Association of Ward Acquired, On-admission, Progressive and Non-progressive AKI with Death among Dengue Patients: A Hidden Relationship

Associação entre Lesão Renal Aguda, Evolutiva e não Evolutiva, Adquirida em Meio Hospitalar e Mortalidade em Doentes com Dengue: Uma Relação Menos Evidente

Keywords: Acute Kidney Injury; Dengue/complications.
Palavras-chave: Dengue/complicações; Lesão Renal Aguda.

Respected Editor,

We retrospectively investigated 7 894 patients admitted during the period of 15 years (2000–2014) and identified 57 fatal cases. By defining mortality as death resulted from or as a consequence of dengue infection, 44 fatal cases were selected. A case-control study was designed by taking five non-fatal controls for every dengue associated death case (study/control group: 44/220 patients). All the confounders i.e. age, gender, baseline kidney disease, co-morbidities and type of dengue infection were matched with control group. Characteristics of patients in study and control group are shown in Table 1. Out of 44 fatal cases, acute kidney injury (AKI) was diagnosed in 35 (79.5%) patients by using Acute Kidney Injury Network (AKIN) criteria: 11.4% with AKIN-I, 22.7% with AKIN-II and 45.5% with AKIN-III. AKI occurred in 24 (10.9%) cases among control group: 5% with AKIN-I, 3.6% with AKIN-II and 2.3% with AKIN-III. In case of disease progression, we classified the worst stage of AKI during hospital stay. Out of 21 fatal cases without AKI on hospital admission, 12 (57.1%) patients developed AKI later during their stay (ward-acquired AKI), including two patients with AKIN-I, three with AKIN-II and seven with AKIN-III. On the other hand, 23 fatal cases had AKI on hospital admission (on-admission AKI) with varying severity. Some of the patients with ward-acquired and on-admission AKI progressed to severe AKI (progressive AKI) i.e. three and five patient respectively. Patients with ward-acquired AKIN-I were associated with greater than two times odds of deteriorating into AKIN-II and AKIN-III. Cox proportional hazards regression analysis suggested AKI as an independent predictor of in-hospital mortality, with *HR* 5.781 ($p < 0.001$). Furthermore,

Table 1 - Characteristics of fatal and non-fatal cases

	Fatal cases n = 44	Non-fatal cases n = 220	*p* value*
Age, mean ± SD	43.5 ± 4.2	38.6 ± 5.4	0.086
Male, n (%)	30 (68.1)	166 (75.5)	0.109
Co-morbidities			
Hypertension, n (%)	6 (13.6)	23 (10.5)	0.071
Diabetes mellitus, n (%)	5 (11.4)	20 (9.1)	0.092
Hyperlipidemia, n (%)	3 (6.8)	17 (7.7)	0.313
Chronic kidney disease, n (%)	2 (3.6)	8 (4.5)	0.062
Severity of dengue infection			
Dengue fever, n (%)	17 (38.6)	89 (40.5)	0.321
Dengue hemorrhagic fever, n (%)	19 (43.2)	130 (46.8)	0.059
Dengue shock syndrome, n (%)	8 (18.2)	28 (12.7)	0.067
AKI, n (%)	35 (79.5)	24 (10.9)	< 0.001
On-admission AKI, n (%)	23 (52.3)	7 (3.2)	< 0.001
Progressive AKI, n (%)	8 (18.2)	12 (5.5)	< 0.001
Serum creatinine, µmol/L	131.5 ± 14.3	82.7 ± 9.8	< 0.001
Aspartate aminotransferase (AST), IU/L	943.5 ± 189.2	188 ± 56.9	< 0.001
Alanine aminotransferase (ALT), IU/L	498.7 ± 112.1	142 ± 67.5	< 0.001
Activated partial thromboplastin time (aPTT), seconds	51.7 ± 6.7	46.9 ± 2.7	0.021
Prothrombin time (PT), seconds	19.8 ± 2.2	13.1 ± 1.8	0.034
Hematocrit, %	46.7 ± 4.6	43.1 ± 2.4	0.002
Hospital stay, days	8.4 ± 2.2	5 ± 1.4	0.001

**p* value is calculated by Chi-square test for categorical variables and by independent student *t* test for continuous variables

the adjusted mortality hazards ratios were 2.331 (95%CI: 1.234 - 3.541, p = 0.003) for severe AKI (AKIN-II/III) in comparison to mild AKI (AKIN-I). Patients with on-admission AKI [HR (95%CI): 1.893 (1.121 - 2.933), p = 0.032)] were more likely to die compared to ward-acquired AKI. Similarly, patients with progressive AKI during hospital stay were signicantly associated [HR (95%CI): 5.121 (3.452 - 8.123), p < 0.001)] with mortality as compared to non-progressive AKI. We also found worsening AKIN class was correlated with increasing linear trends in mortality. All the four serotypes of dengue virus circulate in Malaysia.[1] In our study, we found serotype 2 more prominent among died cases as well as among patients with AKI while serotype 3 was predominant among non-fatal and non-AKI cases. Additionally, serum creatinine criteria to stratify AKI was found to be more predictive (HR: 2.311, p = 0.002) for mortality than urinary output criteria in our analysis. These findings suggest that severity, nature and course of AKI have predictive abilities for hazards of mortality among dengue patients.

It has been documented that even transient AKI is linked to increased mortality[2] but unfortunately relationship between AKI and mortality has not been investigated among dengue patients. Only few studies described dengue associated mortality but no or very less attention was given to AKI.[3,4] Our findings are first description of different relationships of AKI and dengue associated deaths. Furthermore, our preliminary findings presented at European Renal Association-European Dialysis & Transplant Association (ERA-EDTA) 52nd congress demonstrated that all fatal cases with dengue had moderate to severe AKI.[5,6] Conclusively, dengue induced AKI is highly neglected intricacy and portends significant disease burden in terms of morbidity, mortality and cost of care. Therefore it is crucially important to understand the association of AKI with mortality and our analysis is an attempt to underscore the clinician's attention towards this hidden relationship.

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http://dx.doi.org/10.20344/amp.6900