Prognostic value of Red Blood Cell Distribution Width in Acute Kidney Injury Patients: A Systematic Review and Meta-analysis

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Abstract

Background: The conflicting result with regard to Red Cell Distribution Width (RDW) with Acute Kidney Injury (AKI) has been reported. This systematic review and meta-analysis were aimed to investigate RDW and prognostic value in AKI patients.

Methods/Main Results: This meta-analysis included 1251 cases and 1663 controls with a total of 7 enrolled published papers. The results of RDW levels were significantly associated with patients of AKI (WMD=1.127, 95% CI=0.426-1.827; P=0.002), with statistically significant heterogeneity (I^2 =95.80%, $P_{heterogeneity}$ =0.000, random-effects model).

Conclusions: In conclusion, the results of this present meta-analysis suggest that the RDW value is a positive prognostic indicator in patients with AKI. However, these results were obtained on the basis of RCS or small sample sizes studies. Further functional studies with additional data would be needed to validate our findings.

Keywords: Red blood cell distribution width; Acute Kidney Injury; Meta-analysis

Introduction

Acute kidney injury (AKI), one of the most common and serious diseases in the intensive care unit (ICU), is defined as a drastic decrease in glomerular filtration rate with increase in serum creatinine (SCr) or decrease in urine output[1]. Previous studies have confirmed that AKI is an independent risk factor for high mortality range from 36.4% to 50%[1-4], especially in patients with critically illness[5]. In addition, patients with renal function recovery were often suffered from the chronic kidney disease and the major cardiovascular adverse events [6, 7]. Therefore, the early identification of the patients who may progress to AKI and use preventive measures to prevent the occurrence of AKI is crucial. However, AKI was only monitored by SCr which is elevated several hours to days after the renal function loss more than 50%[8, 9].

The red cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes with higher values reflecting greater heterogeneity in cellular sizes. As a part of complete blood cell count, RDW is generally determined among hospitalized patients because of its simplicity and availability[10, 11]. RDW is typically used

to differentiate the different causes of anemia[12], however, the present studies have observed that RDW could be used as a predictive marker in various diseases, including cardiovascular disease [11, 13], malignant tumors[14, 15], acute pancreatitis[16].

Currently, RDW was reported to be an independent predictor in patients with AKI [17-20] and the result remains inconclusion. Our meta-analysis was conducted to screen the current literature to evaluate prognostic value of RDW in the patients with AKI and explain this conflicting result.

Methods

Search strategy

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The association between RDW and AKI was evaluated by two investigators independently. The following databases were electronically searched on 12/6/2019, including PubMed, Embase (host: OVID) from 1980 to June 2019, and Web of Science. The following keywords of the search strategy were used: “acute kidney injury” or “acute kidney failure” or “acute renal injury” or AKI and “red cell distribution width” or RDW.

Inclusion and exclusion criteria

For those studies which were strictly qualified the following criteria were included: (a) studies focus on the association between RDW and AKI; (b) reported the available data on Means and SD values or interquartile range for RDW levels in AKI patients; (c) The diagnosis of AKI was clear; and (d) provided clear clinically relevant outcomes according to the comparisons of AKI versus non-AKI. The studies that met exclusion criteria was excluded and the following was exclusion criteria: (a) not research articles, for example conference abstracts, books, posters, letters, and review articles; (b) studies on animals not human; and(c) underlying disease with early renal injury.

Data Extraction

Based on the previous inclusion and exclusion criteria, the detail information and data of each eligible study was extracted by two review authors (Liu and Wang). An experienced author (Yao) participated to resolve controversy if the outcome and conclusion of the study still remained some uncertainties or discrepancies.

In this meta-analysis, data and information of the individuals of included studies were extracted, including the first authors name, publication year, country, ethnicity (Caucasian, Asian), study design(retrospective cohort study and case-control study), the mean age of the case and control (years), study population, the total (male and female)and male numbers

of cases and controls, definition of AKI, the RDW levels (means and standard deviation (SD) or median and interquartile range) of cases and controls, definition of outcomes, the quality of each study.

Quality Assessment

According to the guidelines of the NewCastle-Ottawa Quality Assessment Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), the quality of the eligible study was assessed. The NOS Cohort Studies for retrospective cohort study (RCS) score system was employed by corresponding to various type of study. Same to date extraction, two review authors did this work first, then the third author resolved controversy when the study still remained some uncertainties. The total NOS quality scores ranged from 0-9, and the NOS scores higher than 5 points indicated better quality and were suitable for meta-analysis.

Statistical analysis

We evaluated the association between RDW and AKI by extracting the mean and standard of RDW levels in each study. The published article of Van Driest et al. [21], which include two studies, did not provide the precise mean and SD values. We attempted to correlate this corresponding author but failed. Therefore, means and SD values in this study was calculated on the basis of the median and interquartile range.

By using random-effects model (DerSimonian and Laird method) or the fixed-effects model (Mantel and Haenszel method), the weighted mean difference (WMD) and 95% CIs were obtained to evaluate the prognostic value of RDW in AKI patients. All statistical analysis was performed using Stata 12.0 software (StataCorp, College Station, Texas, USA). The statistical significance was finally defined as a 2-tailed $P<0.05$.

To obtain the pooled results of heterogeneity in each study, we performed Cochran's Q test and I-squared statistic[22]. For heterogeneity, $P<0.10$ in Q test and/or I^2 value>50% was considered to indicate statistical significance, and the random-effects model (DerSimonian and Laird method) was applied to estimate the summary WMD and 95% CI; otherwise the fixed-effects model (Mantel and Haenszel method) was applied[23]. The sensitivity analysis was also carried out to evaluate the stability of our meta-analysis by omitting one study in total studies. Additionally, subgroup analyses were stratified by ethnicity(Caucasian, Asian), baseline mean age (years) of AKI(≥60, <60), Study population(CI-AKI, CSA-AKI, Other), Sample size in AKI cases(≥100, <100). Finally, we performed the Begg's [24] funnel plot and Egger's[25] tests to explore the potential publication bias, and the P value < 0.05 was considered statistically significant.

Results

Study characteristics

A flow diagram of the data search and study selection is presented in Figure 1. We carefully screened the databases and found a total of 96 articles (PubMed= 37, Embase= 32, Web of Science= 27) in initial search process. With 32 duplicate articles, which were removed, and leaving 64 articles for examining and reading titles and abstracts. Then, the full texts 22 papers were downloaded and examined for further investigation. Finally, a total of 7 enrolled published papers (8 studies) included 1251 cases and 1663 controls were identified meeting the criteria for inclusion in our meta-analysis, with publication years ranging from 2015 to 2018[21, 26-31].

The key features of 8 studies on the association between RDW and AKI are shown in Table 1. In those studies, half of which including Caucasian descents (3 published papers included 4 RCSs)[21, 26, 27] and the other half of which including Asian descents[28-31]. All the included studies were prospective cohort studies, and the mean age years of the patient with AKI range from 6.7 to 68.9. For the study population, 3 focused on contrast-induced acute kidney injury (CI-AKI), 3 focused on cardiac surgery-associated acute kidney injury (CSA-AKI), the other 2 focused on children with sepsis and patients who were receiving extracorporeal membrane oxygenation. The quality assessment of NOS scores range from 7 to 9, which demonstrated that it was suitable for meta-analysis.

Main results and Sub-group analyses

All the availability data from the included RCS were synthesized to evaluate the association between the RDW levels and AKI. The results of RDW levels were significantly associated with patients with AKI (WMD=1.127, 95% CI=0.426-1.827; P=0.002), with statistically significant heterogeneity (I^2 =95.80%, $P_{heterogeneity}$ =0.000, random-effects model; Figure. 2). Then, sub-group analyses were performed according to ethnicity (Caucasian, Asian), baseline mean age years of AKI(≥60, <60), Study population(CI-AKI, CSA-AKI, Other), Sample size in AKI cases(≥100, <100) , and the detailed information was shown in Table 2. When stratifying according to ethnicity, the statistically significant associations between RDW levels and patients with AKI were observed both in Asians (WMD= 1.472, 95% CI=0.392-2.552; P=0.008) and Caucasian (WMD= 0.577, 95% CI=0.308-0.846; P=0.000). For mean age years, a significant association was observed in both AKI patients baseline mean age over 60 years (WMD= 0.725, 95% CI=0.216-1.233; P=0.005) and under 60 years (WMD= 1.941, 95% CI=0.226-3.656; P=0.027). In the study population, the results showed that the RDW levels were of significant prognostic value with AKI patients, including CI-AKI (WMD= 0.582, 95% CI=0.314-0.849; P=0.000), CSA-AKI (WMD= 1.297, 95% CI=1.174-1.420; P=0.000), except the group of others (WMD= 1.751, 95% CI=-0.895-4.397; P=0.195; Table 2). The WMD of RDW levels was significant in studies with sample size more than 100 (WMD= 0.912, 95% CI=0.202-1.623; P=0.012), however, no significant prognostic value was detected in studies with sample size less than 100 (WMD= 1.261, 95% CI=-0.320-2.842; P=0.118).

Heterogeneity and Sensitivity analyses

As was shown in Table 2, we detected significant heterogeneity in the meta-analysis, however, there was no statistically significant heterogeneity according to Caucasian (I^2= 0.00%; $P_{heterogeneity=}$0.692); CI-AKI (I^2= 0.00%; $P_{heterogeneity=}$0.530); CSA-AKI (I^2= 0.00%; $P_{heterogeneity=}$0.781). Then we performed sensitivity analyses by consistently omitting one study to evaluate the influence of each single study on results, and it indicated that the results of this meta-analysis was reliable (Figure. 3). Furthermore, Begg's funnel plot and Egger's test were used to evaluate the publication bias. And there was no publication bias detected in association with RDW and AKI patients, with Begg's funnel plot (P_{Begg}= 0.902) and Egger's regression test (P_{Egger} = 0.824).

Discussion

AKI is a common complication of open heart surgery[32], major abdominal surgery[33] and contrast-associated diseases[34], with similar risk factor and outcome associations across different surgery type[35]. In the current study, AKI is frequently transient condition and strongly associated with increased mortality and morbidity[36]. As far as we know, AKI is interconnected with Chronic Kidney Disease (CKD), which results in end-stage renal disease risk and even death. The rates of death associated with CSA-AKI is maintained as high as 10 years regardless of other risk factors, even for those patients who had fully recovered from renal injury[37]. Although the most surgical treatment of secondary AKI is mild, it is still associated with long-term risk of death, especially in post-operative patients with severe AKI.

RDW is a rapid, simple, routinely laboratory test as a part of complete blood count, which is used to evaluate the abnormal properties of red blood cells and the possible causes of anemia. To our knowledge, high RDW is concerned with several diseases, including cardiovascular diseases[38, 39]; chronic kidney disease[40]; esophageal cancer[41]; upper aerodigestive tract cancer[42]; breast cancer[43]. Low RDW, however, may not be clinically significant. Recently, the predictive value of red blood cell distribution width for acute kidney injury was performed in several studies[44, 45]. RDW is considered as an independent prognostic marker in AKI patients, more importantly, higher RDW means high risk of mortality in AKI[17, 18]. Although RDW are known to be associated with AKI, the result remains unclear.

In present meta-analysis, the results demonstrated that RDW value are significantly higher in patients with AKI compared with that of non-AKI (WMD=1.127, 95% CI=0.426-1.827; P= 0.002). In subgroup analysis, the significant association was observed in CI-AKI (WMD= 0.582, 95% CI=0.314-0.849; P=0.000), and CSA-AKI (WMD= 1.297, 95% CI=1.174-1.420; P=0.000), with no heterogeneity detected. We also observed significant value in the ethnicity, mean age, and sample size in AKI cases. Collectively, this meta-analysis indicated that RDW would be prognostic for patients with AKI, especially for CI-AKI and CSA-AKI.

Although the mechanism of the RDW values in patients with AKI is at present unclear, several potential explanations may account for the relationship between RDW and AKI. Among the risk factors, anemia is the independent related to AKI[46], one present study indicated that the elevated RDW group in AKI was found to have low red blood cell (RBC) which may contribute to increase AKI occurring[28]. Previous studies have demonstrated RDW levels are associated

with inflammation and serum antioxidants which mediate effects on RDW through IL-6[47], and the IL-6 levels in serum may predict the mortality of AKI patients[48]. In addition, the increased of RDW levels was involved in the impaired residual renal functions[49].

Meanwhile, there are some weaknesses and limitations that should be emphasized in current study. First, we cannot disregard that the heterogeneity across the eligible study was observed in ethnicity, mean age, and sample size. Second, the study design of included studies was totally RCS, and the small number of included studies with a limited number of patients was selected for the present meta-analysis. Third, lack of consolidated standards of AKI, and the measurements of RDW is sometime completely discordant in those included studies. Forth, the patients receiving ECMO, which probably have affected on RDW values, could not be exactly evaluated. Finally, due to absence of required information, we did not have an opportunity to understand the mortality, outcome event, presence or absence of anemia.

Conclusions

In conclusion, the results of this present meta-analysis suggest that the RDW value is a positive prognostic indicator in patients with AKI. However, these results were obtained on the basis of RCS or small sample sizes studies. Further functional studies with additional data would be needed to validate our findings.

Authors' Contributions

Zhengsheng Liu and Shanshan Wang contributed equally to this work as first authors.

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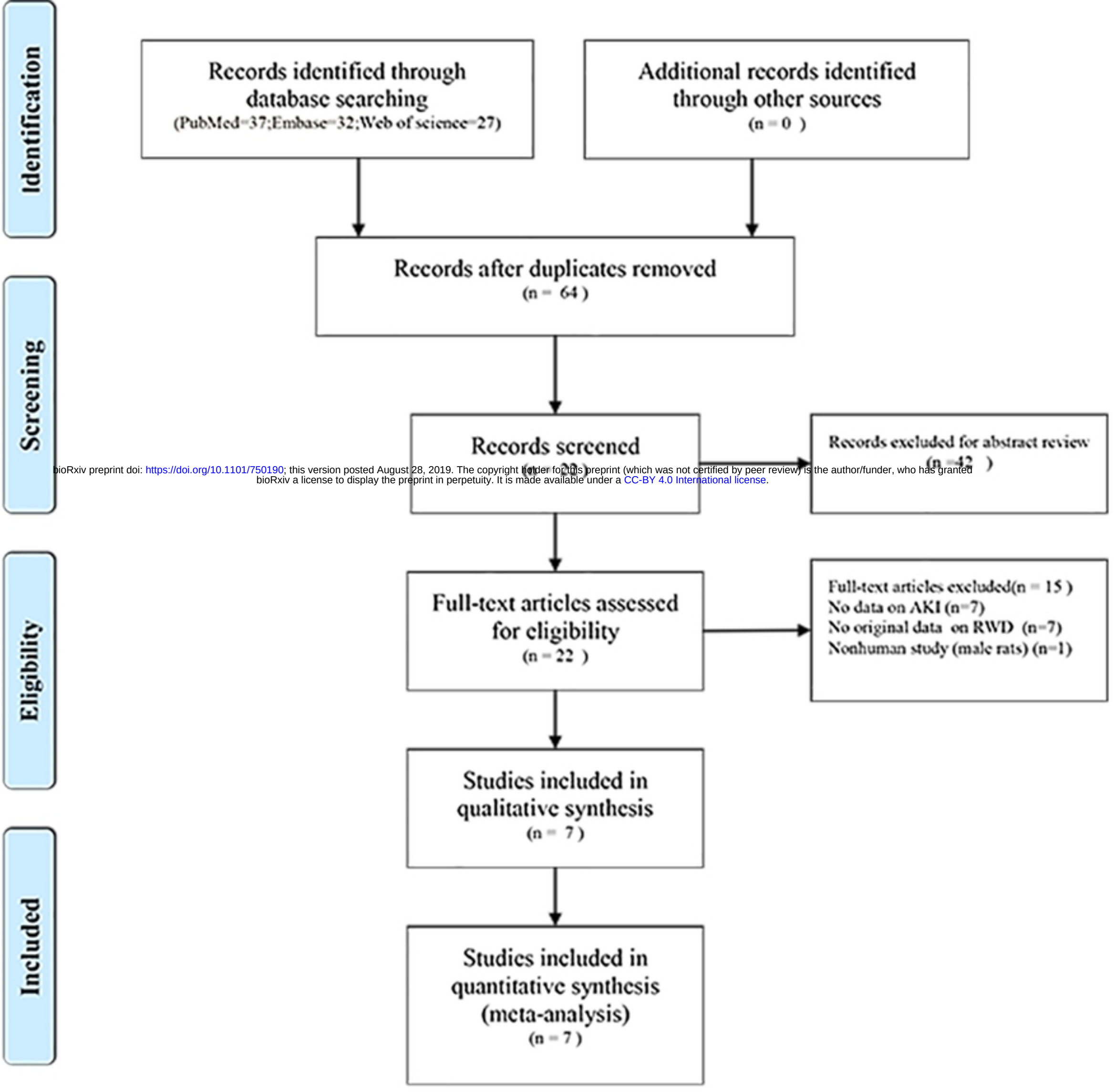

Figure 1:Flow chart of study selection; RDW, AKI, acute kidney injury ;red blood cell distribution width.

folw chart

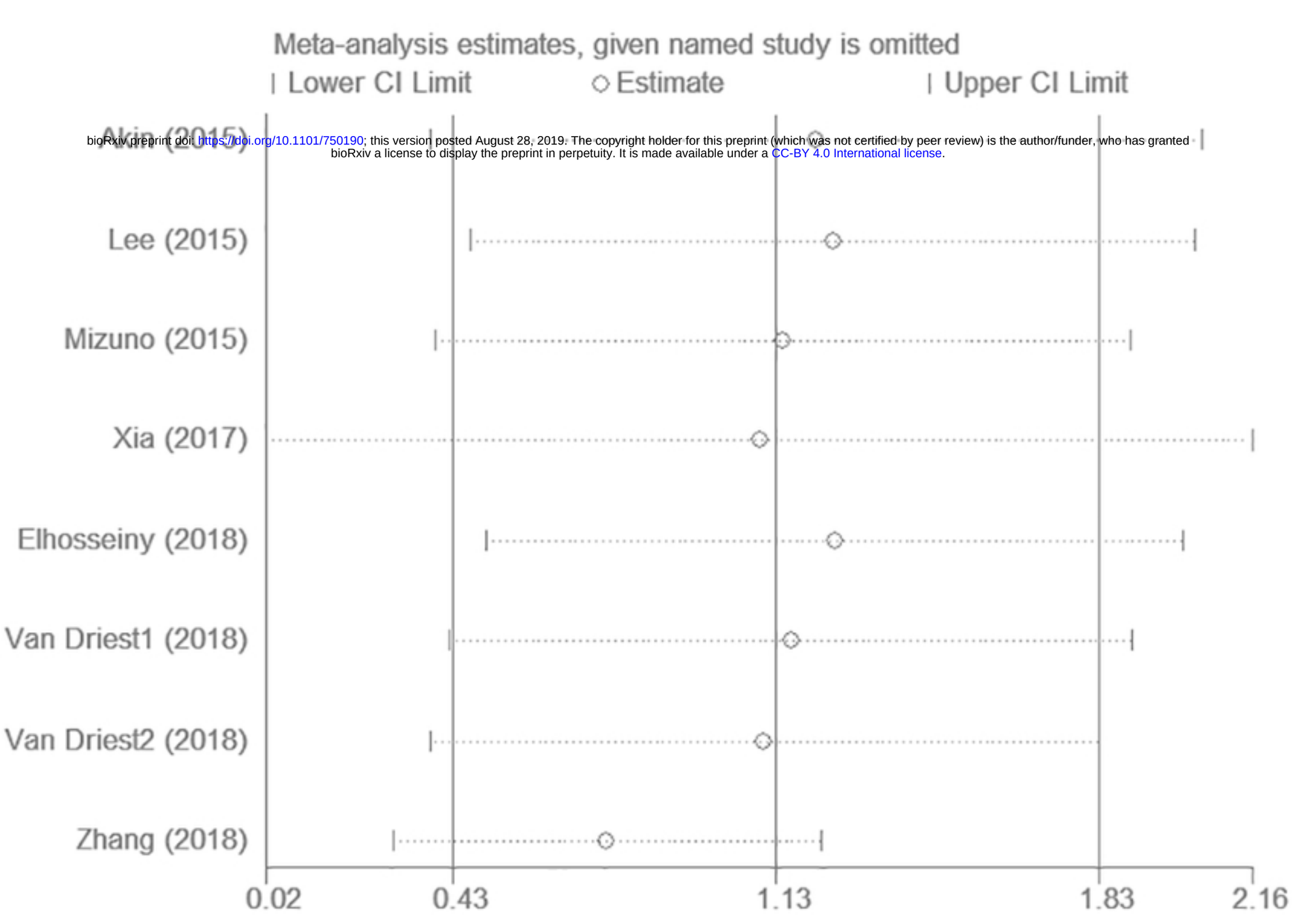

Figure3 WMD pooled value

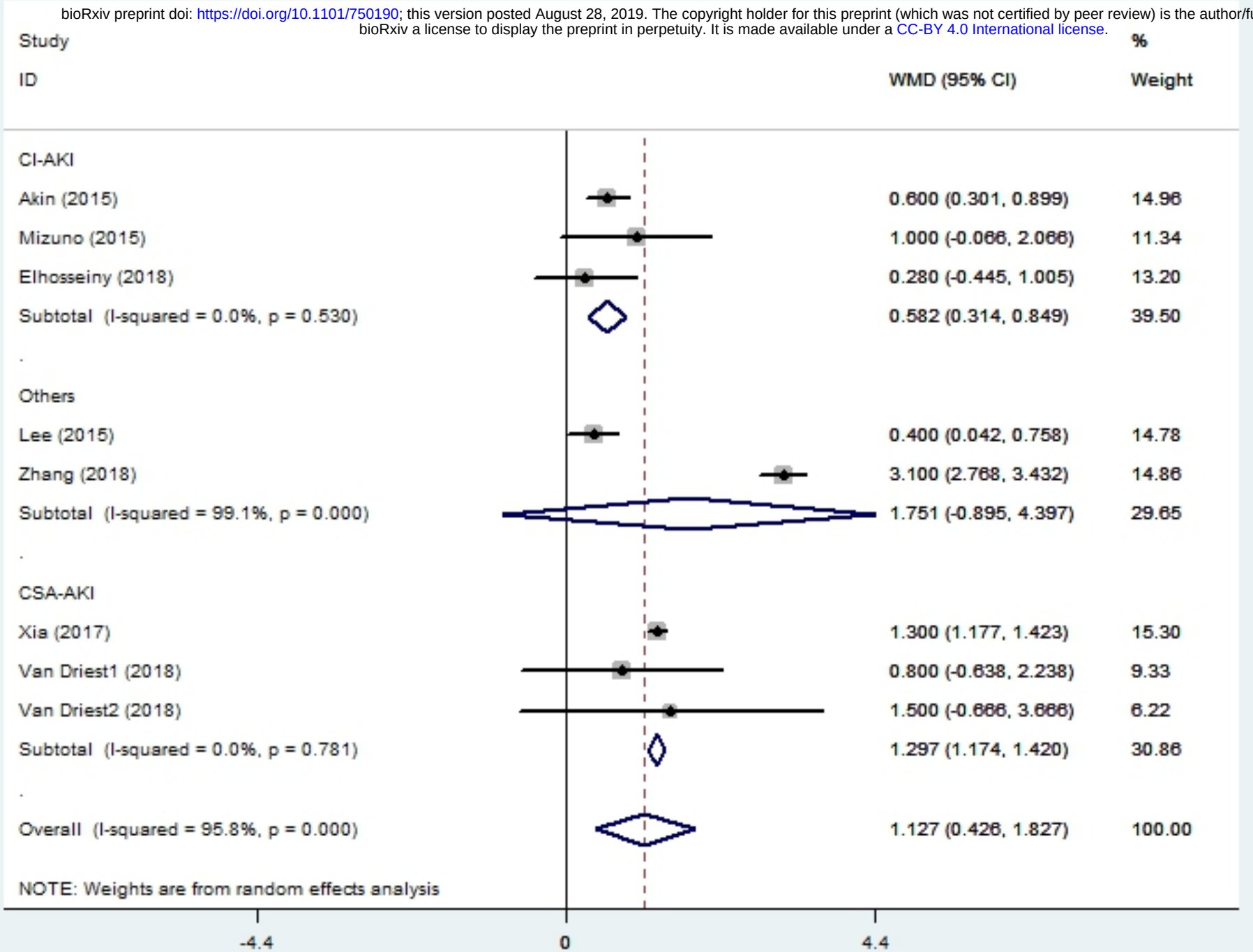

Figure2 forest polt