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Research Article

The Near-Patient Testing Instrument HemoScreen can be used for Rapid Evaluation of Peripheral Blood Cell Counts in Patients with COVID-19

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Abstract

Objectives: Analysis of peripheral blood cell counts are important in the workup of patients with suspected Corona virus disease 2019 (COVID-19). Blood cell counts are usually analyzed on large cell counters that require transport of the samples. Point-of-care (POC) testing reduces the test-turnaround times. The aim of the present study was to evaluate if the HemoScreen™ instrument could be used for point of care testing of blood samples from COVID-19 patients. **Methods:** We compared CBC results from 49 patients with COVID-19 infections analyzed with HemoScreen™ and Sysmex XN-9000. **Results:** There were strong correlations between the results obtained with Sysmex XN-9000 and HemoScreen™ according to Deming correlations for White Blood Cells (WBC): WBCHemoScreen™ = 0.944* WBCSysmex - 0.093; r^2 = 0.988, Neutrophils: NeutrophilsHemoScreen™ = 1.029* NeutrophilsSysmex + 0.090; r^2 = 0.957, Lymphocytes: LymphocytesHemoScreen™ = 0.944* LymphocytesSysmex - 0.107; r^2 = 0.964, Platelets (PLT): PLTHemoScreen™ = 1.056* PLTSysmex + 9.468; r^2 = 0.988, and Red blood cells (RBC) RBCHemoScreen™ = 0.955* RBCSysmex - 0.003; r^2 = 0.991. **Conclusions:** The HemoScreen™ instrument provided fast and accurate test results when analyzing blood samples from COVID-19 patients. This instrument can be used in settings where the transport time to the central laboratory from remote locations such as field hospitals can be long.

Keywords: COVID-19; Red blood cells; White blood cells; Platelets; Point of care testing

Introduction

Corona virus disease 2019 (COVID-19) is a contagious disease and infected persons are most infectious when they show symptoms, including fever, coughing and shortness of breath but also individuals without symptoms may spread the virus. COVID-19 is primarily transmitted from person-to-person through close contact.

Some hematological parameters have been proposed as prognostic criteria in COVID-19 patients: platelet counts, lymphocyte count and neutrophil/lymphocyte ratio [1]. Neutrophil and lymphocyte counts are also important for differential diagnosis of infections e.g., bacterial versus viral. Lymphocyte and neutrophil counts are often followed daily in hospitalized patients with COVID-19 infection. Infections influences not only the number of cells but also changes activation state and subsequently blood cell morphology. Less mature forms especially in the neutrophil lineage can be observed [2]. Toxic granulation or hypogranulation may also occur. These changes in cell morphology prompts warning flags, by the instrument used for analyzing the samples, which then often lead to manual review.

Blood cell counts are mainly analyzed using automated

blood cell counters which requires careful maintenance to work properly. These cell counters are usually located at the central hospital laboratory and the blood samples must be sent to the central laboratory for analysis. The transport times cause delays, and the test results are thus not available until a couple of hours after the blood sampling. POC testing supports a more rapid assessment, differential diagnosis, stratification, and treatment of the patient at the appropriate level of care. It is important especially in facilities such as field hospitals or mobile ambulatory points where the transport times to central laboratory can be long. Also, in settings like primary care where patients with a variety of infections seek care, there is a need for quick differential diagnostic of infections.

HemoScreen™ is a point of care (POC) hematology analyzer that combines viscoelastic focusing and digital imaging in a single instrument [3,4]. The HemoScreen™ utilizes single use cartridges and is suited for POC testing. A complete blood cell count (CBC) analysis takes 3 minutes, while a full CBC test with a five-part differential count of white blood cells (WBC) takes 6 minutes.

HemoScreen was previously shown to perform satisfactory in comparison with automatic hematology analyzers in several patient groups: Influenza [5], intensive care [6], and primary health care [4]. The blood picture in COVID-19 differ from this of other viral infections in respect of lymphopenia and neutrophilia.

The purpose of this study was to evaluate the HemoScreen™ for platelets, neutrophils, lymphocytes, and total white blood cell counts in patients with COVID-19 infections. The HemoScreen™ results were compared with the results obtained with the Sysmex XN-9000™ cell counter at the central laboratory [7].

Materials and Methods

Study design

The present study was performed at Uppsala University Hospital, a tertiary care hospital in Sweden. Samples from the routine testing of CBC from patients with verified COVID-19 were rendered unidentified and used in the study. The only remaining information was gender and age expressed in years. The method comparison study was approved by the ethical committee at Uppsala University (Diary number 01-367). The ethical permit limits the patient information to age and gender. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Samples were collected in K2-EDTA vacutainer tubes (354664, Becton Dickinson, Franklin Lakes, NJ, USA). The samples were first tested with the Sysmex XN-9000™ instrument (Sysmex, Kobe, Japan) and then retested with the HemoScreen™ instrument (PixCell Medical, Yokneam Ilit, Israel). Both measurements were performed within 6 h from blood sampling. The laboratory uses 4.5 mL tubes for the Sysmex instrument. Only a few microliters are used by the instrument while the rest of the blood remains in the sealed Vacutainer tube. The remaining sample volume was used for testing with the HemoScreen instrument. We used venous samples in this study to minimize preanalytical sample variation and to ensure that we got enough material for both measurements. All patient samples were analyzed as singletons on each instrument. Control samples used with the HemoScreen™ analyzer were CBC-3K Whole Blood Controls (R&D Systems, Minneapolis, MN, USA).

Subjects

50 patients treated at the intensive care units or regular COVID-19 wards were included. One patient was excluded because the cell number was under the limit of linearity for the HemoScreen (0.5 x 109/L for leukocyte count). The patient group consisted of 16 women and 34 men, mean age 63 years (range 29 to 90).

Laboratory instruments

The central laboratory cell counter used in this study was the Sysmex XN-9000™ (Kobe, Japan). The instrument analyzes cell count and estimates morphology using three techniques: impedance, fluorescence, and light flow cytometry [7]. The sample volume with the Sysmex instrument is 88 uL. >90% of the Sysmex routine requests are reported within 40 min from the time that the sample reached the laboratory.

The HemoScreen™ (PixCell Medical, Yokneam Ilit, Israel) used image analysis [3]. To align the cells in a single plane HemoScreen utilized a novel technology called viscoelastic focusing. The instrument optics acquired many microscopic images of the focused cells. The images were then analyzed by computer to identify the individual cells. The subcellular data was used to increase the specificity of the measurements. The sample volume was 40 µL and the assay took six min. After the cartridge had been inserted into the instrument, the preparation of the sample and the measurements were performed automatically. The instrument had two modes for operation, with and without the full differential count. If only CBC and not the full differential count was requested the assay time was 3 min and only 20 µL blood was required.

For the HemoScreen analysis, the blood was mixed prior to analysis and 40 µL blood from the vacutainer tube was collected using the HemoScreen capillary device (20 µL in each capillary). The capillaries were inserted into the cartridge and the cartridge was placed in the HemoScreen instrument which automatically started the analysis (Figure 1).

Figure 1: 1. Filling the capillaries with blood. 2. Inserting the capillaries into the cartridge. 3. Placing the cartridge into the analyzer.

Both Sysmex and HemoScreen reports the following 20 blood cell parameters: white blood cell count, red blood cell count, hemoglobin, hematocrit, the red blood cell parameters MCV, MCH, MCHC, and RDW, platelet count, mean platelet volume, percentage and absolute counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Statistical analysis

Deming regression analysis between the methods was calculated using the software Method Validator (Metz, France) The coefficient of variation for the HemoScreen™ instrument and the figures were prepared using Excel 2016 (Microsoft, Seattle, WA, USA).

Results

Correlation between the two analyzers

There were strong correlations between the results obtained with Sysmex XN-9000 HemoScreen™ with Deming correlations: WBCHemoScreen™ = 0.944* WBCSysmex - 0.093; r = 0.986, NeutrophilsHemoScreen™ = 1.029* NeutrophilsSysmex + 0.090; r = 0.972, LymphocytesHemoScreen™ = 0.944* LymphocytesSysmex - 0.107; r = 0.938, PLTHemo-Screen™ = 1.056* PLTSysmex + 9.468; r = 0.988, and RBCHemoScreen™ = 0.955* RBCSysmex - 0.003; r = 0.991. (Table 1, Figures 2A-2D). The correlation between instruments was weaker for monocyte counts.

Analyte	Slope	0.90 CI for slope	Intercept	0.90 CI for intercept	r^2	Bias	0.90 CI for bias
WBC	0.957	0.912 - 1.002	-0.183	-0.580 - 0.214	0.988	-0.62	-0.86 - -0.38
Erytrocytes	0.942	0.904 - 0.979	0.055	-0.093 - 0.203	0.991	-0.17	-0.2 - -0.14
Hb	0.962	0.887 -1.037	-1.963	-10.074 - 6.148	0.978	-6.28	-7.5 - -5.06
Platelets	1.058	0.939 -1.176	9.722	-19.90 - 39.34	0.988	26.4	17.9 - 35.0
Neutrophils	1.016	0.926 -1.107	0.287	-0.505 -1.079	0.957	0.41	0.02 - 0.80
Lymphocytes	0.919	0.762 -1.076	-0.107	-0.245 - 0.086	0.964	-0.18	-0.25 - -0.12
Monocytes	0.212	0.010-0.413	0.101	0.006-0.197	0.493	-0.36	-0.46 - -0.26
Eosinophils	0.821	0.524-1.118	0.048	0.015-0.081	0.824	0.01	-0.04 -0.06
Basophils	0.320	-1.243-1.804	0.001	-0.052-0.049	0.133	-0.03	-0.04 - -0.02

Table 1: Deming correlations between WBC, erythrocytes, hemoglobin, platelets, neutrophils, lymphocytes, monocytes, and eosinophils analyzed with Sysmex XN and HemoScreen.

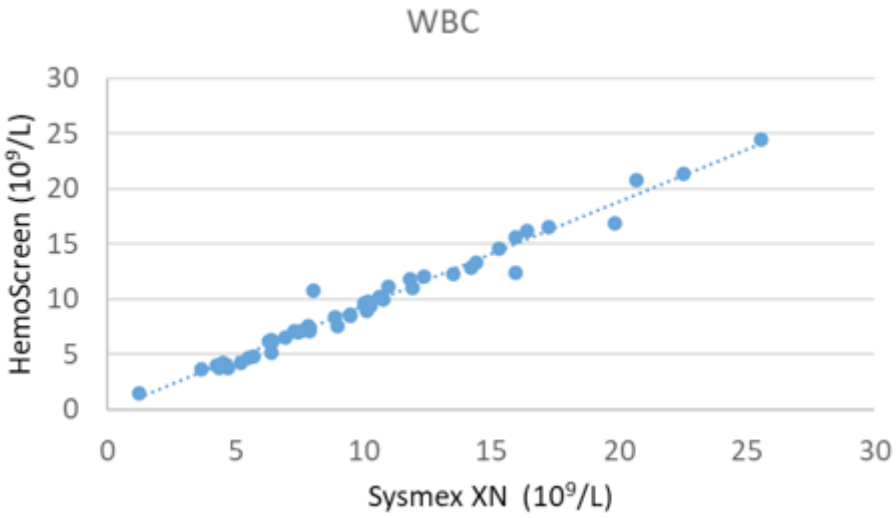

Figure 2A: Correlations between White Blood Cells (WBC) analyzed with Sysmex XN-9000 and HemoScreen.

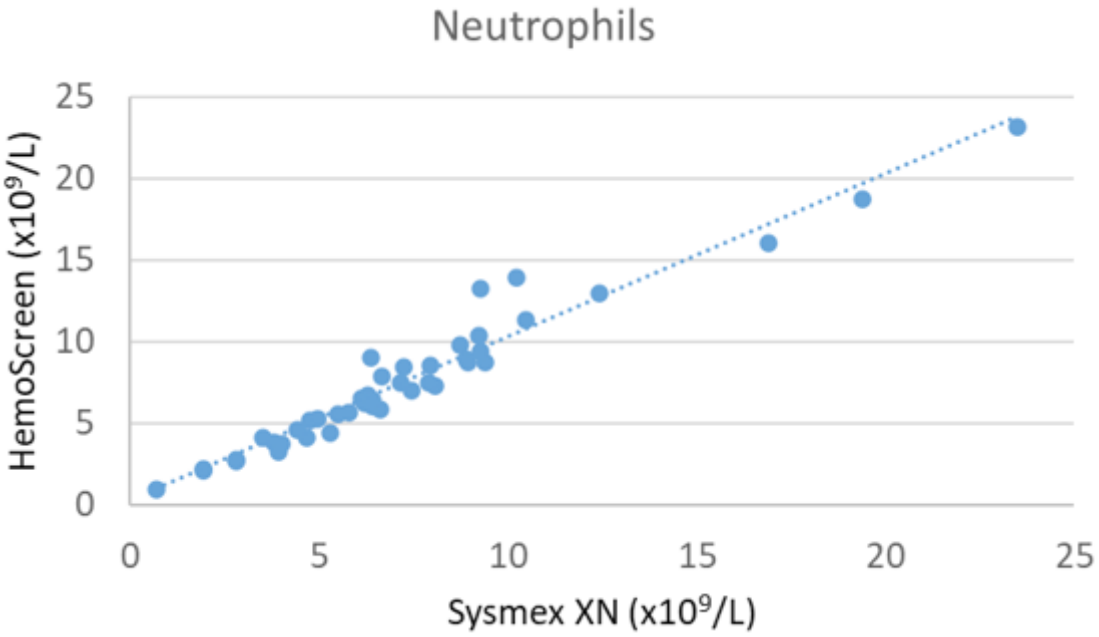

Figure 2B: Correlations between neutrophils analyzed with Sysmex XN-9000 and HemoScreen.

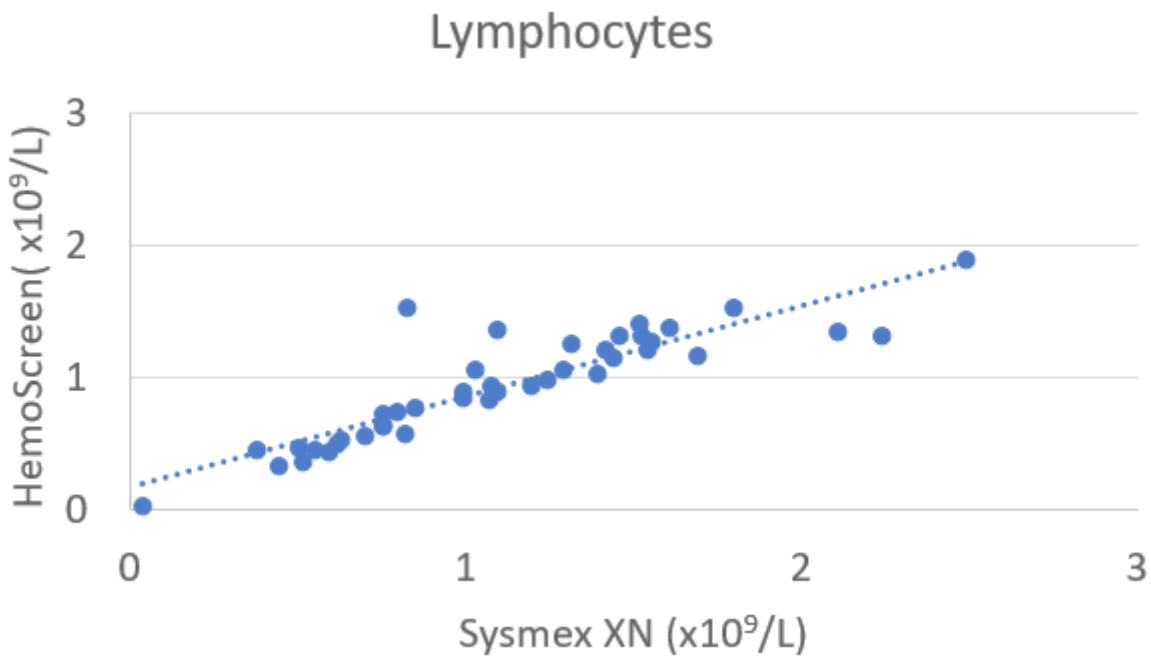

Figure 2C: Correlations between lymphocytes analyzed with Sysmex XN-9000 and HemoScreen.

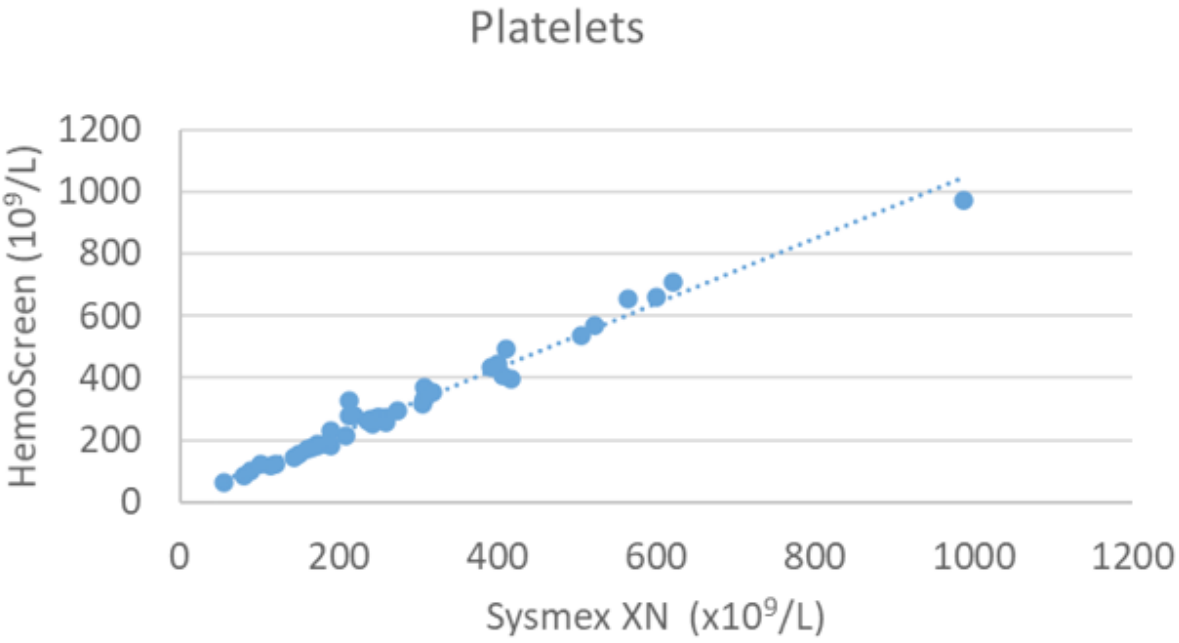

Figure 2D: Correlations between platelets analyzed with Sysmex XN-9000 and HemoScreen.

Flagging of test results

HemoScreenTM creates a text message to the user with recommendation to perform revised testing when abnormal cells can jeopardize the cell number. When morphologically abnormal cells are detected a specific flag for abnormal cells is displayed. When the instrument set a flag, a manual revision was recommended. HemoScreen flagged 18/49 samples.

Sysmex XN-9000 had a complex flagging system which decided which samples should be manually reviewed. Presence of immature granulocytes or suspicion of abnormal lymphocytes or blasts were the main reasons for manual review request by Sysmex XN.

Out of 49 samples Sysmex XN-9000 flagged 20 for manual review. None of the instrument flagged erythrocytes or hemoglobin results. Sysmex XN flagged platelets because of aggregate suspicion in two cases, but manual review did not confirm this suspicion.

Coefficient of variation (CV) for the HemoScreen™ analyzer

Three control levels were used. A total of ten measurements analyzed daily were used to calculate the total CV (Table 2).

	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
WBC (10^9/L)	3.05	6.66	8.22	3.47	20.84	2.51
Erytroc. (10^{12}/L)	2.69	1.78	4.79	1.59	5.56	1.53
Hb (g/L)	7.27	1.08	16.28	2.41	19.31	2.61
Platelets (10^9/L)	67.1	4.32	235.2	3.76	534.7	2.50
Neutrophils (10^9/L)	1.93	7.10	4.79	5.55	12.91	3.27
Lymphocytes (10^9/L)	0.89	12.68	2.49	10.75	6.08	6.95
Monocytes (10^9/L)	0.19	21.70	0.72	11.17	1.55	7.14
Eosinophils (10^9/L)	0.03	33.33	0.09	19.32	0.21	7.65
Basophils (10^9/L)	0.01	0.00	0.03	14.41	0.09	5.81

Table 2: Total coefficient of variation (CV) for the three control levels. Each control was analyzed once daily for 10 days.

Discussion

In the present study we compared blood cell counts analyzed on the central hospital laboratory, a Sysmex XN-9000 cell counter, with POC testing with the HemoScreen™ instrument using blood samples from COVID-19 patients. The most important hematological markers for COVID-19 patients are WBC, neutrophil, lymphocyte, and platelet counts and neutrophil/lymphocyte ratio [8-10]. Red blood cells and Hemoglobin are also used as more general markers in these patients. We thus investigated the correlation between a central laboratory analyzer and the HemoScreen™ POC analyzer for these markers. The same blood samples were used in both instruments. Despite that the Sysmex XN-9000 uses impedance and flowcytometry in combination with fluorescent dyes and HemoScreenTM uses image analysis for cell count there was a good agreement in cell counts be-tween the two instruments. The central laboratory routine price for a CBC performed using Sysmex is €3.5 and an additional €3.4 for the white cell differential count. The cost of the HemoScreen cartridges is estimated to be slightly higher but the price is influenced by many factors, that it is difficult to give an exact figure.

A flag means that there is a degree of uncertainty regarding the results of the flagged parameter. If it is an important parameter for the treatment of the patient the samples should be analyzed by manual microscopy. Both instruments flagged almost 40% of the WBC counts. This high numbers were due to that many subjects were in an advanced stage of COVID-19. Immature granulocytes e.g., left shift was mostly seen in patients with pronounced neutrophilia and this is seen in later stages of COVID-19. The point is that the number of samples directed to the manual review by HemoScreenTM on venous blood was not higher than that of Sysmex XN-9000. Additionally, the number of patients in late stage of disease coming to first contact facilities will probably be lower than in a hospital population which will lower the percentage of required manual reviews for WBC. In a previous pre-Covid study with venous samples collected in primary care we had less than 5% flagged samples. The number of flagged samples in the present study with Covid samples was thus clearly higher [4].

The correlation between the two instruments for monocytes from COVID-19 patients was weaker than previously observed in primary care patients and in other studies. It can only be speculated that this could be an effect of COVID related changes in patients

with severe COVID diseases and that caused the monocytes to be incorrectly classified by one of the instruments. As monocyte count is not one of the prognostic factors in COVID-19 as far as we know to date, one can disregard the monocyte count during the evaluation until comparison with light microscopy morphology are available.

When it comes for CBC erythrocyte parameters including hemoglobin and platelets were accepted by HemoScreen in all cases and could be used for patient assessment.

Generally, the main advantage of Point of Care Devices is the shorter test turnaround time which is achieved by eliminating the time for transport of samples to the laboratory. In addition, the simplicity of performance due to cartridge based system allows non laboratory staff to perform the analysis.

The HemoScreen™ technology was shown previously to be able to operate in primary care setting [4]. Our study shows that it performs satisfactory also in a group of patients with infectious disease COVID-19, which is more difficult to analyze due to possible morphological aberration of white blood cells. It opens the possibility to use HemoScreen™ in field hospitals or triaging centers in case of major infection outbreaks.

Conclusion

The HemoScreen showed good correlation, for the studied parameters, with Sysmex XN-9000 when analyzing samples with patient with COVID-19 infection. The number of samples requiring manual review was similar. HemoScreen™ instrument could be used for COVID-19 patients to permits rapid test results and allow rapid transfer of the patients to designated COVID-19 units or dismissal of the patients thus reducing the risk for spread of the virus.

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