Admission Values of Plasma Biomarkers Predict the Short-Term Outcomes in Acute Aortic Dissection

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ABSTRACT

Background and aims: Acute aortic dissection (AAD) is an emergency disease with high misdiagnosis rate and mortality. The aim of the present study is to explore the impact of blood-related biomarkers, specifically D-dimer, on in-hospital outcomes of patients with AAD.

Materials and methods: A total of 345 patients in our hospital from December 2013 to April 2017 were included. The cutoff value for D-dimer and LDL-C were set as 5.9 mg/l and 1.45 mg/l, respectively. The univariate and multivariate logistic regression models were used to identify the independently prognostic predictors.

Results: The results showed that patients with type A AAD had higher risk of in-hospital mortality compared with those with type B disease. Moreover, results revealed that D-dimer (OR 6.382, 95%CI: 2.423 to 16.812), and LDL-C (OR 0.373, 95%CI: 0.148 to 0.940) were independently associated with in-hospital mortality. Subgroup analysis suggested that D-dimer (OR 2.295, 95%CI: 1.140 to 4.622) was an independently prognostic factor in type A AAD.

Conclusion: In summary, D-dimer ≥ 5.9 mg/L and type A AAD were independently associated with in-hospital mortality in AAD patients. Moreover, subgroup analysis proved that the elevated D-dimer was related to poor prognosis in type A AAD.

INTRODUCTION

Acute aortic dissection (AAD) is increasing in incidence in the emergency department; it comes with a negative influence in prognosis [Aboyans 2017; Nienaber 2012]. A study indicated that the incidence of AAD showed an increasing trend [Meszaros 2000], which still carries a high in-hospital mortality approaching 40% in the short-term [Kalkan 2015]. Therefore, AAD recently has become a hot topic. Also, it was reported that the early misdiagnosis rate is approaching 38%, despite imaging techniques like CT or contrast-enhanced CT. Moreover, a blood test is fast and convenient for the diagnosis of other diseases. So, it is necessary for the patient suspected of having AAD to be tested. Research has reported that high levels of plasma biomarkers related with inflammation include D-dimer [Wen 2013; Eggebrecht 2014; Nazerian 2014; Sbarouni 2017; Hata 2007; Ohlmann 2006] and CRP [Wen 2013; Schillinger 2002].

D-dimer is a degradation product of fibrin, which recently was regarded as an effect of plasma biomarkers. Furthermore, CRP and D-dimer now have become a hotspot of research around the world [Wen 2013]. Many studies have found that CRP and D-dimer play an important role in diagnosis of AAD. Another study has indicated that with the level of D-dimer increasing, the in-hospital mortality of AAD show an increasing rate [Sbarouni 2017; Peng 2015]. However, there is no research about the use of a combination of biomarkers for short-term prognosis of AAD, and no one has done research about different types of AAD. Sakakura et al demonstrated that peak CRP is a predicted factor in patients with AAD in a short-term outcome [Sakakura 2010], and Tian et al indicated that high admission D-dimer levels can increase the incidence mortality of AAD [Tian 2014]. Although there are few previous studies evaluating the prognostic factors in patients with AAD, the sample sizes in some studies were small [Peng 2015; Shimony 2011]. This is the first study to research the short-term prognosis of AAD in the West China District, and we enrolled a large number of patients. Thus, the objective of our research was to elucidate the factors that affected the in-hospital outcome of patients with AAD.
MATERIALS AND METHODS

Patients and data collection: Between December 1, 2013 and April 30, 2017, all the patients consecutively admitted to the emergency units of our hospital (Department of Emergency, West China Hospital, Sichuan University) were enrolled in this retrospective study. Among these 345 patients, 270 patients survived and 75 patients died in a short time. The inclusion criteria were: 1) diagnosed with AAD by imaging examination (CT/MRI); 2) the data from hospital HIS system; 3) diagnosis of AAD; and 4) venous blood was drawn in the first 48 hours after admission. The patients who did not have the blood test were excluded. This study was approved by the Ethics Committee of West China Hospital and for such studies, no informed consent is required. The methods were carried out in accordance with the approved guidelines.

Venous blood measurements: All venous blood was obtained from the patients in the emergency department after admission (within 48 hours). The receiver-operating characteristic (ROC) curve and Youden index (Youden index = sensitivity + specificity - 1) were applied to select the cutoff value of blood laboratory tests, including D-dimer, CRP, HDL-C, LDL-C, TG, TC, Na, K, Ca, and Mg. The cutoff value for D-dimer, CRP, HDL-C, LDL-C, TG, TC, Na, K, Ca, and Mg was set as 5.9 mg/L, 106.5 mg/L, 1.505 mmol/L, 1.455 mmol/L, 0.655 mmol/L, 3.605 mmol/L, 136.55 mmol/L, 4.025 mmol/L, 2.145 mmol/L, and 0.835 mmol/L, respectively.

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22 (IBM Corp, released 2013, Armonk, NY, USA). All continuous variables were presented as means ± standard deviations (S.D.) and categorical variables were expressed as percentages and frequencies. Patients who died in hospital were divided into one group, and the remaining patients were placed into another group. Chi-squared test and student t-test were used to compare the differences between the two groups. The impact of variables on in-hospital mortality were identified by the univariate and multivariate logistic analysis. Factors with P values <0.1 in the univariate analysis were included in the multivariate analysis. The cutoff values of blood-based parameters, such as D-dimer and CRP, were determined by using receiver operating characteristic (ROC) and Youden index. Youden index = sensitivity + specificity - 1. A variable with a two-tailed value of P < .05 was considered statistically significant.

Table 1. Demographics and clinicopathological characteristics of patients diagnosed with AAD in the present study

| Clinical variables | Survival | Death | P       |
|-------------------|----------|-------|---------|
| Patients number   | 270      | 75    | -       |
| Type A AAD, n (%) | 142(52.6)| 63(84)| <.001   |
| Type B AAD, n (%) | 128(47.4)| 12(16)| <.001   |
| Age (years)       | 50.67 ± 11.49| 52.47 ± 12.52| .242 |
| Males, n (%)      | 226(83.7)| 53 (70.7)| .019   |
| History of smoking, n (%) | 164 (60.7)| 33 (44)| .008   |
| History of hypertension, n (%) | 182 (67.4)| 45 (60)| .271   |
| History of drinking, n (%) | 140 (51.9)| 27 (36)| .019   |
| Admission SBP (mm Hg) | 147.54 ± 32.42| 132.69 ± 34.1| .01 |
| Admission DBP (mm Hg) | 84.00 ± 22.64| 74.29 ± 20.86| .01 |
| Serum measurements (mean ± SD) | | | |
| D-dimer, mg/L | 7.9 ± 8.6| 11.7 ± 10.65| .002   |
| CRP, mg/L | 78.15 ± 72.8| 100.59 ± 110.32| .064   |
| HDL-C, mmol/L | 1.27 ± 0.51| 3.32 ± 18.2| .066   |
| LDL-C, mmol/L | 3.03 ± 12.57| 2.14 ± 0.76| .537   |
| TG, mmol/L | 2.49 ± 10.26| 1.46 ± 1.1| .386   |
| TC, mmol/L | 3.96 ± 1.06| 6.48 ± 23.37| .079   |
| Na, mmol/L | 138.65 ± 3.43| 138.60 ± 3.74| .911   |
| K, mmol/L | 3.76 ± 0.56| 5.16 ± 10.89| .035   |
| Ca, mmol/L | 3.69 ± 17.23| 2.16 ± 0.13| .433   |
| Mg, mmol/L | 0.83 ± 0.15| 0.86 ± 0.12| .100   |

SBP = systolic blood pressure, DBP = diastolic blood pressure, CRP = C-reactive protein, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, TC = total cholesterol, Na = sodium, K = kalium, Ca = calcium, Mg = magnesium
A total of 345 patients with AAD during the study period (December 2013 to April 2017) are included in this study. Their clinical features are shown in Table 1. The in-hospital mortality rate was 21.7% in all 345 patients. This study divided the patients into a survived cohort and an in-hospital mortality cohort. Between the two groups, the demographic feature of sex (83.7% versus 70.7%, \(P = .019\)), type A AAD (52.6% versus 84.0%, \(P = .001\)), type B AAD (47.4% versus 16.0%, \(P = .01\)), smoking history (60.7% versus 44%, \(P = .008\)), drinking history (51.9% versus 36%, \(P = .019\)), admission systolic blood pressure (SBP) (147.54 ± 32.42 versus 132.69 ± 34.11 mmHg, \(P = .01\)), admission diastolic blood pressure (DBP) (84.00 ± 22.64 versus 74.29 ± 20.86 mmHg, \(P = .01\)), D-dimer (7.90 ± 8.6 versus 11.7 ± 10.65, \(P = .002\)), and K (3.76 ± 0.56 versus 5.16 ± 10.89, \(P < .035\)) were significantly higher in the in-hospital mortality group than the survival group. However, no difference was found between the two groups in age, CRP, HDL-C, LDL-C, TG, TC, Na, and Ca (as shown in Table 1).

As shown in Table 2, the results of univariate analysis suggested that type A AAD (OR 4.732, 95%CI: 2.441 to 9.174), gender (OR 0.469, 95%CI: 0.259 to 0.848), history of smoking (OR 0.508, 95%CI: 0.303 to 0.852), history of drinking (OR 0.428 to 1.229), and K (3.76 ± 0.56 versus 5.16 ± 10.89, \(P < .035\)) were significantly related to the in-hospital mortality in cases diagnosed with AAD (Table 2).

In multivariate logistic regression analysis, the results demonstrated that only type A AAD (OR 6.382, 95%CI: 2.423 to 16.812), D-dimer (OR 2.433, 95%CI: 1.072 to 4.350), and LDL-C (OR 0.373, 95%CI: 0.148 to 0.940) were independently associated with in-hospital mortality in AAD patients. However, other factors which proved to be statistically significant in univariate analysis were found to be not related to prognosis in multivariate analysis (Table 3). ROC curve analysis revealed that the area under the ROC curve was 0.634 when the cutoff value of D-dimer level was set as 5.9 mg/L. Therefore, when D-dimer level ≥ 5.9 mg/L, the sensitivity and specificity were 63.4% and 58.8%, respectively, in predicting in-hospital mortality in AAD patients (Figure 1).
### Table 3. Multivariate logistic regression analyses to detect the prognostic factors for in-hospital mortality in patients with AAD.

| Clinical variables                                      | OR    | 95%CI             | P     |
|---------------------------------------------------------|-------|-------------------|-------|
| Type of AAD (type A versus B)                           | 6.382 | 2.423 to 16.812   | <.001 |
| Gender (male versus female)                             | 0.396 | 0.143 to 1.098    | .075  |
| History of drinking (yes versus no)                     | 0.823 | 0.344 to 1.969    | .661  |
| History of smoking (yes versus no)                      | 0.812 | 0.325 to 2.029    | .656  |
| Admission SBP (≥120 versus <120), mmHg                  | 0.725 | 0.312 to 1.682    | .454  |
| Admission DBP (≥80 versus <80), mmHg                    | 1.067 | 0.482 to 2.362    | .873  |
| D-dimer (≥5.9 versus <5.9), mg/L                        | 2.160 | 1.072 to 4.350    | .031  |
| CRP (≥106.5 versus <106.5), mg/L                        | 1.320 | 0.619 to 2.815    | .472  |
| LDL-C (≥1.455 versus <1.455), mmol/L                    | 0.373 | 0.148 to 0.940    | .036  |
| TG (≥0.655 versus <0.655), mmol/L                       | 1.950 | 0.676 to 5.624    | .216  |
| Na (≥136.55 versus <136.55), mmol/L                     | 0.479 | 0.224 to 1.102    | .085  |
| K (≥4.025 versus <4.025), mmol/L                        | 2.009 | 0.948 to 4.258    | .069  |
| Ca (≥2.145 versus <2.145), mmol/L                       | 0.703 | 0.352 to 1.404    | .318  |

OR = odds ratio, CI = confidence interval, SBP = systolic blood pressure, DBP = diastolic blood pressure, CRP = C-reactive protein, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, NA = sodium, K = kalium

### Table 4. Univariate logistic analysis in type A and B AAD patients, respectively.

| Clinical variables                                      | Type A AAD | OR    | 95%CI             | P     | Type B AAD | OR    | 95%CI             | P     |
|---------------------------------------------------------|------------|-------|-------------------|-------|------------|-------|-------------------|-------|
| Age (years)                                             | 1.019      | 0.993 | 1.045             | .150  | 0.979      | 1.087 | 1.014             | .243  |
| Gender (male versus female)                             | 0.402      | 0.198 | 0.818             | .012  | 0.165      | 2.618 | 0.657             | .552  |
| History of smoking (yes versus no)                      | 0.536      | 0.295 | 0.977             | .042  | 0.133      | 1.473 | 0.443             | .184  |
| History of hypertension (yes versus no)                  | 1.026      | 0.565 | 1.863             | .934  | 0.237      | 5.612 | 1.154             | .859  |
| History of drinking (yes versus no)                      | 0.472      | 0.256 | 0.868             | .016  | 0.153      | 1.856 | 0.532             | .322  |
| Admission SBP (≥120 versus <120), mmHg                  | 0.509      | 0.276 | 0.938             | .030  | 0.066      | 1.197 | 0.282             | .086  |
| Admission DBP (≥80 versus <80), mmHg                    | 0.739      | 0.396 | 1.357             | .324  | 0.198      | 2.485 | 0.702             | .583  |
| D-dimer (≥5.9 versus <5.9), mg/L                        | 2.432      | 1.281 | 4.617             | .007  | 1.075      | 3.882 | 0.007             | .912  |
| CRP (≥106.5 versus <106.5), mg/L                        | 1.594      | 0.798 | 3.182             | .187  | 0.643      | 17.672 | 3.370             | .151  |
| HDL-C (≥1.505 versus <1.505), mmol/L                    | 0.751      | 0.350 | 1.610             | .461  | 0.182      | 2.751 | 0.707             | .617  |
| LDL-C (≥1.455 versus <1.455), mmol/L                    | 0.392      | 0.283 | 1.236             | .163  | 0.065      | 0.922 | 0.234             | .037  |
| TG (≥0.655 versus <0.655), mmol/L                       | 0.692      | 0.306 | 1.566             | .377  | 0.054      | 0.632 | 0.185             | .007  |
| TC (≥3.605 versus <3.605), mmol/L                       | 1.308      | 0.676 | 2.530             | .425  | 0.313      | 3.867 | 1.100             | .882  |
| Na (≥136.55 versus <136.55), mmol/L                     | 0.533      | 0.272 | 1.044             | .067  | 0.109      | 1.198 | 0.362             | .096  |
| K (≥4.025 versus <4.025), mmol/L                        | 1.882      | 0.988 | 3.584             | .054  | 0.548      | 7.021 | 1.962             | .300  |
| Ca (≥2.145 versus <2.145), mmol/L                       | 0.567      | 0.310 | 1.036             | .065  | 0.172      | 1.990 | 0.576             | .371  |
| Mg (≥2.835 versus <2.835), mmol/L                       | 1.664      | 0.912 | 3.035             | .097  | 1.048      | 3.425 | 0.321             | .938  |

OR = odds ratio, CI = confidence interval, SBP = systolic blood pressure, DBP = diastolic blood pressure, CRP = C-reactive protein, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, TC = total cholesterol, NA = sodium, K = kalium, Ca = calcium, Mg = magnesium
Subgroup analysis in type A AAD and B AAD was performed (Table 4). The results of univariate analysis showed that the male sex (OR 0.402, 95%CI: 0.198 to 0.818), history of drinking (OR 0.472, 95%CI: 0.256 to 0.868), Admission SBP (OR 0.509, 95%CI: 0.276 to 0.938), D-dimer (OR 2.432, 95%CI: 1.281 to 4.617), Na (OR 0.533, 95%CI: 0.272 to 1.044), K (OR 1.882, 95%CI: 0.988 to 3.584), Ca (OR 0.567, 95%CI: 0.310 to 1.036), and Mg (OR 1.664, 95%CI: 0.912 to 3.035) were related to in-hospital mortality in cases diagnosed with A AAD. In addition, Admission SBP (OR 0.282, 95%CI: 0.066 to 1.197), LDL-C (OR 0.246, 95%CI: 0.065 to 0.922), TG (OR 0.185, 95%CI: 0.054 to 0.632), and Na (OR 0.362, 95%CI: 0.109 to 1.198) had a significant association with type B AAD. In multivariate logistic regression analysis, the results showed that sex (OR 0.447, 95%CI: 0.169 to 1.177) and D-dimer (OR 2.295, 95%CI: 1.140 to 4.622) were independent prognostic factors in patients with type A AAD and only TG (OR 0.192, 95%CI: 0.051 to 0.721) had a significant association with B AAD (Table 5).

**DISCUSSION**

AAD is a serious cardiovascular disease with a high mortality rate; it is easily misdiagnosed. In our retrospective study, we found that D-dimer, type of AAD, and LDL-C were independent risk factors in short-term mortality for patients with AAD in our multivariable Cox regression analysis. In addition, a high level of D-dimer plays an important role in the short-term prognosis of AAD. When the D-dimer level was ≥ 5.9mg/l, the sensitivity and specificity were 0.634 and 0.588 in predicting in-hospital mortality, respectively. Moreover, the multivariate logistic regression analysis was performed for different types of AAD, and results found that D-dimer was an independent factor in A AAD and only TG was an independent factor for type B AAD. The type of AAD was an independent risk factor in prognosis of AAD, which was reported by Lingzhi et al. [Lingzhi 2016], and it was the same result in our study. Furthermore, a previous study indicated a similar result as our study, where the patients with type A AAD had a poorer short-term prognosis than patients with type B AAD [Hagan 2000].

D-dimer is a small protein fragment produced by cross-linked fibrin in the blood, and it represents the coagulation and fibrinolytic system activation. D-dimer was also treated as a diagnostic marker to help the diagnosis of AAD [Hata 2007]. The pathogenesis and prognosis of AAD in patients was based on the inflammation. Numerous recent studies have indicated that the value of D-dimer is a reliable diagnosis marker and screening tool for AAD [Eggebrecht 2014; Weber 2003; Taylor 2013]. The sensitivity of D-dimer can reach up to 100%, but with low specificity for the diagnosis of AAD [Nazerian 2014, Weber 2006]. Previously, several studies with a limited number of patients have suggested that high D-dimer levels were associated with poor short-term outcomes and postoperative adverse events [Liu 2020; Yang 2020; Huang 2015]. Studies have revealed the coagulant material from the aortic wall released into the circulation and clotting factors accumulated at the site of the lesion during the aortic tearing, which induced the elevated level

| Clinical variables | Type A AAD | Type B AAD |
|--------------------|------------|------------|
| Gender (male versus female) | 0.447 | 0.230 |
| History of drinking (yes versus no) | 0.766 | 0.241 |
| History of smoking (yes versus no) | 0.800 | 0.192 |
| Admission SBP (≥120 versus <120), mmHg | 0.680 | 0.230 |
| D-dimer (≥5.9 versus <5.9), mg/L | 2.295 | 0.192 |
| Na (≥136.55 versus <136.55), mmol/L | 0.590 | 0.285 |
| K (≥4.025 versus <4.025), mmol/L | 1.854 | 0.192 |
| Ca (≥2.145 versus <2.145), mmol/L | 0.689 | 0.285 |
| Mg (≥0.835 versus <0.835), mmol/L | 1.667 | 0.185 |

Table 5. Multivariate logistic analysis in patients with type A AAD and type B AAD, respectively.

*OR = odds ratio, CI = confidence interval, SBP = systolic blood pressure, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, Na = sodium, K = kalium, Ca = calcium, Mg = magnesium*
of D-dimer [Jan 1975]. Thus, a high level of serum D-dimer may reflect the severe and extensive aortic tearing and may act as a prognostic predictive marker for AAD. As in previously reported studies, our results strongly agree with the predictive value of D-dimer for in-hospital mortality risk in AAD, especially in type A AAD.

CRP is a well-known systemic inflammation marker and was proved to induce the endothelial dysfunction by stimulating the clotting system [Vrsalović 2019]. Previously reported data demonstrated AAD is related to inflammatory response with elevated inflammatory markers, including CRP [Duan 2018]. In a recent study, the authors found that CRP was independently associated with poor prognosis in patients with AAD [Schillinger 2002], while another report indicated that CRP remained in a normal range at admission in most AAD patients [Komukai 2005]. Specifically, in our present study, we found that CRP did not contribute to the in-hospital mortality of AAD in multivariable Cox regression analysis. Compared with previous studies, the average and median CRP values in our cohort was much higher, which reached 82.4 mg/L and 70.8 mg/L, respectively. The cutoff value in another study was also set as 106.5 mg/L, where the Yuden index was maximum, which was far more than that in other studies ranging from 9.8 to 20 mg/L [Vrsalović 2019].

CONCLUSION

In summary, our study has demonstrated that D-dimer ≥5.9 μg/mL, CRP ≥106.5 mg/L, and type A AAD were risk factors and independently associated with in-hospital mortality in AAD patients. Moreover, subgroup analysis proved that the elevated D-dimer was associated with poor prognosis in type A AAD cases. Thus, these patients with high-risk of in-hospital mortality require close medical observation.

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