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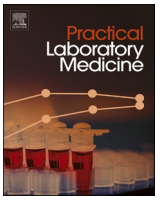

Performance evaluation of the new Sysmex XR-Series haematology analyser

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ABSTRACT

Background: The new XR-Series haematology analyser from Sysmex provides increased throughput and automation, along with a new reagent in WDF channel for optimised WBC differential.
Methods: An analytical performance study for the XR analyser was conducted to evaluate the WDF channel parameters in comparison to the instrument specifications. Additionally, 7460 samples were measured on XR and XN analysers to compare selected parameters and flags, and 930 randomly selected samples were further evaluated with microscopy.
Results: All investigated aspects of the analytical performance study for the XR fell within the manufacturer specifications. The correlation coefficients between the two systems for the parameters tested were greater than 0.983 for the main CBC and DIFF parameters, greater than 0.909 for the Extended Inflammation Parameters, and greater than 0.932 for the parameters used in the workflow rulesets of the *Extended* IPU. Similarly high sensitivities for the detection of abnormal cells were observed for the 'Blasts/Abn Lympho?' flag (XN: 100%, XR: 99.0%) and WPC abnormal flags ('Blasts?' or 'Abn Lympho?') (XN: 97.0%, XR: 96.0%). XN with WPC channel had a 26% reduction of false positive smears compared to XR with 22% reduction, a statistically non-significant difference.
Conclusion: The XR analyser had very good analytical performance, and highly comparable results to the predecessor XN analyser in all investigated parameters, flags and workflow aspects.

1. Introduction

Analyser technology in medical diagnostic laboratories is constantly evolving, driven by the need for optimising laboratory workflows and improved screening and diagnostic methods. In such an environment, Sysmex Corporation had launched the XN-Series automated haematology analyser in 2011. The XN-Series (XN) is equipped with advanced measurement channels and modes such as the PLT-F channel that can analyse platelets with high accuracy revealing the excellent correlation with the immunological platelet

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counting [1,2] and the WPC channel that detects abnormal cells and has contributed to the provision of highly reliable measurement results in clinical practice [3].

In 2021, Sysmex Corporation presented the XR-Series (XR), which has further increased throughput, usability, and automation of the XN analyser. The features of XR are higher throughput than XN, graphical presentation of analytical results through three-dimensional scattergrams and new BT-50 barcode terminal module that automates operations traditionally performed by laboratory staff, including storage and transportation of quality control materials and cleaning materials, automatic device start-up, and mixing of quality control materials and their subsequent measurement. The BT-50 integrated cooler uses thermoelectric cooling to maintain temperature without the need for additional power or the use of harmful refrigerants such as chlorofluorocarbons. The new module, equipped with the automated measurement function of quality control material in a haematology field, will contribute to a reduction in manual operations.

From a measurement principle perspective, XR uses established Sysmex fluorescence flow cytometry technology and provides the same measurement channels and parameters as the predecessor, the XN. For the white blood cell (WBC) differential (measured in WDF channel) Sysmex introduces a new lysing reagent, the Lysercell WDF II to optimise the performance for WBC differential. The WDF channel identifies and counts the subpopulations of WBC and is also the origin of a sensitive flagging to indicate the presence of suspicious cells, alerting to the possibility of an occurrence of malignant as well as immature cells. Moreover, it is capable of functional characterisation of blood cells, including measurement of immune cell activation, which has shown promise for improved diagnosis in infectious diseases [4]. The Sysmex Extended Inflammation Parameters (EIP) of the XN analyser that provide information about the activation status of neutrophils: Neutrophil reactivity intensity (NEUT-RI), Neutrophil granularity intensity (NEUT-GI) [5] as well as about lymphocyte activation: reactive lymphocytes (RE-LYMP), antibody-synthesizing lymphocytes (AS-LYMP) [6,7], and the service parameter with reactive monocytes (RE-MONO), reflecting monocyte activation [4] are also featured on the XR analyser. The EIP are available as additional parameters in Europe, the Middle East and Africa upon activation.

The XN can connect to the *Extended* IPU, a work area manager solution for better sample and result management. Many applications within that work area manager have proven very efficient in terms of laboratory and smear workflow, such as the CBC-O concept which deals with spurious red blood cell-related results leading to an increased mean corpuscular haemoglobin concentration (MCHC) [8], and the Monocyte Workflow Optimisation (MWO) which deals with samples exhibiting monocytosis. The MWO investigates the cause of monocytosis, and thus indication for smear review, by utilising the mono-dysplasia score developed by Schillinger et al. [9]. We investigated the performance of some important parameters and mono-dysplasia score that are used in the CBC-O and the MWO applications.

A performance evaluation of the automated body fluid analysis in the body fluid mode of the Sysmex XR haematology analyser has recently been published [10]. In this work we investigate the whole blood in whole blood mode and the aims of this study are: 1) to evaluate the analytical performance of the WDF channel parameters of the new XR analyser 2) method comparison between XN and XR for selected parameters, flags and mono-dysplasia score 3) assess performance of XR flagging for blasts and abnormal lymphocytes in comparison to the manual differential.

2. Material and methods

2.1. Samples, measurements, and statistical analysis - analytical performance

The analytical performance study was conducted in Sysmex R&D centre (Kobe, Japan) with the use of control blood XN CHECK Level 1/Level 2/Level 3 (Sysmex Corporation, Kobe, Japan) or fresh peripheral blood samples from volunteers. Samples were measured in whole blood mode on Sysmex XR analyser (Sysmex Corporation, Kobe, Japan) with software version SW 2.02. The carryover, precision, linearity, Limit of blank (LoB), detection (LoD) and quantification (LoQ), repeatability, reproducibility and stability were measured as follows.

2.1.1. Carryover

The carryover study was conducted for WBC and differential parameters measured in the WDF channel: neutrophil count (NEUT#), lymphocyte count (LYMPH#), monocyte count (MONO#), eosinophil count (EO#) in accordance with the CLSI H26-A2 method [11]. A controlLine sample with high values (XN CHECK Level 3) was measured in triplicate followed by a diluent (CELLPACK DCL) in triplicate. This process was repeated 3 times.

2.1.2. Repeatability

The repeatability study was conducted for WBC, NEUT#/%, LYMPH#/%, MONO#/%, EO#/%, AS-LYMP#/%, RE-LYMP#/% and NEUT-RI, NEUT-GI parameters. XN CHECK Level 2 was measured 30 times consecutively, and the coefficient of variation (CV) was calculated.

2.1.3. Linearity

The linearity study was conducted for WBC with the linearity verification material WRP CHECK EX Level 3 (Sysmex Corporation, Kobe, Japan). Samples were diluted with CELLPACK DCL to prepare 8-point dilution series with different concentrations, and 5 consecutive measurements were performed at each concentration point on XR and XN. The result data (mean of 5 measurements on XR) were plotted against the target value (mean of 5 measurements on XN), and a regression equation was calculated.

2.1.4. Limit of blank (LoB), detection (LoD) and quantification (LoQ)

The LoB, LoD and LoQ study was conducted for WBC, NEUT#, LYMPH#, MONO#, EO#, AS-LYMP#, and RE-LYMP# in accordance with CLSI EP17-A2 method [12]. For LoB, CELLPACK DCL was measured in a total of 70 replicates. For LoD and LoQ, XN CHECK Level 2 was diluted in 6 target concentrations. Each diluted XN CHECK Level 2 was measured in 5 replicates and for 2 additional test days. This procedure was performed with 2 different lots of reagents.

2.1.5. Precision

The precision study was conducted for WBC, NEUT#/%, LYMPH#/%, MONO#/%, EO#/%, AS-LYMP#/%, RE-LYMP#/% and NEUT-RI, NEUT-GI in accordance with the CLSI EP05-A3 method [13]. Two replicate measurements of XN CHECK Level 1/Level 2/Level 3 were performed in 2 runs (morning and afternoon) for 20 test days. The two-way nested ANOVA test was used to analyse the 80 measurements obtained. Variations within the day, between day and overall, within-laboratory precision were calculated.

2.1.6. Reproducibility

The reproducibility study was conducted for WBC, NEUT#/%, LYMPH#/%, MONO#/%, EO#/%, AS-LYMP#/%, RE-LYMP#/%, NEUT-RI and NEUT-GI in accordance with the CLSI EP05-A3 method [13]. Five replicate measurements of XN CHECK Level 1/Level 2/Level 3 were performed on three XR analysers for five consecutive test days. The two-way nested ANOVA test was used to analyse the 75 measurements obtained.

2.1.7. Stability

The stability study was conducted for WBC, NEUT%, LYMPH%, MONO%, EO%, AS-LYMP%, RE-LYMP%. Fresh blood samples from 3 volunteers on K_2EDTA tubes were stored at room temperature (18–26 °C) and cold temperature (2–8 °C) for up to 72 h. Each sample was measured 3 times at each measurement point and the average value was used to calculate the parameter difference (for NEUT%, LYMPH%, MONO%, EO%, AS-LYMPH% and RE-LYMPH%), and the difference rate (%) (for WBC) with the initial time point.

2.2. Samples and measurements - method comparative study and flagging performance

In total, 7460 venous blood samples from the routine haematology laboratory (Medilys) at Asklepios Clinic Altona in Hamburg, Germany were collected in K_2EDTA anticoagulated tubes (Beckton Dickinson, San Jose, US). The study cohort included all samples received by the laboratory before 12 a.m., and all samples received after 12 a.m. with a request for smear review, for a period of one working week. All samples were measured in the whole blood mode on the Sysmex XN haematology analyser (Sysmex Corporation, Kobe, Japan), software version SW 22.16 upon arrival in the laboratory and the same samples were processed on the Sysmex XR analyser, software version SW 2.02. Before the analysis, samples were handled in accordance with manufacturer instructions. All samples were maximally 6 h old since time of collection and only samples with sufficient residual volume after routine analysis were used. XN and XR analysers were calibrated before the study start. Analytical quality control checks were conducted daily, prior to

Table 1
Parameters from the Whole Blood mode of the Sysmex XN and Sysmex XR analysers investigated in this study.

Main CBC parameters		Units
WBC	White blood cell count	x 10^9/L
RBC	Red blood cell count	x 10^{12}/L
HGB	Haemoglobin concentration	g/dL
HCT	Haematocrit	%
PLT	Platelet count	x 10^9/L
Differential parameters		
NEUT#/%	Neutrophil count/percent	x 10^9/L/%
LYMPH#/%	Lymphocyte count/percent	x 10^9/L/%
MONO#/%	Monocyte count/percent	x 10^9/L/%
EO#/%	Eosinophil count/percent	x 10^9/L/%
IG#/%	Immature granulocyte count/percent	x 10^9/L/%
Extended Inflammation Parameters		
RE-LYMP#/%	Count/percent of reactive lymphocytes with medium and high fluorescence intensity	x 10^9/L/%
AS-LYMP#/%	Count/percent of antibody-synthesizing lymphocytes with high fluorescence intensity	x 10^9/L/%
NEUT-RI	Neutrophil reactivity intensity	FI
NEUT-GI	Neutrophil granularity intensity	SI
Other parameters of interest		
RE-MONO#[a]	Reactive monocyte count	x 10^9/L
RET#	Reticulocyte absolute count	x 10^9/L
RET-H*e*	Reticulocyte haemoglobin equivalent	pg
RBC-H*e*	Red blood cell haemoglobin equivalent	pg
RBC-O[b]	Optical red blood cell count	x 10^{12}/L
NE-WX[b]	Neutrophil side scatter width	

[a] . Service parameter.
[b] . Research parameters.

sample analysis, using XN CHECK quality control materials. Analysis parameters included: (a) main CBC parameters: WBC, red blood cell count (RBC), haemoglobin concentration (HGB), haematocrit (HCT), platelet count (PLT), (b) differential parameters measured in the WDF channel: NEUT#, LYMPH#, MONO#, EO#, IG#, (c) the EIP from WDF channel: RE-LYMP#, AS-LYMP#, NEUT-RI, NEUT-GI, and (d) other parameters of interest: RE-MONO#, reticulocyte count (RET#), reticulocyte haemoglobin equivalent (RET-H*e*), red blood cell haemoglobin equivalent (RBC-H*e*), optical red blood cell count (RBC-O), neutrophil side scatter width (NE-WX) (Table 1). For each parameter, samples with an unreliability mark [*] on at least one output (XN or XR) were excluded from the analysis. The principle of measurement is the same for both the XN and XR analysers except for the new Lysercell WDF II lysing reagent on XR.

2.3. Microscopic evaluation of blood samples and characterisation of selected samples

Blood smears of 930 randomly selected samples were prepared and stained with May-Grünwald Giemsa using the SP-10 automated haematology slide preparation unit (Sysmex Corporation, Kobe, Japan). For each smear, 200 WBC were microscopically evaluated with the DI-60 automated digital cell morphology analyser (Sysmex Corporation, Kobe, Japan) and finally verified and approved by a trained morphologist. According to the presence of cells, all blood smear samples were assigned to one or more of these categories: a) positive for blasts (≥1 blast/200 cells), b) positive for abnormal lymphocytes (≥1 abnormal lymphocyte/200 cells), c) positive for atypical lymphocytes (≥12 variant lymphocytes/200 cells), d) no abnormal cells (no presence for the aforementioned cell types). These categories were used to evaluate the flagging performance of the WDF (‘Blasts/Abn Lympho?‘, ‘Atypical Lympho?‘) and WPC (‘Blasts?‘, ‘Abn Lympho?‘) channel. The microscopic evaluation of samples with discrepant flagging outcome (N = 11) was checked against the medical diagnosis. Based on this approach, four samples positive for abnormal lymphocytes were excluded from the analysis.

2.4. Data analysis for method comparison and flagging performance

All sample results were compared to the XN and data analysis was done using MedCalc® Statistical Software (MedCalc Software, Ostend, Belgium). Correlation coefficients and regression equations were calculated for all parameters and bias between the methods was assessed using Bland-Altman plots. Concordance was defined as the level of agreement between the two systems (number of common negative and positive samples) for any given flag or condition. The sensitivity and specificity were calculated for each individual flag that relates to the presence of abnormal cells. The Chi-squared test was used to compare the XN versus XR smear reduction rate after utilising the WPC reflex test, and the absolute number of smears generated by the ‘Blasts/Abn Lympho?’ flag and the ‘Blasts?’ or ‘Abn Lympho?’ flags from the WPC reflex test. The McNemar test was used to compare the two analysers’ sensitivities for the ‘Blasts/Abn Lympho?’ flag, and the combination of ‘Blasts?’ or ‘Abn Lympho?’ flags. P values smaller than 0.05 are considered statistically significant.

3. Results

3.1. Analytical performance

3.1.1. Carryover

The carryover rate was zero for all the WBC parameters tested (WBC, NEUT#, LYMPH#, MONO#, EO#) in all three sets of measurement.

3.1.2. Repeatability

The repeatability for all tested parameters is shown in Table 2. The CV (%) values ranged from 0.23 (NEUT-GI) to 6.75 (EO#) and all fell within the specifications stated in the instructions for use of XR analyser.

3.1.3. Linearity

The linearity for WBC was excellent ($R^2 = 1.000$) across the whole range of concentrations.

3.1.4. Limit of blank (LoB), detection (LoD) and quantification (LoQ)

LoB for WBC was 0.00 x 10^9/L, while both LoD and LoQ were 0.03 x 10^9/L. LoB for NEUT#, LYMPH#, MONO#, EO#, AS-LYMP#, and RE-LYMP# was 0.00 x 10^9/L, while LoD and LoQ were both 0.03 x 10^9/L.

Table 2
Repeatability study.

	WBC	NEUT#	LYMPH#	MONO#	EO#	AS-LYMP#	RE-LYMP#	NEUT-RI
Mean	6.60	2.73	2.21	0.65	0.70	0.38	0.57	100.03
CV (%)	1.69	2.80	2.55	4.75	6.75	4.25	3.93	0.71
	RBC	NEUT%	LYMPH%	MONO%	EO%	AS-LYMP%	RE-LYMP%	NEUT-GI
Mean	4.37	41.32	33.48	9.78	10.55	5.81	8.69	174.24
CV (%)	0.64	2.18	2.01	4.20	6.51	4.02	3.71	0.23

3.1.5. Precision

The precision (within-laboratory) CV (%) values for selected parameters are shown in Table 3. Precision was excellent for WBC (1.06%–1.98%). Precision for the differential parameters ranged from 1.46% (LYMPH% with XN CHECK Level 3) to 7.75% (MONO% with XN CHECK Level 1). Precision for EIP ranged from 0.17% (NEUT-GI with XN CHECK Level 3) to 5.28% (AS-LYMP% with XN CHECK Level 1) (data not shown). The precision values for all parameters fell within the specifications stated in the instructions for use of XR analyser.

3.1.6. Reproducibility

The reproducibility CV (%) values for selected parameters are shown in Table 3. Reproducibility was excellent for WBC (1.19%–1.93%). Reproducibility for the differential parameters ranged from 1.50% (LYMPH% with XN CHECK Level 3) to 8.17% (EO% with XN CHECK Level 2). Reproducibility for EIP ranged from 0.22% (NEUT-GI with XN CHECK Level 3) to 5.63% (RE-LYMP# with XN CHECK Level 1) (data not shown). The reproducibility values for all parameters fell within the specifications stated in the instructions for use of XR analyser.

3.1.7. Stability

The stability for selected tested parameters from the sample with the highest WBC count is shown in Table 4. The difference rate for WBC between zero and 72 h for all three samples fell within the specifications stated by the manufacturer at both room and cold temperatures (within ±10%). The numerical difference for the differential parameters at 48 h (NEUT%, LYMPH%, MONO% and EO %), and for AS-LYMP% and RE-LYMP% at 24 h (data not shown) for all three samples fell within the specifications as well.

3.2. Method comparison and flagging performance

A total of 7460 blood samples were measured on the XN and XR analysers, and several parameters and flags were compared. A subset of the samples was also evaluated with microscopy to determine the flagging performances of several flags.

3.2.1. CBC, DIFF and Extended Inflammation Parameters comparison

The correlation coefficient (r) for the main CBC and differential parameters studied was excellent; WBC: 1.000, RBC: 0.998, HGB: 0.999, HCT:0.998, PLT: 1.000, NEUT#: 0.999, LYMPH#: 0.996, MONO#: 0.990, EO#: 0.995, and IG#: 0.983. In all cases, the slope of the regression line was close to 1.000 (ranging from 0.997 to 1.038), and the intercept was close to zero (ranging from −0.236 to 0.029) (Figs. 1 and 2; left panels, and Table 5). No significant bias was observed in the Bland-Altman analysis, with the difference of means (XN minus XR) being very close to zero, except for PLT that had a difference of −1.609, ranging from −11.795 to 8.575 (Figs. 1 and 2; right panels, and Table 6).

The two analytical systems also offer a set of parameters termed EIP, that reflect the activation of lymphocytes and neutrophils by measuring changes in the side fluorescence or side scatter signals compared to non-activated cell populations (Table 1). Comparison between the XN and XR showed a very good correlation coefficient for all EIP; RE-LYMP#: 0.909, AS-LYMP#: 0.970, NEUT-RI: 0.929, and NEUT-GI: 0.915. The slope of the regression of line was close to 1.000, and the intercept was close to zero, except for NEUT-RI and NEUT-GI (1.543 and 27.901, respectively) (Fig. 3; left panels, and Table 5). For the lymphocyte related EIP, no significant bias was observed. The neutrophil-related parameters showed a negative bias on the XR; the NEUT-RI difference of means (XN minus XR) was 0.529, ranging from −1.896 to 2.953, and the NEUT-GI difference of means was 2.909, ranging from −0.910 to 6.728 (Fig. 3; right panels, and Table 6).

3.2.2. Flagging comparison of WDF and WPC flags

The two blood count systems offer a set of abnormal and suspect flags for white blood cell abnormalities. In order to have an adequate number of flagged samples the pool of samples was enriched with abnormal samples, giving a higher-than-routine flagging

Table 3
Precision and reproducibility studies.

	WBC	NEUT%	LYMPH%	MONO%	EO%	
Precision (within-laboratory)						
XN CHECK Level 1	Mean	2.83	40.78	36.10	8.42	9.96
	CV (%)	1.98%	3.19%	2.86%	7.75%	7.11%
XN CHECK Level 2	Mean	6.52	42.17	33.36	9.72	9.94
	CV (%)1.10%	2.29%	1.88%	4.47%	6.98%	
XN CHECK Level 3	Mean	14.87	46.98	27.16	9.86	11.19
	CV (%)	1.06%	1.85%	1.46%	2.87%	7.35%
Reproducibility						
XN CHECK Level 1	Mean	2.83	41.20	35.99	8.32	9.72
	CV (%)1.93%	2.97%	2.79%	6.23%	7.22%	
XN CHECK Level 2	Mean	6.51	42.34	33.28	9.69	9.87
	CV (%)1.56%	2.45%	2.07%	4.43%	8.17%	
XN CHECK Level 3	Mean	14.87	47.04	27.07	9.87	11.20
	CV (%)	1.19%	2.04%	1.50%	2.86%	7.03%

Table 4
Stability study (sample 1 with the highest WBC).

	WBC at 72 h	NEUT% at 48 h	LYMPH% at 48 h	MONO% at 48 h	EO% at 48 h
Room temperature					
Mean	5.48	65.73	26.07	4.57	2.87
Difference to 0 h	−4.5%	2.00	−0.87	−1.33	0.20
Cold temperature					
Mean	5.47	65.23	25.33	5.77	2.77
Difference to 0 h	−4.7%	1.50	−1.60	−0.13	0.10

For WBC, difference rate is shown; for the rest, numerical difference is shown.

rate.

The agreement between the two systems (concordance) on WBC-related flags from the WDF channel was over 90% for all the flags studied, and the positive rate was similar between XN and XR (Table 7). Specifically, the 'Blasts/Abn Lympho?' flag, with a concordance of 91.4%, had similar positive rate in our enriched pool of samples; 22.7% for the XN and 21.4% for the XR, compared to average of 18% 'Blasts/Abn Lympho?' from all differentials in a routine operation of haematology laboratory at Asklepios Clinic. The second most common flag was 'Left Shift?' (positive rate 10.9% on XN and 11.5% on XR), followed by 'WBC Abn Scattergram' (positive rate 7.9% on XN and 8.6% on XR) and 'Atypical Lympho?' (positive rate 1.2% on XN and 1.4% on XR) (Table 7).

It is possible to extend XN and XR configurations with additional white precursor and pathological cell (WPC) channel, which only acts as a reflex test when a 'Blasts/Abn Lympho?' flag is generated from the WDF channel. WPC channel can further specify the abnormality ('Blasts?', 'Abn Lympho?', 'Blasts? and Abn Lympho?' flags) or remove the flags. The XN converted slightly more flags into an 'Abn Lympho?' flag (XN: 51.7%, XR: 47.4%), while the XR converted more flags into 'Blasts?' (XN: 28.1%, XR: 35.9%) and 'Atypical Lympho?' (XN: 2.9%, XR: 4.3%) flags. Collectively and considered that most laboratories perform a smear review in the presence of 'Blasts?' or 'Abn Lympho?' flags, 79.8% of the reflex tests on XN and 83.3% on XR retained the abnormal flags (Table 8). This difference did not prove to be statistically significant ($p = 0.401$).

3.2.3. Flagging performance and smear rates

A random set of 926 samples was examined using microscopy and the smear results were compared with selected white blood cell flags. The XR had a sensitivity of 99.0% and specificity of 80.3% for 'Blasts/Abn Lympho?', while the XN had a sensitivity of 100% and specificity of 80.4%. (Table 9). The lower sensitivity of XR is caused by one sample without 'Blasts/Abn Lympho?' that presented with leukopenia (1.6×10^9/L) and Q-flag value of 90. The Q-flag value provides information on the degree of positivity on a scale of 0–300 and at a threshold of 100 'Blasts/Abn Lympho?' is triggered.

Expanding this analysis in the flags from the WPC channel, we focused on conditions that trigger a smear, as mentioned previously. The presence of either 'Blasts?' or 'Abn Lympho?' had a sensitivity of 97.0% on XN and 96.0% on XR in detecting abnormal white blood cells, and a specificity of 88.3% and 86.8% respectively. Looking collectively the performance of the WPC reflex test in terms of smear rate, the XN exhibited a 26% reduction in false positive smears: 261 smears triggered initially by 'Blasts/Abn Lympho?'; 193 smears due to abnormal cells after reflex. Similarly, the XR showed a 22% reduction in false positive smears (261 initial smears; 204 after reflex) (Table 9). This difference was not statistically significant ($p = 0.678$).

Finally, in the case of the 'Atypical Lympho?' flag, we consider the necessity for a smear to evaluate the presence of reactive lymphocytes only in the presence of lymphocytosis ($>3.75 \times 10^9$/L or $>$ 50% of WBC) and in the absence of abnormal lymphocytes. With these conditions, the XN had a sensitivity of 42.9% and a specificity of 97.3% for alerting about the presence of reactive lymphocytes. The XR had a sensitivity of 44.6% and a specificity of 97.3%. The sensitivity for both analysers is lower compared to very high specificity. Thus, reactive samples might be missed, but this is not clinically relevant for our laboratory. Importantly, low number of false positive samples keeps the rate of smear trigger due to the 'Atypical Lympho?' flag very low.

3.2.4. Reactive monocytes and parameters used by extended IPU applications CBC-O and MWO

Additionally, we examined a service parameter termed RE-MONO# that counts monocytes with high side fluorescence signal. The correlation coefficient for RE-MONO# was 0.949 (with an intercept of 0.001 and slope of 0.991), and no bias (Tables 5 and 6).

The CBC-O application of the *Extended* IPU uses information from RET channel parameters and compares the results with the impedance channel values to detect inconsistencies. All RET channel parameters tested (RET#, RET-H*e*, RBC-H*e*, and RBC-O; Table 1) had excellent correlation coefficients between XN and XR, a regression slope close to 1.000 and an intercept close to zero (Table 5). RET# and RET-H*e* showed a slight positive bias for the XR with a difference of means (XN minus XR) at −1.383 and −1.073 respectively. The rest of the parameters showed no significant bias (Table 6).

The MWO assesses the probability of monocytosis being due to non-reactive causes, and thus indication for smear review for confirmation by utilising the mono-dysplasia score developed by Schillinger et al. [9]. The two analysers had an excellent concordance of 97.4% for detecting monocytosis based on the criteria of the application (MONO# $\geq 1.0 \times 10^9$/L and MONO% $\geq$ 10%), with similar positive rates (12.5% for the XN and 12.4% for the XR) (Table 10). The MWO then calculates the mono-dysplasia score (derived from a polynomial equation that includes values from MONO#, NEUT# and NE-WX) in the samples that meet the monocytosis criteria and uses a threshold of $>$0.16 to deem a sample positive [9]. In our pool of samples, 761 samples met the monocytosis criteria in both analysers: the concordance for the mono-dysplasia score was 97.5%, and the positive rates were similar (18.3% for the XN and 19.2%

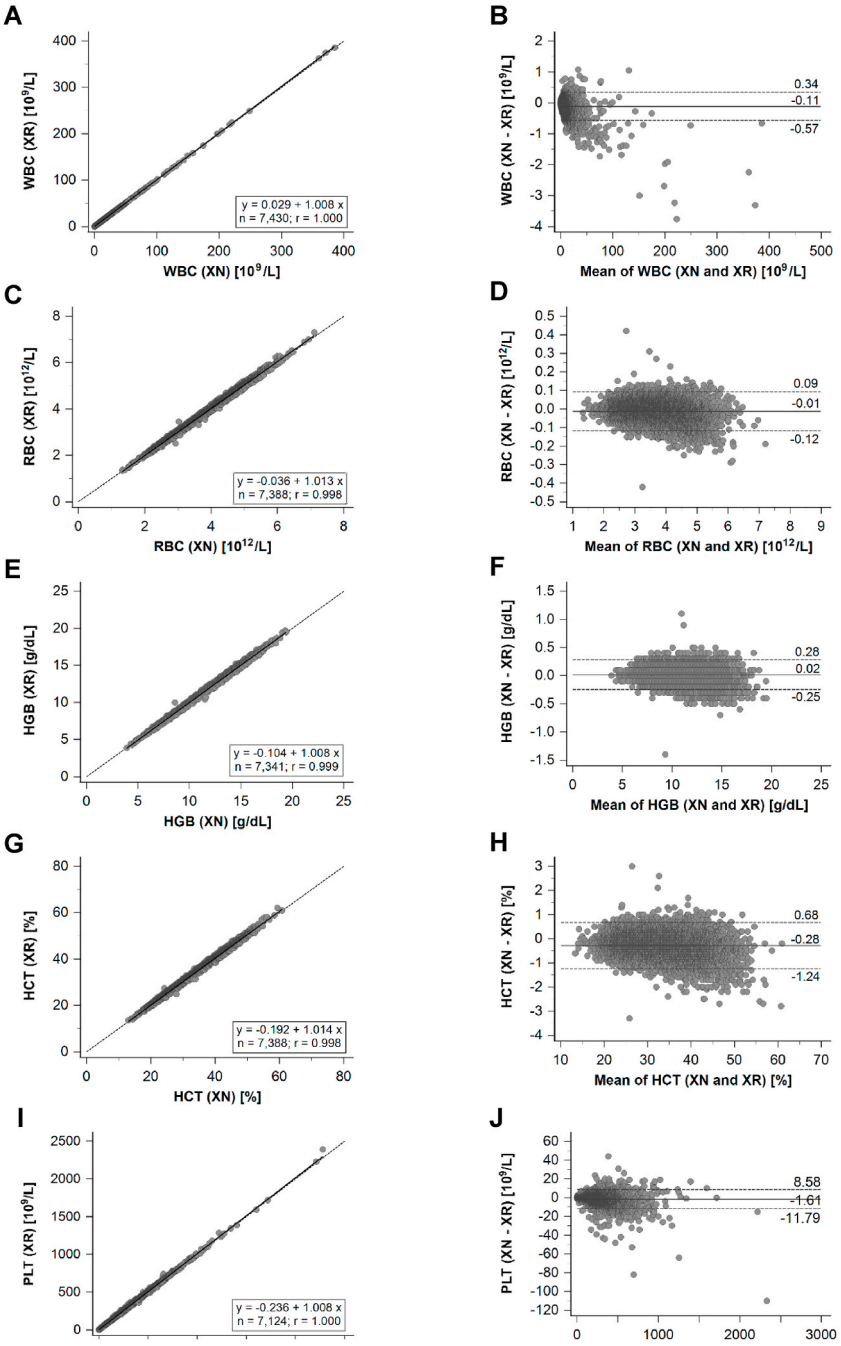

Fig. 1. Comparison of XR and XN main CBC parameters

Blood samples (n = 7460) were measured on the Sysmex XR and on the Sysmex XN analysers. Correlation graphs with regression line (solid line) and line of equality (dashed line) are shown for white blood cell count (WBC) (n = 7430) (A), red blood cell count (RBC) (n = 7388) (C), haemoglobin (HGB) (n = 7431) (E), haematocrit (HCT) (n = 7388) (G), and platelet count (PLT) (n = 7124) (I). Bland-Altman plots with difference of means (XN – XR) and range (1.96SD) are shown for WBC (B), RBC (D), HGB (F), HCT (H), and PLT (J). For each parameter, samples with an unreliability mark [*] on either XN, XR or both analysers were excluded from the analysis.

for the XR). NE-WX, a research parameter that measures the side scatter width of neutrophil population in relation to median side scatter position of neutrophil cloud and is used in the mono-dysplasia score, had a correlation coefficient of 0.932, with a positive bias for the XR (difference of means −3.212) (Fig. 4, Tables 5 and 6).

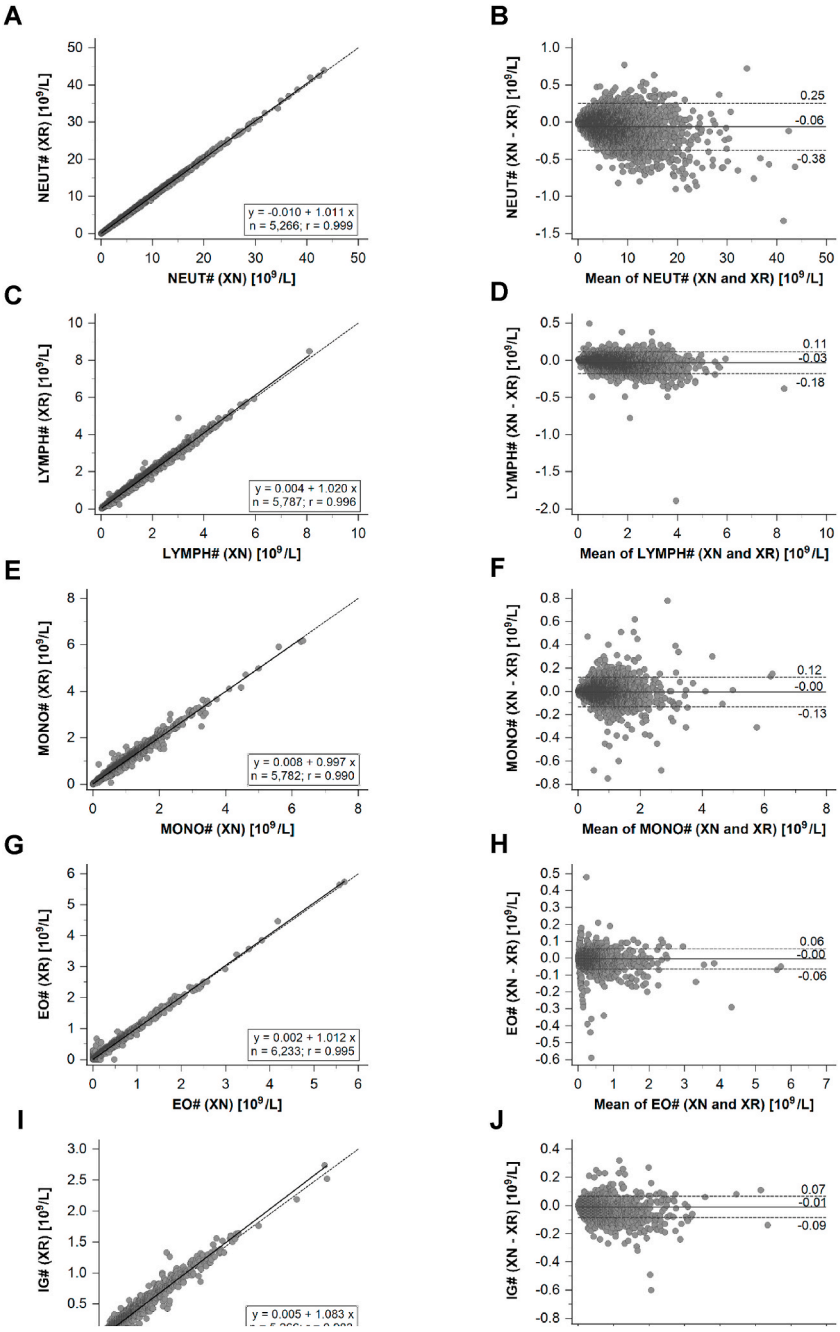

Fig. 2. Comparison of XR and XN differential parameters
Blood samples (n = 7460) were measured on the Sysmex XR and on the Sysmex XN analysers. Correlation graphs with regression line (solid line) and line of equality (dashed line) are shown for neutrophil count (NEUT#) (n = 5266) (A), lymphocyte count (LYMPH#) (n = 5787) (C), monocyte count (MONO#) (n = 5782) (E), eosinophil count (EO#) (n = 6233) (G) and immature granulocyte count (IG#) (n = 5266) (I). Bland-Altman plots with difference of means (XN – XR) and range (1.96SD) are shown for NEUT# (B), LYMPH# (D), MONO# (F), EO# (H), and IG# (J). For each parameter, samples with an unreliability mark [*] on either XN, XR or both analysers were excluded from the analysis.

4. Discussion

The XR is a new high-throughput haematology instrument that is based on the well-established technological platform of the XN analyser. Moreover, XR poses technical improvements that enhance certain clinical and workflow aspects such as enhanced DIFF parameters separation as well as by up to 10% higher throughput and automated quality control material handling. The Sysmex XN

Table 5
Regression statistics between XN and XR Whole Blood mode parameters.

	Sample size	Correlation coefficient	Intercept	Slope
Main CBC parameters				
WBC	7430	1.000	0.029	1.008
RBC	7388	0.998	−0.036	1.013
HGB	7431	0.999	−0.104	1.008
HCT	7388	0.998	0.192	1.014
PLT	7124	1.000	−0.236	1.008
Differential parameters				
NEUT#	5266	0.999	−0.010	1.011
LYMPH#	5787	0.996	0.004	1.020
MONO#	5782	0.990	0.008	0.997
EO#	6233	0.995	0.002	1.012
IG#	5266	0.983	0.005	1.038
Extended Inflammation Parameters				
RE-LYMP#	5787	0.909	0.011	0.942
AS-LYMP#	1963	0.970	0.000	1.018
NEUT-RI	5284	0.929	1.543	0.957
NEUT-GI	5284	0.915	27.901	0.790
Other parameters of interest				
RE-MONO#	7459	0.949	0.001	0.991
RET#	7262	0.994	0.001	0.995
RET-He	7228	0.985	−0.410	1.046
RBC-He	7269	0.995	−1.269	1.051
RBC-O	7450	0.996	0.006	0.985
NE-WX	7447	0.932	15.028	0.964

Table 6
Bland-Altman analysis for the XN and XR Whole Blood mode parameters.

	Sample size	Difference of means (XN minus XR)	Lower limit	Upper limit
Main CBC parameters				
WBC	7430	−0.115	−0.566	0.337
RBC	7388	−0.013	−0.117	0.092
HGB	7431	0.015	−0.249	0.280
HCT	7388	−0.279	−1.236	0.677
PLT	7124	−1.609	−11.795	8.575
Differential parameters				
NEUT#	5266	−0.064	−0.379	0.251
LYMPH#	5787	−0.033	−0.179	0.113
MONO#	5782	−0.006	−0.134	0.122
EO#	6233	−0.004	−0.064	0.055
IG#	5266	−0.011	−0.087	0.065
Extended Inflammation Parameters				
RE-LYMP#	5787	−0.006	−0.077	0.066
AS-LYMP#	1963	0.000	−0.023	0.023
NEUT-RI	5284	0.529	−1.896	2.953
NEUT-GI	5284	2.909	−0.910	6.728
Other parameters of interest				
RE-MONO#	7459	0.000	−0.277	0.276
RET#	7262	−1.383	−10.040	7.273
RET-He	7228	−1.073	−2.583	0.438
RBC-He	7269	−0.293	−0.886	0.300
RBC-O	7450	0.047	−0.103	0.198
NE-WX	7447	−3.212	−53.381	49.957

analyser was first evaluated in 2012 for both whole blood mode and body fluid mode [3,14,15]. Furthermore, the Sysmex XN performance has been described for various sample types and pathological conditions and compared with other haematology analysers in several follow-up studies [16–24]. All the XN technology and measurement channels are also used in XR: a complete blood count and differential is based on the impedance methodology in RBC/PLT channel and fluorescence flow cytometry used in WNR and WDF channels. Optionally, the XR can be also extended with RET, PLT-F and WPC channels and a body fluid mode. The XR analyser uses a new lysing reagent Lysercell WDF II for enhanced separation of parameters measured in the WDF channel resulting in superior differentiation of WBC subpopulations.

In this study, we undertook an analytical performance evaluation for carryover, precision, linearity, limit of blank, detection and quantification, repeatability, reproducibility, and stability. Furthermore, we evaluated the XR analyser by comparing all whole blood parameters and flags from WDF and WPC channels between the XN and the XR analyser. Except for method comparability of basic

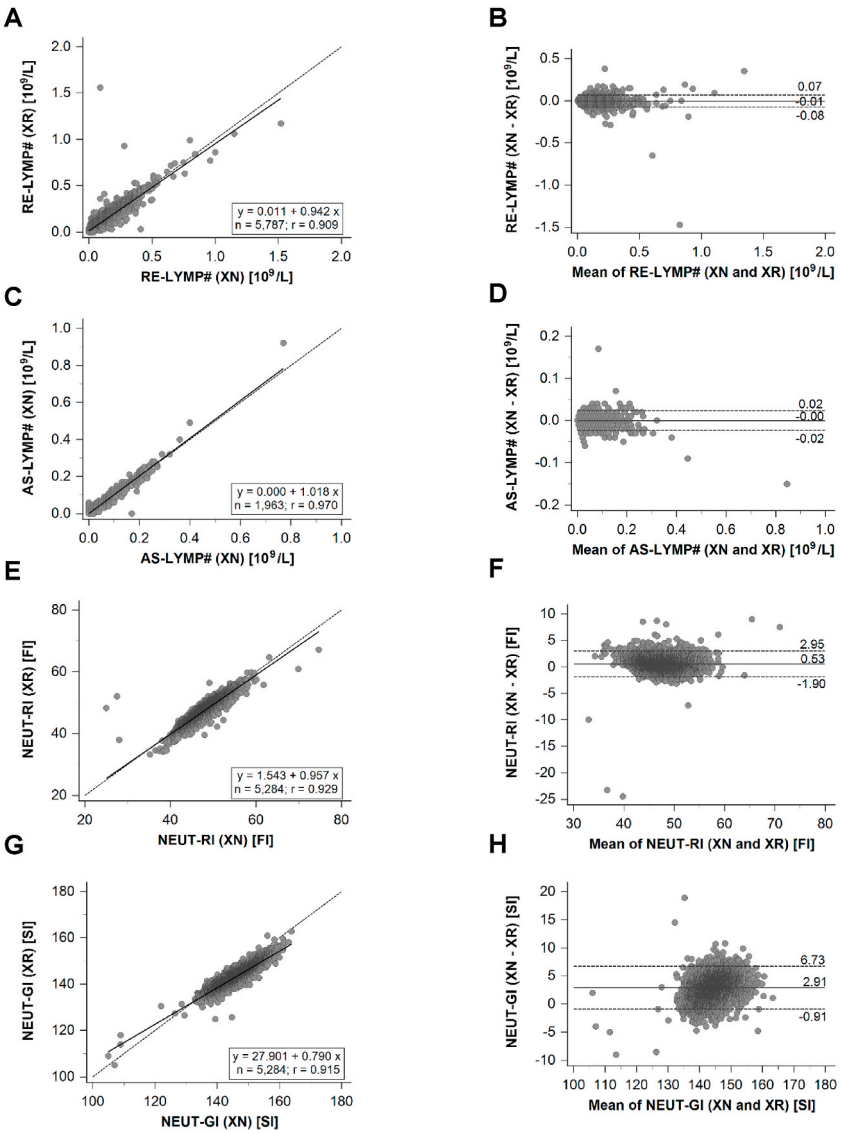

Fig. 3. Comparison of XR and XN Extended Inflammation Parameters
Blood samples (n = 7460) were measured on the Sysmex XR and on the Sysmex XN analysers. Correlation graphs with regression line and line of equality (thin orange line) are shown for reactive lymphocyte count (RE-LYMP#) (n = 5787) (A), antibody-synthesizing lymphocyte count (AS-LYMPH#) (n = 1963) (C), neutrophil reactivity intensity (NEUT-RI) (5284) (E), and neutrophil granularity intensity (NEUT-GI) (n = 5284) (G). Bland-Altman plots with difference of means (XN – XR) and range (1.96SD) are shown for RE-LYMPH# (B), AS-LYMPH# (D), NEUT-RI (F), and NEUT-GI (H). For each parameter, samples with an unreliability mark [*] on either XN, XR or both analysers were excluded from the analysis.

Table 7
Flagging comparison between Sysmex XN and Sysmex XR in WDF.

	Concordance (%)	Positive rate XN (%)	Positive rate XR (%)
WBC Abn Scattergram	97.3	7.9	8.6
Blasts/Abn Lympho?	91.4	22.7	21.4
Atypical Lympho?	98.8	1.2	1.4
Left Shift?	97.9	10.9	11.5

parameters (WBC, RBC, HGB, HCT, and PLT) we focused only on parameters and flags that originate in the WDF or WPC channels. Moreover, we investigated additional parameters of interest and score that are used in the CBC-O and the MWO *Extended* IPU applications.

Overall, the performance results of the XR analyser were consistent and accurate compared to the XN. The carryover rates for all

Table 8
Flagging conversion rates of 'Blasts/Abn Lympho?' in WPC.

		XN	XR
WDF	Blasts/Abn Lympho?	1691 flags	1597 flags
WPC	Blasts?	28.1%	35.9%
	Abn Lympho?	51.7%	47.4%
	Blasts? and Abn Lympho?	6%	6%
	Atypical Lympho?	2.9%	4.3%
	Negative	23.3%	18.4%

Table 9
Smear rate with 'Blasts/Abn Lympho?' and WPC reflex test.

	Flags triggering smears	XN		XR	
		Smears triggered	Sensitivity/Specificity (%)	Smear triggered	Sensitivity/Specificity (%)
WDF	Blasts/Abn Lympho?	261	100/80.4	261	99.0/80.3
WPC	Abnormal flags (Blasts? or Abn Lympho?)	193	97.0/88.3	204	96.0/86.8
Reduction of false positive smears		**26%**		**22%**	

Table 10
MWO monocytosis criteria and score results agreement.

	Sample size	Concordance (%)	Positive rate XN (%)	Positive rate XR (%)
Monocytosis criteria	6743	97.4	12.5	12.4
Mono-dysplasia score	761	97.5	18.3	19.2

parameters assessed were well below the acceptance criteria (1%), indicating very good performance. Results for other performance characteristics, such as precision, repeatability, reproducibility, LoB, LoD, LoQ and linearity were also excellent and within the specification stated in the instructions of use of XR analyser (Tables 2–4).

Results for the comparison of parameters between the XN and XR instruments ranged from very good to excellent (Tables 5 and 6, Figs. 1–4). The parameters comparability results show low biases for most parameters between the two instruments, despite the different reagents utilised in the WDF channels, without potential clinical impact (except of NEUT-GI and NE-WX). In some cases, we observed samples outside the limits of agreement, but given the large number in the cohort, Bland-Altman analysis did not reveal any systematic difference between the measurements. The correlation coefficient of 15 out of 19 investigated parameters was above 0.96. NEUT-GI and NE-WX had r of 0.915 and 0.932 respectively, with higher intercept (27.9 and 15.0, respectively). The results for NEUT-GI and NE-WX show that the new Lysercell WDF II reagent has some impact on these structural neutrophil parameters. This highlights the need for careful validation of reference intervals for these parameters on the XR analyser as the reference intervals might differ from the ones recently published for the XN analyser [25].

The good performance of flagging of the XN analyser has been published previously [16,17,22]. Thus, the flagging performance of the XR analyser was assessed by comparing it to XN analyser flagging as well as to the microscopical classification of pathological cells on smear. The impact of the reagent change on the XR analyser is only on the WDF channel therefore only flags related to that channel and WDF-dependent reflex test on WPC have been evaluated in this comparative study. The overall concordance was above 97% for all flags, except for 'Blasts/Abn Lympho?' (91.4%). The positive flag rate was highly comparable (Table 7) meaning that the actual laboratory smear rate impact due to the difference between the analysers would be very small (Tables 7 and 8).

However, as the 'Blasts/Abn Lympho?' is one of the most important flags that can inform about suspected blast or abnormal lymphocytes cells in patient blood samples, we also investigated the performance of this flag in an unbiased selection of 926 samples against manual smear review results. The results revealed very similar performance for detection of these abnormal cells either with 'Blasts/Abn Lympho?' (sensitivity: XN 100%, XR 99.0%) or with the WPC reflex measurement (sensitivity of abnormal flags: XN 97.0%, XR: 96.0%) (Table 9). The two analysers flagged mostly the same samples, and the small differences observed between them were not significant ('Blasts/Abn Lympho?' $p = 1.000$, WPC reflex $p = 1.000$). The abnormal sample that did not trigger 'Blasts/Abn Lympho?' on the XR presented with leukopenia and thus would not be missed by the laboratory. Similarly, samples from the reflex measurements (3 on XN and 3 on XR) that did not alert for the presence of blasts or abnormal lymphocytes had other WBC-related flags, such as 'WBC Abn Scattergram', 'IG Present', 'NRBC Present', 'Atypical Lympho?', and Left Shift?'. Only one sample from the XN had no other WBC-related flag, but severely decreased WBC count of 0.7 x 10^9/L.

This means that when abnormal cell populations are present, the WDF and WPC detect them with high confidence, and WPC channel can additionally give more information about this aberrant cell type and thus support morphological smear review as in most cases the samples are classified in distinct categories. This allows the morphologist to focus on specific cell types in the follow-up smear review.

In our study, WPC reflex testing would lead to a theoretical (without consideration of other abnormality flags) blood smear review

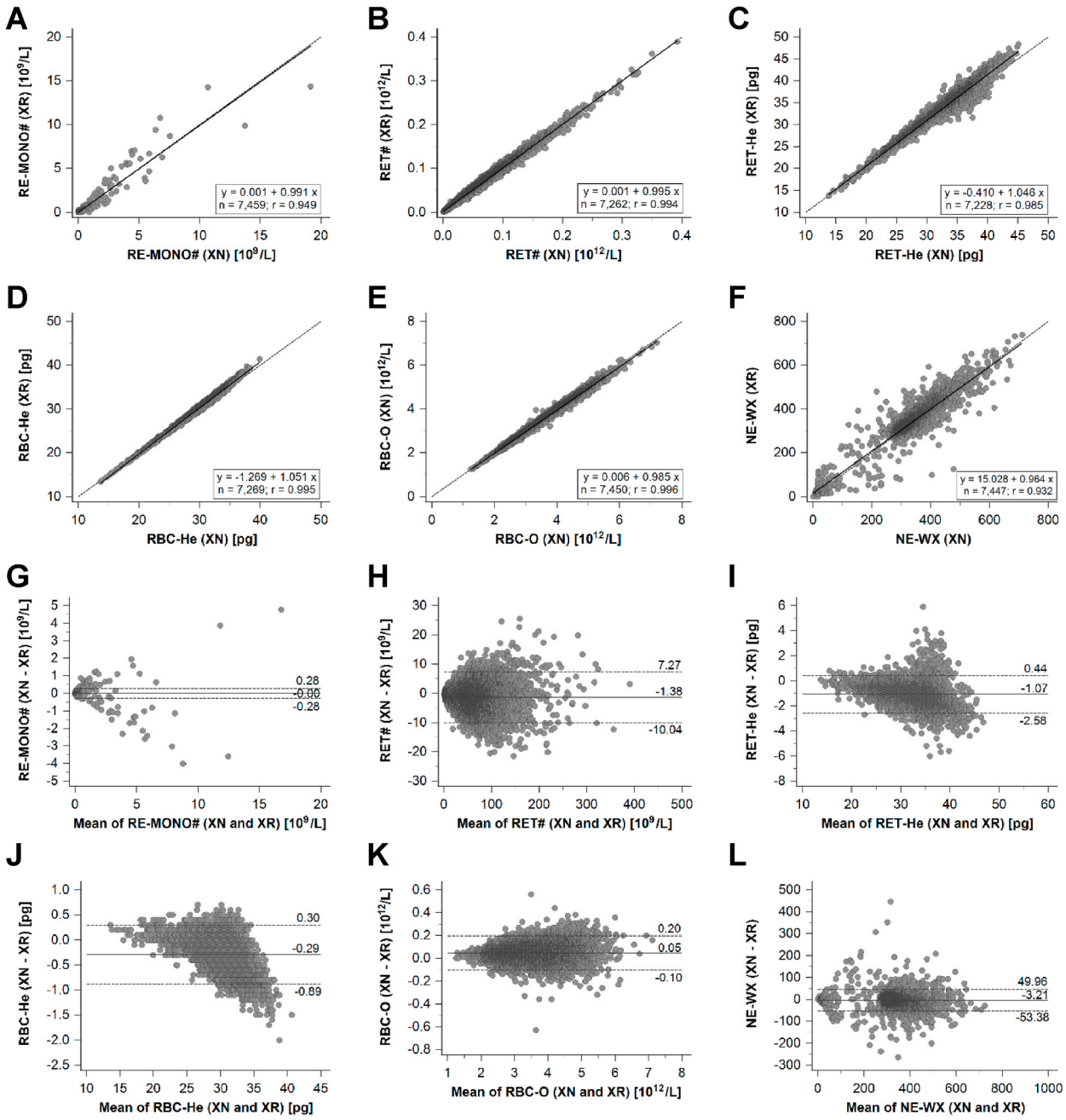

Fig. 4. Comparison of other XR and XN parameters
Blood samples (n = 7460) were measured on the Sysmex XR and on the Sysmex XN analysers. Correlation graphs with regression line (solid line) and line of equality (dashed line) are shown for reactive monocytes (RE-MONO#) (n = 7459) (A), reticulocyte absolute count (RET#) (n = 7262) (B), reticulocyte haemoglobin equivalent (RET-H*e*) (n = 7228) (C), red blood cell haemoglobin equivalent (RBC-H*e*) (n = 7269) (D), optical red blood cell count (RBC-O) (n = 7450) (E), and neutrophil side scatter width (NE-WX) (n = 7447) (F). Bland-Altman plots with difference of means (XN – XR) and range (1.96SD) are shown for RE-MONO# (G), RET# (H), RET-H*e* (I), RBC-H*e* (J), RBC-O (K) and NE-WX (L). For each parameter, samples with an unreliability mark [*] on either XN, XR or both analysers were excluded from the analysis.

rate reduction of 26% (68/261) on XN and 22% (57/261) on XR (Table 9), a non-significant difference between the two systems. This reduction of potential false positive results from WDF would lead to decreased smear review. Other reduction rates have been published by several investigators ranging from 12% to 34% and the differences might be due to earlier XN software versions, different criteria for sample selection, different applied cut-off for flag triggers and differences in patient populations served by the laboratories [21,22,26–29].

The *Extended* IPU CBC-O concept indicates the origin of an increased MCHC and offers the laboratories corrective actions, using the RET channel technology [8]. As the RET channel parameters used in CBC-O concept investigated in this study (RET#, RET-H*e*, RBC-H*e*, and RBC-O) showed excellent correlation coefficients between XN and XR (Table 5) it shows that the CBC-O concept can also be used on the XR analyser. Mono-dysplasia score showed very high concordance and positive rate between XN and XR analysers (Table 10). The score showed similar positive rate on XR compared to XN (146 *vs* 139 samples). Still, thirteen samples were positive on XR but negative on XN, and six samples were positive on XN but negative on XR. As showed in the results of our study, the impact of the new reagent on NE-WX parameter and the difference between NE-WX parameter on XN and XR might be a plausible explanation of the differences in score positivity rate. Further studies investigating the performance like study by Schillinger et al. [9] are needed to evaluate MWO concept in real laboratory setting including the assessment of the performance to manage microscopic examination of samples with monocytosis of the confirmed reactive or chronic myelomonocytic leukaemia origin. CBC-O is already available for the XR while the MWO application is under further investigation.

This study has two limitations. For the analytical performance, except for the stability results made on fresh blood samples, the quality control material was used for the analytical performance results. Ideally, these characteristics (except of LoB) should also be measured on fresh blood samples, as this would have occurred naturally in the laboratory. Moreover, since our intention was to compare the outcome of the two similar analytical systems, and not necessarily investigate the clinical performance in detail, the performances of the abnormal WBC flags derived after smear observations from a single microscopist. For this study, we found this approach sufficient as XN has been previously found to have a high performance for flagging of pathological samples [16,17,22], but further studies would be warranted to see the performance of XR in the broader diagnostic context beyond the smear investigation in the laboratory.

5. Conclusions

In conclusion, this first XR analyser study showed very good analytical performance for the new XR analyser and in all investigated parameters, flags and workflow aspects, with highly comparable results to the current XN state-of-the-art routine haematology analyser.

Ethics approval

The analytical performance was approved by the Sysmex Corporation Ethics Committee (Kobe, Japan), and was conducted in strict adherence to the guidelines by the Declaration of Helsinki. As part of the approval, the Internal Review Boards at Sysmex corporation explicitly waived the need for written informed consents from the patients as all the samples were de-identified.

For the method comparative study and flagging performance, no ethical approval and consent from study participants was required given the fact that samples used in this study were remnant blood samples after a routine laboratory measurement. All the data were treated anonymously without any personal data.

Research funding

For the method comparative study and flagging performance, the Sysmex XR haematology analyser and all consumables and reagents were provided by Sysmex Europe SE.

CRediT authorship contribution statement

Kenichi Fujimaki: Conceptualization, Data curation, Formal analysis, Investigation, Methodology. **Kornelia Hummel:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Immaculate Magonde:** Formal analysis. **Katharina Dammert:** Data curation, Formal analysis, Writing – review & editing. **Yoshiko Hamaguchi:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Konstantinos Mintzas:** Data curation, Formal analysis, Visualization, Writing – original draft. **Jarob Saker:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology. **Ondrej Valina:** Formal analysis, Writing – original draft. **Klaus-Martin Otte:** Conceptualization, Investigation, Methodology, Supervision.

Declaration of competing interest

Katharina Dammert, Konstantinos Mintzas, Jarob Saker and Ondrej Valina are employed by Sysmex Europe SE. Kenichi Fujimaki and Immaculate Magonde are employed by Sysmex R&D center Europe. Yoshiko Hamaguchi is employed by Sysmex Corporation. Other authors have no competing interests.

Data availability

Data will be made available on request.

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