Research Article

Preoperative red cell distribution width: Not a useful prognostic indicator for 30-day mortality in patients who undergo major- or ultra-major noncardiac surgery

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Abstract

Background: Red cell distribution width (RDW) has been shown to be associated with mortality in cardiac surgical patients. This study investigates the association of RDW with the 30-day mortality for those patients who undergo major- or ultra-major noncardiac surgery. **Methods:** Patients who received major- or ultra-major noncardiac surgery between July 2012 and May 2013 were included in the study and patients those with preoperative hemoglobin <10 g/day were excluded from the study. Patients were followed till day 30 from the date of surgery or death, whichever occurred earlier. **Results:** The overall 30-day mortality for major- and ultra-major surgery was 11.4%. The mean RDW of the 30-day survivors was 13.6 ± 1.6 and that of nonsurvivors was 14.2 ± 2.1 ($P < 0.001$). Other factors that were significantly different ($P < 0.05$) between survivors and nonsurvivors included age, sex, preoperative pulse rate, current or ex-alcoholic, the American Society of Anesthesiologists score, diabetes mellitus, use of antihypertensives, sepsis with 48 h before surgery, preoperative hemoglobin, white cell count, sodium, urea, creatinine, albumin, international normalized ratio (INR), pH, base excess, estimated blood loss, and emergency surgery. Logistic regression revealed that preoperative RDW > 13.35% ($P = 0.025$, odds ratio [OR]: 1.52), INR ($P = 0.008$, OR: 4.49), albumin level ($P < 0.001$, OR: 1.10), use of antihypertensives ($P = 0.001$, OR: 1.82), and preoperative pulse rate ($P = 0.006$, OR: 1.02) independently predicted the 30-day mortality. However, the area under receiver operating characteristic curve for the prediction of 30-day mortality using RDW was only 0.614. **Conclusions:** Although preoperative RDW independently predicted 30-day mortality in patients who underwent major- or ultra-major noncardiac surgery, it may not serve as an influential prognostic indicator in view of its low sensitivity and specificity.

Keywords: Erythrocyte indices, operative, red cell distribution width, risk assessment, surgical procedures

Introduction

Red cell distribution width (RDW) serves as a parameter to measure variation in red blood cell size or red blood cell volume. The term "width" refers to the width of the volume distribution curve but not the actual width of

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the red blood cell. RDW is calculated with the following formula: (standard deviation [SD] of mean corpuscular volume (MCV)/mean MCV) × 100. Marked anisocytosis is expected on peripheral blood smear when RDW is elevated. RDW may reflect nutritional deficiencies, bone marrow dysfunction, or systemic inflammation.[1]

RDW was shown to be an important prognostic indicator in various conditions, such as patients with severe sepsis and septic shock,[2,3] critically ill,[2,4] heart failure,[5-7] acute myocardial infarction,[8,9] and those undergoing cardiac catheterization.[10] The prognostic significance of RDW in internal medicine, newly hospitalized patients, and all-cause mortality was also explored.[11-13] The application of RDW for perioperative prognostication involved mainly in coronary artery bypass graft surgery or cardiac surgery,[14-16] and its application in noncardiac surgery was less common.[17,18] RDW interpretation needs to be taken in conjunction with hemoglobin level and it offers better mortality prediction among nonanemic patients.[19]

This study investigates the significance of RDW on mortality and morbidities among patients who received major- or ultra-major noncardiac surgery. The primary objective is to study the associations of RDW with 30-day hospital mortality. The secondary objective is to look for the association with hospital and Intensive Care Unit (ICU) length of stay.

Methods

This study was approved by the Hong Kong East Cluster Ethics Committee with approval number HKEC-2014-028. Written informed consent was waived. It was a retrospective, single-centered, cohort study conducted at a regional acute care tertiary hospital that provides comprehensive care except cardiothoracic surgery, transplant surgery, and burns. Patients who received major- or ultra-major operations (n = 1598) between July 01, 2012, and May 31, 2013, who may require ICU care were recruited for the study. Cases with hemoglobin (Hb) level <10 g/dL were excluded from the study to optimize the mortality predictive value of RDW.[19] Patients' demographics, comorbidities, the American Society of Anesthesiologists (ASA) physical status classification, smoker and drinking history, presence of sepsis within 48 h before surgery, blood parameters within 48 h before surgery (included complete blood count (CBC), clotting profile, arterial or venous blood gas, renal and liver function tests), and outcome data (mortality, significant morbidities, and hospital length of stay) were collected. All measurements were taken preoperatively and were

performed in a single laboratory. For the blood tests, CBC and RDW were determined from whole blood using Sysmex XE_5000 analyzer (Sysmex Canada, Inc., Canada, USA). The reference range for RDW was between 11.8% and 15.8%. It was validated by local protocols adopted from the Clinical and Laboratory Standards Institute (CLSI)-approved guideline C28-A3. The international normalized ratio (INR) was processed by ACL TOP 500 (Instrumentation Laboratory, Massachusetts, USA). Renal function, albumin, and C-reactive protein were measured by ABBOTT Architect C16000 (Abbott Diagnostics, Illinois, USA). Arterial blood gas was studied by SIEMENS RL1265 (Siemens AG, Munich, Germany).

Definitions

The 30-day mortality was defined as death occurred within 30 days after the first operation. Hospital mortality was defined as death that occurred in that single episode of hospitalization regardless of the length of stay. Current smoker was defined as those who reported smoking at least 100 cigarettes in their lifetime and who, at the time of survey, smoked either every day or some days. Those who had 15 or more drinks per week for men and eight or more drinks per week for women were treated as alcoholics. Diabetes mellitus (DM) referred to either type I or type II DM.

Statistical analysis

We assumed the mean RDW of those 30-day survivors to be 13% ± 2.5% while nonsurvivors to be 14% ± 2.5%, with alpha 0.05, power 0.9, survivor versus nonsurvivor ratio of 10, and the calculated sample size to be 798.[20] Comparisons were performed between 30-day survivors and nonsurvivors. Results were expressed as mean ± SD or as number of cases and percentages as appropriate. Univariate analysis was performed using Student's t-test or Mann–Whitney U-test for continuous variables. Categorical variables were analyzed using Pearson's Chi-square test or Fisher's exact test as appropriate. A two-tailed $P < 0.05$ was considered statistically significant. Significant factors with $P < 0.05$ were reassessed by backward stepwise logistic regression analysis to identify factors associated with 30-day mortality in patients. Trend analysis was performed using Chi-squared test for trend in proportions. On conversion of continuous variables to categorical variables, the appropriate cutoff values were determined by the receiver operating characteristic (ROC) method. The performance of the 30-day mortality prediction model (discrimination and calibration) was assessed by C-index and Hosmer–Lemeshow goodness-to-fit test. All analyses were performed using the Statistical Package for the Social Sciences software for Windows version 20.0 (SPSS Inc.,

Chicago, USA) and R statistical program version 3.2 (R Foundation, Vienna, Austria, http://www.r-project.org/).

Results

A total of 1598 patients received major- or ultra-major operations during the study period (July 01, 2012–May 31, 2013). Among them, 200 patients with Hb level below 10 g/dL were excluded from the study. The characteristics of the population studied (*n* = 1398) are shown in Table 1. The overall 30-day mortality was 11.4%, while hospital death was 1.1% that signified most of the mortality (90.4%) occurred after hospital discharge. Mean RDW was 13.7% ± 1.7%.

Univariate analysis

Table 2 shows the demographic, biochemical parameters, and outcome data for those 30-day survivors and nonsurvivors. Nonsurvivors were older, preferentially male, had more significant comorbidities (including hypertension and DM), being current or ex-alcoholic, and had poorer physical status with ASA score >2. They were more likely to receive emergency surgery and develop sepsis within 48 h before surgery as compared with survivors. Nonsurvivors also had a higher level of preoperative pulse rate with more significant derangement of blood parameters (including RDW, white cell count, urea, creatinine, INR, Hb, sodium, albumin, pH, and base excess). The estimated blood loss was higher in nonsurvivors. Hospital length of stay and high dependence unit/ICU length of stay were significantly longer among nonsurvivors. The 30-day mortality rate increased with RDW level (30-day mortality 8.0% with RDW level <12.7%, 7.9% with RDW level between 12.7% and 13.1%, 14.3% with RDW level between 13.2% and 14.0%, and 15.7% with

RDW ≥14.1%, *P* < 0.001). The area under receiver operating characteristic curves (AUROC) for prediction of 30-day mortality using RDW was only 0.614. The best cutoff value for RDW was 13.35% (sensitivity: 0.625 and specificity: 0.443).

Multivariate analysis

Logistic regression (C-index: 0.705, Hosmer–Lemeshow test; *P* = 0.412, *n* = 1239), as shown in Table 3, demonstrated that preoperative RDW > 13.35% (*P* = 0.025, odds ratio [OR]: 1.52), INR (*P* = 0.008, OR: 4.49), albumin level (*P* < 0.001, OR: 1.10), use of antihypertensives (*P* = 0.001, OR: 1.82), and preoperative pulse rate (*P* = 0.006, OR: 1.02) were independent risk factors for 30-day mortality in patients receiving major- or ultra-major operation.

Discussion

RDW is a well-known independent mortality and morbidity predictor in patients who undergo cardiac surgery.[15,21,22] It is considered as a sensitive and low-cost prognostication marker, which may combine with other hematological parameters (such as mean platelet volume or neutrophil-to-lymphocyte ratio) to provide better outcome predictive value.[23] However, the use of RDW among noncardiac surgical condition is less common.[18,24] This study evaluated the value of preoperative RDW for prediction of 30-day mortality in patients who received major- or ultra-major noncardiac surgery. We found that preoperative RDW, together with INR, albumin, pulse rate, and presence of hypertension, independently predicted 30-day mortality in this group of patients. In fact, similar findings were reported by Hirahara *et al.*, Zehir *et al.*, Warwick *et al.*, Zhao *et al.*, and Yilmaz *et al.* among those patients who underwent esophagectomy, hip fracture operation, lung cancer surgery, liver cancer surgery, and pancreatic cancer surgery.[17,18,24-26] The 30-day mortality rate also increased with RDW level, which was 8% when RDW <12.7% and reached 15.7% when RDW ≥ 14.1. Again, Warwick *et al.* reported similar findings, which indicated a linear relationship between mortality and RDW level.[18] To reduce the risk of confounding, we adjusted for a comprehensive list of factors/parameters known to influence the clinical outcome. We also determined factors that were associated with higher levels of RDW preoperatively and omitted those patients with significant anemia (Hb <10 g/dL). However, the discrimination power of RDW is limited as reflected by its small AUROC (0.614), which correlated well with that reported by Sun *et al.* with AUROC of 0.562 among those patients with ST-elevated myocardial infarction.[9]

Table 1: Patients' demographic (*n*=1398)

Parameters	Results
Age (year)	63.7±15.7
Sex, female (%)	588 (42.1)
BMI	23.6±4.1
Systolic BP (mmHg)	129±18)
Pulse rate (beat/min)	76±13
RDW (%)	13.7±1.7
Operation type (%)	
Abdominal	655 (46.9)
Urology	392 (28.0)
Vascular	106 (7.6)
Endocrine	91 (6.5)
Thorax	14 (1.0)
Others	140 (10.0)
Hospital length of stay (days)	6.8±11.8
ICU or HDU length of stay (days)	0.3±1.1

Continuous variables are shown as mean±SD. Categorical variables are shown as frequency (%). BP: Blood pressure; RDW: Red blood cell distribution width; ICU: Intensive Care Unit; HDU: High Dependence Unit; BMI: Body mass index; SD: Standard deviation

Table 2: Comparison between those 30-day survivors and nonsurvivors

Parameters	30-day postoperative survivors (n=1238)	30-day postoperative nonsurvivors (n=160)	P
Age (years)	62.9±15.7	69.9±13.9	<0.001
Sex, female (%)	535 (43.2)	53 (33.1)	0.015
BMI	23.5±4.2	24.0±4.2	0.32
Current smoker within 1 year (%)	195 (15.8)	23 (14.4)	0.845
Current alcoholic or ex-alcoholic (%)	62 (5.0)	14 (8.7)	0.018
DM (%)	208 (16.8)	39 (24.4)	0.018
Use of antihypertensives (%)	576 (46.5)	103 (64.4)	<0.001
ASA >2 (%)	330 (26.7)	79 (49.4)	<0.001
Emergency surgery (%)	316 (25.5)	68 (42.5)	<0.001
Sepsis 48 h before surgery (%)	51 (4.1)	21 (13.1)	<0.001
Preoperative parameters			
Systolic BP (mmHg)	129±17	131±21	0.176
Pulse rate (beat/min)	75±13	81±17	<0.001
RDW (%)	13.6±1.6	14.2±2.1	<0.001
Hb (g/dL)	13.1±1.5	12.7±1.5	0.001
WCC (×10⁹/L)	7.79±3.89	8.64±4.15	0.01
Platelet (×10⁹/L)	228±70	228±77	0.969
Urea (mmol/L)	5.78±3.05	7.18±4.78	<0.001
Creatinine (μmol/L)	85.2±81.6	107±111	0.004
Sodium (mmol/L)	139±3.2	138±3.8	0.001
Albumin (g/L)	39.7±4.1	36.8±5.6	<0.001
INR	1.02±0.10	1.10±0.29	<0.001
pH	7.40±0.72	7.38±0.11	0.041
Base excess (mmol/L)	−1.56±3.20	−2.85±4.55	0.004
Estimated blood loss (ml)	288±368	500±652	<0.001
Hospital length of stay (days)	5.6±10.5	16.5±16.0	<0.001
ICU/HDU length of stay (days)	0.1±0.5	1.5±2.5	<0.001

Continuous variables are presented as mean±SD. Categorical variables are presented as frequency (%). BMI: Body mass index; BP: Blood pressure; RDW: Red blood cell distribution width; Hb: Hemoglobin; WCC: White cell count; INR: International normalized ratio; ICU: Intensive Care Unit; HDU: High Dependence Unit; Sepsis 48 h: Sepsis within 48 h before surgery; ASA: The American Society of Anesthesiologists Physical Status classification; DM: Diabetes mellitus; SD: Standard deviation

Table 3: Multivariate analysis to identify factors associated with 30-day mortality

Variable	OR	95% CI (OR)	P
RDW ≥13.35	1.52	1.05-2.19	0.025
INR	4.49	1.49-13.6	0.008
Albumin	1.10	1.06-1.14	<0.001
Use of antihypertensives	1.82	1.26-2.62	0.001
Preoperative pulse rate	1.02	1.01-1.03	0.006

Backward stepwise analysis excluded age, sex, preoperative hemoglobin level, white cell count, creatinine, urea, sodium, pH, base excess, the ASA score, diabetes mellitus, presence of sepsis within 48 h prior to surgery, estimated blood loss, and emergency surgery. INR: International normalized ratio; ASA: The American Society of Anesthesiologists Physical Status classification; RDW: Red blood cell distribution width; CI: Confidence interval; OR: Odds ratio

The mechanism of association with mortality is not clear. Elevated RDW or anisocytosis reflects greater heterogeneity in red blood cell size, caused by the presence of circulating immature red blood cells. Systemic inflammation response has a significant contribution to great variation on the size of the erythrocytes.[27,28] Inflammation not only limits the survival of erythrocytes, but also deforms RBC membranes,[27,29,30] suppresses the activity of erythropoietin, and increases the production of ineffective erythrocytes, which ultimately leads to enhanced reticulocytosis.[27,28,31] In fact, RDW showed a strong and graded association with inflammatory markers, which was independent of ferritin, age, sex, and other hematological variables.[30] Multiple factors are associated with heightened inflammatory response.[32-34] Therefore, elevated preoperative RDW level may signify the presence of underlying sepsis, malnutrition, impaired cardiovascular function, or malignancy, which contributed to an increased overall mortality.

RDW alone may not serve as an influential prognostic indicator given its considerably low sensitivity and specificity at the cutoff value of 13.35. However, the value of RDW lies on its ready availability with the results produced from automated CBC. The use of RDW in combination with other known prognostic markers may increase the performance of risk models. For example, a combination of RDW with mean platelet volume and neutrophil-to-lymphocyte ratio might offer better adverse events (defined as myocardial infarction, cardiac reoperation, prolonged mechanical ventilation, prolonged hospital stay, rehospitalization, and mortality) predictions among patients who received cardiac surgery.[23] Mizuno *et al.* also illustrated the potential benefit of RDW combined with Mehran Risk Score for the prediction of contrast-induced acute kidney injury in patients with ST-elevated myocardial infarction.[35]

Zhao *et al.* combined the predictive value of RDW and GRACE risk score to yield a more accurate predictive value for long-term cardiovascular events in acute coronary syndrome patients who underwent percutaneous coronary intervention as compared to each measure alone.[36] Recently, Yin *et al.* reported that a combination of RDW and the ASA score may provide a more powerful and effective strategy (AUC increased from 0.700 to 0.723) for the prediction of all-cause mortality in hip fracture patients.[37] Considered it is one of the essential components derived from CBC, RDW adds minimal administrative cost without additional blood test and provides a potential advantage in improving prognostic evaluation. Its potential application in preoperative assessment in combination with other hematological parameters or scoring system warrants further investigations.

Limitations of the study

First, this study was a single-center study where the majority of patients (98%) were Chinese. The result might not be applicable for other ethnicities. Second, the RDW values in this study were produced by our institution's laboratory catered to local population with reference to the CLSI-approved guideline. Variability with international models might exist, which may be explained by the fact that different analyzers use different algorithms to analyze cell distribution. Third, there was no consensus on the optimal cutoff value of RDW for its prognostic purpose. We employed Youden index to determine the optimal cutoff value within the ROC curve. However, this cutoff value may not be applicable in other clinical situations. Finally, patients who had elective surgery in our hospital might not necessarily have regular blood test monitoring, hence rendering us unable to investigate the importance of the RDW trend in postoperative period.

Conclusions

Although preoperative RDW independently predicted 30-day mortality in patients who underwent major- or ultra-major noncardiac surgery, it may not serve as an influential prognostic indicator in view of its considerably low sensitivity and specificity. Its potential application in preoperative assessment in combination with other hematological parameters or scoring system warrants further investigations.

Conflicts of interest

There are no conflicts of interest.

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