Original Article

Exploring the value of routinely measured hematology parameters for identification of elderly patients at high risk of death at the Emergency Department

RS Bindraban, MJ ten Berg, S Haitjema, IE Hoefer, M de Regt, MHH Kramer, WW van Solinge, PWB Nanayakkara & CA Naaktgeboren

Renuka S Bindraban[1,2] MD

Maarten J ten Berg[1] PharmD, PhD

Saskia Haitjema[1] MD, PhD

Imo E Hoefer[1] MD, PhD

Marieke de Regt[3] MD, PhD

Mark H H Kramer[2] MD, PhD, FRCP

Wouter W van Solinge[1] PhD

Prabath W B Nanayakkara[2]* MD, PhD, FCRP

Christiana A Naaktgeboren[1,4] PhD

[1] Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Section Acute Medicine, Department of Internal Medicine, Amsterdam University Medical Centers, VU University Medical Center, Amsterdam, The Netherlands
[3] Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
[4] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence
Prabath W.B. Nanayakkara MD, PhD, FRCP
Head, Section Acute Medicine, Department of Internal Medicine
Amsterdam University Medical Centers, VU University Medical Center
De Boelelaan 1118, 1081 HZ, Amsterdam, The Netherlands
Email: p.nanayakkara@vumc.nl

Abstract

Of the warning scores in use for recognition of high-risk patients at the Emergency Department (ED), few incorporate laboratory results. Although hematological characteristics have shown prognostic value in small studies, large studies in elderly ED populations are lacking. We studied the association between blood cell and platelet counts and characteristics as well as C-reactive protein (CRP) at ED presentation with mortality in non-multitrauma patients ≥ 65 years. Comparison between survivors and non-survivors showed small, significant differences with AUROCs ranging between 56.6% and 65.2% for 30-day mortality. Combining parameters yielded an evident improvement (AUROC of 70.4%). Efforts should be pursued to study the added value of hematological parameters on top of clinical data when assessing patient risk.

Keywords

red blood cell, leukocyte count, blood platelet, mortality, emergency care

Key points

- Individual blood cell and platelet counts, their (morphological) characteristics and CRP measured in elderly patients at Emergency Department presentation display moderate predictive ability for short-term mortality
- Combining hematological parameters yields an evident improvement in predictive ability for short-term mortality
- Efforts should be pursued to study the additive value of these promising combinations of hematological parameters on top of clinical data

Introduction

Early recognition and prioritization of acutely ill patients at the Emergency Department (ED) can be challenging, especially in elderly, in whom illness often presents in an atypical fashion.[1, 2] At least 36 warning scores have been developed to support quick recognition of patients that are most likely to deteriorate, with variable rates of implementation in hospitals worldwide.[3] These scores include variables such as heart rate, respiratory rate and temperature. Of the many scoring systems in use in emergency medicine, laboratory results are incorporated in only a few,[3] even though they are routinely obtained and almost immediately available.[4]

The predictive value of inflammatory biomarkers at the ED for poor outcomes has been studied extensively. Studies report on the positive association between C-reactive protein (CRP) taken at or early after hospital presentation and (short-term) mortality.[5-9] In addition, previous work has demonstrated associations between leukocyte counts early after hospital presentation, and mortality.[4, 10-12] Other parameters associated with mortality include high neutrophil and low lymphocyte counts,[13-14] a high corresponding neutrophil-lymphocyte ratio[15-17] and a high platelet-lymphocyte ratio.[18] Although these parameters are directly associated with short-term mortality, their predictive value is limited. Therefore the search for better markers for mortality prediction continues.

In addition to blood cell and platelet counts and their ratios, it is possible that morphologic characteristics measured by modern hematology analyzers are also predictive of mortality. These devices provide information such as cell size, intrinsic properties and cell viability.[19, 20] Until now, morphologic parameters have mainly been studied for diagnostic purposes, such as for diagnosing bacterial infections,[21] defining asthma phenotypes[22] and discriminating between lymphocyte pathologies.[23] Yet several smaller studies suggest that some of these parameters, such as neutrophil volume,[24, 25]

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coefficient of variation (CV) for lymphocyte cell size,[19] platelet volume and distribution width[26] and red cell distribution width (RDW),[27] might also be of prognostic value in selected patient populations.

Large-scale studies on the association between early blood cell and platelet counts and characteristics with mortality in elderly populations are lacking. The aim of this study was to explore the associations of these parameters with 7- and 30-day mortality in an elderly population presenting to the ED, aiming to see if they are more useful in predicting mortality than the well-known markers, CRP and leukocyte count. Additionally, the predictive performance of the combination of these parameters will be assessed, to assess whether prediction models that include these parameters show promise. We specifically chose to study a largely unselected population to explore whether we could identify parameters useful in patients for whom only little clinical information is known so that they might potentially serve as a triage tool for prioritization of elderly ED patients.

Methods

Study design

In this retrospective observational study using routinely collected healthcare data, we assessed the association of (morphological) red blood cell (RBC), leukocyte and platelet characteristics and CRP at ED presentation with mortality, aiming to identify parameters more useful in predicting mortality than CRP or leukocyte count.

Setting and study population

For this study, data from the Utrecht Patient Oriented Database (UPOD) were used. UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the University Medical Center Utrecht (UMC Utrecht) since 2004. UPOD data acquisition and management is in accordance with current regulations concerning privacy and ethics. The structure and content of UPOD have been described in more detail elsewhere.[28]

The UMC Utrecht is a 1,042-bed academic teaching hospital in the center of the Netherlands, with around 28,000 clinical and 15,000 day-care hospitalizations and 334,000 outpatient visits annually. The hospital has a large ED, providing emergency care to approximately 21,300 patients annually for all medical specialties.

We retrospectively evaluated patients aged 65 years or older presenting to the ED of the UMC Utrecht from June 1st, 2011 to December 31st, 2017 for whom mortality outcomes and hematology parameters were available. Patients for whom a multi-trauma was registered at the ED were excluded from analyses. For patients who had more than one ED visit during the study period, all visits were included.

Data

The following clinical data were obtained per ED visit: sex, age, treating specialty, the first result for CRP and hematological tests at hospital presentation and data on 7-day and 30-day mortality.

Hematological parameters

The hematological parameters used in this study were obtained through complete blood count analysis, using the Cell-Dyn Sapphire hematology analyzer (Abbott Diagnostics, Santa Clara, USA). The analyzer provides information on RBC count, leukocyte count and blood platelet count and their characteristics, using spectrophotometry, electrical impedance, laser light scattering and three-color fluorescent technologies.

RBC parameters are measured through impedance measurement and optically using intermediate angle scatter (IAS, 7° scatter) for cell complexity/granularity and FL-3 fluorescence for cell viability. Leukocyte characteristics are measured using the following five optical scatter signals: axial light loss (ALL, 0° scatter) for cell size, intermediate angle scatter (IAS, 7° scatter) for cell complexity/granularity, polarized side scatter (PSS, 90° scatter) for nuclear lobularity, depolarized side scatter (DSS, 90° scatter) for depolarization and red fluorescence (FL-3) for viability. Platelet parameters are measured through IAS scatter (7° scatter) for platelet complexity/granularity and PSS (90° scatter) for platelet lobularity.

Outcomes

Our primary outcome was mortality within 30 days of ED visit, our secondary outcome was mortality within 7 days of ED visit. Information on mortality was extracted from the hospital database and was not available for all patients. A patient was confirmed 'deceased' if death occurred within 7 or 30 days (1) at the ED or during hospitalization or (2) if the date of death was communicated and registered in the hospital system. Patients were confirmed alive after 7 or 30 days if there was contact with the patient any time after 30 days until data extraction was performed in April 2018. For the remainder of patients, mortality status was unknown.

Statistical analysis

For comparison of laboratory values between groups (mortality vs. no mortality), Student's T-test or Mann-Whitney-U test was used as appropriate. We corrected for multiple testing using a Bonferroni

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correction and considered p-value < 0.0008 (p-value 0.05/62 laboratory tests) significant. The predictive power of parameters was expressed as area under the receiver operating curve (AUROC). We adjusted for age and nonlinearity of the data. The shape of the relation with outcome was studied for each parameter using the Hosmer-Lemeshow test, in which we assumed linearity for p-values > 0.05. Parameters displaying a nonlinear relation with mortality were transformed by adding splines until the optimal AIC value was reached at which the AUROC was calculated. We also studied the risk of mortality within deciles of laboratory values.

We then explored the predictive power of combinations of hematological parameters for 30-day mortality. Note that CRP was not included as the goal was only to study hematological parameters. The hematological parameters, together with age and gender, were entered into a random forest classification model. No variable selection was performed. We built 100 decision trees and considered 5 variables at each split in the individual trees to acquire the smallest out-of-bag error. Predictive power was expressed as AUROC.

All analyses were performed using R version 3.4.3. The random forest model was built using the 'randomForest' package.

Missing data

If mortality outcomes or any of the hematological parameters were missing for a visit, this visit was excluded from all analyses. If CRP was missing for a visit, this visit was still included for analyses regarding hematological parameters, yet excluded for analyses regarding CRP.

Results

Between June 1st, 2011 and December 31st, 2017, there were 34,672 visits to the ED by 17,462 unique patients older than 65 years for non-multitrauma causes. Of these, 17,319 visits were excluded due to either missing mortality data or hematological parameters. We included 17,353 visits for analysis of hematological parameters, of which 16,705 were included for analyses regarding CRP. Characteristics of the study population are presented in **Table I**.

Characteristics of excluded visits are presented in **Appendix I**. Of visits that were excluded due to missing mortality data, the vast majority resulted in ED discharge (90.0%). For visits with missing hematology parameters, slightly more than half (50.8%) were followed by ED discharge.

Comparison of laboratory values between groups

Table II presents the results of the studied laboratory parameters (n=62), stratified by the occurrence of death within 30 days. From the acquired hematology parameters, the following ratios were also calculated: neutrophils-to-lymphocytes, platelets-to-lymphocytes and monocytes-to-lymphocytes. After correction for multiple testing, 50 parameters showed statistically significant differences between the two groups, yet, the differences in absolute values were small for the majority of tests.

Table I. Characteristics of study population.

	Mortality data and hematology available	Mortality data, CRP and hematology available
Number of ED visits, n	17,353	16,705
Male sex, n (%)	9,804 (56.5)	9,420 (56.4)
Age in years, median (IQR)	74 (69-80)	74 (69-80)
Top 5 ED specialties, n (%)		
Cardiology	3,590 (20.7)	3,531 (21.1)
Neurology	2,646 (15.2)	2,600 (15.6)
Internal medicine	2,562 (14.8)	2,488 (14.9)
Pulmonary medicine	1,581 (9.1)	1,565 (9.4)
Surgery	1,245 (7.2)	1,145 (6.9)
Destination after ED presentation, n (%)		
Continued care within UMCU	14,165 (81.6)	13,714 (82.1)
Transfer to other institution	219 (1.3)	215 (1.3)
Died at ED	64 (0.4)	58 (0.3)
Discharge	2,726 (15.7)	2,561 (15.3)
Other	179 (1.0)	157 (0.9)
Outcome, n (%)		
30-day mortality	1,842 (10.6)	1,784 (10.7)
7-day mortality	870 (5.0)	845 (5.1)

Abbreviations: ED, emergency department; IQR, interquartile range; UMCU, University Medical Center Utrecht.

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Table II. All laboratory values, stratified by occurrence of death within 30 days.

Laboratory value, unit	Alive after 30 days, n (visits)=22 143	Deceased within 30 days, n (visits)=2634	P value	AUROC (95% CI)
CRP, mg/L	15.00 (3.50-64.00)	40.00 (8.00-121.00)	< 0.0008	63.8 (62.4-65.2)
Leukocyte count, 10^9/L	9.37 (7.07-12.49)	11.31 (8.21-15.97)	< 0.0008	65.1 (63.8-66.4)
Subsets and morphology				
Neutrophils				
Count, 10^9/L	6.75 (4.60-9.84)	8.84 (5.83-13.02)	< 0.0008	65.2 (63.9-66.5)
% of total leukocyte count	74.12 (63.95-82.79)	80.26 (70.41-87.14)	< 0.0008	64.4 (63.1-65.7)
Mean cell size, AU	150.10 (144.80-156.0)	151.90 (145.80-159.90)	< 0.0008	60.8 (59.4-62.2)
Mean complexity/granularity, AU	136.33 (131.99-140.71)	135.70 (131.40-140.30)	0.0009	58.0 (56.6-59.4)
Mean lobularity, AU	123.40 (115.19-131.39)	120.31 (110.50-128.87)	< 0.0008	60.1 (58.7-61.5)
Mean depolarization, AU	27.59±4.18	27.04±4.81	< 0.0008	58.6 (57.2-60.0)
Mean viability/red fluorescence, AU	70.99 (69.34-72.67)	71.63 (69.80-73.34)	< 0.0008	59.6 (58.3-61.0)
CV of cell size, %	2.78 (2.45-3.17)	2.83 (2.50-3.23)	< 0.0008	57.2 (55.8-58.6)
CV of complexity/granularity, %	3.66±0.65	3.77±0.78	< 0.0008	59.6 (58.2-61.0)
CV of lobularity, %	8.82 (7.18-9.96)	9.28 (7.88-10.40)	< 0.0008	60.0 (58.6-61.4)
CV of depolarization, %	15.49±2.43	15.78±3.06	< 0.0008	58.7 (57.3-60.1)
CV of viability/red fluorescence, %	8.03 (7.12-8.76)	8.05 (7.17-8.74)	0.38	57.0 (55.6-58.4)
Segments				
Count, 10^9/L	6.67 (4.57-9.59)	8.53 (5.62-12.17)	< 0.0008	64.9 (63.6-66.2)
% of total leukocyte count	72.56 (62.99-80.37)	76.63 (65.30-83.14)	< 0.0008	61.8 (60.5-63.2)
Lymphocytes				
Count, 10^9/L	1.36 (0.88-1.97)	1.15 (0.72-1.84)	< 0.0008	60.4 (59.0-61.8)
% of total leukocyte count	15.24 (8.95-23.56)	10.82 (6.15-18.33)	< 0.0008	64.1 (62.8-65.4)
Mean cell size, AU	100.75±5.60	99.25±6.83	< 0.0008	60.7 (59.3-62.1)
Mean complexity/granularity, AU	76.91±3.45	76.78±3.98	0.17	58.3 (56.9-59.7)
CV of cell size, %	4.26 (3.11-5.24)	3.97 (2.67-5.03)	< 0.0008	58.3 (56.9-59.7)
CV of complexity/granularity, %	4.37±1.17	4.16±1.28	< 0.0008	59.3 (57.9-60.7)
Monocytes				
Count, 10^9/L	0.70 (0.51-0.95)	0.75 (0.49-1.07)	< 0.0008	60.6 (59.3-62.0)
% of total leukocyte count	7.68 (5.74-9.77)	6.65 (4.59-8.95)	< 0.0008	62.0 (60.6-63.3)
Eosinophils				
Count, 10^9/L	0.09 (0.04-0.18)	0.13 (0.02-0.14)	< 0.0008	60.5 (59.1-61.9)
% of total leukocyte count	0.98 (0.38-2.14)	0.55 (0.21-1.39)	< 0.0008	62.9 (61.5-64.2)
Basophils				
Count, 10^9/L	0.03 (0.01-0.05)	0.02 (0.01-0.05)	< 0.0008	58.9 (57.5-60.3)
% of total leukocyte count	0.32 (0.14-0.58)	0.21 (0.08-0.42)	< 0.0008	61.7 (60.4-63.0)
Red blood cells				
Count, 10^9/L	4.17±0.73	3.99±0.80	< 0.0008	60.4 (59.0-61.7)
MCV, fL	90.64±6.77	91.47±7.75	< 0.0008	58.4 (57.0-59.8)
% red blood cells with MCV>120 fL	1.96 (1.11-3.67)	2.60 (1.45-5.34)	< 0.0008	61.3 (59.9-62.7)
% red blood cells with MCV<60 fL	0.94 (0.61-1.73)	1.16 (0.72-2.19)	< 0.0008	60.2 (58.8-61.5)
RDW, %	12.93 (12.09-14.38)	13.70 (12.52-15.57)	< 0.0008	63.4 (62.1-64.7)
Hb, mmol/L	7.91±1.43	7.55±1.48	< 0.0008	60.7 (59.3-62.0)

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MCH, fmol	1.91 (1.82-2.00)	1.90 (1.80-2.00)	0.44	56.6 (55.2-58.0)
MCHC, mmol/L	0.21 (0.21-0.22)	0.21 (0.20-0.21)	< 0.0008	60.6 (59.3-62.0)
% red blood cells with Hb<28 g/dL	3.64 (1.47-8.97)	5.80 (2.32-13.71)	< 0.0008	61.8 (60.5-63.2)
% red blood cells with Hb>41 g/dL	0.01 (0.00-0.10)	0.00 (0.00-0.07)	< 0.0008	58.2 (56.8-59.6)
CV of Hb concentration, %	7.42 (6.74-8.22)	7.52 (6.84-8.33)	< 0.0008	57.2 (55.8-58.6)
Ht, L/L	38.28 (33.77-42.10)	36.68 (31.75-41.29)	< 0.0008	60.2 (58.8-61.6)
Mean complexity/granularity, AU	181.80 (180.10-183.40)	182.20 (180.60-183.80)	< 0.0008	58.4 (57.0-59.8)
Mean viability/red fluorescence, AU	82.90±9.21	82.92±9.85	0.93	56.6 (55.2-58.0)
CV of complexity/granularity, %	1.64 (1.52-1.80)	1.65 (1.52-1.80)	0.79	56.8 (55.4-58.2)
CV of viability/red fluorescence, %	12.17 (10.86-13.73)	12.33 (11.02-14.05)	< 0.0008	57.3 (55.9-58.7)
Reticulocytes				
Count, 10^9/L	66.78 (50.48-87.42)	69.90 (50.44-94.50)	< 0.0008	58.9 (57.5-60.3)
% of RBC	1.57 (1.19-2.12)	1.69 (1.27-2.42)	< 0.0008	59.7 (58.3-61.0)
Immature reticulocyte fraction	0.30 (0.28-0.37)	0.33 (0.26-0.41)	< 0.0008	61.8 (60.4-63.2)
MCV, fL	98.29±13.10	99.24±14.56	0.008	59.5 (58.1-60.9)
MCH, fmol	29.61 (27.32-31.32)	29.31 (26.68-31.37)	0.009	58.3 (56.9-59.7)
MCHC, mmol/L	29.14 (28.02-30.18)	28.54 (27.42-29.66)	< 0.0008	61.4 (60.1-62.8)
Platelets				
Count, 10^9/L	239.00 (184.80-309.90)	238.20 (169.60-325.30)	0.07	60.8 (59.4-62.2)
MPV, fL	7.57 (6.89-8.37)	7.74 (7.01-8.64)	< 0.0008	58.6 (57.2-60.0)
PDW, 10 (GSD)	16.16 (15.74-16.62)	16.15 (15.74-16.64)	0.47	57.5 (56.1-59.0)
PCT, mL/L	0.18 (0.15-0.23)	0.18 (0.14-0.24)	0.69	61.1 (59.7-62.5)
Reticulated platelets, %	2.66 (1.89-3.84)	3.47 (2.35-5.13)	< 0.0008	64.9 (63.5-66.2)
Mean complexity/granularity, AU	144.40±6.76	144.20±7.88	0.33	56.7 (55.3-58.1)
Mean lobularity, AU	124.20 (121.30-127.30)	123.20 (120.10-126.60)	< 0.0008	59.2 (57.8-60.6)
CV of complexity/granularity, %	17.27 (16.64-17.93)	17.54 (16.80-18.36)	< 0.0008	61.0 (59.7-62.4)
CV of lobularity, %	13.36 (12.76-14.15)	13.70 (12.93-14.65)	< 0.0008	60.8 (59.4-62.1)
Ratios				
Neutrophil-to-lymphocyte ratio	5.00 (3.00-9.00)	7.32 (3.84-14.01)	< 0.0008	63.2 (61.9-64.5)
Platelet-to-lymphocyte ratio	178.00 (115.00-284.00)	206.00 (113.00-338.00)	< 0.0008	56.7 (55.3-58.1)
Monocyte-to-lymphocyte ratio	0.50 (0.33-0.80)	0.61 (0.36-1.03)	< 0.0008	61.8 (60.4-63.2)

Values are expressed in "median (interquartile range)" for non-normally distributed data and in "mean±SD" for normally distributed data. After Bonferroni correction, p-values < 0.0008 were considered significant. AUROCs after adjustment for age and nonlinearity are presented. **Abbreviations:** AUROC, area under the receiver operating curve; CRP, C-reactive protein; AU, arbitrary unit; CV, coefficient of variation; MCV, mean corpuscular volume; RDW, red blood cell distribution width; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Ht, hematocrit; MPV, mean platelet volume; PDW, platelet distribution width; GSD, geometric standard deviation; PCT, plateletcrit.

For 7-day mortality, 36 parameters differed significantly between the two groups (**Appendix II**). Here too, absolute differences were small for the majority of tests. Absolute values for most tests did not differ much from those in survivors and non-survivors after 30 days.

Predictive ability of individual laboratory parameters for 30-day mortality

To study the predictive ability of laboratory parameters for 30-day mortality, we assessed the AUROC for individual parameters. AUROCs ranged between 50.2% and 62.5% (data not shown). When adjusted for age and nonlinearity, AUROCs ranged between 56.6% and 65.2% (**Table II**).

We found an AUROC of 65.1% for leukocyte count and 63.8% for CRP. Neutrophil count (65.2%) performed similarly to leukocyte count and marginally better than CRP. Segment count and percentages of reticulated platelets (both 64.9%), neutrophils (64.4%) and lymphocytes (64.1%) performed better than CRP.

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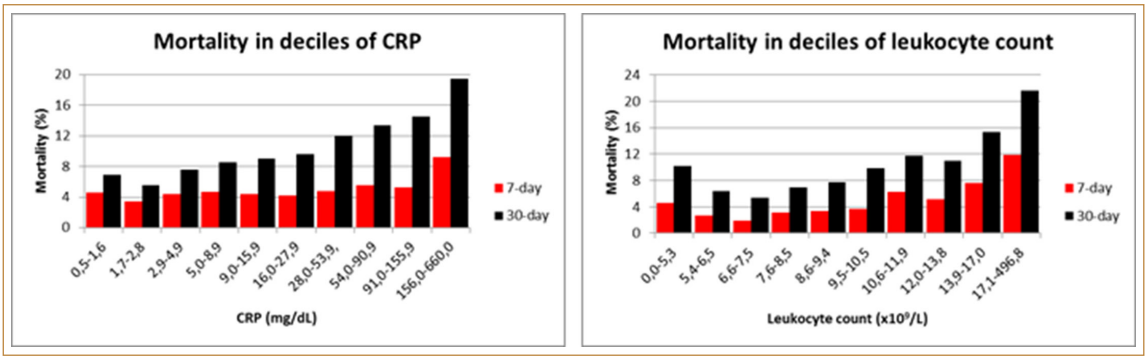

Figure I. Mortality rates within deciles of CRP and leukocyte count

Risk of mortality

To study the association between absolute values and mortality, we studied the risk of mortality within deciles of values. In our study population, 30-day mortality rate was approximately 11% and 7-day mortality rate was approximately 5%. Mortality rates within deciles of CRP and leukocytes are displayed in **Figure I**. For other parameters, mortality rates within deciles are plotted in **Appendices III** (for 30-day mortality) and **IV** (for 7-day mortality).

CRP

Mortality rates increase in a linear fashion with increasing CRP values. 30-day mortality rates were higher than the overall rate for patients within 6th (12.0%) to 10th (19.5%) decile. For 7-days, mortality rate was higher than the overall rate for patients within the 10th decile (9.2%).

Leukocytes

Leukocyte counts display a U-shaped relation with mortality. Both 30- and 7-day mortality rates were higher than the overall rates for patients within the 9th (15.3% and 7.6%) and 10th decile (21.6% and 11.9%). For patients in the first decile, both 30- and 7-day mortality rates were almost equal to the overall rates.

Predictive ability of combinations of hematological parameters for 30-day mortality

Joint modeling of all hematology parameters through a random forest model yielded an evident improvement in predictive ability compared with the individual parameters, with an AUROC of 70.4%. Importance of parameters in the random forest model is plotted in **Figure II**. Importance is expressed as "mean decrease in accuracy", which represents how much the model accuracy would decrease if we were to drop that variable.

According to variable importance, leukocyte count is the most predictive for mortality. Counts and percentages of neutrophils, monocytes, lymphocytes and segments were also important parameters, as were platelet counts and the platelet-to-lymphocyte ratio. In addition, reticulocyte and RBC MCV appeared important, as did RDW and parameters related to hemoglobin concentration.

Discussion

In this paper, we explored the associations of blood cell and platelet counts and characteristics and CRP, at presentation, with short-term mortality in an elderly ED population from a Dutch academic hospital. We found that the differences in absolute values for the studied parameters were statistically significant, yet small and AUROCs ranged between 56.6% and 65.2% for 30-day mortality. When combining parameters, an evident improvement in predictive ability was found over individual parameters, with

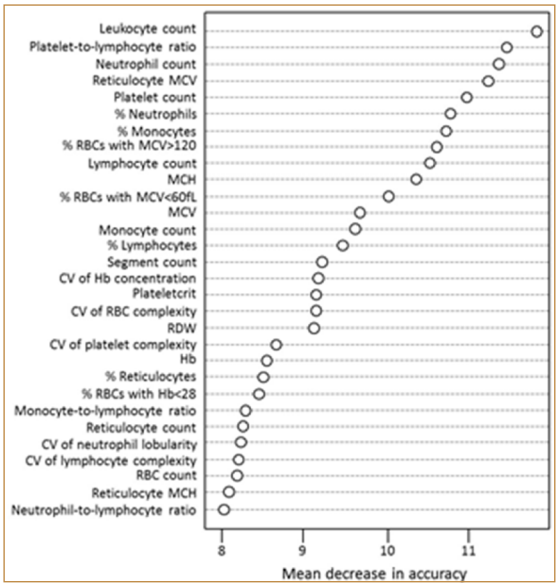

Figure II. Variable importance in random forest classification model. **Abbreviations:** MCV, mean corpuscular volume; RBC, red blood cell; MCH, mean corpuscular hemoglobin; CV, coefficient of variation; Hb, hemoglobin; RDW, red blood cell distribution width.

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an AUROC of 70.4%. Leukocyte count, counts and percentages of most subsets, platelet count, platelet-to-lymphocyte ratio, and measures of reticulocyte and RBC cell size were among the most important variables.

Leukocyte and differential

Upon exploration of our random forest model, leukocyte count seemed to be the most important predictor. Previous studies established a clear positive association between leukocyte count and short-term mortality in acutely admitted patients.[4, 10] Although we found, in line with these studies, that leukocyte count was associated with mortality and that counts were significantly higher in non-survivors, the absolute difference between groups was small.

The higher leukocyte count in deceased patients seemed mainly attributable to an increase in neutrophil and segment counts, parameters that also appeared to be important predictors in our random forest model. It is known that the production of these cells increases in response to stress and inflammation and that they can contribute to tissue injury.[29, 30] This association of neutrophils with short- as well as long-term mortality was also established in other studies.[8, 31]

Monocyte percentage and count were also important variables in our model. Compared to survivors, non-survivors had significantly higher counts of monocytes, which matches previous research. Although a high monocyte count is often mentioned in the context of cardiovascular disease, it was also identified as a prognostic marker for 30-day mortality in patients with a wide range of pathologies presenting to the ED.[19, 32]

Furthermore, lymphocyte count and percentage appeared to be important predictors and, in line with previous studies, we found lower lymphocyte counts in non-survivors.[14, 33, 34] One of the explanations proposed for this finding is that a low lymphocyte count is a marker of the stress response commonly encountered in acutely ill patients.[30, 33]

Red blood cells

From our random forest model, it becomes clear that both the proportions of RBCs with a high MCV as RBCs with a low MCV are important mortality predictors. The red blood cell distribution width (RDW) is a measure of this variability in RBC size. Although the pathways through which higher RDW levels are associated with mortality have not been fully elucidated, it is believed that inflammation and oxidative stress can reduce RBC survival and disrupt erythropoiesis, leading to more heterogeneity in cell sizes.[35] The increased risk of mortality as RDW increases was confirmed by our findings, although its AUROC was not as high as described by some other authors.[27, 36, 37] For parameters such as hemoglobin and RBC count, their association with mortality is widely known.[38, 39]

Platelets

Among platelet parameters, the platelet-to-lymphocyte ratio was a highly important parameter in our random forest model. Its prognostic value has been demonstrated in patients with sepsis,[26] acute coronary syndrome,[40] acute pulmonary embolism[41] and several malignancies.[42-44] Platelet count also appeared an important predictor of mortality. High counts are believed to reflect underlying inflammation as their proliferation is stimulated by inflammatory mediators, while on the other hand, a low lymphocyte count is believed to be a result of the stress response encountered upon acute illness.[30, 33]

Strengths and limitations

To our knowledge, this is the first paper reporting the exploration of (morphological) blood cell and platelet characteristics and counts in an elderly ED population. The size of this study population allows us to explore the combination of multiple hematological parameters in a model.

This study suffers from several limitations. First, mortality outcomes were missing for a large group of patients. Although these patients were similar to the patients we studied in terms of age and presenting specialty, the vast majority of their visits resulted in discharge, which leads us to believe that their risk of mortality was deemed lower than in patients for whom mortality outcomes were known. Secondly, hematological parameters were missing for a large amount of visits. Thirdly, we did not study subgroups of patients. Although this might have led to increased performance, our aim was to identify parameters useful in an unselected population. A final limitation is the lack of validation in a different patient population, such as in patients visiting the ED at a non-academic hospital.

Conclusions and implications

We performed an explorative study on the value of hematological characteristics in predicting short-term mortality in a large, elderly population presenting to the ED and found that a combination of hematological parameters showed good predictive ability. Especially seeing as how these parameters are inexpensive and rapidly available, future research should assess the place of such prediction models in clinical practice, whether that be to add such markers to existing models or to provide these predictions along with laboratory results. Also, the prognostic

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value of serial measurements of hematological parameters might be an interesting sequel to our study. Applications such as clinical decision support systems provide the opportunity to integrate different types of patient data into information that might aid clinicians' decision making, ideally through yielding a risk prediction for each individual patient.

Conflict of interest

None declared.

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Appendix I. Characteristics of excluded visits.

	Missing data on mortality		Missing hematology parameters	
Number of ED visits, n	9,895		12,697	
Male sex, n (%)	5,231 (52.9)		7,163 (56.4)	
Age in years, median (IQR)	73 (68-78)		73 (69-79)	
Top 5 ED specialties, n (%)				
1	Cardiology	2,304 (23.3)	Cardiology	2,399 (18.9)
2	Surgery	1,137 (11.5)	Neurology	1,469 (11.6)
3	Neurology	1,092 (11.0)	Surgery	1,195 (9.4)
4	Internal medicine	987 (10.0)	Internal medicine	1,019 (8.0)
5	Urology	669 (6.8)	Pulmonology	899 (7.1)
Destination after ED presentation, n (%)				
Continued care within UMCU	220 (2.2)		5,541 (43.6)	
Transfer to other institution	424 (4.3)		232 (1.8)	
Died at ED	-		70 (0.6)	
Discharge	8,902 (90.0)		6,444 (50.8)	
Other	349 (3.5)		410 (3.2)	
Outcome, n (%)				
30-day mortality	-		792 (6.2)	
7-day mortality	-		356 (2.8)	
Unknown	9,895 (100.0)		5,273 (41.5)	

The *'Number of ED visits, n'* for the columns (9,895 + 12,697) do not add up to the actual number of visits that were excluded (n=17,319), as overlap exists between both exclusion criteria. For a part of the visits, both mortality data and hematology parameters were missing. **Abbreviations:** ED, emergency department; IQR, interquartile range; UMCU, University Medical Center Utrecht.

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Appendix II. Laboratory values, stratified by occurrence of death within 7 days.

Laboratory value, unit	Alive after 7 days, n (visits)=22 143	Deceased within 7 days, n (visits)=2634	P value
CRP, mg/L	16.00 (3.80-68.00)	27.00 (5.43-113.00)	< 0.0008
Leukocyte count, 10^9/L	9.44 (7.10-12.64)	11.89 (8.58-16.55)	< 0.0008
Subsets and morphology			
Neutrophils			
Count, 10^9/L	6.85 (4.63-9.97)	9.45 (6.15-13.58)	< 0.0008
% of total leukocyte count	74.50 (64.31-83.11)	80.87 (69.48-87.79)	< 0.0008
Mean cell size, AU	150.10 (144.80-156.20)	152.50 (145.80-160.60)	< 0.0008
Mean complexity/granularity, AU	136.30 (131.95-140.69)	135.70 (131.50-140.60)	0.049
Mean lobularity, AU	123.20 (114.85-131.17)	121.40 (111.55-130.69)	< 0.0008
Mean depolarization, AU	27.53±4.22	27.39±4.90	0.40
Mean viability/red fluorescence, AU	71.03 (69.37-72.71)	71.58 (69.73-73.21)	< 0.0008
CV of cell size, %	2.78 (2.45-3.17)	2.85 (2.52-3.23)	0.0009
CV of complexity/granularity, %	3.66±0.65	3.79±0.81	< 0.0008
CV of lobularity, %	8.84 (7.22-9.99)	9.31 (7.93-10.41)	< 0.0008
CV of depolarization, %	15.51±2.45	15.66±3.37	0.21
CV of viability/red fluorescence, %	8.03 (7.12-8.76)	8.03 (7.25-8.71)	0.64
Segments			
Count, 10^9/L	6.75 (4.59-9.73)	9.03 (5.95-12-65)	< 0.0008
% of total leukocyte count	72.78 (63.12-80.55)	75.92 (63.20-83.49)	< 0.0008
Lymphocytes			
Count, 10^9/L	1.35 (0.87-1.95)	1.26 (0.71-2.18)	0.06
% of total leukocyte count	14.92 (8.74-23.26)	10.72 (5.92-19.98)	< 0.0008
Mean cell size, AU	100.67±5.68	98.98±6.89	< 0.0008
Mean complexity/granularity, AU	76.89±3.49	77.03±3.93	0.30
CV of cell size, %	4.24 (3.09-5.23)	4.04 (2.77-5.01)	< 0.0008
CV of complexity/granularity, %	4.36±1.18	4.26±1.40	0.04
Monocytes			
Count, 10^9/L	0.70 (0.51-0.96)	0.74 (0.48-1.05)	0.05
% of total leukocyte count	7.65 (5.69-9.76)	6.20 (4.25-8.33)	< 0.0008
Eosinophils			
Count, 10^9/L	0.09 (0.04-0.18)	0.06 (0.02-0.14)	< 0.0008
% of total leukocyte count	0.95 (0.37-2.10)	0.47 (0.18-1.26)	< 0.0008
Basophils			
Count, 10^9/L	0.03 (0.01-0.05)	0.02 (0.01-0.05)	< 0.0008
% of total leukocyte count	0.31 (0.13-0.57)	0.21 (0.08-0.42)	< 0.0008
Red blood cells			
Count, 10^9/L	4.16±0.74	4.06±0.82	< 0.0008
MCV, fL	90.72±6.84	91.82±7.64	< 0.0008
% red blood cells with MCV > 120 fL	0.96 (0.62-1.77)	1.05 (0.64-1.94)	< 0.0008
% red blood cells with MCV < 60 fL	1.99 (1.12-3.76)	2.59 (1.49-5.26)	0.01
RDW, %	12.99 (12.11-14.48)	13.34 (12.33-15.24)	< 0.0008
Hb, mmol/L	7.88±1.44	7.71±1.48	0.001

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MCH, fmol	1.91 (1.81-2.00)	1.92 (1.81-2.02)	0.11
MCHC, mmol/L	0.21 (0.20-0.22)	0.21 (0.20-0.21)	< 0.0008
% red blood cells with Hb < 28 g/dL	3.77 (1.51-9.22)	5.44 (2.05-13.88)	< 0.0008
% red blood cells with Hb > 41 g/dL	0.01 (0.00-0.10)	0.00 (0.00-0.08)	< 0.0008
CV of Hb concentration, %	7.44 (6.76-8.24)	7.44 (6.75-8.22)	0.93
Ht, L/L	38.15 (33.58-42.02)	37.64 (32.79-41.99)	0.08
Mean complexity/granularity, AU	181.80 (180.10-183.40)	182.30 (180.60-183.90)	< 0.0008
Mean viability/red fluorescence, AU	82.89±9.27	83.06±9.44	0.62
CV of complexity/granularity, %	1.65 (1.52-1.80)	1.65 (1.51-1.79)	0.79
CV of viability/red fluorescence, %	12.19 (10.87-13.75)	12.17 (10.92-13.88)	0.36
Reticulocytes			
Count, 10^9/L	66.97 (50.48-87.98)	69.34 (50.25-93.99)	0.02
% of RBC	1.58 (1.19-2.14)	1.65 (1.24-2.36)	< 0.0008
Immature reticulocyte fraction	0.30 (0.24-0.37)	0.32 (0.25-0.41)	< 0.0008
MCV, fL	98.34±13.18	99.46±14.72	0.03
MCH, fmol	29.59 (27.27-31.32)	29.47 (27.04-31.32)	0.57
MCHC, mmol/L	29.14 (27.94-30.18)	28.63 (27.42-29.79)	< 0.0008
Platelets			
Count, 10^9/L	239.10 (184.20-311.30)	234.00 (167.40-311.30)	0.001
MPV, fL	7.58 (6.89-8.38)	7.81 (7.13-8.76)	< 0.0008
PDW, 10 (GSD)	16.15 (15.74-16.62)	16.20 (15.78-16.71)	0.07
PCT, mL/L	0.18 (0.15-0.23)	0.18 (0.14-0.24)	0.13
Reticulated platelets, %	2.70 (1.91-3.90)	3.37 (2.21-4.99)	< 0.0008
Mean complexity/granularity, AU	144.40±6.83	144.50±7.85	0.67
Mean lobularity, AU	124.20 (121.20-127.30)	123.40 (120.20-126.80)	< 0.0008
CV of complexity/granularity, %	17.29 (16.65-17.96)	17.52 (16.83-18.40)	< 0.0008
CV of lobularity, %	13.37 (12.76-14.17)	13.77 (12.95-14.84)	< 0.0008
Ratios			
Neutrophil-to-lymphocyte ratio	5.00 (3.00-9.00)	7.35 (3.49-14.60)	< 0.008
Platelet-to-lymphocyte ratio	179.00 (115.00-289.00)	189.00 (94.00-329.00)	0.57
Monocyte-to-lymphocyte ratio	0.51 (0.33-0.82)	0.55 (0.30-1.01)	0.03

Values are expressed in "median (interquartile range)" for non-normally distributed data and in "mean±SD" for normally distributed data. After Bonferroni correction, p-values < 0.0008 were considered significant.
Abbreviations: C-reactive protein; AU, arbitrary unit; CV, coefficient of variation; MCV, mean corpuscular volume; RDW, red blood cell distribution width; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Ht, hematocrit; MPV, mean platelet volume; PDW, platelet distribution width; GSD, geometric standard deviation; PCT, plateletcrit,

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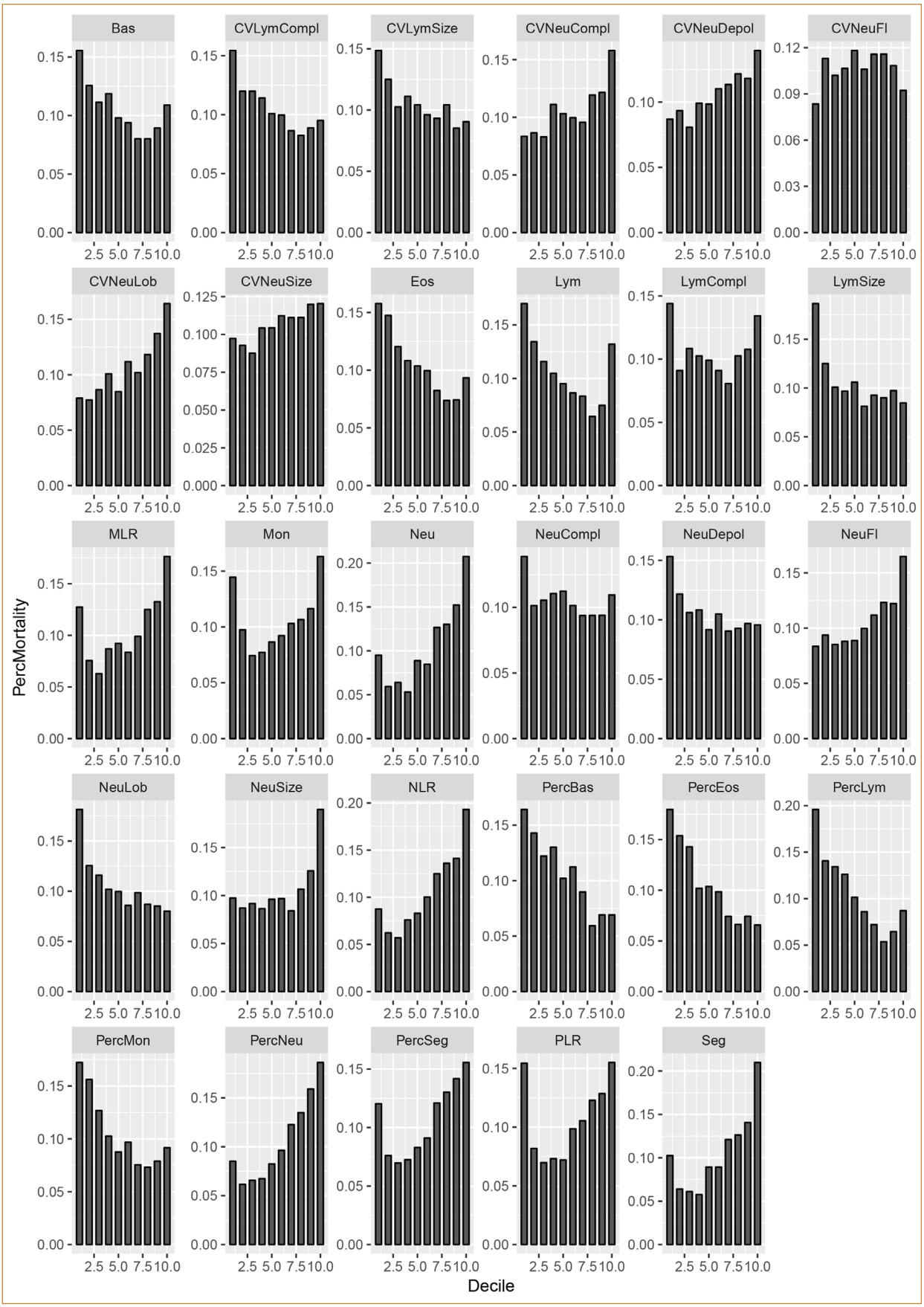

Appendix III. 30-day mortality in deciles of laboratory values

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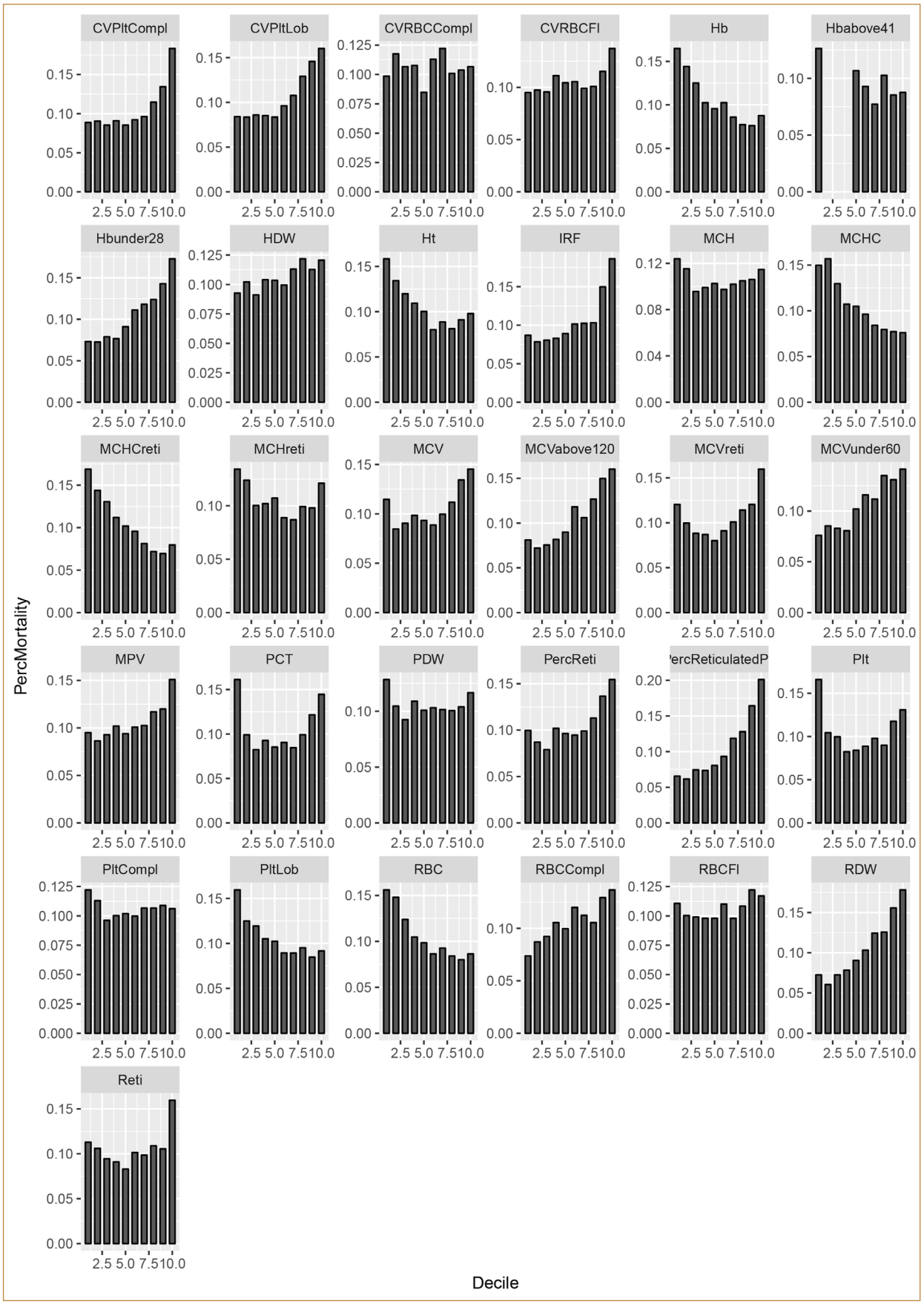

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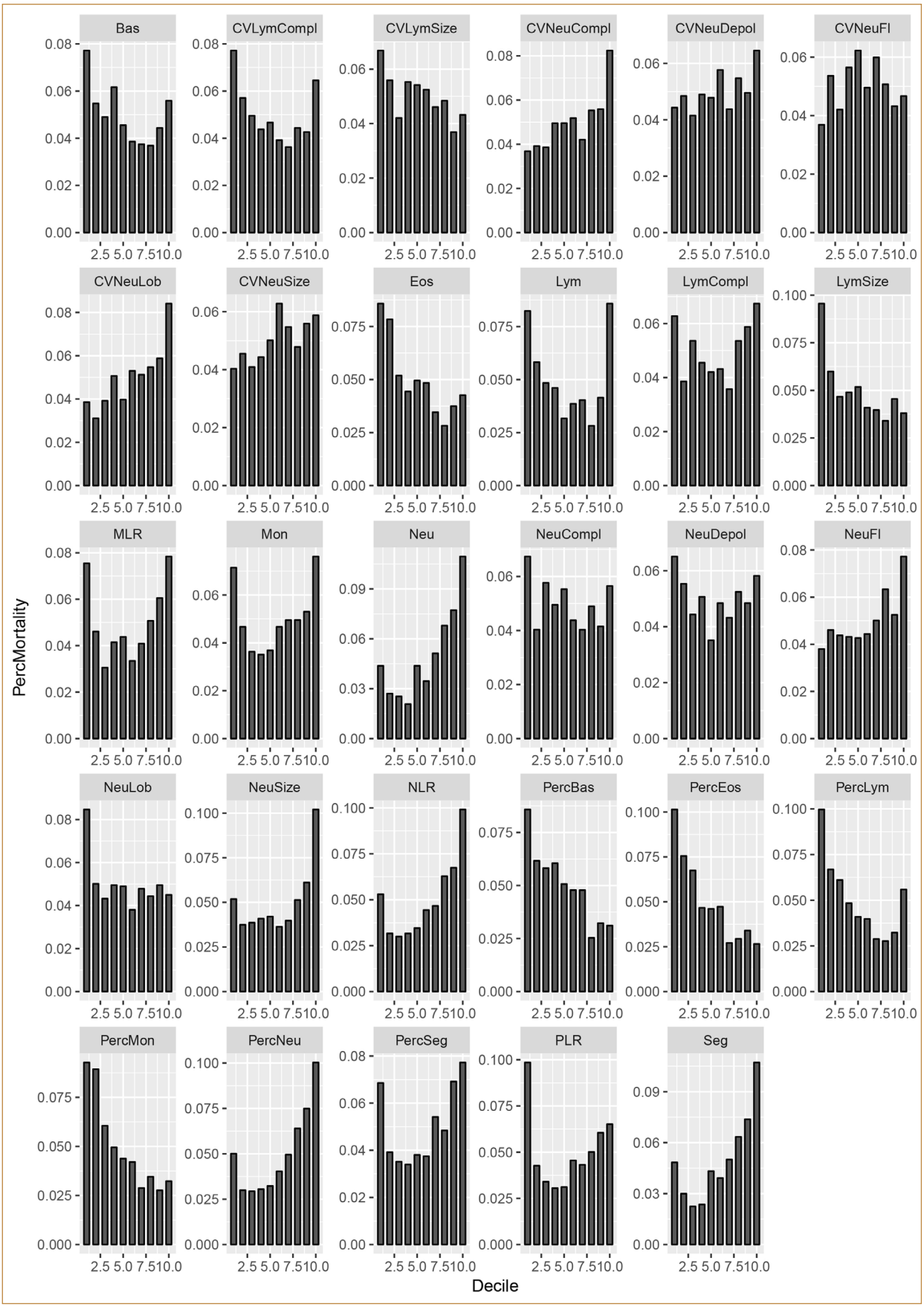

Appendix III. 7-day mortality in deciles of laboratory values

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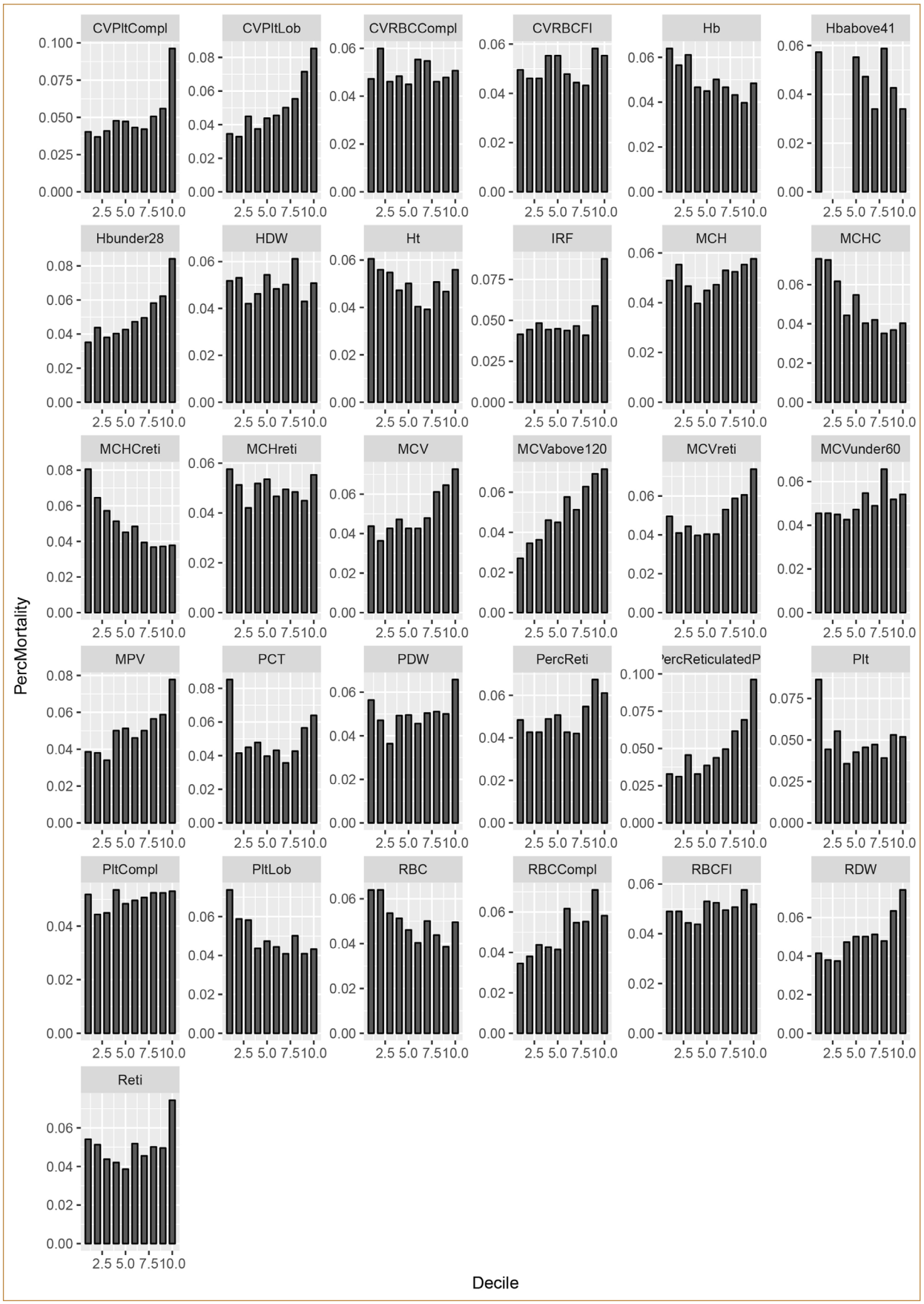
Exploring the value of routinely measured hematology parameters for identification of elderly patients at high risk of death at the Emergency Department



Appendix III. 7-day mortality in deciles of laboratory values

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