

Generating Evidence Based Interpretation of Hematology Screens via Anomaly Characterization

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Abstract: *Introduction:* We propose a simple, workable algorithm that provides assistance for interpreting any set of data from the screen of a blood analysis with high accuracy, reliability, and inter-operability with an electronic medical record. This has been made possible at least recently as a result of advances in mathematics, low computational costs, and rapid transmission of the necessary data for computation.

Materials and Methods: The database used for this study is a file of 22,000 laboratory hemograms generated by two Beckman-Coulter Gen-S analyzers over a two month period in a 630 bed acute care facility in Brooklyn. All control samples, patient identifiers, and patients under 23 years old were stripped from the dataset. An experienced medical practitioner reviewed all of the data used in generating the algorithm described. The differential diagnoses were outlined prior to beginning the study, and preliminary studies were done to determine the reference ranges for each predictor. An algorithm for anomaly detection and classification via anomaly characterization is proposed. For each patient, the algorithm characterizes its anomalous profile and builds a differential metric to identify similar patients who are mapped into a classification.

Results: The algorithm successfully classified patients into the diagnosis that were sufficient in sample size, and others are still under observation. The algorithm correctly classified the patients as follows: Microcytic Anemia - 99.63%, Normocytic Anemia - 98.03%, Mild SIRS - 73.42%, Thrombocytopenia - 99.52%, Leukocytopenia - 84.83%, Moderate / Severe SIRS - 96.69% and Normal - 93.18%.

Discussion: This limited analysis of automated hematological results can be extended to the case of more complicated conditions than presented, and can be extended to a combination of chemistry, hematology, immunology, and other data.

Keywords: Hemogram, Systemic Inflammatory Response Syndrome (SIRS), anemia, thrombocytopenia, structured data, interpretative comment, anomaly detection, anomaly characterization, non-linear differential diagnosis.

1. INTRODUCTION

Healthcare-associated infection (HAI) occurs in 5%-10% of hospitalized patients [1] and accounts nearly 100,000 deaths in US hospitals annually [2]. The risk of serious complications due to HAIs is particularly high for patients requiring intensive care [3, 4]. Preventing HAIs is one of 20 Priority Areas for National Action [5], and resulted in preventive measures tied to financial reimbursement. In addition, wider use of electronic data platforms to measure, report, and improve quality, National Quality Forum (NQF) has been endorsed by the NQF endorsed measures that combine data from two or more common electronic sources, including pharmacy, and laboratory systems, and other records, which cover sixteen conditions, including bone and joint conditions, cardiovascular disease, asthma and respiratory illness, and diabetes [6].

The timely identification of sepsis risk in acutely ill patient populations depends on an effective protocol for screening for risk to minimize the prospect of a suboptimal outcome in association with the systemic inflammatory response syndrome (SIRS), age, and disease related comorbidities, to allow for early antibiotic administration, to minimize the emergence of antibiotic resistance, and to shorten the stay and costs of intensive care unit stay, and to avoid the development of multiple organ dysfunction syndrome followed by death. Severe infection and sepsis, common causes of morbidity and mortality in intensive care units, are accompanied by clinical and laboratory signs such as changes in body temperature, leukocytosis, and tachycardia. However, these signs and symptoms of systemic inflammation may have an infectious or non-infectious aetiology and are neither specific nor sensitive for sepsis. A similar inflammatory response occurs in patients suffering from pancreatitis, major trauma, and burns without infectious complications. Patients with systemic infection and organ dysfunction or shock are often difficult to distinguish from patients with similar clinical signs and laboratory findings without infection. Since these common clinical and laboratory measurements lack sensitivity and

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specificity, other tests are needed to give an early marker of the infectious cause of a generalized inflammatory response, to allow early diagnosis and the use of specific treatment.

This is a significant basis for the study we have undertaken to construct a software agent that can be applied to the instantaneous interpretation of the hemogram, which carries rapidly generated information about the most common conditions, such as, infection, anemia, and disordered coagulation. The hemogram is the most commonly performed test done on all patients seen in the emergency department, in the physicians' offices, and in the hospital population. It is the most essential test for anemia in children and adults, worldwide. This could be expanded to subset classifications, and can be combined with chemistry data once a firm foundation is set. While there is an example of the use of neural networks in cytological analysis, this work is unique in exploring multiple variables predicting one or several diagnostic endpoints and estimated the weighted probabilities of the results.

Predictive diagnostics is an emerging science. An underlying principle lies in the work in bacterial taxonomy by Eugene Rypka that illustrated a method of forming clusters of elements with a high degree of similarity, with the provision that each cluster (and its elements) will be disjoint or separable to some degree from other clusters. The development of Latent Class Clustering by the method of Magidson and Vermunt [7-12] has held unfulfilled promise in medical sciences. The introduction of LCM models developed by Magidson and Vermunt allowed for examining the structure of combinations of ordinal and continuous variables in a data set, and the validity of the classes formed. The possibility of examining a large data set with several predictors and several disease states and a combination of them in an individual patient is elusive, and there is still a need to embed a classifying agent that could provide instantaneous second opinion.

Anomaly detection identifies patterns in a given dataset that do not conform to an established normal behavior. The detected patterns are called anomalies and often translated to critical and actionable information in several application domains since they deviate from their normal behavior. Anomalies are also referred to as outliers, deviation, peculiarity, etc. The anomaly detection problem, in its most general form, is not easy to solve. In fact, most of the existing anomaly detection techniques solve a specific formulation (instance) of the problem. The formulation is induced by various factors such as nature of the data, availability of labeled data, type of anomalies to be detected, etc. Often, these factors are determined by the application domain in which the anomalies have to be detected.

Usually, in addition to the challenge of detecting anomalies in a dataset, the analyzed data is also high-dimensional. High-dimensional data, meaning data which require more than three dimensions to be represented, are difficult to analyze and interpret. Since the data in most modern systems can be described by hundreds and even thousands of parameters (features), then the dimensionality of the data is very high and its processing becomes impractical.

“Curse of dimensionality” [13] is associated with high-dimensional data. This is due to the fact is that as the dimensionality of the input data space increases, it becomes exponentially more difficult to process and analyze the data. Furthermore, adding more dimensions can increase the noise, and hence the error and in certain situations, the number of observations is insufficient to produce satisfactory dimensionality reduction. The “curse of dimensionality” is a significant obstacle for high-dimensional data analysis, since a local neighborhood in high dimensions is no longer local. Therefore, high-dimensional data is incomprehensible to understand, to draw conclusions from or to find anomalies that deviate from their normal behavior.

Although anomaly detection identifies the anomalies in the system, it lacks the characterization of these deviations. This characterization is crucial since it provides a better understanding of the anomalies and it enables a more accurate classification of them. Anomaly characterization is a subject of recent researches. It aims at understanding the statistical, temporal or spatial behavior of the anomalies in order to characterize them and, as a result, provide a more accurate and sophisticated anomaly detection.

In this paper, we propose a novel method for anomaly detection and classification *via* anomaly characterization. For a given hemogram in the system, we characterize its anomalous behavior *via* non-linear differential diagnosis processes. Then, once its characterization profile, which is its unique differential metric, is constructed, we identify other anomalous hemograms that match this differential profile. Last, in case we deal with supervised anomaly detection, we use the labels of the matching hemograms to label and classify the given hemogram.

2. MATERIALS AND METHODS

The database used for this study is 22,000 hemograms generated by the Beckman-Coulter Gen-S (Brea, Ca) over a two month period in a 630 bed acute care facility in Brooklyn. All control samples, patient identifiers, and patients under 23 years old were stripped from the dataset. An independent source experienced in medicine reviewed all of the data. The differential diagnoses were outlined prior to beginning the study, and preliminary studies were done to determine the reference ranges for each predictor.

Systematic Inflammatory Response Syndrome (SIRS) is defined as a condition in which a patient displayed any two of the following abnormal vital signs [14]:

- Temperature < 36 °C (hypothermia) or Temperature > 38 °C (hyperthermia);
- Heart Rate > 90 beats/min;
- Respiratory Rate > 20 breath/min;
- Systolic Blood Pressure < 90 mm Hg;
- White blood cell count > 12,000 cells/mm³ or < 4,000 cells/mm³.

It may be difficult to distinguish a moderate state of disease such as pneumonia with SIRS from the severe and progressive state of sepsis, septicemia or even septic shock. CRP [15], an acute phase protein, may reduce errors from using the standard clinical criteria, and is used in assessing

children. Procalcitonin [16] has emerged as a biomarker of sepsis, but it would have a high cost for overuse, making the algorithm based on WBC and percent neutrophils a necessary first step. The most commonly used screening methods for the presence of iron deficiency in a population are the measurements of hemoglobin/hematocrit concentration [16]. Because iron deficiency is often the most common cause of anemia, the presence of microcytic anemia is also used as a screening tool for iron deficiency. It is assumed that a population with a high anemia prevalence is likely to also have a high prevalence of iron deficiency, if we remove those with chronic disease. A number of physiologic characteristics such as age, sex and stage of pregnancy influence hemoglobin concentration [16, 17]. Anemia was defined according to World Health Organization (WHO) criteria as a hemoglobin concentration below 12 g/dL in women and below 13 g/dL in men.

Our database organized to enable linking a given profile to known profiles. This is achieved by associating a patient to a peer group of patients having an overall similar profile, where the similar profile is obtained through a randomized search for an appropriate weighting of variables. Given the selection of a patients' peer group, we build a metric that measures the dissimilarity of the patient from its group. This is achieved through a local iterated statistical analysis in the peer group. We then use this metric to locate other patients with similar anomalous profiles, for each of whom we repeat the procedure described above. This leads to a network of patients with similar anomalous condition. Then, the classification of the patient is inferred from the medical known condition of some of the patients in the linked network.

Given a set of points (the database) and a newly arrived sample (point), we characterize the anomalous behavior of the newly arrived sample, according to the database. Then, we detect other points in the database that match this unique characterization. This collection of detected points defines the differential neighborhood of the newly arrived sample. We use the differential neighborhood in order to classify the newly arrived sample. This process of differential diagnosis is repeated for every newly arrived point.

Fig. (1) presents the flow of the algorithm.

Let $X = \{x_1, \dots, x_m\}$ be a set of n -dimensional points in \mathbb{R}^n where each point $x_i \in X$ is described by n variables $x_i = \{x_{i1}, \dots, x_{in}\}$. X is the database of the system. Let y be a n -dimensional point in \mathbb{R}^n . y is the newly arrived point.

We apply the following algorithm in order to classify y :

2.1. Random Selection of Weighting of Variables

In order to analyze the data using different viewpoints, we apply random weights on the data. A random weighting r is a random vector in \mathbb{R}^n that assigns a random weight to each parameter in the data. X^r is the result of the application of the random weighting r on the data X . $X^r = \{x_1^r, \dots, x_m^r\}$ where each point $x_i^r \in X^r$ is described by n variables $x_i^r = \{x_{i1}^r, \dots, x_{in}^r\}$, $x_{ij}^r = x_{ij} \cdot r_j, i = 1, \dots, m, j = 1, \dots, n$. In the

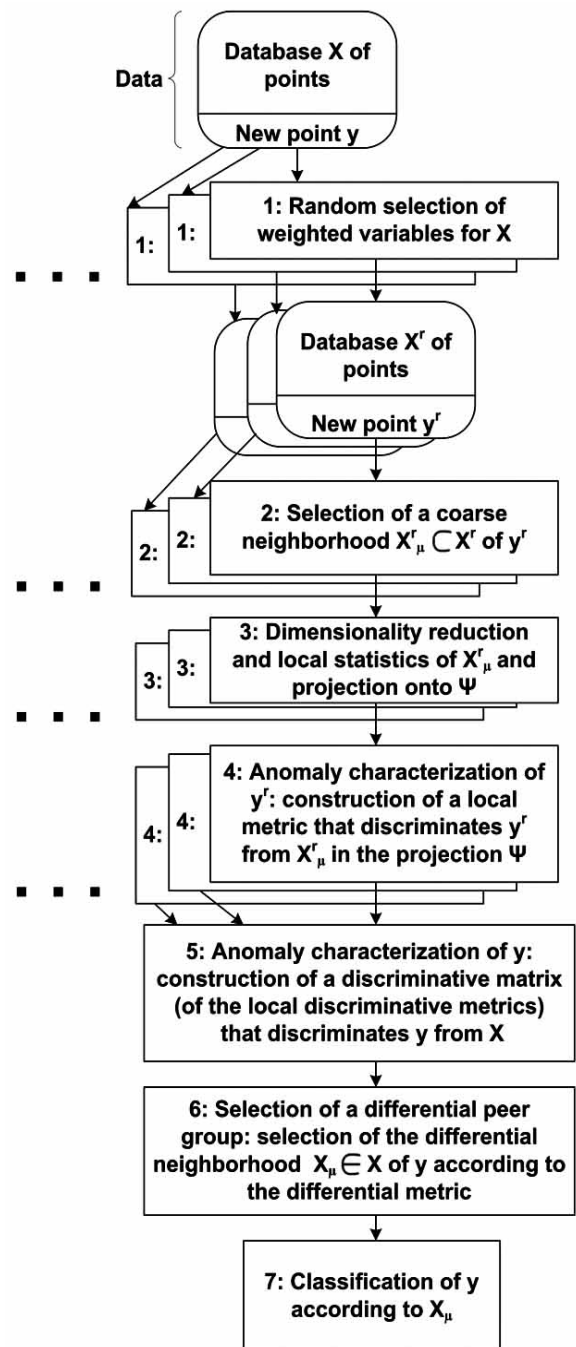


Fig. (1). Anomaly characterization and differential diagnosis.

same way, y is transformed into y^r . There are several ways to choose the random weighting r . Most often, the elements r_j of r are Gaussian distributed with different Gaussian widths, whose role is to select and weigh a small number of coordinates. We use the absolute values of the Gaussian distributed vector.

2.2. Selection of a Coarse Neighborhood

In order to select a coarse neighborhood $X_\mu^r \subset X^r$ of y^r , we find all the points in X^r that are included in a ball of radius μ around y^r . Therefore, $X_\mu^r = \{x^r \mid x^r \in X^r \wedge \|x^r - y^r\| < \mu\}$.

X_μ^r is the coarse neighborhood of y^r according to the viewpoint that was provided by the random weighting r .

2.3. Dimensionality Reduction and Local Statistics

We reduce the dimension of X_μ^r in order to find the most significant directions of X_μ^r corresponding to y^r . First, we center X_μ^r according to y^r . $\bar{X}_\mu^r = \left\{ \bar{x}_1^r, \dots, \bar{x}_{|X_\mu^r|}^r \right\}$,

$\bar{x}_{ij}^r = x_{ij}^r - y_j^r, i = 1, \dots, |X_\mu^r|, j = 1, \dots, n$. Then, we compute the Singular Value Decomposition (SVD) of the normalized centered neighborhood. $\frac{\bar{X}_\mu^r}{\sqrt{|X_\mu^r|}} = \mathbf{U}\Sigma\mathbf{V}^T$, where \mathbf{U} are the

left singular vectors, the diagonal elements of Σ are the singular values and \mathbf{V} are the right singular vectors. Since \bar{X}_μ^r was centered according to y^r , then the singular vectors are the directions that correspond to y^r . Observe that each selection of r can introduce a different neighborhood and therefore the SVD should be computed independently for each such neighborhood since we cannot compute the SVD of the data once and then multiply the singular values by the current r .

We sort the singular values Σ from larger to smaller and then order \mathbf{V} accordingly. We project the data \bar{X}_μ^r onto the most significant right singular vectors $\{\mathbf{V}_1, \dots, \mathbf{V}_\eta\}$. η is determined according to the decay point of the spectrum (where the singular values decay toward zero). Let Ψ be the set of these projections: $\Psi = \{\psi_1, \dots, \psi_{|\bar{X}_\mu^r|}\}$, where $\psi_i = (\bar{x}_i^r \cdot \mathbf{V}_1, \dots, \bar{x}_i^r \cdot \mathbf{V}_\eta)$, $i = 1, \dots, |\bar{X}_\mu^r|$ and \cdot denotes the inner product operator. Similarly, we project y^r onto the right singular vectors and denote this projection by ψ_y .

Last, we calculate the distance between the points in the projection Ψ to ψ_y . We denote the function that transforms the points in the coarse neighborhood into the distance in the projection by $f: X_\mu^r \rightarrow \delta$, where $f(x_i^r) = \delta_i = \|\psi_i - \psi_y\|$, $x_i^r \in X_\mu^r$ and $i = 1, \dots, |X_\mu^r|$.

2.4. Local Discrimination

In this step, we try to discriminate y^r from its coarse neighborhood X_μ^r in the projection Ψ . A good discrimination will significantly separate y^r and some of its very close neighbors (its peer group) from the rest of the coarse neighborhood. A significant separation means that there is a big gap between y^r (and its peer group) and the majority of its neighborhood. In this case, we consider the random weighting r as discriminative and we use it in the next steps in order to construct the differential metric. On the other hand, if no significant gap is found, y^r cannot be

separated from its neighborhood, the random weighting r is not discriminative, and therefore we ignore it.

We sort the distances δ from smaller to larger and denote the ordered distances by: $\bar{\delta} = \{\bar{\delta}_1, \dots, \bar{\delta}_{|X_\mu^r|}\}$, where $\bar{\delta}_1 < \bar{\delta}_2 < \dots < \bar{\delta}_{|X_\mu^r|}$. Then, we look for a significant jump in the rate of change of $\bar{\delta}$. The existence of this spike implies that there is a significant gap and r is discriminative. Otherwise, y^r is not separated from its neighborhood. If r is discriminative, we denote by α_r the normalized radius of the peer group of y^r that is centered with y^r . α_r introduces a weight for the random weighting r . A small value of α_r implies that the peer group of y^r is very unique and therefore r is more discriminative than when α_r has a big value.

2.5. Construction of a Discriminative Matrix for Anomaly Characterization

In the first step of this algorithm, we applied random weighting on the data. X_μ^r is the selected coarse neighborhood of y^r that was provided by the random weighting r . Different random weightings provide different viewpoints of the data and as a result, different coarse neighborhoods of y^r are selected. In the fourth step of the algorithm, we decided whether the random weighting r is discriminative or not. The whole process (steps 1-4) depends on the random weighting r . Therefore, steps 1-4 are repeated several times using different random weightings to search for the appropriate random weightings. Each random weighting is classified as discriminative or not. In this step, we fuse all the discriminative random weightings and construct a discriminative matrix.

Let $\{r_1, \dots, r_k\}$ be the set of k discriminative random weightings that were found. We build the discriminative matrix R and denote the i^{th} row of R by: $R_i \triangleq (R_i^1, \dots, R_i^n), i = 1, \dots, k$. We denote by $\alpha = \{\alpha_1, \dots, \alpha_k\}$ their corresponding peer groups' radii. R and α characterize the anomalous profile of y .

2.6. Selection of the Differential Neighborhood

In this step, we select the differential neighborhood of y that defines its differential peer group. First, we use the differential matrix R of y and its corresponding radii α to calculate the distance between y to the points in X . Then we discriminate y from X to find its differential peer group.

We denote the distances between y to the points $x_i \in X, i = 1, \dots, m$ by $\omega_i \triangleq \frac{1}{k} \sum_{j=1}^k \|x_i - y\|_j^2$, where $\|x_i - y\|_j^2 = \sum_{p=1}^n \frac{1}{\alpha_j} (R_p^j)^2 (x_{ip} - y_p)^2$.

We sort the distances ω from smaller to larger and denote the ordered distances by: $\bar{\omega} = \{\bar{\omega}_1, \dots, \bar{\omega}_m\}$, where $\bar{\omega}_1 < \bar{\omega}_2 < \dots < \bar{\omega}_m$. As described in step 4, we look for a significant jump in the rate of change of $\bar{\omega}$. We use this spike to discriminate y from X and to select its differential peer group. We denote by $X_\mu \subset X$ the differential neighborhood of y , as discriminated by the spike, according to the differential matrix R and the corresponding radii α .

2.7. Classification

In case the dataset is labeled, we use the labels of X_μ in order to classify y . Let $L = \{l_1, \dots, l_q\}$ be a set of classes (labels). For each point $x_i \in X$, the corresponding label vector c_i is constructed: $c_i \triangleq (c_{i1}, \dots, c_{iq})$, where

$$c_{ij} = \begin{cases} 1 & \text{if } x_i \text{ has the label } l_j, 1 \leq j \leq q \\ 0 & \text{otherwise.} \end{cases}$$

Each point can be associated to several classes, and therefore have multiple labels. c_i denotes the set of classes that x_i belongs to. In order to classify y according to X_μ , we build a corresponding label vector $c_y = (c_{y1}, \dots, c_{yq})$, where $c_{yj} = \sum_{x_i \in X_\mu} c_{ij} \cdot e^{-\omega_i}$, $1 \leq j \leq q$. The classification of y is the stochastic vector $p_y = (p_{y1}, \dots, p_{yq})$, where $p_{yj} = \frac{c_{yj}}{\sum_{s=1}^q c_{ys}}$. p_y denotes the probability of y to belong to each one of the classes $\{l_1, \dots, l_q\}$.

3. RESULTS

The reviewer labeled manually 4,900 hemograms that were used as the database of the algorithm. 2,200 unlabeled hemograms were used as the testing set. The algorithm labeled each testing hemogram according to the labeled database. The reviewer analyzed the results of the algorithm regarding the testing set.

Table 1 shows the overall accuracy results. The overall accuracy measures the accuracy of the results of the classification as follows:

Table 1. Overall Accuracy Results

	% of patients (hemograms)
Full agreement	95.70
Partial agreement	4.14
Disagreement	0.16

1. Full agreement: the algorithm identified all the labels that were given by the reviewer to the patient;

2. Partial agreement: the algorithm identified some of the labels that were given by the reviewer to the patient;
3. Disagreement: the algorithm did not identify any of the labels that were given by the reviewer to the patient.

Table 2 shows the class accuracy results. The class accuracy measures the detection rate for each class of anomalies according to the labels that were given by the reviewer and the labels that were given by the algorithm.

DISCUSSION

This is the first application of anomaly detection and characterization to be applied to medical laboratory data, specifically the hemogram. Our results are quite remarkable as shown in the tables. Patients with iron deficiency anemia and normocytic anemia, patients with moderate and severe SIRS, and patients with thrombocytopenia are easily segmented. Those with microcytic indices who had thalassemia are readily identified using the ratio of the MCV to RBC count, but the sample is too sparse for inclusion in the prediction model. Even though the patients with SIRS had defining features, they are not homogeneous, as some have hemolytic anemia (normocytic) and/or thrombocytopenia, and there are a recognizable group of patients who have either a normal or a mild leukocytosis. They are recognized by the high percentage population of neutrophils. The childhood population and newborns would present issues of either lymphocyte population or neutropenia, quite unlike the adult population, not to mention the nucleated red cells that require a corrected leukocyte count. Although there were unsurprisingly more than a single diagnosis in a number of cases, such as, microcytic anemia with mild SIRS, the separation of combinatorial classes is not the purpose of this phase of the study.

The use of computational methods has increased in volume and complexity in the last decade. Much of this work is done with large databases for epidemiological studies. The most similar example, but different in intent and complexity is a data mining study predicting risk of mortality using the basic metabolic panel carried out using almost 280,000 adult patients seen at any Intermountain Healthcare facility between 1999 and 2005 who had at least one basic metabolic panel (BMP), and subsequent follow-up at 30-days, 1-year, and 5-years with a mortality followup record. The researchers used a logistic regression model, and the model was validated [18]. The study uses a scaling of test results to be used in a logistic regression and further modeled using an ROC curve. The resulting score could be applied to predict for each patient. The BMP that includes the measures of glucose, electrolyte balance, and kidney function is performed on virtually all patients, like the CBC. While our study does not consider the binary question either dead or alive, the model of the study referred to is binary, and is parametric. Our study is beyond the bounds of a two class prediction, and it is nonparametric, important for reducing errors from nonlinearities. The artificial neural network is used specifically with the preference for a nonlinear discriminant solution, but also has limitations in the number

Table 2. Class Accuracy Results

	Number of labels given by the reviewer	Number of labels given by the algorithm	% detection of the algorithm
Microcytic Anemia	545	543	99.63
Normocytic Anemia	508	498	98.03
Mild SIRS	79	58	73.42
Thrombocytopenia	629	626	99.52
Leukocytopenia	178	151	84.83
Moderate / Severe SIRS	151	146	96.69
Normal	44	41	93.18

of outputs, which is not an issue with our proposed model and the class of structural equations models.

We are able to find a number of applications of anomaly detection in engineering problems, mainly fault tolerance [19-23]. An application in medical studies is work on blood oxygen saturation and heart rate in obstructive sleep apnea [24-26].

In order to have clear results, we selected the groups of sufficient size that the results would be valid. In the case of leukocytosis - elevation of neutrophils, lymphocytes, or indeterminate - we pooled severe and moderate SIRS, indicative of pneumonia, abdominal infection, or sepsis, into one pool, and kept mild SIRS, elevation to about 13,000, in another pool. The percent of neutrophils and lymphocytes is a criterion that would be needed as a next step, even though it is very useful. The ability for measuring accurately the amount of the subpopulation of immature neutrophilic series was technically limiting in the method used. The small size of the leukemia population and requirement for peripheral smear for final secondary analysis required that we not include that in the calculations. The requirement for a corrected neutrophil count on children because of immature nucleated red cells was sufficient reason for limiting the study to patients 23 and older.

This limited analysis of automated hematological results can be extended to the case of more complicated conditions than presented, and can be extended to a combination of chemistry, hematology, immunology, and other data, and is currently being compared with the findings of a large database of results from the Sysmex series hematology analyzer with measurement of immature granulocytes, and the manual differential. As this method is anticipated to be of practical value as a presentation of an expected assessment to the practicing physician (as in a dashboard of an airplane), and unanticipated benefit to the laboratory is a considerable reduction in necessary manual differentials in a highly productive laboratory, with possible future applications to communication of critical findings to medical staff.

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Received: November 25, 2010

Revised: December 28, 2010

Accepted: January 05, 2011

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