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RED BLOOD CELL DISTRIBUTION WIDTH IMPROVES RECLASSIFICATION OF PATIENTS ADMITTED TO THE EMERGENCY DEPARTMENT WITH ACUTE DECOMPENSATED HEART FAILURE

ŠIRINA DISTRIBUCIJE ERITROCITA POBOLJŠAVA REKLASIFIKACIJU PACIJENATA PRIMLJENIH U HITNU SLUŽBU ZBOG AKUTNE SRČANE DEKOMPENZACIJE

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Summary

Background: The usual history of chronic heart failure (HF) is characterized by frequent episodes of acute decompensation (ADHF), needing urgent management in the emergency department (ED). Since the diagnostic accuracy of routine laboratory tests remains quite limited for predicting short-term mortality in ADHF, this retrospective study investigated the potential significance of combining red blood cell distribution width (RDW) with other conventional tests for prognosticating ADHF upon ED admission.
Methods: We conducted a retrospective study including visits for episodes of ADHF recorded in the ED of the University Hospital of Verona throughout a 4-year period. Demographic and clinical features were recorded upon patient presentation. All patients were subjected to standard Chest X-ray, electrocardiogram (ECG) and laboratory testing including creatinine, blood urea nitrogen, B-type natriuretic peptide (BNP), complete blood cell count (CBC), sodium, chloride, potassium and RDW. The 30-day overall mortality after ED presentation was defined as primary endpoint.

Kratak sadržaj

Uvod: Istoriju hronične srčane insuficijencije (SI) obično karakterišu česte epizode akutne dekompenzacije (ASD), koja zahteva urgentno lečenje u odeljenjima hitne službe (HS). Kako dijagnostička tačnost rutinskih laboratorijskih testova i dalje ima znatna ograničenja kad se radi o predviđanju kratkoročnog smrtnog ishoda u ASD, ova retrospektivna studija istraživala je potencijalni značaj kombinovanja širine distribucije eritrocita (ŠDE) i drugih uobičajenih testova za prognoziranje ASD posle prijema u HS.
Metode: Sproveli smo retrospektivnu studiju koja je uključila posete zbog epizoda ASD zabeležene u HS Univerzitetske bolnice u Veroni tokom perioda od 4 godine. Demografske i kliničke odlike su zabeležene posle prijema pacijenata. Svi pacijenti su podvrgnuti standardnom rendgenu grudnog koša, elektrokardiogramu (EKG) i laboratorijskom testiranju koje je obuhvatilo kreatinin, ureu u krvi, natriuretski peptid B-tipa (BNP), kompletnu krvnu sliku (CBC), natrijum, hlorid, kalijum i širinu distribucije eritrocita. Ukupan broj smrtnih ishoda u roku od 30 dana posle prijema u HS je definisan kao primarna krajnja tačka.

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Results: The values of sodium, creatinine, BNP and RDW were higher in patients who died than in those who survived, whilst hypochloremia was more frequent in patients who died than in those who survived. The multivariate model, incorporating these parameters, displayed a modest efficiency for predicting 30-day mortality after ED admission (AUC, 0.701; 95% CI, 0.662–0.738; p=0.001). Notably, the inclusion of RDW in the model significantly enhanced prediction efficiency, with an AUC of 0.723 (95% CI, 0.693–0.763; p<0.001). These results were confirmed with net reclassification improvement (NRI) analysis, showing that combination of RDW with conventional laboratory tests resulted in a much better prediction performance (net reclassification index, 0.222; p=0.001).
Conclusions: The results of our study show that prognostic assessment of ADHF patients in the ED can be significantly improved by combining RDW with other conventional laboratory tests.

Keywords: acute decompensated heart failure, red blood cell distribution width, net reclassification improvement, laboratory parameters

Rezultati: Vrednosti natrijuma, kreatinina, BNP i ŠDE bile su više kod pacijenata koji su umrli nego kod onih koji su preživeli, dok je hipohloremija bila češća kod pacijenata koji su umrli nego kod onih koji su preživeli. Multivarijantni model koji je uključio ove parametre pokazao je umerenu efikasnost za predviđanje smrtnog ishoda u roku od 30 dana po prijemu u HS (AUC, 0,701; 95% CI, 0,662–0,738; p=0,001). Primećeno je da je uključivanje ŠDE u ovaj model značajno poboljšalo efikasnost predikcije, sa AUC od 0,723 (95% CI, 0,693–0,763; p<0,001). Ovi rezultati su potvrđeni analizom neto pobošljanja reklasifikacije (net reclassification improvement, NRI), koja je pokazala da kombinovanje ŠDE sa uobičajenim laboratorijskim testovima ima za rezultat mnogo bolju predikciju (indeks neto reklasifikacije, 0,222; p=0,001).
Zaključak: Rezultati ove studije pokazuju da prognostička procena pacijenata sa ASD u HS može biti značajno pobošljana ukoliko se ŠDE kombinuje sa drugim uobičajenim laboratorijskim testovima.

Ključne reči: akutna srčana dekompenzacija, širina distribucije eritrocita, pobošljanje neto reklasifikacije, laboratorijski parametri

Introduction

Heart failure (HF) is a leading cause of hospitalization and death in Western countries. It has been recently estimated that more than 500,000 patients are hospitalized each year with a first diagnosis of HF in the United States (1). Due to the progressive aging of the population and improved management of other chronic conditions such as diabetes, hypertension and cardiac valvular disorders, the prevalence of HF is also constantly increasing, so that the epidemiologic burden of this condition now resembles a real epidemics, associated with considerable risk of mortality, morbidity and healthcare expenditure (2, 3).

The usual history of chronic HF is characterized by frequent episodes of acute decompensation (ADHF) needing urgent management in the emergency department (ED), which is then frequently followed by hospitalization (4, 5). Despite some progresses observed in the past decades, the mortality for ADHF remains considerably high, approaching 12% at 30 days after ED assessment (6), with a 30 days re-hospitalization rate as high as 20% (6, 7). This last aspect is mainly due to the fact that the frequent recurrence episodes contribute to worsen cardiac function, thus ultimately compromising the prognosis (7).

Laboratory diagnostics plays a crucial role during the initial evaluation of ADHF patients (8). Both traditional laboratory tests (hemoglobin, chloride, sodium, blood urea nitrogen (BUN), creatinine, natriuretic peptides) routinely performed upon ED admission (9, 10) and the vast array of innovative cardiac biomarkers (i.e., galectin-3, interleukin 1 and 6, soluble ST2) (11, 12) were found to be variably associated with, and predictive of, the clinical history of disease. Whilst the use of innovative biomarkers is an appealing perspective, still confined to highly specialized or research laboratories, several lines of evidence attest that the diagnostic accuracy of routine laboratory tests remains quite limited for predicting short-term mortality in ADHF (11–12).

The red blood cell (RBC) distribution width (RDW) has been largely investigated for establishing the prognosis of patients admitted to the ED with many acute disorders (13). Notably, increased values of RDW measured upon ED admission were found to be associated with increased short-term mortality also in ADHF patients (14, 15). It is hence conceivable that the combination of RDW with other routine laboratory tests may enhance the efficiency of prognostic information provided by laboratory diagnostics in patients with ADHF.

Therefore, this study was aimed at assessing whether RDW determination during initial laboratory assessment of ADHF patients may allow to better predict 30-day mortality risk, by using an approach based on net reclassification improvement (NRI).

Materials and Methods

Patient population

We conducted a retrospective study based on reassessment of all urgent visits for an episode of ADHF recorded in the ED of the University Hospital in Verona between January 1, 2013 and December 31, 2016. HF has always been diagnosed according to the recent guidelines of the European Society of Cardiology (ESC), and thus based on the presence of suggestive diagnostic signs and symptoms including

respiratory distress, dyspnea, paroxysmal nocturnal dyspnea, peripheral edema, jugular turgor, hepatojugular reflux, tachypnea and pulmonary stasis (16). The main demographic and clinical features were recorded upon patient presentation to the ED. The patients were all subjected to standard Chest X-ray, electrocardiogram (ECG) and laboratory testing. According to the local protocol, the following laboratory tests were performed: creatinine, BUN, B-type natriuretic peptide (BNP), complete blood cell count (CBC), sodium, chloride and potassium.

The patients records were then reevaluated by two emergency physicians to confirm the correctness of the diagnosis and to delete wrong records (i.e., all diagnoses not complying with the ESC diagnostic criteria). Additional exclusion criteria included: 1) impossibility to immediately perform standard Chest X-ray examination in the ED; 2) diagnosis of acute myocardial infarction (AMI) according to the ESC guidelines (17); 3) patients missing follow-up; 4) incomplete data of laboratory testing at ED presentation. The 30-day overall mortality after ED presentation was defined as the primary endpoint. Mortality data was obtained by consultation of the registry office. This retrospective study was carried out in agreement with the Helsinki Declaration, according to the terms of relevant local legislation, and was cleared by the local institutional review board.

Statistical analysis

Categorical variables were reported both as percentages and as number of events, and differences were analyzed with Fisher Exact Test or Chi-square Test. Continuous variables were reported as median and interquartile range (IQR), and differences were analyzed with Mann-Whitney U Test.

The results of laboratory tests were logarithmically transformed and then standardized (mean of 0 and SD of 1), as suggested by Schnabel et al. (18). The parameters that were found to be significantly different in ADHF patients who died or survived within 30 days after ED admission were then entered into a multivariable logistic regression analysis with the backwards elimination method (likelihood-ratio test). The odds ratio (OR) and the relative 95% confidence interval (95% CI) were finally estimated for variables which independently predicted the risk of death 30 days after ED admission. The diagnostic performance of the final model, obtained from multivariate analysis and including the significant predictors of 30-day mortality (i.e., $p<0.05$), was assessed by calculating the area under the curve (AUC) in an operating receiver characteristic (ROC) analysis.

The NRI approach (19) was used to verify whether the RDW value may ameliorate the overall prognostication by reclassification of patients whose risk had been previously estimated using conventional laboratory analyses. The NRI hence was applied to all patients who died or survived 30 days after ED admission, using the following risk categories: <5%, 5–10% and >10% (20, 21). These different cut-offs were then analyzed with survival analysis (Log-Rank test) to compare the 30-day cumulative mortality among the three risk groups. The statistical analysis was performed using STATA statistical software (Stata Corp LP, College Station, TX, USA). The statistical significance was set at $p<0.05$.

Results

A total number of 2278 visits for an episode of ADHF were recorded in the ED of the University Hospital of Verona throughout the 4-year study period. Of these, 554 ought to be excluded due to discordant diagnosis with ESC criteria (n, 122), diagnosis of AMI (n, 73), missing follow-up (n, 35) or lack of complete laboratory testing immediately at ED admission (n, 344). Therefore, the final study population consisted of 1704 ED visits (mean age 83 years, 51.6% women). *Table I* shows the demographic, clinic and laboratory data of the study population divided into patients who died (217/1704; 12.7%) and those who survived at 30 days. The values of sodium, creatinine, BNP and RDW were found to be higher in patients who died than in those who survived, whilst hypochloremia was more frequent in patients who died than in those who survived. In backward stepwise selection multivariable logistic regression, the risk of 30-day mortality was 67% higher per SD increase of BNP value, 39% higher per SD increase of creatinine value, 38% higher per SD increase of sodium value, and 66% higher per SD decrease of chloride value (*Table II*). The multivariate model, incorporating these parameters, displayed a modest efficiency for predicting 30-day mortality after ED admission (AUC, 0.701; 95% CI, 0.662–0.738; $p=0.001$). Notably, the inclusion of RDW in the model significantly enhanced the prediction efficiency, displaying a significant increase of AUC (0.723; 95% CI, 0.693–0.763; $p<0.001$) (*Figure 1*). The NRI resulting from the combination of RDW with the previous model based on BNP, creatinine, sodium and chloride is shown in *Table III*. In the category of ADHF patients who died within 30 days after ED admission, the incorporation of RDW in the predictive model allowed to reclassify 27 patients in higher risk categories (i.e., more accurate classification, bold font), whilst 20 patients were inaccurately reclassified as having a lower risk (i.e., less accurate classification, italic font). As regards the category of patients who survived, the incorporation of RDW in the predictive model allowed to reclassify 437 patients in a lower risk category (i.e., more accurate classification, bold font), whilst 155 patients were inaccurately reclassified as having a higher risk (i.e., less accurate classification, italic font). Overall, the NRI net reclassification index,

Table I Demographic, clinical and laboratory data of the study population.

Variable	Patients survived	Patients died	p
ADHF episodes, n (%)	1487 (87.3)	217 (12.7)	
Sex, n (%)			0.310
Men	712 (47.9)	112 (51.6)	
Women	775 (52.1)	105 (48.4)	
Age (years)	83 (76–88)	87 (80–92)	0.001
Clinical history			
Ischemic heart disease	410 (27.6)	53 (24.3)	0.353
Hypertensive cardiomyopathy	1167 (78.5)	154 (70.9)	0.019
Atrial fibrillation	666 (44.8)	101 (46.8)	0.598
Valvular heart disease	300 (20.2)	39 (18.2)	0.574
Chronic renal failure	280 (18.8)	47 (21.7)	0.340
Pacemaker	232 (15.6)	41 (18.7)	0.260
Drugs			
Loop diuretics	868 (58.4)	131 (60.3)	0.641
Potassium-sparing diuretics	247 (16.6)	37 (17.0)	0.918
Beta-Blockers	671 (45.1)	79 (36.6)	0.031
ACE inhibitors/sartans	578 (38.9)	64 (29.4)	0.011
Laboratory data			
Hb (g/L)	124 (110–138)	119 (105–134)	0.002
Creatinine (µmol/L)	101 (81–134)	120 (89–172)	0.000
Sodium (mol/L)	136 (135–138)	138 (134–142)	0.035
Chloride (mol/L)	99 (96–102)	97 (93–101)	0.000
Potassium (mol/L)	4.3 (4.1–5.2)	4.4 (3.9–5.1)	0.122
Leukocytes ($x10^9$/L)	9.1 (7.1–11.6)	9.2 (6.7–13.2)	0.516
BNP (pg/mL)	7517 (3031–13504)	11743 (6347–18376)	0.000
RDW (%)	14.3 (13.4–15.6)	15.2 (14.2–16.6)	0.000

ACE, angiotensin converting enzyme; BNP, B-type natriuretic peptide; RDW, red blood cell distribution width.

Table II Multivariable logistic regression analysis for prediction of 30-day mortality in patients with acute decompensated heart failure (BNP, creatinine, serum natrium and chloride are considered as continuous variables).

Coefficient	Standard error	Odds ratio	95% CI	p	
Final model					
BNP	0.511	0.088	1.666	1.403–1.979	<0.001
Creatinine	0.331	0.071	1.392	1.212–1.599	<0.001
Hypernatremia	0.323	0.110	1.381	1.112–1.715	0.003
Hypochloremia	0.509	0.111	1.665	1.340–2.068	<0.001
Final model + RDW					
BNP	0.460	0.088	1.584	1.333–1.882	<0.001
Creatinine	0.278	0.072	1.321	1.148–1.520	<0.001
Hypernatremia	0.306	0.110	1.358	1.094–1.686	0.006
Hypochloremia	0.496	0.111	1.642	1.322–2.039	<0.001
RDW	0.379	0.074	1.461	1.263–1.690	<0.001

BNP, B-type natriuretic peptide; RDW, red blood cell distribution width.

which expresses prediction performance gained by adding a specific parameter, was 0.222 (p=0.001). Better reclassification was especially evident in the intermediate risk group, where 40.3% (25/62) of patients who died and 34.9% (275/787) of those who survived were more accurately classified versus 9.6% (6/62) and 17.8% (140/787) of patients whose risk was instead less accurately stratified. Overall, the inclusion of RDW in the model allowed achieving a better risk stratification of 16.9% of the patients admitted to the ED with ADHF (*Figure 2*).

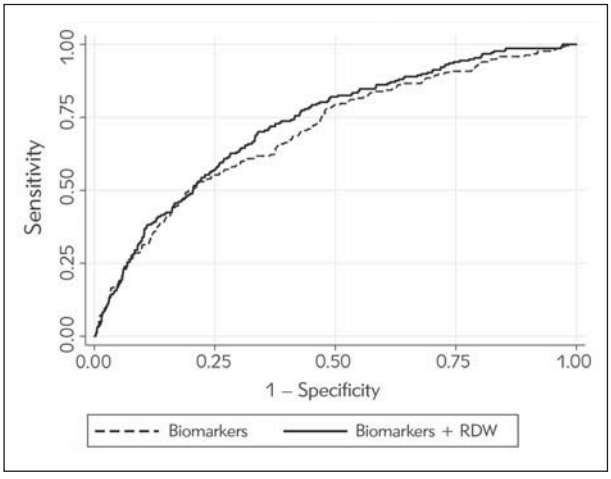

Figure 1 Receiver operating characteristics (ROC) curve analysis of a predictive model for 30-day mortality in patients with acute decompensated heart failure (ADHF). Comparison of a predictive model based on conventional laboratory tests (i.e., B-type natriuretic peptide, creatinine, sodium and chloride), with or without red blood cell distribution width (RDW).

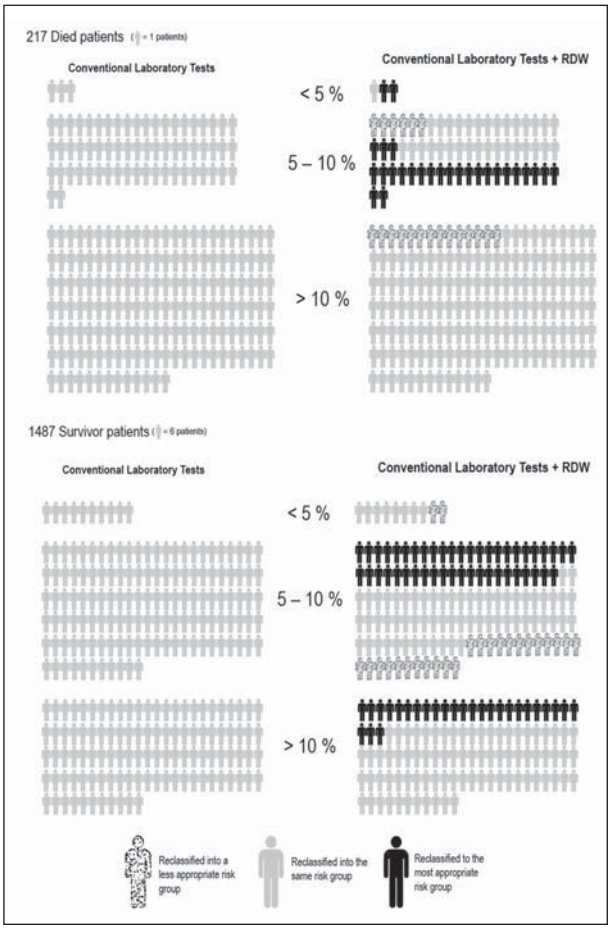

Figure 2 Results of the net reclassification improvement (NRI) after including red blood cell distribution width (RDW) in a predictive model based on conventional laboratory tests (i.e., B-type natriuretic peptide, creatinine, sodium and chloride).

Table III Results of net reclassification improvement (NRI) obtained by combining red blood cell distribution width (RDW) with conventional laboratory tests (B-type natriuretic peptide, creatinine, sodium and chloride).

	Conventional Tests	Conventional Tests + RDW		
		< 5%	5–10%	> 10%
Patients died				
< 5%	3	1	**2**	0
5–10%	62	*6*	31	**25**
> 10%	152	*0*	*14*	138
Total	217	7	47	163
	Conventional Tests	Conventional Tests + RDW		
Patients survived		< 5%	5–10%	> 10%
< 5%	61	46	*10*	*5*
5–10%	787	**275**	372	*140*
> 10%	639	**7**	**155**	477
Total	1487	328	537	622

Bold font, more accurate risk classification; *italic* font, less accurate risk classification.

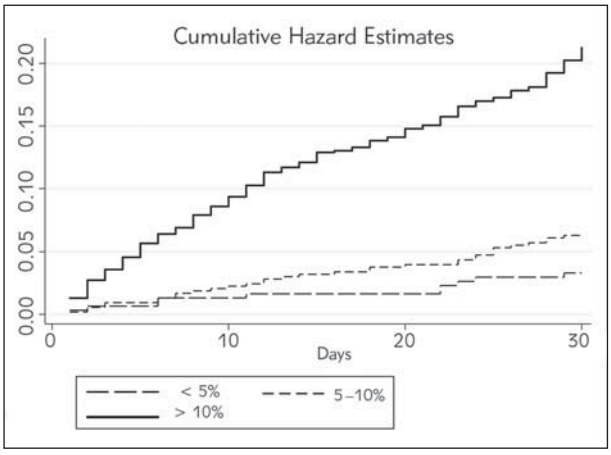

Figure 3 Survival curve analysis after including red blood cell distribution width (RDW) in a predictive model based on conventional laboratory tests (i.e., B-type natriuretic peptide, creatinine, sodium and chloride).

Figure 3 shows the comparison of 30-day cumulative mortality risk after ED assessment among the three risk thresholds after NRI. Notably, patients belonging to the >10% risk category were more likely to die at 30 days than those in lower risk categories (Log Rank Test, $p<0.001$).

Discussion

Heart failure (HF) is currently diagnosed in over 10% of subjects aged 65 years or older in developed countries (2, 22). The frequent and often life-threatening episodes of ADHF occurring in HF patients need timely therapeutic management and are associated with a remarkably high rate of hospitalization and mortality (2, 23). Like in other potentially lethal conditions that are frequently observed in the ED, timely diagnosis and prognostication are the mainstays for optimizing management of patients with ADHF, and thus lowering the risk of long-term hospitalization and death (24, 25). Nevertheless, consolidated evidence suggests that clinical history, physical examination, laboratory testing and even diagnostic imaging are not accurate enough to timely rule out a diagnosis of ADHF in the ED (24, 26).

Laboratory testing (i.e., ions, hemoglobin, creatinine, BUN, natriuretic peptides) upon ED admission may provide early prognostic information, which can support clinicians in the medical management of ADHF (26, 27). The prognostic role of chloride (28), sodium (29), creatinine and BNP (31, 32) measured at ED presentation has been extensively studied over the last decade. Albeit these tests were found to be associated with severity and risk of cumulative mortality of HF, their diagnostic accuracy was far below satisfactory, especially for predicting medium-term outcomes (26, 33–35).

The results of our study show that combination of RDW with some conventional tests such as BNP, creatinine, sodium and chloride, may improve 30-day prognostication of ADHF patients in the ED. More specifically, NRI showed that implementation of RDW in the clinical practice management of ADHF would definitely help to improve the prognostic accuracy provided by other routine laboratory tests. Notably, the role of RDW in HF has been critically acclaimed during the past decade, but definitive conclusions have been lacking.

The RDW value in ADHF, as well as in other acute cardiovascular disorders, is associated with disease severity (36, 37). Section et al. first demonstrated that RDW value >14.5% was independently associated with medium and long term survival in a prospective cohort of 707 patients (36). These results were confirmed by Van Kimmenade et al. (38) who showed that increased RDW was associated with 1-year mortality irrespective of BNP value and inflammatory state in 205 patients with ADHF. More recently, the evidence that RDW may be a significant prognostic factor in ADHF patients has been strengthened by the publication of studies with larger sample size and including specific patients' populations (e.g., African Americans, subjects with diabetes or cardiovascular disease) (39, 40, 41). Notably, Sotiropoulos et al. (42) recently carried out a prospective study in patients hospitalized for ADHF and with preserved left ventricular ejection fraction (LVEF), showing that high RDW values were associated with 1-year all-cause mortality. This concept has been recently reinforced by demonstrating that RDW variations (i.e., DeltaRDW) during the acute phase of hospitalization were better markers of adverse prognosis in patients with ADHF than the baseline values (43, 44).

Taken together, the results of our study demonstrate that routine assessment of RDW upon ED presentation may improve the risk assessment of patients with ADHF, improving especially the risk classification for 30-day mortality provided by other conventional laboratory tests. In particular, NRI analysis allowed to estimate that combination of RDW with BNP, creatinine, sodium and chloride could improve risk prediction in as many as 17% of patients admitted to the ED with ADHF, thus providing more accurate information for timely and appropriate patient management.

Our study, however, has some limitations. First, the retrospective design introduces a possible bias in the collection of clinical information, although the large sample size and the systematic and accurate exclusion of unclear records may have probably mitigated this drawback. Then, some clinical variables (e.g., echocardiographic assessment of ventricular function) which are significantly associated with disease severity, were unavailable in our investigation. Notably, the main scope of our study was to assess the prognostic efficiency of conventional laboratory

tests (with or without RDW). Therefore, future reclassification studies, including additional useful parameters such as echocardiography, may be advisable to verify whether or not risk stratification of ADHF patients may be further improved.

Conclusions

ADHF is an extremely severe condition still characterized by an inefficient diagnostic approach and high mortality rate (26). Nevertheless, our results show that the prognostic assessment of ADHF patients in the ED can be significantly improved by combining RDW with other conventional laboratory tests.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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