Review Article

Prognostic value of admission red blood cell distribution width in acute pancreatitis: a systematic review

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Background: Red blood cell distribution width (RDW) has been proved to be a strong prognostic marker in various diseases such as cardiovascular diseases, renal failure, viral hepatitis etc. But its prognostic value in acute pancreatitis (AP) remains controversial. The aim of this systematic review is to determine the prognostic value of RDW in AP.

Methods: PubMed, Cochrane, Google scholar, and Web of Science were searched on March 2, 2017 to identify studies that investigated the association between RDW and the prognosis of AP. The eligible studies were reviewed and summarized.

Results: In total, 2008 articles were screened. Seven studies were included in the final analysis. Five studies estimated the prognostic value of RDW using receiver operating characteristic (ROC) curve analysis, and multivariable analysis was performed in only four studies. The major design weaknesses of eligible studies are their retrospective design and some of potential confounding factors were not adjusted.

Conclusions: Current evidence and findings support that high admission RDW can be used as a biomarker to identify the AP patients who are at high risk of mortality. However, due to the weaknesses of available studies, further well-designed studies with large sample size and various outcome endpoints are needed to rigorously evaluate the prognostic value of RDW in AP.

Keywords: Red blood cell distribution width (RDW); acute pancreatitis (AP); prognosis; systematic review

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Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal cause of hospital admissions in US with approximately 275,000 hospitalizations in the year 2009 and annual incidence of up to 13–45/100,000 persons (1). Clinical manifestation and effects of AP, range from a mild, self-limited disease to severe and sometimes fatal disease. However, reported mortality from AP is about 1% but this risk increases with age, co-morbidities and development of complications, and varies from 7–42% in severe disease (1). Early identification of these patients who are at high risk of mortality in emergency room can help us with rational use of more aggressive treatment leading to decreased mortality rate (1). Therefore, there is a need for simple, easily obtainable and inexpensive markers to determine the prognosis of AP. In previous studies, several AP scoring systems and laboratory tests have been proposed and developed to estimate the prognosis of AP, such as Ranson's score, Balthazar score, BISAP score and SIRS score, C-reactive protein (CRP), serum blood urea nitrogen

(BUN), D-dimer and pro-calcitonin levels (2). However, there are multiple disadvantages associated with score systems such as hassle of calculation and need for ordering specific tests (2).

Red blood cell distribution width (RDW) is an easily obtained, inexpensive, routinely reported parameter as a part of the complete blood count test. It is commonly performed in the assessment of almost all the patients at the time of admission (3). Conventionally, RDW has been used as a tool to explore the etiologies of anemia (3). During the past decade, however, accumulated studies have shown that RDW is associated with the risk, disease activity and prognosis of various diseases, such as malignancies (4), heart failure (5), autoimmune diseases (6) and hepatocellular carcinoma (7) etc.

To date, multiple studies have investigated the usefulness of RDW in determining the prognosis of AP at the time of admission, but the results have not been consistent. Our aim is to perform a systematic literature review to summarize the published evidences from available studies on use of RDW at the time of admission to predict prognosis and mortality in AP.

Methods

Literature retrieval

We searched Medline (using PubMed as search engine), Cochrane, Google scholar, and Web of Science in March 02, 2017 to identify studies investigating the association between RDW and AP. The search algorithms used in PubMed were: ["red blood cell distribution width" or "red cell distribution width" or "RDW" or Erythrocyte Indices (mesh)]and pancreatitis. Similar strategies were used in Web of Science. Additionally, the references of each article were also searched for relevant citations.

Study selection and data extraction

After all the potential studies were retrieved, we performed a title and abstract screening to exclude irrelevant studies. For the remaining studies, a full text review was performed to justify the eligibility of the study. We only included studies investigating the prognostic value of RDW in AP patients, with outcomes of all-cause mortality, hospital mortality, pancreatitis specific mortality, intensive care unit (ICU) supervision, hospital length of stay, severity of disease, or presence of organ failure. Non-English publications were excluded.

The following data were extracted from eligible studies: first author, sources of subjects, publication year, sample size, type of data collection (prospective or retrospective), outcomes studied, mortality rate, area under receiver operating characteristic (ROC) curve (AUC) and its 95% confidence interval (95% CI), whether multivariable analysis was performed, and adjustment for confounding factors.

Results

Study selection process

Figure 1 is a flowchart of study selection. After screening and assessment, seven of them met the eligibility criteria and were included in our systematic review (9-15).

Summary of eligible studies

The characteristics of eligible studies are summarized in *Table 1*. The sample size of eligible studies ranged from 102 to 359 (9-15). Three studies were performed in Turkey (9,11,12), three studies (13-15) were performed in China, and one study (9) was based on clinical database named Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) from USA (16). All of the studies were retrospective design except one study did not report the type of data collection (13). The outcomes studied by the eligible studies included hospital mortality (9-11), AP mortality (13), and mortality within 48 hours (12) or within three months (14,15). The mortality rate ranges from 4.3% to 13.3%. All studies reported that the non-survivors have significantly higher admission RDW compared to survivors. Five studies (10,11,13-15) evaluated the prognostic value of RDW using ROC curve analysis, and three reported AUC values higher than 0.80 (11,13,14). While in the MIMIC II database study, the AUC was 0.66 (10).

By comparing the clinical characteristics of those who died *vs.* those who survived during hospitalization, the studies found that age, renal function, calcium and white blood cell count (WBC) were potential predictors for mortality (*Table 1*). However, only five studies analyzed the association between RDW and mortality using multivariable analysis (9-12,15), and four studies (9-11,15) reported that RDW was independently associated with mortality. The common confounding factors adjusted for in multivariable analysis including age (9,10,12,15), WBC (9,11), albumin

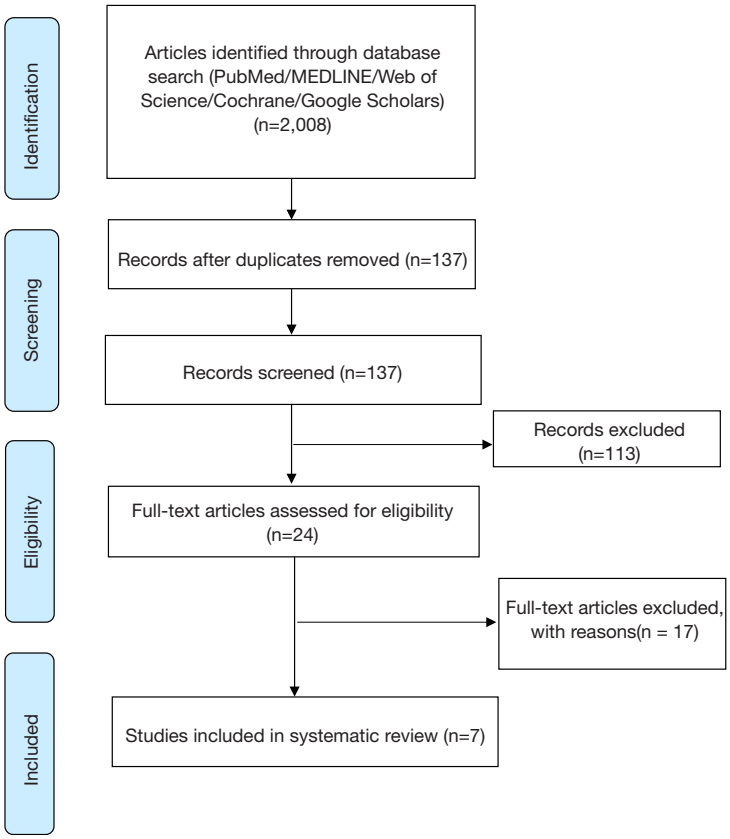

Figure 1 Flowchart of study selection (8).

(9,11), BUN (9,11), creatinine (10), calcium (9,11), platelet count (9,11). None of the studies investigated the association between RDW and ICU care, hospital length of stay or presence of organ failure. One study investigated the association between RDW and severity of AP and found that RDW is increased in severe acute pancreatitis (SAP) (15).

Discussion

This systematic review identified seven retrospective studies which investigated the prognostic value of RDW in AP. Employing different methodology and various RDW cut-off values, all of the included studies demonstrated that admission RDW significantly predicted clinical outcomes and mortality in AP. However, these studies, only adjusted for a limited range of potential confounding factors.

Using ROC curve analyses, three studies reported that the AUC of RDW for predicting mortality is more than 0.80. It is noteworthy that, also by using ROC curve analysis, many studies have investigated the predictive value of some well-recognized score systems in AP, including acute physiology and chronic health evaluation (APACHE) score (17), bedside index of severity in AP (BISAP) (18), Ranson score (19), Glasgow score (20), and the AUCs of these score systems are approximately 0.80 (20-26) which is comparable to that of RDW. These results indicate that RDW is a strong prognostic factor for AP. Additionally, five studies analyzed the association between RDW and mortality of AP using multivariable analysis, and four of them found that RDW is independently associated with mortality in AP. Taken together; these studies indicated that RDW has a utility in estimating the prognosis of AP.

The underlying pathophysiologic mechanism of association between RDW and prognosis of AP remains unclear. We postulate that the prognostic value of RDW in AP is mediated by inflammation response. This hypothesis is also supported by some previous studies. First, previous studies have suggested that RDW is an inflammatory marker and is positively correlated with inflammatory

Table 1 Summary of eligible studies

Author	Source country	Number of patients	Cause of AP	Data collection	Endpoint	Mortality rate (%)	AUC (95% CI)	Multivariable analysis	Potential predictors for mortality
Senol (11)	Turkey	102	75 ABP; 27 AAP	Retrospective	Hospital mortality	13/102 (12.7)	0.82 (0.69–0.95)	Performed	WBC, age, RDW, BUN, PLT, calcium, albumin
Yao (13)	China	106	NA	NR	AP mortality	8/106 (7.5)	0.85 (0.73–0.96)	Not performed	Age, BUN, creatinine, calcium, albumin, TP, LDH, WBC, RDW
Cetinkaya (9)	Turkey	102	75 ABP; 37 AAP	Retrospective	Hospital mortality	13/102 (12.7)	NR	Performed	Age, WBC, PLT, calcium, BUN, RDW, RPR, albumin
Gülen (12)	Turkey	322	226 ABP; 46 AAP; 60 other	Retrospective	Mortality within 48 h	14/322 (4.3)	NR	Performed	NLR
Wang (14)	China	120	75 ABP; 18 AAP; 27 NANB	Retrospective	Mortality within 3 months	16/120 (13.3)	0.89 (0.82–0.97)	Not performed	Calcium, albumin, TP, age, BUN, RDW, calcium
Hu (10)	USA database	162	NA	Retrospective	Hospital mortality	17/162 (10.5)	0.66 (0.52–0.81)	Performed	RDW, WBC, creatinine, SAPI, SOFA
Li (15)	China	359	39 AAP 181 ABP 139 others	Retrospective	100 day mortality	31/359 (8.64)	0.74 (0.70–0.79)	Performed	Age, NLR, CRP, PNI, LMR

AUC, area under receiver operating characteristic curve; WBC, white blood cell; BUN, blood urea nitrogen; PLT, platelet count; NR, not reported; AP, acute pancreatitis; TP, total protein; RPR, red blood cell distribution width to platelet ratio; LDH, lactate dehydrogenase; CI, confidence interval; SAPSI, simplified acute physiology score I; SOFA, sequential organ failure assessment; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PNI, prognostic nutritional index; CRP, C-reactive protein; ABP, acute biliary pancreatitis; AAP, acute alcoholic pancreatitis; NANB, non-alcoholic non-biliary pancreatitis.

markers in unselected outpatients (27) and apparently healthy individuals (28). Second, it is well-accepted that inflammation impairs the bone marrow function, iron metabolism and erythrocyte homeostasis (29). Increased inflammatory cytokines such as tumor necrosis factor α, interleukin-1 and interleukin-6 due to sepsis in AP, have been shown to suppress maturation of erythrocytes leading to entry of larger reticulocytes in the peripheral blood (30) causing elevation in RDW. Third, inflammatory markers such as CRP (31), pro-calcitonin (32,33) and tumor necrosis factor (TNF) (34,35) have been shown/used as a prognostic marker in AP. Fourth, Ucar Karabulut *et al.* retrospectively analyzed patient with AP and found that RDW value was significantly higher during the bout of AP when compared to the samples obtained after complete recovery (36). Taken together, these studies support that inflammation, at least partially, mediates the association between RDW and prognosis of AP.

During the past decades, several scoring systems have been proposed for early identification of increased morbidity, outcomes and mortality in AP such as acute physiologic assessment and chronic health evaluation II (APACHE II) score (17), systemic inflammatory response syndrome (SIRS) score (37), bedside index of severity in acute pancreatitis (BISAP) (18), Glasgow score (20) and sequential organ failure assessment (SOFA) (38). However, when compared with these scoring systems, RDW has its strengths. First, RDW is routinely ordered as part of a complete blood count (CBC), and is easily obtained without any additional costs (39). Second, it is readily available and easy to use in comparison to score systems as no calculations are needed.

Although available studies have indicated that RDW is a useful index for estimating the prognosis of AP, some limitations of these studies are worth mentioning. First, confounding factors should be considered when performing observational studies. Only five studies (9-12,15) adjusted for the effects of confounding factors using multivariable analyses, and four studies (9-11,15) reported that RDW is independently associated with mortality after potential confounding factors have been adjusted. However, most of the studies that adjusted for confounders might have failed to adjust for potential confounders including gender (40,41), unrecognized deficiency of iron, vitamins B12, and folate (42). Besides, RDW is also affected directly by alcohol intake which is the second most common cause of AP (42).

Second, all the available studies are observational and retrospective in design, and therefore, the reliability of the results is greatly affected by the representativeness of the subjects. Further studies with prospective design, with appropriate samples are needed to rigorously evaluate the prognostic value of RDW in AP.

Third, all of the studies included in the review have investigated the predictive value of RDW for hospital mortality, but none have investigated the prognostic value of RDW to predict the severity of AP or persistent organ failure. Additionally, the association between RDW and ICU care (admission or transfer), or length of hospital stay, were not studied. Further studies examining the possible prognostic value of RDW for predicting various outcomes related to AP are warranted.

In conclusion, the available evidences support that RDW is a useful index for predicting mortality in patients with AP. Future prospective studies with larger samples, robust analyses, and examining various outcomes related to AP are needed to rigorously evaluate the prognostic value of RDW in AP.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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