Abstract

Objective: To perform a systematic review and meta-analysis to comprehensively evaluate the prognostic role of C-reactive protein (CRP) in Type A acute aortic dissection (AAD).

Methods: PubMed, Web of Science, CNKI, SciELO, and EMBASE were searched until October 2017 for studies reporting data on the prognostic role of CRP measured at admission in Type A AAD patients. Inclusion criteria were a diagnosis of Type A AAD, CRP levels obtained, and a prospective or retrospective cohort study. Relevant outcome data were extracted, and pooled hazard ratios (HRs) were calculated using a random-effects model. Study quality was assessed using the Newcastle–Ottawa Scale (NOS). Subgroup analyses by type of dissection type were carried out.

Results: Of 319 articles identified, 9 (1693 patients) studies met the inclusion criteria and were included in this meta-analysis. The number of Type A patients ranged from 36 to 570 where elevated CRP was significantly and independently associated with increased risks of in-hospital mortality in patients with type A - AAD. The results of primary pooled statistics (n=1693 patients) showed that elevated CRP level was associated with a significantly increased risk of in-hospital mortality in patients with type A AAD (HR = 1.17, 95%CI: 1.04-1.33, p =0.01; Table 3 and Figure 1). No heterogeneity was observed among these studies (I^2 = 0%; Chi^2:1.21; Cochrane Q, p = 1.00). No publication bias was detected. The pooled sensitivity of CRP in Type A AAD patients was 77% (95% CI 69%–84%, P<0.001), and the specificity was 72% (95% CI 66%–78%, P<0.001).

Conclusion: Elevated CRP level is significantly associated with increased risks of in-hospital patients with Type A acute aortic dissection. CRP is a convenient prognostic factor in acute aortic dissection patients.

Keywords: C-reactive protein; Acute aortic dissection; Mortality; Prognosis

Statistical analysis

The extracted data were combined through meta-analysis to calculate a pooled HRs with 95% CIs to assess the prognostic significance of hs-CRP in Type A AAD. An HR >1.0 indicated worse prognosis in patients with elevated CRP levels. Heterogeneity across the studies was evaluated using the Cochrane's Q and the I^2 statistics. A p-value of <0.10 for the Cochrane's Q test or an I^2 value of > 40% indicated significant heterogeneity [39], [40]. A random-effects model was used when significant heterogeneity was present [41]; otherwise, a

fixed-effects model was used [40]. Subgroup analyses were conducted by data type, types of AAD, and adjusted status of HRs. Funnel plot and the Egger's test were used to evaluate the risk of publication bias. Stata version 12.0 (STATA Corporation, College Station, TX, USA) was used for all statistical analyses. A two-sided *p* value of < 0.05 was considered statistically significant.

Results

Study selection

A total of 319 potentially eligible studies were identified through the search of the electronic databases (Figure 1). After reviewing the titles and abstracts, 270 studies were excluded, and 24 studies were retained for a further detailed evaluation [16]–[19], [27], [28], [30]–[33], [42]–[54]. Based on the inclusion and exclusion criteria, 16 studies were excluded [16]–[19], [31], [32], [49]–[54]. Thus, 9 studies, with a total of patients with Type A acute aortic dissection, were included in this meta-analysis [27]–[30], [33], [43]–[48], [55].

Characteristics of included studies

Table 1 presents the characteristics of the included studies. All nine studies were published between 2002 to 2017, and the number of patients ranged from 36 to 570. In the studies, the numbers of patients in the deceased group ranged from 5 to 94 (total=360), and the number of patients in the survival group ranged from 31 to 509 (total=1301). Out of nine studies, six studies [46]–[48], had NOS score over 6 points while the other three studies [42], [43], [45] met five points. All included studies were retrospective cohort studies that examined the CRP level at admission and assessed the prognostic role of at-admission CRP in Type A AAD patients. Seven studies were performed in China, one in Austria and one in Croatia. The sample sizes of the studies ranged from 36 to 570, with most studies having enrolled more than 100 patients. All eight studies reported data on in-hospital mortality [43], [45], [47], [48]. Eight studies reported unadjusted risk estimates, while five studies only reported unadjusted risk estimates. CRP values in two [27], [45] study was dealt as a binary variable, with different cut-off values while six studies presented CRP as continuous variable [32], [42], [43], [45], [47] (Table 1).

Primary Outcome

The results of primary pooled statistics (n=1693 patients) showed that elevated CRP level was associated with a significantly increased risk of in-hospital mortality in patients with type A AAD (HR = 1.17, 95%CI: 1.04-1.33, *p* =0.01; Table 3 and Figure 1). No heterogeneity was observed among these studies (I^2 = 0%; Chi^2:1.21; Cochrane Q, p = 1.00). Only eight studies (n = 1442 patients) reported univariate adjusted HRs on the association

between CRP level and in-hospital mortality. Elevated CRP level was associated with a significantly increased risk of in-hospital mortality in patients with type A acute aortic dissection (HR =1.27, 95%CI: 1.12-1.45, p =0.0003; Table 4 and Figure 2). No heterogeneity was observed among these studies (I^2 = 0%; 95% Chi^2: 2.30; Cochrane Q, p = 0.94).

Sensitivity and Specificity of CRP in predicting inhospital mortality

All 4 studies provided complete sensitivity and specificity data, and were included in the analysis. Forest plots summarizing the sensitivity and specificity of CRP levels are shown in Table 5 and Figure 3, respectively. A random-effects analysis was applied because there was evidence of heterogeneity among the studies (sensitivity: Heterogeneity chi-squared = 29.54, I^2=89.8%, P<0.001; Table 5 and Figure 3) and (specificity: Heterogeneity chi-squared = 34.29, I^2=91.3%, P<0.001; Table 6 and Figure 4). The pooled sensitivity of CRP in Type A AAD patients was 77% (95% CI 69%–84%, P<0.001), and the specificity was 72% (95% CI 66%–78%, P<0.001). CRP levels were used as continuous variable, and different cut off in each study but all four studies did have minimum CRP cut off value of ≥9.5, which had sensitivity 77% and specificity was 72% to predict in-hospital mortality among Type A patients.

Subgroup Analyses

The results of subgroup analyses were conducted separately for the studies that had CRP as a continuous and categorical variable. The six studies [32], [42], [43], [45], [47], [48] had used CRP as continuous variable where elevated CRP level (n=1151 patients) was significantly associated with an increased risk of in-hospital mortality in patients with type A AAD (HR = 1.18, 95%CI: 1.02-1.37, p =0.03; Table 7 and Figure 5). No heterogeneity was observed among these studies (I^2 = 0%; Chi^2: 0.57; Cochrane Q, p = 0.99).

Two studies [27], [45] [elevated >6.3 mg/L and ≥12.05 mg/L (categorical)] CRP level as categorical variable (n=291 patients). However, CRP was not associated with increased risk of in-hospital mortality in patients with type A AAD (HR = 1.22, 95%CI: 0.93-1.61, p =0.14; Table 8 and Figure 6). No heterogeneity was observed among these studies (I^2 = 0%; Chi^2=0.24; Cochrane Q, p = 0.63).

Publication bias

To evaluate the risk of publication bias, a funnel plot and Egger's test was employed. No obvious publication bias was observed in this meta-analysis in case of association between high CRP level and in-hospital mortality (p value of eggers?).

Table 1 Characteristics of all studies included in the meta-analysis

Study[Ref.]	Country	Design	Participants	Outcome (Data type)	Age(y)	Men n(%)	CRP level	Adjustment	NOS score
Zhou et al. [48]	China	Retrospective	98 patients with acute type A aortic dissection	In-hospital mortality (H vs L)	55.9±10.3 VS 50.8±9.2	69(70.4)	14.7 (10.5,21.6) VS 5.9 (2.6,10.3)	Yes	6
Li et al. [47]	China	Retrospective	103 patients with type-A acute6767 aortic dissection	In-hospital mortality (per unit)	56.5±13.8 VS 53.3±13.2	71(68.9)	9.8±7.8 VS 14.3±10.1	Yes	6
Huang et al. [43]	China	Retrospective	212 consecutive patients with type A acute aortic dissection	In-hospital mortality (per unit); Long-term mortality after a median follow-up of 8.8 months (per unit)	47.7±11.6 VS 51.2±10.7	161(75.9)	30.9 (6.5-85.1) VS 74.2(8.6-132.0)	No	5
Fan et al. [42]	China	Retrospective	570 consecutive patients with type A aortic dissection	Long-term mortality after a median follow-up of 1.89 years (per unit)	46.7±12.7 VS 46.9±10.9	429(75.3)	60.0(56.3-69.0) VS 52.0 (31.6-60.9)	No	5
Wen et al. [46]	China	Retrospective	114 patients with acute aortic dissection	In-hospital mortality (H vs L)	48.9±7.6 VS 48.6±7.6	96(84.2)	11.18±1.85 VS 14.08±2.81	Yes	6
Wen et al. [45]	China	Retrospective	36 patients with acute type A acute aortic dissection	In-hospital mortality (H vs L)	50.6±10.4 VS 67.4±2.3	30(83.3)	11.81±1.87 VS 15.67±5.04	Yes	5
Schillinger et al. [27]	Austria	Retrospective	255 patients with acute aortic disease	Long-term mortality after a median follow-up of 50 months (H vs	Median: 66 VS 72	179(70.2)	<0.5 to >6.30 in Quartiles	Yes	7

Study[Ref.]	Country	Design	Participants	Outcome (Data type)	Age(y)	Men n(%)	CRP level	Adjustment	NOS score
				L)					
Vrsalovic et al. [32]	Croatia	Retrospective	54 patients with Type A	CRP has independent prognostic value in type A AAD and the addition of CRP to IRAD score improved discriminative capacity of in-hospital mortality irrespective of symptom duration and treatment strategy.	62±12 VS 77±13	34(63.0)	5.0 (2.5-8.5) VS 15.7 (10.8-21.4)	No	6
Liu et al [55].	China	Retrospective	251 patients with Type A	PCT levels measured in patients undergoing Type A aortic dissection (TAAD) were used to determine prognostic values for complications and surgical outcomes	48.94±12.85 VS 49.67±12.87	197(78.5)	92.82±57.29 VS 128.10±156.80	No	6

(NOS, Newcastle-Ottawa Scale; H vs L, high CRP level versus low CRP level; Mean±SD

Table 2 C-reactive protein Outcomes of the Included Studies

Studies (Publication year)	Number of Patients	CRP Cutoff Value, (mg/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Zhou et al. [48]	32	≥9.5	80	69	56.5	88.5	0.69
Li et al. [47]	36	14	48.9	94.3	81.8	77.8	0.70
Huang et al. [43]	50	na	na	na	na	na	na
Fan et al. [42]	61	na	na	na	na	na	na
Wen et al. [46]	31	11.21	100	54.2	44.9	100	0.822
Wen et al. [45]	5	na	na	na	na	na	na
Vrsalovic et al. [32]	24	>9.8	83	80	76.9	85.7	0.79
Schillinger et al. [27]	94	na	na	na	na	na	na
Liu et al.[55]	27	na	na	na	na	na	na

Table 3 Forest plot for CRP levels between Death and Survival (overall, Univariate and Multivariate)

Study or Subgroup	Death Events	Death Total	Survivor Events	Survivor Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Fan X 2015	61	570	509	570	7.432	54.47	21.8%	1.15 [0.88, 1.49]
Huang B 2015	50	212	162	212	3.121	38.21	15.3%	1.09 [0.79, 1.49]
Li G 2016	36	103	67	103	5.129	23.42	9.4%	1.24 [0.83, 1.87]
Liu et al 2017	27	251	224	251	1.173	24.09	9.7%	1.05 [0.70, 1.57]
Schillinger 2002	94	255	129	255	8.661	47.55	19.1%	1.20 [0.90, 1.59]
Vrsalovic 2015	24	54	30	54	3.195	13.33	5.3%	1.27 [0.74, 2.17]
Wen D 2011	5	36	31	36	1.841	4.306	1.7%	1.53 [0.60, 3.94]
Wen D 2013	31	114	83	114	4.832	22.57	9.0%	1.24 [0.82, 1.87]
Zhou Q 2016	32	98	66	98	4.768	21.55	8.6%	1.25 [0.82, 1.90]
Total (95% CI)		**1693**		**1693**			**100.0%**	**1.17 [1.04, 1.33]**
Total events	360		1301					

Heterogeneity: Chi² = 1.21, df = 8 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)

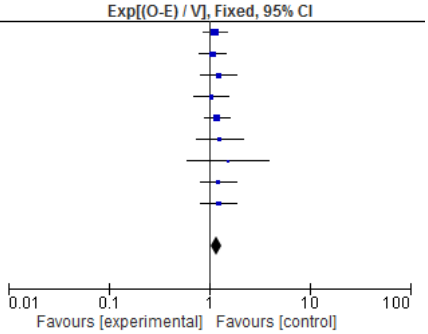

Figure 1 Funnel plot for CRP levels between Death and Survival

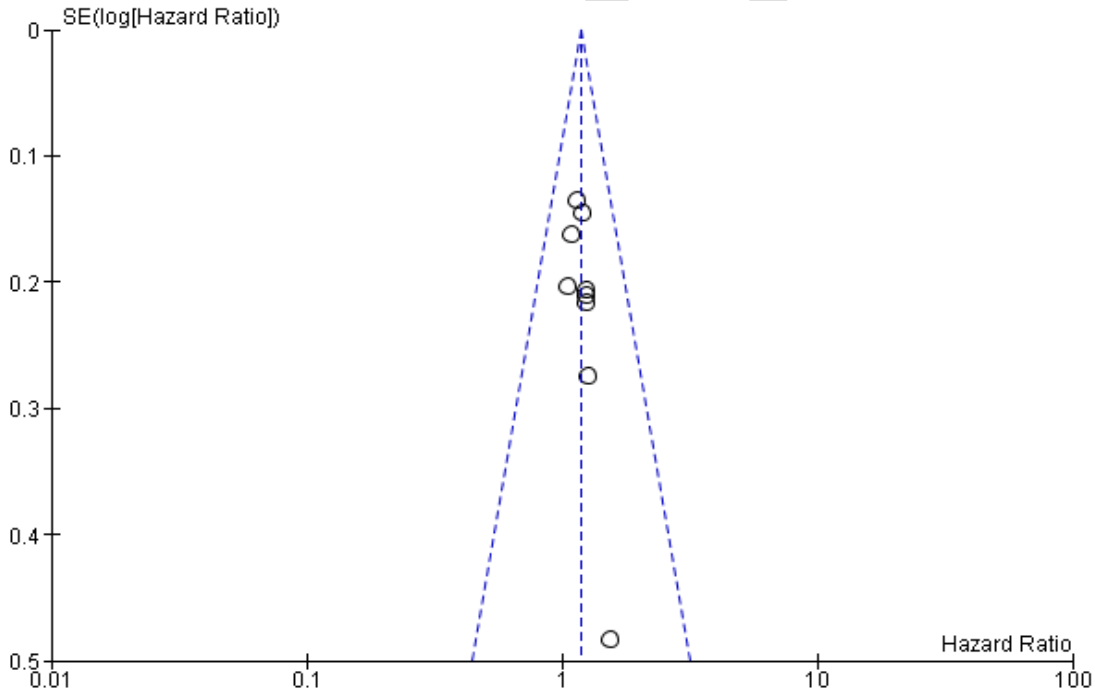

Table 4 Forest plot for CRP levels in univariate Cox regression between Death and Survival

Study or Subgroup	Death Events	Death Total	Survivor Events	Survivor Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Zhou Q 2016	32	98	66	98	6.156	21.55	9.6%	1.33 [0.87, 2.03]
Wen D 2013	31	114	83	114	7.34	22.57	10.0%	1.38 [0.92, 2.09]
Wen D 2011	5	36	31	36	3.206	4.306	1.9%	2.11 [0.82, 5.41]
Vrsalovic 2015	24	54	30	54	4.381	13.33	5.9%	1.39 [0.81, 2.38]
Schillinger 2002	94	255	129	255	8.661	47.55	21.1%	1.20 [0.90, 1.59]
Li G 2016	36	103	67	103	7.476	23.42	10.4%	1.38 [0.92, 2.06]
Huang B 2015	50	212	162	212	9.55	38.21	17.0%	1.28 [0.94, 1.76]
Fan X 2015	61	570	509	570	7.432	54.47	24.2%	1.15 [0.88, 1.49]
Total (95% CI)		**1442**		**1442**			**100.0%**	**1.27 [1.12, 1.45]**
Total events	333		1077					

Heterogeneity: Chi² = 2.30, df = 7 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.61 (P = 0.0003)

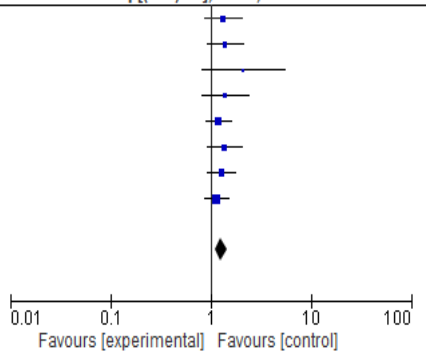

Figure 2 Funnel plot for CRP levels in univariate Cox regression between Death and Survival

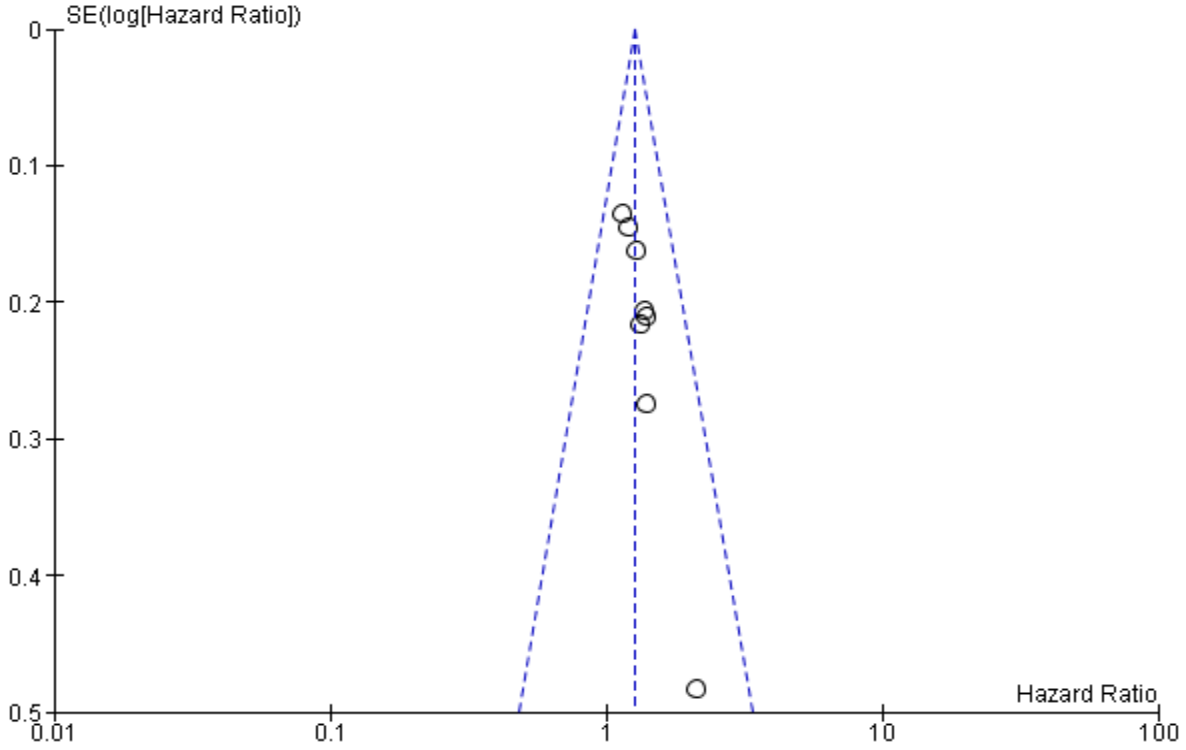

Table 5 Sensitivity for C reactive protein levels

Study	Sensitivity	[95% Conf. Interval.]	TP/(TP+FN)	TN/(TN+FP)
Zhou 2016	0.813	0.636-0.928	26/32	46/66
Li G 2016	0.500	0.329-0.671	18/36	63/67
Wen D 2013	1.000	0.888-1.000	31/31	45/83
Vrsalovic 2015	0.833	0.626-0.953	20/24	24/30
Pooled Sensitivity	**0.772**	**0.688-0.843**		

Heterogeneity chi-squared = 29.54 (d.f.= 3) p = 0.000
Inconsistency (I-square) = 89.8 %
No. studies = 4.

Figure 3 Forest plot evaluating the sensitivity for C reactive protein levels

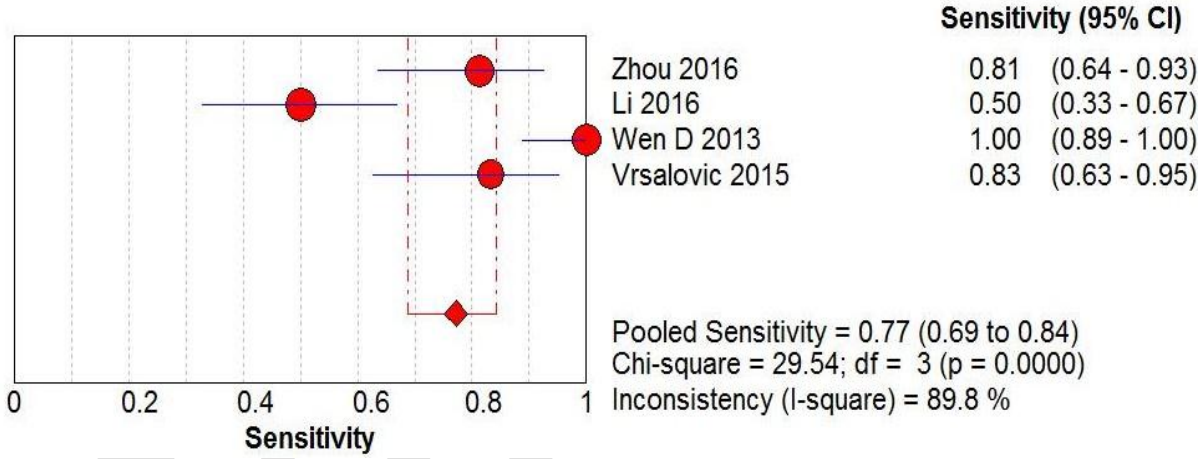

Table 6 Specificity for C reactive protein levels

Study	Specificity	[95% Conf. Interval.]	TP/(TP+FN)	TN/(TN+FP)
Zhou 2016	0.697	0.571-0.804	26/32	46/66
Li G 2016	0.940	0.854-0.983	18/36	63/67
Wen D 2013	0.542	0.429-0.652	31/31	45/83
Vrsalovic 2015	0.800	0.614-0.923	20/24	24/30
Pooled Sensitivity	**0.724**	**0.663-0.778**		

Heterogeneity chi-squared = 34.29 (d.f.= 3) p = 0.000
Inconsistency (I-square) = 91.3 %
No. studies = 4.

Figure 4 Forest plot evaluating the specificity for C reactive protein levels

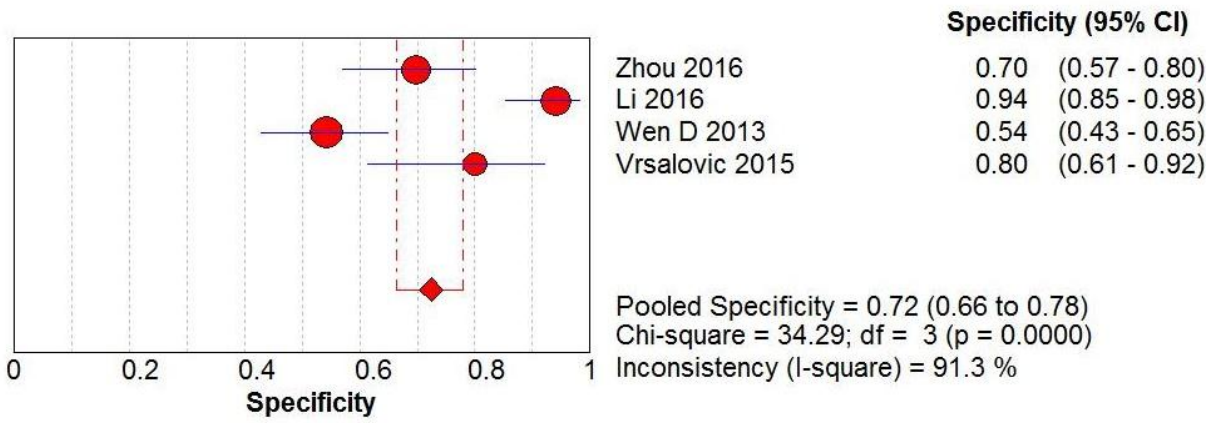

Table 7 Forest plot for Subgroup CRP levels (Continuous) between Death and Survival

Study or Subgroup	Death Events	Death Total	Survivor Events	Survivor Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Zhou Q 2016	32	98	66	98	4.768	21.55	12.4%	1.25 [0.82, 1.90]
Wen D 2013	31	114	83	114	4.832	22.57	13.0%	1.24 [0.82, 1.87]
Vrsalovic 2015	24	54	30	54	3.195	13.33	7.7%	1.27 [0.74, 2.17]
Li G 2016	36	103	67	103	5.129	23.42	13.5%	1.24 [0.83, 1.87]
Huang B 2015	50	212	162	212	3.121	38.21	22.0%	1.09 [0.79, 1.49]
Fan X 2015	61	570	509	570	7.432	54.47	31.4%	1.15 [0.88, 1.49]
Total (95% CI)		**1151**		**1151**			**100.0%**	**1.18 [1.02, 1.37]**
Total events	234		917					

Heterogeneity: Chi² = 0.57, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)

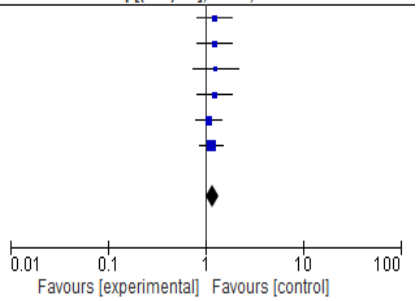

Figure 5 Funnel plot for Subgroup CRP levels (Continuous) between Death and Survival

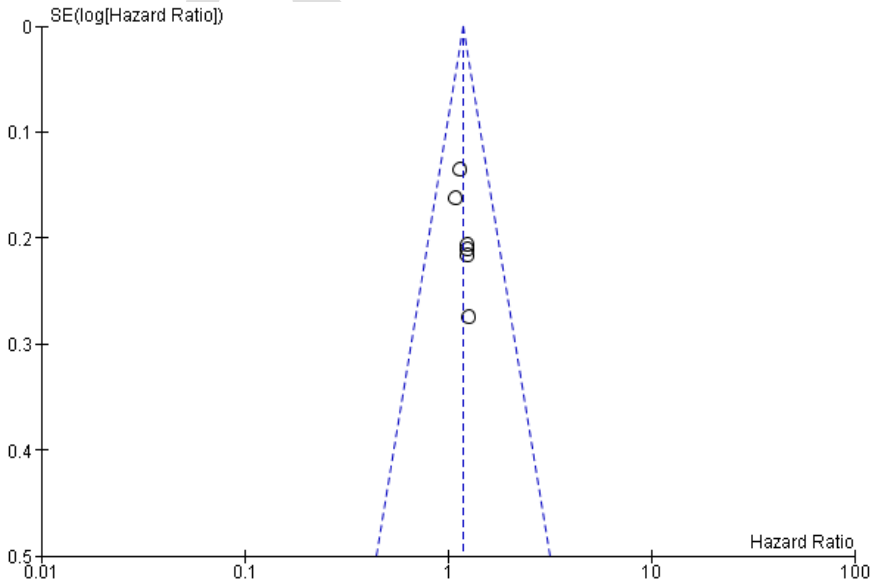

Table 8 Forest plot for Subgroup CRP levels (Categorical) between Death and Survival

Study or Subgroup	Death Events	Death Total	Survivor Events	Survivor Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Schillinger 2002	94	255	129	255	8.661	47.55	91.7%	1.20 [0.90, 1.59]
Wen D 2011	5	36	31	36	1.841	4.306	8.3%	1.53 [0.60, 3.94]
Total (95% CI)		**291**		**291**			**100.0%**	**1.22 [0.93, 1.61]**
Total events	99		160					

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)

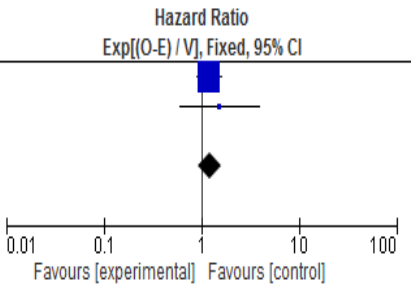

Figure 6 Funnel plot for Subgroup CRP levels (Categorical) between Death and Survival