Renal Dysfunction on Admission as a Predictor for In-Hospital Mortality of Patients with Stanford Type B Acute Aortic Dissection

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Stanford type A and open false lumen are accepted predictors for in-hospital mortality in patients with acute aortic dissection (AAD). However, the association of renal dysfunction on admission with in-hospital mortality is not well known. The aim of this study was to investigate the prognostic value of renal dysfunction in patients with AAD. A total of 250 patients with type B AAD admitted to our institution between January 2003 and August 2011 were enrolled in this study. In multivariate logistic regression analysis, the significant predictors of in-hospital mortality were age (odds ratio [OR] 1.575, 95% confidence interval [CI] 1.078–2.864, $p = 0.024$), maximum aortic diameter measured by an initial computed tomography (CT) (OR 1.740, 95% CI 1.029–2.940, $p = 0.039$), decreased enhancement of kidney (OR 7.716, 95% CI 2.335–25.501, $p = 0.001$) and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m² on admission (OR 2.782, 95% CI 1.062–7.283, $p = 0.037$). In conclusions the results identified a renal dysfunction on admission as the independent predictor of in-hospital mortality in type B AAD. Further investigations are needed to evaluate therapies and strategies for decreasing the deterioration of renal function to improve in-hospital mortality in patients with AAD.

Keywords: aortic diseases, renal function, prognosis

INTRODUCTION

Acute aortic dissection (AAD) is a life-threatening disease with an incidence of approximately 3 per 100000/year.¹⁾ Both diversity of symptoms and variability of the severity of symptoms lead emergency room physicians to miss AAD in about 1 in 6 cases of AAD.²⁾ While emergent or sub-emergent surgery is usually indicated as the treatment for Stanford type A AAD, patients with Stanford type B AAD are prescribed medical treatment, including complete rest and aggres-

sive blood pressure lowering as the initial choice of treatment.³⁾ Blood pressure lowering therapy sometimes induces renal dysfunction in cases with renal dysfunction on admission and it might relate to adverse outcomes. Although Stanford type A and open false lumen are accepted predictors for in-hospital mortality in patients with AAD,⁴⁻⁶⁾ prognostic value of renal dysfunction is not well known. Hence, the objective of this study was to investigate the associations of renal dysfunction with in-hospital mortality in patients with Stanford type B AAD.

MATERIALS AND METHODS

Study patients

A case record review identified patients that met following criteria: (1) AAD presenting within 14 days of symptom onset,⁷⁾ (2) computed tomography (CT) with contrast confirmation of a dissected descending aorta

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containing both true and false lumens, (3) CT confirmation of that the ascending aorta was not involved and (4) not on maintenance hemodialysis. Definitions of the following clinical criteria include: hypertension: blood pressure $\geq 140/90$ mmHg or treatment for hypertension before admission; dyslipidemia: LDL-cholesterol level ≥ 140 mg/dl or treatment for dyslipidemia before admission; diabetes mellitus: treatment for diabetes mellitus before admission and smoking: ever smoking habit. Baseline blood sample was obtained on admission to the coronary care unit. Estimated glomerular filtration rate (eGFR) is widely recognized as a useful marker to evaluate renal function. eGFR was calculated as follows; eGFR (male) = $194 \times \text{Scr}^{-1.094} \times \text{age}^{-0.287}$ ml/min/1.73m², eGFR (female) = eGFR (male) $\times 0.739$ (Scr: serum creatinine).⁸⁾ Patients were divided into two groups: eGFR ≥ 60 ml/min/1.73m² group and eGFR < 60 ml/min/1.73m² group. In accordance with the Acute Dialysis Quality Initiative (ADQI) Group,⁹⁾ acute renal failure was defined for increased Scr within 2 days on admission 1.5 times or greater.

Computed Tomography

Computed tomography with a bolus intravenous injection of contrast medium was performed on admission in all 250 patients. The initial examination was used in the statistical analysis. At first, the extension of the dissection was evaluated and a Stanford type was confirmed, then the false lumen closure status was evaluated. The thrombosed type was defined as a false lumen that was not enhanced entirely by contrast whereas the non-thrombosed type was defined as a false lumen that was enhanced by contrast. In addition, partial enhancement of the false lumen was defined as the non-thrombosed type and intramural hematoma of the aorta was included in the definition of the thrombosed type. The maximum aortic diameter of the dissected aorta was measured in all patients. Decreased enhancement of kidney was defined as an enhancement of kidney decreased by narrowed or obstructed renal artery due to intimal flap or false lumen etc.

Statistical analysis

Quantitative variables were presented as mean $\pm$ SD and categorical variables as percentages. Continuous variables were compared with the Student's t-test and categorical data with the Fisher's exact or chi-square tests. Univariate and multivariate logistic regression analyses were performed to identify the predictors of

in-hospital mortality. The odds ratio (OR) and the 95% confidence interval (CI) were also calculated. A $p < 0.05$ was considered to indicate statistical significance. All analyses were performed using statistical software, Dr. SPSS 2/Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Study population and baseline characteristics

Between January 2003 and August 2011, there were 259 patients with Stanford type B AAD admitted to our institution. Nine patients were excluded from the study because of maintenance hemodialysis. Thus, a total of 250 Stanford type B AAD patients were included in this analysis. The mean age was 68.2 ± 13.1 years, with the majority of patients being male. 158 (63.2%) had a history of hypertension, 53 (21.2%) had a history of dyslipidemia, 22 (8.8%) had a history of diabetes mellitus and 156 (62.4%) had a history of smoking. Compared with the patients with eGFR ≥ 60 ml/min/1.73m², the patients with eGFR < 60 ml/min/1.73m² were significantly older. Time intervals between onset of symptom and admission were similar in the patients of both groups.

C-reactive protein (CRP) on admission was significantly higher in the patients with eGFR < 60 ml/min/1.73m² than the patient with eGFR ≥ 60 ml/min/1.73m². EGFR of the overall patients was 72.2 ± 27.8 ml/min/1.73m². The rate of acute renal failure in the patients with eGFR < 60 ml/min/1.73m² was higher than the patients with eGFR ≥ 60 ml/min/1.73m². CT findings were similar in the patients of both groups. All patients were initially subjected to intense medical therapy that focused on blood pressure lowering; of these, 232 patients (92.8%) continued to receive medical therapy for treatment of their Stanford type B AAD whereas 18 (7.2%) underwent surgery. While both groups were similar in many respects except for calcium channel blocker and angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) in medical therapy. Calcium channel blocker and ACE-I/ARB were more often prescribed in the patients with eGFR ≥ 60 ml/min/1.73m² (Table 1).

The mean duration of hospitalization was 28.9 ± 20.2 days. In-hospital complications such as stroke, intestine ischemia, limb ischemia and rupture were similar in both groups. The rate of acute respiratory distress syndrome was higher in the patients with eGFR < 60 ml/min/1.73m² than the patients with eGFR ≥ 60 ml/min/1.73m². Compared with the patients with eGFR ≥ 60 ml/min/1.73m², the patients with eGFR < 60 ml/min/1.73m² were significantly

Table 1 Patients characteristics, laboratory data, CT findings and therapies

	Overall (n = 250)	eGFR $\geq$ 60 ml/ min/1.73m ² (n = 170)	eGFR <60 ml/ min/1.73m ² (n = 80)	p value
<i>Patient characteristics</i>				
Age (years)	68.2 $\pm$ 13.1	66.5 $\pm$ 13.3	71.9 $\pm$ 12.0	0.002*
Female sex (%)	73 (29.2)	45 (26.5)	28 (35.0)	0.166
Hypertension (%)	158 (63.2)	107 (62.9)	51 (63.8)	0.902
Dyslipidemia (%)	53 (21.2)	34 (20.0)	19 (23.8)	0.499
Diabetes Mellitus (%)	22 (8.8)	15 (8.8)	7 (8.8)	0.985
Smoking (%)	156 (62.4)	104 (61.2)	52 (65.0)	0.560
Time interval onset-admission (h)	14.2 $\pm$ 36.0	12.5 $\pm$ 30.6	17.8 $\pm$ 45.5	0.272
<i>Laboratory data</i>				
White blood cell counts (/mm ³)	1127 $\pm$ 465	1108 $\pm$ 400	1168 $\pm$ 581	0.401
CRP on admission (mg/dl)	2.5 $\pm$ 5.5	1.9 $\pm$ 5.3	3.6 $\pm$ 5.7	0.026*
Peak CRP (mg/dl)	12.8 $\pm$ 6.8	12.4 $\pm$ 6.9	13.6 $\pm$ 6.7	0.293
eGFR (ml/min/1.73m ²)	72.2 $\pm$ 27.8	86.2 $\pm$ 20.7	42.3 $\pm$ 14.2	<0.001 [#]
Acute renal failure	74 (29.6)	42 (24.7)	32 (40.0)	0.013*
<i>CT findings</i>				
Non-thrombosed type (%)	91 (36.4)	62 (36.5)	29 (36.3)	0.973
Maximal aortic diameter (mm)	38.6 $\pm$ 7.7	38.1 $\pm$ 7.6	39.9 $\pm$ 7.9	0.083
Decreased enhancement of kidney (%)	22 (8.8)	12 (7.1)	10 (12.5)	0.157
<i>Therapy</i>				
Medical therapy only (%)	232 (92.8)	158 (92.9)	72 (90.0)	0.424
Emergent operation (%)	4 (1.6)	2 (1.2)	2 (2.5)	0.595
Elective operation (%)	14 (5.6)	8 (4.7)	6 (7.5)	0.386
<i>Medical therapy</i>				
Calcium channel blocker (%)	243 (97.2)	168 (98.8)	75 (93.8)	0.036*
Nitrate (%)	142 (56.8)	94 (55.3)	48 (60.0)	0.483
ACE-I/ARB (%)	200 (80.0)	147 (86.5)	53 (66.3)	<0.001 [#]
β blocker (%)	189 (75.6)	130 (76.5)	59 (73.8)	0.640
α blocker (%)	101(40.4)	66 (38.8)	35 (43.8)	0.459

Figures are mean $\pm$ SD or number (%) of patients. Time interval onset-admission, time interval between onset of symptom and admission. CT: computed tomography; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate. ACE-I: angiotensin-converting enzyme-inhibitor; ARB: angiotensin receptor blocker. * $p < 0.05$ eGFR $\geq$ 60 ml/min/1.73m² vs. eGFR <60 ml/min/1.73m². [#] $p < 0.001$ eGFR $\geq$ 60 ml/min/1.73m² vs. eGFR <60 ml/min/1.73m²

Table 2 Outcomes

	Overall (n = 250)	eGFR $\geq$ 60 ml/ min/1.73m ² (n = 170)	eGFR <60 ml/ min/1.73m ² (n = 80)	p value
Hospital stay (days)	28.9 $\pm$ 20.2	28.8 $\pm$ 19.7	29.3 $\pm$ 21.4	0.833
Stroke (%)	4 (1.6)	2 (1.2)	2 (2.5)	0.595
Intestine ischemia (%)	7 (2.8)	5 (2.9)	2 (2.5)	1.00
Limb ischemia (%)	8 (3.2)	5 (2.9)	3 (3.8)	0.713
Rupture (%)	4 (1.6)	1 (0.6)	3 (3.8)	0.098
ARDS (%)	50 (20.0)	25 (14.7)	25 (30.0)	0.002*
Death (%)	24 (9.6)	10 (5.9)	14 (17.5)	0.004*

Figures are mean $\pm$ SD or number (%) of patients. eGFR: estimated glomerular filtration rate; ARDS: acute respiratory distress syndrome. * $p < 0.05$, eGFR $\geq$ 60 ml/min/1.73m² vs. eGFR <60 ml/min/1.73m²

more likely to die in hospital (**Table 2**). In-hospital mortality occurred in 24 patients. Twelve patients died because of renal failure and respiratory failure. Four patients died because of aortic rupture and the other patients died because of gastrointestinal hemorrhage, limb ischemia, respiratory failure, severe infection or

intestine ischemia (**Table 3**).

Predictors for in-hospital mortality

In univariate logistic regression analysis, age (each having a 10 years increment: OR 1.790, 95% CI 1.150–2.785, $p = 0.010$), diabetes mellitus (OR 3.235, 95% CI 1.075–

Table 3 In-hospital Death; Patients Characteristics

Patient no.	Age/Gender	eGFR	Cause of death	Medical history	Admission CT findings	Other remarks
1	85 F	D	Gastrointestinal hemorrhage	HTN	60 mm, non-thrombosed	None
2	77 M	D	Rupture	HTN	46 mm, thrombosed	Spinal cord ischemia
3	86 M	D	Rupture	Smoking	29 mm, thrombosed	None
4	82 M	D	Rupture	HTN, smoking	33 mm, thrombosed	Cerebral infarction
5	70 F	D	Renal failure, respiratory failure	DM	48 mm, thrombosed	Abdominal aorta aneurysm, CHDF
6	80 M	D	Renal failure, respiratory failure	HTN, DM, smoking	33 mm, thrombosed	CHDF
7	78 M	D	Renal failure, respiratory failure	HTN, smoking	41 mm, thrombosed	Abdominal aorta aneurysm, CHDF
8	77 M	D	Renal failure, respiratory failure	Dyslipidemia, DM, smoking	29 mm, thrombosed	CHDF
9	64 M	D	Renal failure, respiratory failure	Smoking, s/p total arch replacement	64 mm, non-thrombosed	None
10	78 F	D	Renal failure, respiratory failure	Smoking	37 mm, non-thrombosed	Peripheral arterial disease
11	64 M	D	Renal failure, respiratory failure, Limb ischemia	HTN, smoking	47 mm, non-thrombosed	CHDF
12	85 M	D	Renal failure, respiratory failure	HTN	34 mm, thrombosed	None
13	82 F	D	Renal failure, respiratory failure	HTN	46 mm, thrombosed	CHDF
14	90 M	D	Renal failure, respiratory failure	HTN	60 mm, thrombosed	None
15	56 M	N	Rupture	HTN	62 mm, thrombosed	Emergent operation
16	57 M	N	Renal failure, respiratory failure	DM, smoking	30 mm, thrombosed	CHDF
17	75 M	N	Renal failure, respiratory failure	Dyslipidemia, smoking	35 mm, non-thrombosed	Abdominal aorta aneurysm
18	64 M	N	Limb ischemia, DIC	HTN, smoking	43 mm, non-thrombosed	Elective operation, CHDF
19	61 M	N	Respiratory failure	HTN, smoking	38 mm, thrombosed	None
20	74 M	N	Acute cholecystitis, sepsis	Smoking, HTN, DM	32 mm, thrombosed	Positive blood culture
21	76 M	N	Pneumonia, sepsis	s/p Y graft	48 mm, thrombosed	Abdominal aorta aneurysm
22	86 M	N	Intestine ischemia	HTN	35 mm, non-thrombosed	None
23	73 M	N	Intestine ischemia, DIC	Smoking	40 mm, non-thrombosed	Emergent operation
24	81 M	N	Intestine ischemia	Smoking, DM	38 mm, non-thrombosed	Acute myocardial infarction

eGFR: estimated glomerular filtration rate; CT: computed tomography; D: eGFR <60 ml/min/1.73m² on admission; N: eGFR 60 >= ml/min/1.73m² on admission; DIC: disseminated intravascular coagulation; HTN: hypertension; DM: diabetes mellitus; CHDF: continuous hemodiafiltration

Table 4 Univariate logistic regression model for prediction of in-hospital mortality

Clinical characteristic	OR	95% CI	p value
Age (10 years increase)	1.790	1.150–2.785	0.010*
Female gender	0.455	0.150–1.382	0.165
Hypertension	0.660	0.283–1.541	0.337
Dyslipidemia	0.312	0.071–1.371	0.123
Diabetes mellitus	3.235	1.075–9.740	0.037*
Smoking	1.005	0.421–2.396	0.992
Time interval onset-admission	1.001	0.991–1.012	0.810
White blood cell (100/mm ³ increase)	1.000	0.991–1.009	0.950
CRP on admission	1.039	0.980–1.102	0.199
Peak CRP	1.155	1.063–1.256	0.001*
Non-thrombosed type	1.861	0.354–2.099	0.743
Maximum aorta diameter (10 mm increase)	1.684	1.063–2.667	0.026*
Decreased enhancement of kidney	5.791	2.080–16.129	0.001*
Acute renal failure	4.718	1.960–11.352	0.001*
eGFR <60 ml/min/1.73m ²	3.392	1.435–8.020	0.005*

Time interval onset-admission, time interval between onset of symptom and admission. OR: odds ratio; 95% CI: 95% confidence interval; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; * p < 0.05

Table 5 Multivariate logistic regression model for prediction of in-hospital mortality

Clinical characteristic	OR	95% CI	p value
Age (10 years increase)	1.575	1.078–2.864	0.024*
Diabetes mellitus	2.572	0.674–9.807	0.167
Maximum aorta diameter (10 mm increase)	1.740	1.029–2.940	0.039*
Decreased enhancement of kidney	7.716	2.335–25.501	0.001*
eGFR <60 ml/min/1.73m ²	2.782	1.062–7.283	0.037*

OR: odds ratio; 95% CI: 95% confidence interval; eGFR: estimated glomerular filtration rate; * p < 0.05

9.740, $p = 0.037$), peak CRP (OR 1.155, 95% CI 1.063–1.256, $p = 0.001$), maximum aortic diameter measured by an initial CT (each having a 10 mm increment: OR 1.684, 95% CI 1.063–2.667, $p = 0.026$), decreased enhancement of kidney (OR 5.791, 95% CI 2.080–16.129, $p = 0.001$), acute renal failure (OR 4.718, 95% CI 1.960–11.352, $p = 0.001$) and eGFR <60 ml/min/1.73m² (OR 3.392, 95% CI 1.435–8.020, $p = 0.005$) were significant predictors of in-hospital mortality (**Table 4**).

In multivariate logistic regression analysis, the significant predictors on admission were age (each having a 10 years increment: OR 1.575, 95% CI 1.078–2.864, $p = 0.024$), maximum aortic diameter measured by an initial CT (each having a 10 mm increment: OR 1.740, 95% CI 1.029–2.940, $p = 0.039$), decreased enhancement of kidney (OR 7.716, 95% CI 2.335–25.501, $p = 0.001$) and eGFR <60 ml/min/1.73m² on admission (OR 2.782, 95% CI 1.062–7.283, $p = 0.037$) (**Table 5**).

DISCUSSION

While renal dysfunction independently predicted higher mortality in patients with acute coronary syndrome,^{10,11)} predictors of in-hospital events in Stanford type B AAD patients including renal function have not been clearly established. The present study results showed that a renal dysfunction was the independent predictor of in-hospital mortality for the patients with Stanford type B AAD. Thus, higher risk patients might be identified by acquiring eGFR in cases of confirmed dissected descending aorta.

We could have discriminated chronic kidney disease and acute kidney injury clearly if we had the data about renal function before admission. Since time intervals between onset of symptom and admission were relatively short and CT findings were similar in the patients of both groups, we speculated that low eGFR on admission was

due to basal renal dysfunction.

The usage of calcium channel blocker and ACE-I or ARB in the group with $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$ was infrequent. Since the rate of acute renal failure in the patients with $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$ on admission was higher than the patients with $\text{eGFR} \geq 60 \text{ ml/min/1.73m}^2$, we thought that was because those patients were intolerant to the medications. This study was not a prospective study and we controlled the blood pressure of the patients with the target blood pressure, so we cannot exclude the possibility that the patients required less amount of medication due to relatively well-controlled blood pressure.

Predictors of in-hospital mortality

In an International Registry of Acute Aortic Dissection (IRAD) report, a dilated aorta ($\geq 6 \text{ cm}$) was associated with in-hospital mortality in univariate analysis.¹²⁾ Our study also confirmed that the maximum aortic diameter was a determinant of in-hospital mortality in univariate and multivariate analysis.

A patent false lumen during the acute phase is reported to be a predictor of aortic dissection enlargement.¹³⁾ The non-thrombosed type was not a significant predictor of in-hospital events in univariate analysis in this study. One of the explanations about this difference is that the present study only adopts initial CT findings and does not provide information about gradual enlargement of the aorta during hospitalization. Further research is warranted to determine the efficacy of serial CT analyses in this clinical setting.

As aortic dissection is associated with systemic inflammation, fibrinolytic marker D-dimer, heart-type fatty acid-binding protein and inflammatory markers such as white blood cell (WBC) and CRP are known to increase in the acute phase.¹⁴⁻¹⁷⁾ Sugano, et al., reported that the greater peaks of CRP levels predicted poor clinical outcomes.¹⁸⁾ In our study, neither WBC nor CRP on admission was a significant predictor for in-hospital mortality. However, peak CRP was a significant predictor for in-hospital mortality. One explanation for this difference might be the timing of the CRP measurements. The initial evaluation of the WBC and CRP might be less important than the peak evaluation of that for risk stratification.

Multiple organ failure (MOF) including renal failure and respiratory failure was more frequent than rupture as a cause of in-hospital mortality in the patient with type B AAD. Renal function after admission tended to deteri-

orate in the patients with renal dysfunction on admission. The patients with renal dysfunction tended to have respiratory failure including ARDS. Since MOF was often complicated with respiratory failure for renal dysfunction, blood pressure lowering therapy preventing deterioration of renal function such as moderate blood lowering might lead to reduce the MOF and mortality.

Intravascular ultrasound-guided percutaneous fenestration of the intimal flap in the dissected aorta can effectively relieve the patient's symptom.¹⁹⁾ Nishida, et al., reported that a case of acute Stanford type B thoracic aortic dissection complicated with malperfusion, which was successfully treated with emergent thoracic endovascular aortic repair.²⁰⁾ The decreased enhancement of kidney related with renal dysfunction and predicted to the in-hospital mortality. Hence treatment to improve renal flow such as fenestration or endovascular repair might be useful for the decrease of in-hospital mortality in patients with Stanford type B AAD.

Study limitations

This study was performed at a single center, thus posing a risk for possible patient selection bias. Furthermore, these are observational data, and the conclusions are not based on prospective and randomized study results. Although the patient number used in this study was not low, it might have been underpowered for identifying other predictive factors. Our analyses of patient outcomes were based on the results from the initial admission. For example, the creatinine levels on admission used to calculate eGFR were not discriminate chronic and acute kidney injury that may occur as a result of hemodynamic compromise and inflammatory response. More recently, it has been shown that cystatin C-based formulas are more reliable and reproducible than creatinine-based ones, but cystatin C was not available when this database started to collect.^{21,22)} The available data are limited to in-hospital mortality and do not provide information on mid-term to long-term outcomes.

CONCLUSIONS

The present study results identified a renal dysfunction on admission as the independent predictor of in-hospital mortality in the patients with Stanford type B AAD. Further investigations are needed to evaluate therapies and strategies for decreasing the deterioration of renal function to improve in-hospital mortality in patients with Stanford type B AAD.

DISCLOSURE STATEMENT

The authors have no financial or related disclosures and conflict of interest.

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