ORIGINAL RESEARCH

Which Observations from the Complete Blood Cell Count Predict Mortality for Hospitalized Patients?

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BACKGROUND: Information on the prognostic utility of the admission complete blood count (CBC) and differential count is lacking.
OBJECTIVE: To identify independent predictors of mortality from the varied number and morphology of cells in the complete blood count defined as a hemogram, automated five cell differential count and manual differential count.
DESIGN: Retrospective cohort study and chart review.
SETTING: Wishard Memorial Hospital, a large urban primary care hospital.
PATIENTS: A total of 46,522 adult inpatients admitted over 10 years to Wishard Memorial Hospital—from January 1993 through December 2002.w
INTERVENTION: None.
MEASUREMENTS: Thirty-day mortality measured from day of admission as determined by electronic medical records and Indiana State death records.
RESULTS: Controlling for age and sex, the multivariable regression model identified 3 strong independent predictors of 30-day mortality—nucleated red blood cells (NRBCs), burr cells, and absolute lymphocytosis—each of which was associated with a 3-fold increase in the risk of death within 30 days. The presence of nucleated RBCs was associated with a 30-day mortality rate of 25.5% across a range of diagnoses, excluding patients with sickle-cell disease and obstetric patients, for whom NRBCs were not associated with increased mortality. Having burr cells was associated with a mortality rate of 27.3% and was found most commonly in patients with renal or liver failure. Absolute lymphocytosis predicted poor outcome in patients with trauma and CNS injury.
CONCLUSIONS: Among patients admitted to Wishard Memorial Hospital, the presence of nucleated RBCs, burr cells, or absolute lymphocytosis at admission was each independently associated with a 3-fold increase in risk of death within 30 days of admission.
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KEYWORDS: diagnostic decision making, laboratory testing, electronic medical record.

The complete blood count (CBC) bundles the automated hemogram, an automated differential count of 5 types of cells, and a reflex manual differential count (when required by protocol) and is one of the most frequently ordered laboratory tests on admission to the hospital. In practice, it is a routine ingredient of all hospital admission orders—physicians order a hemogram either alone or as part of a complete blood count for 98% of our medical/surgical admissions, and the same is true at most institutions.[1] We know that the white blood cell count and hematocrit from the automated hemogram predict disease severity and mortality risk.[2–5] For example, elevated WBC counts predict a worse prognosis in patients with cancer or coronary artery disease,[6,7] and anemia predicts increased risk of death of patients with heart

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failure.[8,9] Further, these two tests provide direct management guidance in common circumstances, for example, bleeding and infection.

The CBC describes the number and morphology of more than 40 cell types, from acanthocytosis to vacuolated white blood cells. Disagreement exists about the clinical significance of many of these observations.[10–13] And only a few components of the manual differential, for example, nucleated red blood cells (NRBCs) and lymphocytosis, have been quantitatively evaluated to determine their prognostic significance.[14–17] But these two observations have not been examined to determine their independent contributions to predictions of mortality when taken in conjunction with their accompanying CBC observations. Which of the numerous cell types and cell counts in the commonly ordered CBC, indicate that a patient is at high risk of death? In this article we report an inpatient study that used univariate and multivariate analyses of admission CBCs to predict 30-day mortality in order to answer that question.

METHODS

Patients and Protocol

The institutional review board of Indiana University, Purdue University, Indianapolis, approved this study. We included in the study all adult patients (those at least 18 years old) admitted to Wishard Hospital between January 1, 1993, and December 31, 2002, except for prisoners (for IRB reasons) and obstetric patients (because their 30-day mortality is very close to zero—0.07% at our institution). Wishard Hospital is a large urban hospital that serves a diverse but predominantly inner-city population in Indianapolis. If a patient was admitted more than once during the 10 years of observation, we included only the first admission in the analysis in order to assure statistical independence of the observations. We extracted data from the Regenstrief Medical Record System (RMRS), a comprehensive medical records system that has demographic data, vital signs, diagnoses, results of clinical tests, and pharmacy information on all inpatient, emergency department, and outpatient encounter sites.[18]

We obtained the admission and discharge ICD9 and DRG codes to assess the disease patterns associated with individual CBC abnormalities. We obtained these codes from routine hospital case abstractions performed by Wishard Hospital's medical records department using NCoder+ and Quadramed. Patients assigned DRG codes 370-384 were identified as obstetric and therefore excluded. Using the ICD9 and CPT codes according to the Charlson algorithm, we calculated a Charlson Comorbidity Index value[19] for each patient as a marker of coexisting conditions.

Outcomes

The primary outcome was 30-day mortality counted from the date of admission. We used information from the hospital record (inpatient deaths) and the Indiana state death tapes to determine the dates of death of all patients. Patients were matched to the Indiana death tapes by an algorithm using name, social security number, date of birth, and sex.[20]

Hemogram and Differential Count Test Methods

The hemogram, differential counts, and blood smear exam results included in this study all came from Wishard Hospital's laboratory. During this study, the hospital used only 2 cell counters, the Coulter STK-S and the Gen-S automated blood analyzer (Beckman Coulter, Brea, California), to produce hemogram and automated blood differential counts. Both instruments provided automated differential counts of 5 cell types: neutrophils, lymphocytes, monocytes, basophils, and eosinophils. The latter machine also produced platelet counts and reticulocyte counts, but during the study period these counts were not routinely reported to physicians unless ordered specifically, so we did not include them in the analyses. The laboratory reflexively performed 100-cell manual differential counts and blood smear exams when abnormalities as defined by College of American Pathologists (CAP) criteria were observed in the automated measures. Both automated blood analyzers used the same automated CAP criteria to decide when to add a manual differential count and blood smear analysis, and these criteria were constant throughout the study. This protocol predicts manual differential abnormalities with high sensitivity, missing less than 1% of important findings in a manual differential.[21] When the CAP criteria did not require a manual differential count and blood smear exam, we assumed that those counts unique to a manual count, for example, blast cell count, were zero and that there were no abnormalities in blood smear morphology.

Laboratories may report white blood cells as absolute counts (eg, number of cells/mm^3) and/or

as percentages. We converted all counts reported as percentages to absolute numbers (eg, WBC count $\times$ 1000 $\times$ cell type percent/100). For absolute counts that have both high and low ranges, such as white blood cell (WBC) count, we constructed two binary variables. WBC-low was 1 when the WBC was below the lower limit of normal; otherwise it was 0. WBC-high was 1 if the WBC was above the upper limit of normal; otherwise it was 0. For continuous variables such as NRBCs or blasts where any presence on the manual differential count is abnormal, we constructed binary variables with 0 indicating absence of the cell type and 1 indicating a cell count was at least 1.

Measurements of many cell types in the manual differential count and smear assessment (eg, burr cells) are reported in qualitative terms such as "occasional," "few," "increased," or "present," if observed, or "none seen," "unremarkable," or "no mention," if not observed. We dichotomized all such results as present or absent for analysis purposes.

Statistical Analysis

For all the original variables, we plotted cell counts against 30-day mortality to graphically show this univariate association. To screen the effects of these 45 binary CBC variables univariately, we used each as the sole independent variable in a logistic regression model with 30-day mortality as the dependent variable.

The simultaneous effects of the 45 CBC measures on mortality were investigated using multiple logistic regression models, always controlling for patient age (in years, as a continuous variable) and sex (as a dichotomous variable). Two approaches were taken to handle the large number of predictors in the model. First, we formed subgroups of predictors based on clinical judgment (eg, the subgroup of "bands," Dohle bodies, and toxic granules associated with infections) and ran logistic regressions of each subgroup to choose the significant predictors of these subgroups to fit them into an overall prediction model of 30-day mortality. The results were verified using a second approach that did not depend on subjective judgment. Both backward and forward stepwise variable selection procedures were used to choose the subset of significant predictors ($P < .005$) of 30-day mortality in logistic regression, again controlling for age and sex. To be sure that the predictive power of the models was not decreased by converting continuous variables into categorical variables, we also ran models that included the continuous variables as potential predictors. We used the *c* statistic as a measure of the goodness-of-fit of the models. We included the Charlson Index and the 10 most common admission diagnoses in our model to control for comorbidities and prime reason for admission, respectively.

We performed the analysis using SAS software, version 8.02 (SAS Institute, Inc., Cary, NC).

Chart Review

For each independent predictor of 30-day mortality that was both statistically significant and had a very high relative risk (>2.5), one author (A.K.) took a random sample of 100-200 patients with positive values for this predictor and reviewed the dictated discharge summaries in order to asses the clinical correlates of these findings.

RESULTS

During the 10 years from January 1993 through December 2002, physicians admitted 46,522 unique eligible patients to Wishard Memorial Hospital. Each patient averaged 2 admissions during the study period, for a total of 94,582 admissions. The overall 30-day mortality of these admissions was 3.4%. Automated hemograms (white blood cell count, hemoglobin, red cell count, and red blood cell indices) were performed on blood samples from 45,709 of these patients (98%) within one day of admission. Seventy-seven percent (35,692) had a complete blood count that included an automated differential count plus a reflex manual count and smear when required by the CAP protocol, as well as an automated hemogram. The patients with an admission CBC with differential count had a 30-day mortality rate of 4%, slightly higher than that of patients who had only a hemogram. The patients' mean Charlson score for the CBC with differential count was 0.83, which was lower than the national average, which is closer to 1.[22] Table 1 shows the demographics of this study population.

Predictors of 30-Day Mortality

We examined the univariate effect of age, sex, and the 45 CBC variables (Table 2) on 30-day mortality. Most of these variables showed a significant ($P < .0001$) effect on mortality. Only a few abnormalities, for example, a low WBC (< 5000/μL), basophilia (>200/μL), and eosinophilia (>450/μL), were

TABLE 1
Characteristics of 35,692 Unique Patients with a CBC and Automated Differential Count

Characteristic	Value
Average age (years)	46.2 ± 17.7
Average LOS (days)	6.5 ± 8.1
Male (%)	55.4
Race	
White (%)	52.9
Black (%)	43.4
Other (%)	3.7
Charlson Index (mean)	0.83 ± 1.5
Most common admission diagnoses (ICD9)	Chest pain
	Pneumonia, organism unspecified
	Other symptoms involving abdomen or pelvis
	Unspecified heart failure
	Intermediate coronary syndrome
	Unspecified hemorrhage of GI tract
	Acute but ill-defined cerebrovascular disease
	Diseases of pancreas
	Cellulitis and abscess of leg except foot
	Convulsions

unrelated to 30-day mortality. Increasing age and male sex were associated with increased mortality. Of the 45 CBC variables, 29 were strong ($P < .0001$) univariate predictors of mortality and had odds ratios (ORs) greater than 2.5. Eight variables had univariate ORs greater than 4: toxic granules, Dohle bodies, smudge cells, promyelocytes, myelocytes, metamyelocytes, NRBCs, and burr cells. All but 2 of these are white blood cell observations.

All the statistical approaches produced essentially the same model for predicting mortality. Table 3 shows that age, sex, and 13 of the CBC variables were retained in the final model of dichotomous variables using backward and forward selection. Lymphocytosis, burr cells, and NRBCs were the greatest independent predictors of mortality, with odds ratios greater than 2.5. Only 1 variable, sickle cells, predicted reduced mortality (with an odds ratio well below 1).

The *c* statistic (the ratio of the area under the ROC curve to the whole area, which reflects the overall predictive power of the final model), was about 0.80 by any approach, which compared favorably with previous prediction models.[3,4] Using continuous measures of CBC in the model did not increase the predictive power. Inclusion of the Charlson Index and the top 10 admission diagnoses did not significantly change the prediction model, although 2 admission diagnoses, chest pain and acute but ill-defined cerebrovascular disease, emerged as independent predictors of 30-day mortality, with odds ratios of 0.314 and 2.033, respectively, at $P < .0001$.

TABLE 2
Univariate Risk of 30-Day Mortality in Patients with an Admission CBC and Automated Differential Count

		Number (%)	Odds ratio	*P* value
	Age (≥ 18 years)	35,688 (100)	1.039	< .0001
	Sex (male)	19,788 (55.4)	1.420	<.0001
Hemogram	WBC > 12,000	11,124 (31.2)	2.049	<.0001
	WBC < 5000	2176 (6.1)	0.938	.5765
	Hematocrit (>54)	212 (0.6)	2.633	<.0001
	Hematocrit (<37)	8687 (24.3)	2.359	<.0001
	MCV (>94)	6552 (18.4)	1.584	<.0001
	MCV (<80)	2815 (7.9)	1.258	.0121
	High RDW (>14.5)	9478 (26.6)	2.647	<.0001
	High MCH (>32)	5308 (14.9)	1.367	<.0001
	Low MCH (<26)	2064 (5.8)	1.392	.0011
	High MCHC (>36)	28 (0.1)	3.964	.0109
	Low MCHC (<32)	738 (2.1)	2.190	<.0001
Automated differential count	Neutrophilia (>7700)	10,578 (37.8)	1.601	<.0001
	Neutropenia (<1500)	469 (1.3)	2.831	<.0001
	Basophilia (>200)	1137 (3.2)	1.362	.0215
	Eosinophilia (>450)	1529 (4.3)	1.074	.5788
	Monocytosis (>800)	10,066 (28.2)	1.262	<.0001
	Lymphocytosis (>4000)	3046 (8.5)	2.495	<.0001
Manual differential count	Blast cells (Y/N)	31 (0.1)	1.638	.5001
	Myelocytes (Y/N)	215 (0.6)	8.231	< .0001
	Promyelocytes (Y/N)	25 (0.1)	13.429	< .0001
	Metamyeloctyes (Y/N)	905 (2.5)	5.798	< .0001
	Atypical lymphocytes (Y/N)	1303 (3.7)	1.881	< .0001
	Hypersegmented neutrophils (Y/N)	141 (0.4)	3.061	< .0001
	Microcytes (Y/N)	3452 (9.7)	2.578	< .0001
	Macrocytes (Y/N)	3475 (9.7)	3.282	< .0001
	Hypochromic RBCs (Y/N)	2252 (6.3)	2.290	< .0001
	Basophilic stippling (Y/N)	273 (0.8)	3.553	< .0001
	Target cells (Y/N)	1140 (3.2)	2.866	< .0001
	Polychromasia (Y/N)	1675 (4.7)	3.622	< .0001
	Toxic granules (Y/N)	1063 (3.0)	4.021	< .0001
	Dohle bodies (Y/N)	524 (1.5)	4.821	< .0001
	Ovalocytes (Y/N)	1555 (4.4)	2.558	< .0001
	Spherocytes (Y/N)	465 (1.3)	3.132	< .0001
	Schistocytes (Y/N)	1484 (4.2)	3.150	< .0001
	Sickle Cells (Y/N)	62 (0.2)	0.389	.3490
	Howell-Jolly bodies (Y/N)	71 (0.2)	3.025	.0033
	Pappenheimer bodies (Y/N)	67 (0.2)	2.344	.0468
	Burr cells (Y/N)	253 (0.7)	9.297	<.0001
	Teardrop cells (Y/N)	538 (1.5)	2.150	< .0001
	Vacuolated cells (Y/N)	897 (2.5)	3.667	< .0001
	Giant platelets (Y/N)	781 (2.2)	3.102	< .0001
	Smudge cells (Y/N)	50 (0.1)	5.237	< .0001
	Cleaved cells (Y/N)	8 (0.0)	3.393	.2533
	Band forms (Y/N)	7594 (21.3)	2.964	< .0001
	NRBCs (Y/N)	467 (1.3)	8.756	< .0001

TABLE 3
Multivariate Model of Statistically Significant ($P < .005$) Predictors of 30-Day Mortality from the CBC and Automated Differential Count Pared Stepwise Backward Selection

Parameter	Odds ratio	Confidence interval	*P* value
Age (years)	1.040	1.037-1.043	< .0001
Sex (male)	1.965	1.746-2.213	< .0001
WBC > 12,000	1.701	1.508-1.919	< .0001
Hematocrit (>54)	2.331	1.438-3.780	< .0006
Hematocrit (<37)	1.714	1.514-1.941	< .0001
MCV (>94)	1.352	1.186-1.543	< .0001
High RDW (>14.5)	1.463	1.291-1.658	< .0001
Lymphocytosis (>4000)	2.848	2.435-3.332	< .0001
Metamyeloctye (Y/N)	2.074	1.666-2.581	< .0001
Macrocytes (Y/N)	1.317	1.127-1.539	< .0005
Toxic granules (Y/N)	1.494	1.200-1.859	.0003
Sickle cells (Y/N)	0.039	0.005-0.292	.0016
Burr cells (Y/N)	3.254	2.347-4.513	< .0001
Band forms (Y/N)	1.586	1.386-1.814	< .0001
NRBCs (Y/N)	2.906	2.240-3.770	< .0001

Chart Review

Of the 200 cases with NRBCs, the leading probable causes for this finding were severe hypoxia (average A-a gradient = 326 mm Hg), acute anemia (average hgb = 6.1 gm/dL), and sickle-cell anemia. Other diseases associated with NRBCs were infection/sepsis, HIV, solid tumors (breast/lung/colon/prostate), and leukemia or multiple myeloma. Having even a single NRBC at admission correlated with a 25.5% mortality rate. Of note, 30%-40% of patients with sickle-cell disease had NRBCs and moderate anemia (hgb = 8.7 gm/dL) on admission to the hospital, but there was no excess risk of mortality. Indeed, the 49 patients with sickle-cell disease who had NRBCs at admission had a 30-day mortality of 0%.

Most of the patients with NRBCs reviewed exhibited overt signs of severe disease, for example, shock, respiratory failure, or severe trauma, in addition to having NRBCs. However, in 2 patients the NRBCs were the only strong signal of disease severity. Both had NRBCs on the day of discharge and were readmitted within 3 days *in extremis* and died. One was readmitted in fulminant septic shock, likely from a bacterial peritonitis or urinary tract infection, and the other was readmitted in shock, likely from decompensated heart failure.

In univariate analysis, burr cells at admission correlated with a mortality rate of 27.3%. A review of 100 randomly chosen patients with burr cells revealed a pattern of associated diseases, that is, acute renal failure, liver failure, and congestive heart failure, different from that of patients with NRBCs. There was little overlap in the presence of burr cells and NRBCs, but the 12% who had burr cells *and* NRBCs had a high mortality rate (57%).

Absolute lymphocytosis was associated with a mortality rate of 8.6%. Although univariate analysis showed that the risk with lymphocytosis was not as high as that for patients with NRBCs or burr cells at admission, lymphocytosis was much more common (8.5%), and within the logistic model its presence explained more of the chi-square statistic than any other variable except age. Indeed, lymphocytosis was a stronger predictor of 30-day mortality than was high WBCs or anemia. Chart review of 200 patients with lymphocytosis showed a preponderance of them had large physiologic stressors, for example, traumatic tissue injury (surgery) or cerebrovascular injury. In one subset, half the patients (50.9% of 53 patients) who underwent craniotomy for trauma and had absolute lymphocytosis at admission died, compared with 20.8% of 101 patients admitted for the same diagnosis without absolute lymphocytosis.

DISCUSSION

Some investigators have incorporated selected CBC measures, for example, white blood cell count and hemoglobin/hematocrit, into multivariable models that predict mortality or rehospitalizations.[6,7,9,23] However, CBC reports can include a spectrum of more than 40 distinct counts and morphologic findings. Our study was the first to take into account all the different variables in the complete blood count and differential to determine elements that independently predict a high risk of mortality.

In addition to age and sex, our multivariable analysis of the 45 CBC variables found 13 independent predictors of mortality. Five were observations about white blood cells: absolute leukocytosis, high band form cell count, the presence of metamyelocytes, the presence of toxic granules, and absolute lymphocytosis. Eight were observations about red blood cells: high hematocrit, low hematocrit, high MCV and the presence of macrocytes, high red cell distribution width, the presence of NRBCs, the presence of burr cells, and the presence of sickle cells. Because controlling for severity of illness by Charlson comorbidity scores did not significantly change the model, the CBC abnormalities among the predictors of mortality did not simply reflect how sick the patients were. Including the 10 most

common admission diagnoses did not significantly attenuate our reported odds ratios, suggesting the CBC predictors did not merely reflect the primary reason for admission. Interestingly, however, admission for chest pain did correlate with a greatly reduced risk of 30-day mortality, which may reflect the low threshold that physicians have for admitting patients with this complaint. Admission for acute but ill-defined cerebrovascular disease independently predicted a 2-fold increased risk of 30-day mortality.

What is the message to physicians from this analysis? Physicians commonly order CBCs and may rely on quick heuristics to sift through the myriad findings in CBC reports. Our analysis focuses physician attention on high-impact findings in the CBC. We assume that physicians already consider low hematocrit, high hematocrit (a sign of fluid loss and/or chronic hypoxia), high WBC count, high band cell count, and the presence of metamyeloctes (left shift) as important prognostic indicators. These abnormal findings are routinely mentioned at morning report and in a physician's notes.

Physicians, however, may not appreciate the importance of other CBC findings that our analysis found are predictive of mortality. Macrocytosis and a high RDW count (indicating an abnormally wide distribution of red blood cell size) have not previously been reported as predictors of mortality. And although other studies have suggested that bands are not predictors of mortality,[11] our study found they *were* an important prognostic indicator, with an OR =1.59, approaching those of leukocytosis and anemia.

The most impressive predictors of mortality were burr cells, NRBCs, and absolute lymphocytosis. The multivariate ORs of these 3, ranging from 2.8 to 3.2, were the highest of any CBC finding. In univariate analysis, the first 2 were associated with mortality rates 8 to 10 times higher than that of the average admitted patient. There are anecdotal reports in the literature of burr cells being associated with ominous prognoses[24-26] and more robust statistical analyses showing NRBCs to be associated with increased mortality.[14] Lymphocytosis has also been reported as a mortality risk in patients with trauma and emergency medical conditions.[15,16] Our analysis has shown that, indeed, all 3 of these findings are strong *independent* predictors of mortality.

The presence of sickle cells was also a strong predictor, but of decreased mortality. Patients with sickle cells in their smear had a risk of death one third that of patients without sickle cells. This does not indicate a protective effect. Rather, patients with sickle-cell disease typically are young and admitted for pain control and other non-life-threatening conditions. The presence of NRBCs in patients with sickle-cell disease appears to be intrinsic to the disease itself and did not have the same implications for mortality as it did for other patients in our study.

The overall logistic model including age, sex, and admission CBC variables had a respectable *c* statistic for predicting 30-day mortality of 0.80. This compares well with findings in other multivariable models. For example, the APACHE II score used to predict the mortality of hospitalized critical care patients has a *c* statistic that ranges from 0.78 to 0.86.[3,27,28] The APACHE score uses the worst value from the first 2 days after admission for some of its predictors so it cannot provide as early a warning as the admission CBC, and it requires collection of significantly more data. The inclusion of more CBC findings in the APACHE model might increase its predictive accuracy.

Our multivariate analysis was based on a very large number of patient samples using data collected through routine clinical care. However, our study has a number of limitations. The analysis was done at only a single institution, and the exact logistic regression model may not apply to other institutions that have different case mixes and laboratory procedures. Our institution's reported 30-day mortality rate of 3.4% was lower than the 4.6%-11.9% reported in studies of patients admitted to general ward services,[29–31] but this may be accounted for by the lower-than-average Charlson comorbidity scores in our study population. Our risk adjustment by Charlson comorbidity scores may not be as precise as a risk adjustment tailored for our particular institution.[32] Our 30-day mortality rate was calculated using state death tapes, which means we would have missed patients who died outside the state, although we believe this rarely happens. We developed predictive equations on the basis of 30-day mortality, so we cannot comment on whether the CBC elements predict mortality beyond 30 days. We analyzed most variables as either high or low or as present or absent. Increasing degrees of abnormality may further increase the predictive power of some variables. Finally, the CBC is only one of many tests and clinical findings;

it may be that some of these other variables would displace some CBC variables and/or improve the overall predictive power at the time the admission laboratory tests were performed. In this initial study, we have described the prognostic implication of the CBC across a wide range of diagnoses. Future work will focus on the predictive power of commonly gathered variables in more specific conditions (eg, low white blood cell count in sepsis).

Physicians generally have an intuitive ability to identify patients who are seriously ill and at high risk of dying[33] and adjust their diagnostic and therapeutic efforts accordingly. Our analysis highlights the value that certain observations in the CBC, notably burr cells, NRBCs, and absolute lymphocytosis, add to physicians' assessments of mortality risk. Even after adjustment for age, sex, comorbidities, common admission diagnoses, and other variables in the CBC, the presence of these findings predicted a 3-fold increase in 30-day mortality. Identifying the "red flags" within this ubiquitously performed test can make the difference in premature discharge or inappropriate triage of patients. Busy physicians can choose from a wide selection of ever-improving diagnostic tests, yet the workhorse CBC can serve as a simple and early identifier of patients with a poor prognosis.

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