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Quantitative Determination of Volume Conductivity and Scatter Parameters to Predict Mortality of Patients in Intensive Care Units

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Abstract: Prediction of patient's mortality in intensive care unit was a debatable topic and still remains elusive. Numerous clinical scores and biomarkers were identified but none considered as a gold standard modality due to their complexity and non availability of laboratory tests in certain hospitals. A simple cost effective mortality predictor is always expected in ICU settings. Volume Conductivity and Scatter (VCS) parameters are WBC research population data generally developed to compute differential count. In the current study, these 24 parameters were analysed to know if they can be used as a mortality predictor. A total of 100 patients who were admitted, treated and expired in intensive care units were enrolled in the study. For control, 100 age and sex matched patients who were admitted, treated and recovered in intensive care units included in the study. In this retrospective analysis of 200 cases, VCS parameters were noted from automated hematology analyser and analysed. To achieve mean and standard deviation of each parameter, Mann Whitney test was performed. Receiver's operating characteristics was analysed on significant parameters to derive cut-off values, sensitivity and specificity. Out of 24 parameters, significant parameters with area under the curve more than 7.0 were neutrophil-volume distribution width (cut-off ≥23.5, sensitivity 85%,specificity 50%), neutrophil-conductance distribution width (cut-off ≥6.5,sensitivity 86%, specificity 54%) , mean lymphocyte scatter (cut-off ≥54.5, sensitivity 85%, specificity 60%), lymphocyte-scatter distribution width (cut-off ≥18.5, sensitivity 82%, specificity 52%), monocyte-conductance distribution width (cut-off ≥5.5, sensitivity 66%, specificity 69%), mean monocyte scatter (cut-off ≥79.5, sensitivity 84%, specificity 60%) and mean eosinophil scatter (cut-off ≥186.5, sensitivity 81%, specificity 50%). These significant VCS parameters either alone or in combination can serve as a simple, cost effective and reliable predictor of mortality in ICU patients in comparison to the complex clinical scores and more sophisticated laboratory markers.
Keywords: Mortality predictor, volume, conductivity, scatter, intensive care unit.

INTRODUCTION

Mortality prediction of ICU cases is still an ongoing clinical research. Mortality rate varies depending on the underlying disease process. A variety of severity assessment scores are often used in ICU settings to predict outcomes including death such as APACHE scores, the Simplified Acute Physiology Score (SAPS), the Mortality Probability Model (MPM), and the Sequential Organ Failure Assessment (SOFA) score. Although these scoring systems predict mortality with better sensitivity and specificity, they are yet considered too complex for clinical use.

Various biomarkers have also been identified to predict mortality such as C-reactive protein, Interleukin-6, parathyroid hormone, homocysteine and troponins [1]. However to assess patient outcome, repetitive periodic analysis of these markers are required which are not strictly followed due to the costs of these tests. Studies showed that terminal illness elicits systemic inflammatory response which in turn influences the hematological and biochemical parameters [2]. Systemic inflammation an integral part of disease in critical illness, more commonly associated with the sepsis. Studies have shown that these could occur during the period of terminal illness. There had been various studies evaluating the utility of basic and cost effective hematological parameters like Red cell distribution width(RDW), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio

PLR in predicting mortality and sepsis. In addition to these diagnostic parameters, there are certain research parameters in automated hematology analyzer which are far beyond reach for clinical utility. Such research parameters of WBC are called WBC Research population data (RPD). WBC RPD is measured by VCS (volume, conductivity, and scatter) technology hence also called VCS parameters. When WBCs pass between the electrodes in an analyzer it creates impedance in the circuit which gives the value of cell volume. Volume increases during cellular activation and shift-to-left. Conductivity is measured using a radiofrequency probe that determines nuclear shape, globularity, density, and nuclear/cytoplasmic ratio. Scatter is analyzed by laser beam which measures cytoplasmic granules; hence scatter value increases when there is an increase in size or number of granules or both [3]. All these were applied to each cell for approximately 8000cells to provide differential count [4].

Our study was based on the hypothesis that hematological alterations which occur during terminal illness could also be reflected in VCS parameters. In view of this, we sought to evaluate 24 VCS hematological parameters to derive a simple and effective assessment tool to predict mortality of ICU cases.

AIM AND OBJECTIVES

- To identify VCS parameters which can predict mortality in patients admitted in intensive care units
- To determine cut-off values for significant VCS parameters to predict mortality in ICU patients

MATERIALS AND METHODS

The present study was a retrospective analysis of patients admitted in intensive care units in a tertiary care hospital. A total of 200 patients were included in the study which comprised of 100 cases and 100 controls. Patients who succumb to the illness during ICU stay were the cases (non survivors) and those who recovered and discharged from ICU were taken as controls (survivors). From the data storage system of Beckman LH 750 automated hematology analyzer, 24 VCS parameters were noted for both survivors and non survivors. Volume conductivity and scatter parameters for four WBC cell types are listed below.

- Mean neutrophil volume (MNV)
- Volume distribution width (Std deviation) of neutrophils (Neutrophil-VDW)
- Mean neutrophil conductivity (MNC)
- Conductivity distribution width of neutrophils (Neutrophil-CDW)
- Mean neutrophil scatter (MNS)
- Scatter distribution width of neutrophils (Neutrophil-SDW)
- Mean lymphocyte volume (MLV)
- Volume distribution width of lymphocytes (Lymphocytes-VDW)
- Mean lymphocyte conductivity (MLC)
- Conductivity distribution width of lymphocytes (Lymphocytes-CDW)
- Mean lymphocyte scatter (MLS)
- Scatter distribution width of lymphocytes (Lymphocytes-SDW)
- Mean monocyte volume (MMV)
- Volume distribution width (Std deviation) of monocytes (Monocyte-VDW)
- Mean monocyte conductivity (MMC)
- Conductivity distribution width of Monocytes (Monocyte-CDW)
- Mean monocyte scatter(MMS)
- Scatter distribution width of monocyte (Monocyte-SDW)
- Mean eosinophil volume (MEV)
- Volume distribution width of eosinophil (Eosinophil -VDW)
- Mean eosinophil conductivity (MEC)
- Conductivity distribution width of eosinophil (Eosinophil -CDW)
- Mean eosinophil scatter (MES)
- Scatter distribution width of eosinophil (Eosinophil -SDW)

Exclusion criteria

- Test group (non survivors) without laboratory VCS data within last 48hours of life were excluded from the study
- Control patients (survivors) without laboratory VCS data within last 48hours of discharge from ICU were excluded from the study.
- All pediatric patients (in test and control groups) were excluded from the study
- Patients (cases and controls) with hematological malignancies were excluded from the study.

Statistical analysis

Data collected were entered into Microsoft Excel program and analysis was carried out using Statistical Package for Social Sciences (SPSS) version 22. Mean and standard deviation were provided for continuous variables. The means of various VCS parameters were compared between cases and controls by Mann-whitney test since values in cases and controls were not equally distributed. As further analysis, Receiver Operating Characteristics (ROC) curves were constructed to estimate the usefulness of each VCS parameter in terms of sensitivity and specificity in predicting mortality. A p-value of <0.05 was considered to be statistically significant.

RESULTS

During the study period, 24 VCS parameters of 100 cases (non-survivors) were compared with 100

control subjects (survivors). Of 100 patients in study group, 62% were between 20-60 years of age and 38% were more than 60 years. The mean age among study group was 56.25 years. This was in comparison to the mean age among the control group which is 51.28 years. With regard to sex distribution, males constituted 60% and females were 40% in both the study and control groups. The values of all 24 VCS parameters were noted for both the study and control groups and their respective mean and standard deviation were shown in Table 1.

Table-1: Comparison of mean and standard deviation of VCS parameters in study and control groups

S. No	Parameters	Control Group (Mean±SD)	Study Group (Mean±SD)	P value
1	MNV	151.6 ± 13.88	159.4 ± 23.82	0.153
2	Neutrophil-VDW	24.54 ± 4.53	30.09 ± 7.87	<0.0001
3	MNC	145.2 ± 4.58	145.2 ± 7.75	0.943
4	Neutrophil-CDW	7.24 ± 2.78	10.22 ± 5.43	<0.0001
5	MNS	128.7 ± 9.43	133.4 ± 10.67	0.0015
6	Neutrophil-SDW	11.07 ± 1.55	12.08 ± 3.03	0.0078
7	MLV	84.24 ± 11.40	79.90 ± 9.63	<0.0001
8	Lymphocytes-VDW	15.52 ± 3.51	15.84 ± 3.38	0.389
9	MLC	116.4 ± 5.66	123.0 ± 16.23	0.0011
10	Lymphocytes-CDW	15.02 ± 7.21	20.46 ± 11.87	<0.0001
11	MLS	57.53 ± 13.02	65.55 ± 12.81	<0.0001
12	Lymphocytes-SDW	19.24 ± 5.06	24.68 ± 16.14	<0.0001
13	MMV	170.0 ± 13.33	169.7 ± 23.49	0.945
14	Monocyte-VDW	21.34 ± 4.58	25.41 ± 12.63	0.0004
15	MMC	124.1 ± 4.74	136.9 ± 115.1	0.0015
16	Monocyte-CDW	5.50 ± 2.08	14.68 ± 67.99	<0.0001
17	MMS	79.32 ± 12.37	86.57 ± 11.29	<0.0001
18	Monocyte-SDW	9.92 ± 1.37	11.40 ± 15.39	0.970
19	MEV	137.7 ± 45.40	133.3 ± 42.10	0.026
20	Eosinophil -VDW	17.57 ± 14.05	19.32 ± 18.68	0.501
21	MEC	143.3 ± 48.18	149.5 ± 49.68	0.0392
22	Eosinophil -CDW	11.07 ± 14.71	17.53 ± 25.62	0.0395
23	MES	174.9 ± 51.42	185.4 ± 56.51	<0.0001
24	Eosinophil -SDW	8.84 ± 7.09	19.80 ± 109.7	0.944

Of 24 parameters analyzed, 17 parameters showed significant difference between survivors and non-survivors. Conductivity distribution width and mean scatter of all the four WBC types showed difference between the groups. In addition it was noted that among the parameters that were significant, mean values of mean lymphocyte volume and mean eosinophil volume were greater in control group compared to study group. ROC curves were plotted for 17 significant parameters and those that showed relatively good curves with area under the curve more than 7.0 were evaluated for further analysis (Fig:1) Area under the curve, cut-off values, sensitivity and specificity were depicted in table 2.

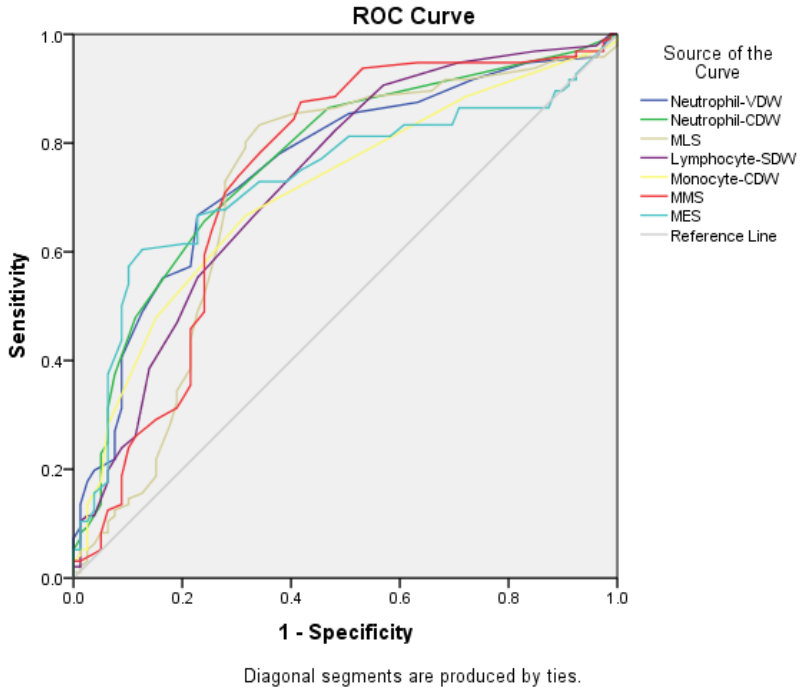

Fig-1: ROC curve for 7 VCS parameters that can mortality of patients admitted in intensive care units

Table-2: Cut-off values, sensitivity and specificity of VCS parameters evaluated by ROC analysis

VCS parameters	Area under the curve	Cut-off values	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
Neutrophil-VDW	.756	≥23.5	85%	50%	.683	.828
Neutrophil-CDW	.766	≥6.5	86%	54%	.695	.837
MLS	.716	≥54.5	85%	60%	.634	.798
Lymphocytes-SDW	.730	≥18.5	82%	52%	.655	.806
Monocyte-CDW	.711	≥5.5	66%	69%	.634	.787
MMS	.737	≥79.5	84%	60%	.659	.816
MES	.733	≥186.5	81%	50%	.656	.809

DISCUSSION

Mortality predictors help to triage patients and provide appropriate care for a favourable outcome. Costliness of laboratory biomarkers and complexity of existing clinical scores compels the clinicians to look for a simple, cost effective and reliable tool in every tertiary care hospitals.

Volume conductivity scatter parameters are research datas in automated analysers which provide differential count for a given blood sample. In the current study, seventeen parameters were identified to show significant difference between survivors and non survivors in intensive care units Of 17 parameters, seven parameters namely neutrophil-VDW, neutrophil-CDW, mean lymphocyte scatter, lymphocyte-scatter distribution width, monocyte-conductivity distribution width, mean monocyte scatter and mean eosinophil scatter were considered to predict mortality due to their high area under the curve, sensitivity and specificity. Among the haematological parameters, mortality prediction was widely studied in mean platelet volume [5], neutrophil-lymphocyte ratio [6] and red cell distribution width [7].

VCS was not evaluated earlier for mortality prediction. Rather, they were widely used to identify sepsis of critically ill patients [8]. Studies have shown that bacterial sepsis is the major cause of mortality in intensive care units. A large retrospective study quoted that mortality rate of septic patients admitted in intensive care unit was 44.6% compared with 26.2% in non-septic patients [9]. Bacterial infection leads to disturbance in haematological equilibrium causing leucocytosis, leucocyte activation and increased shift-to-left, in short what is known as leukemoid reaction. Earlier study stated that leukemoid reaction was associated with mortality irrespective of bacterial sepsis. This might denote that during terminal illness systemic inflammation was activated by cytokines irrespective of infection similar to certain previous

studies where cytokine stimulation noted in non-infectious diseases [10,11].

In the present study, shift-to-left was identified by significant increase in values of neutrophil-VDW, neutrophil-CDW and monocyte-CDW. Increased cytoplasmic granularity was seen in WBC cell types either during cellular activation or shift-to-left which are identified by change in scatter values. In the current study, significant increase in MLS, MMS and MES were identified in non-survivors which suggested that either cellular activation or shift-to-left occur in terminally ill patients. ROC curve plotted showed greater area under the curve for neutrophil-CDW (0.766). Table 3 demonstrates area under the curve of different clinical and laboratory markers studied earlier in predicting mortality.

Table-3: Comparison of Area under Receiver's Operating Characteristic Curve (AUROC) of different markers in predicting mortality

S.No	Mortality predictors	Area under the curve	References
1	MPM (Mortality probability model) II_{24}	0.823	Yaseen *et al.*[12]
2	MPM (Mortality probability model) II_{24}	0.806	Yaseen *et al.*[12]
3	SAPS (Simplified Acute Physiology Score) II	0.797	Yaseen *et al.* [12]
4	APACHE (Acute Physiology and Health Evaluation)II	0.782	Yaseen *et al.*[12]
5	Troponin T	0.708	Artunc *et al.*[1]
6	Troponin I	0.746	Artunc *et al.*[1]
7	Procalcitonin	0.83	Kim *et al.*[13]
8	C-Reactive protein	0.72	Kim *et al.*[13]
9	Delta neutrophil index	0.8	Kim *et al.*[13]
10	Neutrophil-VDW	0.756	Current study
11	Neutrophil-CDW	0.766	Current study

The above table shows that our study was comparable to the other previous studies in terms o area of under the curve. To increase the effectiveness of predictability those cut off values of the 7 significant parameters obtained can be used in combination. Surprisingly, MNV which was frequently studied in correlation with sepsis and mortality showed no significant difference in cases compared to controls in the current study which might be due to the sample size.

CONCLUSION

Volume conductivity and scatter parameters are research datas which will predict mortality in patients admitted in intensive care units. Since the datas are easily available in hematology analyser which is easily interpretable, demands no additional sample and carries no extra cost, VCS parameters can be used as a mortality predictor in patients admitted in intensive care units with good reliability.

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