-2.8]	0.5 [0.1-5.3]	79.4 [4.8-428.3]
True negatives	122	61 [22-99]	8.2 [0.4-37.6]	5.7 [0.1-34.8]	1.5 [0.2-6.6]	0.6 [0.1-2]	6.8 [<1-350.3]
False negatives	34	64 [25-93]	5.7 [2.2-15.6]	4.1 [0.9-13.3]	1.0 [0.3-3.2]	0.5 [0.1-1.4]	23.1* [<1-360.4]
False positives	14	77 [40-97]	10.4** [4.5-38.6]	8.4** [3.4-34.6]	1.1 [0.4 - 1.8]	0.8 [0.1-2.6]	126.3 [21.6-415.3]

Note: Statistical comparisons (Mann-Whitney test) were done between false negatives and true positives (\* $P < .001$ ) and false positives and true positives (\*\* $P < .001$ ).

Abbreviations: CRP, C-reactive protein; LY, lymphocytes; MO, monocytes; NE, neutrophils; WBC, white blood cells.

count above  $7.2 \times 10^9/L$  could be in favor of a false positive (sensitivity 71.4%, specificity 78.8, AUC 0.803).

Lastly, in the 178 patients where no COVID-19 was suspected after clinical examination, in 8 cases (4.5%), a SARS-CoV-2 infection could be suspected using this discriminating protocol. This frequency was like the frequency of false positives observed in the cohort of October 2019. In 4 cases out of 8, a bacterial infection was diagnosed.

## 4 | DISCUSSION

Diagnosis of COVID-19 is complex, first because it is a new pathology whose clinical signs seem to be highly variable and nonspecific, some patients being asymptomatic.<sup>1,2</sup> RT-PCR is considered as the gold standard method for the etiological diagnosis of SARS-CoV-2

infection. However, the large demand for RT-PCR tests due to the worldwide spread of the virus is highlighting the limitations of this type of diagnosis. Moreover, its sensitivity is a matter of debate, some studies have reported as much as 20% false-negative results for this type of test.<sup>12,13</sup> Chest CT scan has been proposed in patients in whom RT-PCR was negative despite a high clinical suspicion of COVID-19, but it can be negative in the early phases of the pathology.<sup>4</sup> Lastly, both tests are quite expensive, require some time to be carried out, and are not available in all hospital structures, while precautions must be taken to isolate the patient due to the high contagiousness of the virus.

Thereby, different approaches have been proposed to identify patients with SARS-CoV-2 infection based on routine biological tests. CBC and Diff constitute a part of these routine assays.<sup>14,15</sup> As it has been shown that CPD could contribute to the diagnosis of different infectious pathologies,<sup>6-9</sup> we wondered if the CPDs were modified

in COVID infection and could contribute as an aid to detect COVID-19. Indeed, important variations of CPD were observed, mainly for lymphocytes and monocytes, whereas CPD of Polymorphonuclear leukocytes (PMN) were less affected. This last point is not surprising since PMN are not involved in the defense of the body against viruses. Variations in lymphocyte CPD were expected since lymphocytes are largely involved in case of viral infection. Surprisingly, monocytes CPD were also largely modified by SARS-CoV-2 infection, possibly because monocytes are an important source of cytokines, the levels of which are particularly high in COVID-19.<sup>1,2</sup> Therefore, we built and tested a discriminating protocol, based on monocytes CPD, in order to identify patients with a possible SARS-CoV-2 infection. Our aim was to develop the algorithm which can be implemented as decision rules on our routine hematology analyzer, DxH 800. The specificity was 89.7%, and the sensitivity was 60.5%, comparable to that of the other tests currently offered: sensitivity of RT-PCR varied between 63% and 78%,<sup>16</sup> and a recent meta-analysis of CT scan described a pooled sensitivity of 94.6%, but a low specificity (46%).<sup>17</sup> The main advantage of this methodology is that it gives a rapid answer and is free since it is an integral part of the CBC and Diff from the Beckman Coulter analyzer.

Most of the cases of false positives were due to sepsis. This was observed in a series of patients from which the blood had been drawn in last autumn 2019, when SARS-CoV-2 infections were non-existent in France. This is not surprising, since variations of monocytes CPD were shown to be of interest for the identification, in EmU, of patients with sepsis.<sup>6,8,9</sup> However, clinical profiles are different for patients with sepsis, and therefore, these false positives can be eliminated by the clinicians and the flag given by the analyzer with CBC-Diff result must be taken within the clinical context of each individual patient.

During winter, in the northern hemisphere, flu, due to another respiratory virus, is frequent. To our knowledge, variations of CPD on DxH800 of patients infected by influenza virus were not reported. We performed a retrospective study in our institution and also observed similar variations in the parameters used in our discriminating protocol, but the increase in SD-UMALS-MO was less pronounced than in patients with COVID-19 (data not shown). At this time, we therefore cannot exclude that our discriminating protocol would be less efficient when both viruses can be present, but the pattern of WBC differential results is different between patients with flu and patients with COVID-19. Indeed, in agreement with others,<sup>18</sup> we observed a higher monocyte count in patients with flu, while monocytes count is usually normal in patients with COVID-19.<sup>19</sup>

Another limitation of this study is that CPD levels on DxH 800 are not standardized on different hematology analyzers, therefore the cutoff proposed by this algorithm must be adapted for each laboratory. An external control to calibrate CPD would be very helpful to use CPD levels in routine and make possible a multicentric evaluation of this protocol. Another limitation is the identification of patients without COVID-19 considered for the discriminating protocols. We selected patients with a negative RT-PCR (in some cases, this test was performed twice) and negative CT scan, when available,

but because of the sensitivity of these tests, as well as the versatility of the clinical signs, we cannot exclude that some patients considered negative actually suffered from the SARS-CoV-2 infection, therefore limiting the power of the discriminating protocol. In contrast, the characteristics of the population of patients COVID + are clearly like that previously described in terms of age, gender, lower lymphocyte, eosinophils, and platelet counts.<sup>20</sup>

This preliminary study suggests that consideration of CPD could constitute a first step and potentially aid in the early diagnosis of COVID-19 in the EmU. Its use can be beneficial to developing countries and, in those countries, suffering from a shortage of RT-PCR reagents and/or specialized laboratories as an inexpensive and available alternative to identify potential COVID-19 patients.

#### ACKNOWLEDGEMENTS

MV, ES, TP, and EF. conceived the study and designed experimental procedures; MCB recruited patients, DA, FD, FH, EJ, and EF collected patients' data; MV, ES, and DS performed statistical analysis; MV and ES wrote the paper. All authors reviewed and approved the final version.

#### CONFLICT OF INTEREST

Elena Sukhacheva is director medical and scientific affairs in the Beckman-Coulter company.

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#### REFERENCES

- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2019;382:1708-1720.
- Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill*. 2020;25(3):e2000045.
- Bernheim A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology*. 2020;20:200463.
- Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect*. 2020;80:388-393.
- Park DH, Park K, Park J, et al. Screening of sepsis using leukocyte cell population data from the Coulter automatic blood cell analyzer DxH800. *Int J Lab Hematol*. 2011;33:391-399.
- Jung YJ, Kim JH, Park YJ, et al. Evaluation of cell population data on the UniCel DxH 800 Coulter Cellular Analysis system as a screening for viral infection in children. *Int J Lab Hematol*. 2012;34:283-289.
- Crouser ED, Parrillo JE, Seymour C, et al. Improved early detection of sepsis in the ED with a novel monocyte distribution width biomarker. *Chest*. 2017;152:518-526.
- Van de Geijn GM, Denker S, Meuleman-van Waning V, et al. Evaluation of new laboratory tests to discriminate bacterial from nonbacterial chronic obstructive pulmonary disease exacerbations. *Int J Lab Hematol*. 2016;38:616-628.

10. Deslandes A, Berti V, Tandjaoui-Lambotte Y, et al. SARS-COV-2 was already spreading in France in late December 2019. *Int J Antimicrob Agents*. 2020;55:106006.
11. Jean A, Boutet C, Lenormand B, et al. The new haematology analyzer DxH 800: an evaluation of the analytical performances and leucocyte flags, comparison with the LH 755. *Int J Lab Hematol*. 2011;33:138-145.
12. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology*. 2020;296:E32-E40.
13. Xiao AT, Tong YX, Zhang S. False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: rather than recurrence. *J Med Virol*. 2020.
14. Mardani R, Ahmadi Vasmehjani A, Zali F, et al. Laboratory parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study. *Arch Acad Emerg Med*. 2020;8(1):e43. eCollection 2020.
15. Ferrari D, Motta A, Strollo M, Banfi G, Locatelli M. Routine blood tests as a potential diagnostic tool for COVID-19. *Clin Chem Lab Med*. 2020;58(7):1095-1099.
16. Zitek T. The appropriate use of testing for COVID-19. *West J Emerg Med*. 2020;21(3):470-472.
17. Adams HJA, Kwee TC, Yakar D, Hope MD, Kwee RM. Systematic review and meta-analysis on the value of chest CT in the diagnosis of coronavirus Disease (COVID-19): *Sol Scientiae Illustrata Nos. AJR Am J Roentgenol*. 2020;1-9.
18. Wang L, Liu Y, Zhang T, et al. Differentiating between 2019 novel coronavirus pneumonia and influenza using a nonspecific laboratory marker-based dynamic nomogram. *Open Forum Infect Dis*. 2020;7(5):ofaa169.
19. Sun S, Cai X, Wang H, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. *Clin Chim Acta*. 2020;507:174-180.
20. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-847.

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