Red Cell Distribution Width Predicting In-Hospital Mortality in Patients with Acute Coronary Syndrome and Chronic Kidney Disease

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ABSTRACT

The prognostic value of red cell distribution width (RDW) in predicting in-hospital mortality in patients with acute coronary syndrome (ACS) has been validated in several surveys. Our aim was to assess the predictive value of RDW and whether the RDW has additional prognostic value on the GRACE RS in prediction of in-hospital mortality in patients with ACS and CKD. We retrospectively studied the medical data of 344 consecutive patients with a diagnosis of ACS and CKD between January, 1st 2011 and July, 30th 2014. The discrimination of RDW and GRACE RS to predict in-hospital all-cause mortality was evaluated by the C-statistic test. Multivariate logistic regression analysis was performed to assess the independent predictors of in-hospital mortality. The predictive value and discriminative ability of the model with GRACE RS alone and of the model with inclusion of RDW was both assessed. 66 patients (19.2%) died during hospitalization. RDW of in-hospital death was significantly higher than that of in-hospital survivors [14.3(13.7, 14.8) vs 13.4(12.8, 13.9), P<0.001]. After multivariate logistic analysis, RDW was an independent predictor of in-hospital mortality (OR 1.357, 95% CI 1.067 to 1.724, P =0.013). The best cut-off for RDW was 13.6%. Compared with the GRACE RS, inclusion of RDW improved the AUC from 0.866 (95% CI 0.821 to 0.911) to 0.882 (95% CI 0.838 to 0.926) (P=0.035). As an independent predictor of in-hospital mortality, RDW was useful in risk stratification of patients with ACS and CKD. RDW added the predictive value of GRACE RS for in-hospital mortality.

Key words: Red cell distribution width, acute coronary syndrome, chronic kidney disease, GRACE risk score, mortality.

INTRODUCTION

Despite advances in the diagnosis and treatment, Acute Coronary Syndromes (ACS) still accounts for most of the mortality and disability all over the world (Lopez et al, 2006). It is important for ACS patients receiving early risk estimation because patients who have higher risk may benefit from earlier and more aggressive treatment (Mehta et al, 2009). Chronic kidney disease (CKD) has a high prevalence in ACS population nowadays. Several researches
showed that CKD is an independent risk factor for the development of coronary artery disease, and for more adverse outcomes in patients with cardiovascular diseases (Masoudi et al., 2004; Banerjee et al., 2007; Beattie et al., 2001; Ix et al., 2005).

The Global Registry of Acute Coronary Events risk score (GRACE RS) was developed from a large multinational registry to predict the outcomes across the whole spectrum of ACS population (Eagle et al., 2004; Granger et al., 2003; Lyon et al., 2007). The validity of the score has been demonstrated in many studies and it is recommended in current guidelines for the risk stratification of ACS patients (Elbarouni et al., 2009; Fujii et al., 2014; Lin and Kerr, 2014).

Red cell distribution width (RDW) represents the variation in the size of red blood cell and is routinely reported as part of the complete blood count. RDW was often used as an indicator to differentiate types of anemia. Recent studies showed that high RDW is associated with poor prognosis in patients with heart failure, stable angina pectoris and ACS (Felker et al., 2007; Tonelli et al., 2008; Lappe et al., 2011).

It was also demonstrated that high RDW is an independent predictor of high GRACE RS, and it is associated with high in-hospital mortality in ACS patients (Polat et al., 2014).

Our aim was to investigate the predictive value of RDW and whether the RDW has additional prognostic value on top of the GRACERS in predicting in-hospital mortality in the relative high risk population that is, patients with CKD and ACS.

MATERIALS AND METHODS

Design

Our study was a single-center, observational study. We retrospectively studied the medical data of 344 consecutive patients with a diagnosis of ACS and CKD between January, 1st 2011 and 30th July, 2014, in Beijing Chao-Yang Hospital, Capital Medical University, China. The present study enrolled 349 patients at first, 5 patients died before we got the necessary data to calculate the GRACERS; they were excluded from the study. Information of patients’ demographic characteristics, such as risk factors for coronary artery disease, previous disease history and vital signs during hospitalization were collected and preserved with a high quality. We did not obtain informed consent from participants involved in our study because we used anonymous data compiled from electronic medical record. The present cohort did not take part in the original cohort used for the development of the international multicenter GRACE registry. Endpoint was in-hospital all-cause mortality. All blood samples were obtained on patients’ admission. Baseline values of RDW and creatinine level were determined using the Sysmex XE-2100™ and Dimension RxL Max™ automated analyzer, respectively. Normal reference range for RDW is 10 to 15%. Normal reference range for creatinine level is 53 to 115 μmol/L in men and 35 to 106 μmol/L in women.

Definitions

ACS

ACS includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). NSTEMI and UAP are also known as non-ST-segment elevation ACS (NSTEACS).

STEMI

This is defined as symptoms consistent with cardiac ischemia, and ≥ 1 positive cardiac biochemical marker of necrosis with electrocardiogram (ECG) changes: ST-segment elevation >1 mm in 2 contiguous leads with reciprocal ST depression, new or presumed new left bundle branch block.

NSTEMI was diagnosed in the presence of symptoms with ≥ 1 positive cardiac biochemical marker of necrosis and without new ST-segment elevation seen on ECG.

UAP was diagnosed when patients had typical symptoms of cardiac ischemia with the absence of ST-segment elevation on ECG and negative found in serum cardiac biochemical marker of necrosis. Prominent T-wave inversion and/or ST-segment depression can be seen on NSTEACS patients’ ECG. The diagnosis of ACS was followed by the contemporary universal definition (Thygesen et al., 2012).

CKD

CKD is defined as glomerular filtration rate (GFR) ≤ 60 ml/(min· 1.73 m²). GFR was calculated by the modified modification of diet in renal disease (MDRD) formula: GFR[ml/(min·1.73 m²)] = 186 ×[serum creatinine (mg/dl)]⁻¹.¹⁵⁴ ×[age (y)]⁻⁰.²⁰³ ×[0.742 (female)] (Tarantini et al., 2015). Serum creatinine level was from the blood samples obtained on admission.

Hypertension (HT) and diabetes mellitus (DM)

HT and DM were defined as either previously known or on specific therapy.

The GRACE RS

As previously described, GRACE is a multinational,
prospective observational registry enrolling full spectrum of ACS patients. The GRACE RS was developed from it and designed to predict short-term and long-term mortality. It was calculated from 8 factors: age, heart rate, systolic blood pressure (SBP), Killip class, cardiac arrest, ST segment deviation, serum creatinine and elevated cardiac enzyme levels (Granger et al., 2003).

Statistical analysis

Normality of variables was tested by Kolmogorov-Smirnov test. Normally distributed continuous variables were presented as mean ± SD. Student’s t-test was used to determine statistically significant differences between the two (2) different groups. Abnormally distributed data were given as median (interquartile range). Mann–Whitney U-test was used to determine statistically significant difference between the two (2) different groups. Pearson’s chi-squared test was used for dichotomous variables expressed as percentages. Multivariate logistic regression analysis was performed to assess the independent predictors of in-hospital mortality. Receiver operating characteristic (ROC) curve analysis and the area under the ROC curve (AUC) was used to evaluate the accuracy of RDW and the GRACE RS to predict in-hospital all-cause mortality. AUCs were compared by z-statistics. The best cut-off point of RDW was selected by maximizing the sum of sensitivity and specificity. P value less than 0.05 was considered statistically significant. All statistical calculations were performed in SPSS 16.0 (IBM, Xi An, China).

RESULTS

Three hundred and forty-four (344) patients with a diagnosis of ACS and CKD were enrolled in our study. Seventy patients were diagnosed with STEMI (22.4%), others (77.6%) presented with NSTEMI. The mean RDW of all patients was 13.5% (12.9 and 14.1%) respectively. The mean GRACE RS of all patients was 164.7 ± 45.1. 66 patients died during hospitalization (19.1%), including 57 cardiac death (86.4%), 7 hemorrhagic death (10.6%) and 2 infectious death (3%). According to the outcomes, patients were separated into 2 groups (Table 1).

RDW of in-hospital death was significantly higher than that of in-hospital survivors [14.3 (13.7, 14.8) vs 13.4 (12.8, 13.9), P < 0.001]. Multivariate logistic regression analysis was performed to assess the independent predictors of in-hospital mortality. The logistic regression model included all significant variables found in Table 1 (gender, STEMI, Current smoker, SBP, HR, KILLIP class, ST segment deviation, Elevated cardiac enzyme, HDL-C, RDW, Hb and NT-proBNP). After multivariate analysis, RDW was an independent predictor of in-hospital mortality (OR: 1.357, 95% CI: 1.067-1.724, P = 0.013). Because several variables earlier mentioned are the components of the GRACE RS, we did the multivariate analysis again with only GRACE RS and RDW was included. The result turned out to be similar (OR: 1.351, 95% CI: 1.088-1.678, P = 0.006).

In ROC analysis, the best cut-off for RDW identified in-hospital mortality was 13.55, with a sensitivity of 88.9% and a specificity of 61.4% (AUC=0.78, 95% CI: 0.721-0.84, P < 0.001, Figure 1). The GRACE RS showed a high discriminatory capacity in all patients (AUC=0.866 95% CI 0.821-0.911, P < 0.001, Figure 2). AUC increased significantly after the inclusion of RDW in the GRACE RS model (from 0.866 to 0.881, P=0.035, Figure 3).

DISCUSSION

RDW reflects variability in circulating red blood cell size and is routinely reported as part of the complete blood counts. It is based on the width of red blood cell volume distribution curve, with larger values indicating greater variability. The present study demonstrated that high RDW was an independent predictor of in-hospital mortality and added the predictive value of the GRACE RS. To the best of our knowledge, this is the first time the addition of RDW to the GRACE RS for the prediction of in-hospital mortality in patients with CKD and ACS was evaluated.

The important value of RDW in patients with cardiovascular disease was shown in recent studies. High RDW was an independent predictor of reinfarction, heart failure, short-term and long-term mortality in ACS patients (Felker et al., 2007; Tonelli et al., 2008; Wang et al., 2011; Cavusoglu et al., 2010). High RDW was also associated with the severity of coronary lesions, thrombus burden, poor reperfusion, in-hospital mortality, and long-term mortality in patients with STEMI treated with primary percutaneous coronary intervention (PCI) (Isik et al., 2012; Tanboga et al., 2014). Our study demonstrated that RDW was an independent predictor of in-hospital all-cause death in the particular ACS population (OR: 1.357, 95% CI: 1.067-1.724, P = 0.013), which was consistent with previous studies. RDW is usually increased in conditions of deficiency of iron, B12 or folate, increased red cell destruction, hemoglobinopathies and blood transfusion (Forhecz et al., 2009). The mechanisms by which RDW is associated with unfavorable outcomes in ACS patients are still not known. Systemic inflammation and oxidative stress related to the ACS might be involved between elevated RDW and increased mortality (Allen et al., 2010; Wen 2010). Inflammation possibly contributes to an increased RDW by impairing iron metabolism and inhibiting the production response to erythropoietin. Exposure to greater oxidative stress can cause anisocytosis by reducing red cell survival, thus increasing the RDW values. However, hypotheses aforementioned should be further confirmed and there should be new studies in this issue.

The GRACE RS were developed from a large multinational registry to predict the outcomes across the broad spectrum of ACS population (Eagle et al., 2004; Granger et al., 2003;
The validity of it has been demonstrated in many studies and the GRACE RS is recommended in current guidelines for ACS patients' risk stratification (Elbarouni et al., 2009; Fujii et al., 2014; Lin and Kerr, 2014). The score was calculated from 8 factors: age, heart rate, systolic blood pressure (SBP), Killip class, cardiac arrest, ST segment deviation, serum creatinine and elevated cardiac enzyme levels. All concerned data were recorded on presentation. Our results presented that the GRACE RS was also suitable for predicting in-hospital all-cause mortality in patients with ACS and CKD, with AUC=0.866 (95% CI 0.821-0.911, P < 0.001). Combined Value of RDW and the GRACE RS was proved in several studies. Manuela et al (2014) showed that RDW might provide additional information over the GRACE RS in patients with acute myocardial infarction (AMI) (Manuela et al., 2014). In a study of Zhao et al (2015) the predictive value of adding RDW to the GRACE RS was superior to the predictive value of the GRACE score alone for major adverse cardiac events (MACEs) in ACS patients who underwent PCI (Zhao et al., 2015). With aging of the population, the number of CKD patients is increasing and CKD patients constitute a significant proportion of ACS patients nowadays (Dudek et al., 2008). A number of studies have demonstrated the mortality of patients with ACS and CKD is higher than general ACS population (Beattie et al., 2001; Ix et al., 2005; Dudek et al., 2008). However, no present study focused on the usage of RDW and the GRACE RS in the particular high risk population, whom we mean patients with CKD and ACS. Our results showed that RDW was useful in risk stratification of patients with ACS and CKD. Compared with the GRACE RS alone, inclusion of RDW improved the AUC from 0.866 (95% CI 0.821 to 0.911) to 0.882 (95% CI 0.838 to 0.926) (P=0.035).

There are few limitations in our study. First, as a retrospective study, the present study might undervalue the diagnostic accuracy of the GRACE risk score in patients with ACS and CKD because of the relatively small sample size. Second, 5 (1.4%) patients were excluded from the study because of the incomplete data to calculate the GRACE score.

### Table 1. Baseline characteristics of patients with ACS and CKD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death in hospital (n=66)</th>
<th>Survivors in hospital (n=278)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>77(72.82)</td>
<td>74(64.79)</td>
<td>0.001</td>
</tr>
<tr>
<td>male</td>
<td>37(56.1)</td>
<td>181(65.1)</td>
<td>0.089</td>
</tr>
<tr>
<td>STEMI</td>
<td>29(43.9)</td>
<td>48(17.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>34(51.5)</td>
<td>129(46.4)</td>
<td>0.478</td>
</tr>
<tr>
<td>HT</td>
<td>55(83.3)</td>
<td>232(83.5)</td>
<td>0.874</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>15(22.7)</td>
<td>48(17.3)</td>
<td>0.441</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>6(9.1)</td>
<td>37(13.3)</td>
<td>0.314</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>4(6.1)</td>
<td>24(8.6)</td>
<td>0.436</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10(15.2)</td>
<td>70(25.2)</td>
<td>0.026</td>
</tr>
<tr>
<td>Prior smoker</td>
<td>14(21.2)</td>
<td>65(23.4)</td>
<td>0.795</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125(110,150)</td>
<td>140(120,160)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 (65,80)</td>
<td>80 (70,90)</td>
<td>0.016</td>
</tr>
<tr>
<td>HR at admission (bpm)</td>
<td>86 (73,105)</td>
<td>75 (66,84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6(7.6)</td>
<td>174(62.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>14(21.2)</td>
<td>60(21.6)</td>
<td>0.904</td>
</tr>
<tr>
<td>III</td>
<td>32(48.5)</td>
<td>37(13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV</td>
<td>15(23.8)</td>
<td>8(2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>48(42.56)</td>
<td>50(45.56)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiac arrest at admission</td>
<td>2(3)</td>
<td>4(1.4)</td>
<td>0.222</td>
</tr>
<tr>
<td>ST segment deviation</td>
<td>60(90.9)</td>
<td>170(61.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated cardiac enzyme</td>
<td>57(86.4)</td>
<td>129(46.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>2.3(1.8,2.66)</td>
<td>2.28(1.83,2.82)</td>
<td>0.838</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>1.17(0.95,1.41)</td>
<td>1.04(0.86,1.23)</td>
<td>0.007</td>
</tr>
<tr>
<td>LP(a) (mg/dl)</td>
<td>25.5(19.2,47.9)</td>
<td>26.15(18.03,41.50)</td>
<td>0.512</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>14.3(13.7,14.8)</td>
<td>13.4(12.8,13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb</td>
<td>108.4±22.8</td>
<td>116.1±23.4</td>
<td>0.017</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>11.9(9.95,12.3)</td>
<td>10.8(10.11,11.5)</td>
<td>0.079</td>
</tr>
<tr>
<td>PDW (%)</td>
<td>12.65(10.48,14.5)</td>
<td>12.1(10.83,13.5)</td>
<td>0.303</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>6279(2269,16100)</td>
<td>2001.5(393.26986.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.81(1.51,2.32)</td>
<td>1.74(1.45,2.31)</td>
<td>0.638</td>
</tr>
<tr>
<td>GFR (ml/minute/1.73 m²)</td>
<td>34.22(23.80,45.28)</td>
<td>36.74(25.12,48.65)</td>
<td>0.266</td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>212.7±3.5</td>
<td>153.6±4.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are number (%), mean (SD), or median (IQR).
Figure 1. Receiver operating characteristic curve for predicting in-hospital mortality by the RDW in patients with ACS and CKD. (n=344, C-statistic AUC=0.78, 95% CI: 0.721-0.84, P<0.001).

Figure 2. Receiver operating characteristic curve for predicting in-hospital mortality by the GRACE risk score in patients with ACS and CKD. (n=344, C-statistic 0.866, 95% CI 0.821-0.911, P<0.001).
risk score, which might cause some bias to the results.

Conclusions

RDW was proved to be an independent predictor of in-hospital mortality in patients with CKD and ACS. Moreover, RDW might add the predictive value over the GRACES in this population. Our findings discovered a new method to estimate the risk of CKD patients with ACS. We suggest when this kind of patients are present, both RDW and the GRACES should be used to help physicians make treatment strategies.

REFERENCES


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