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Intensive Care Unit Fluid Therapy in Severe Dengue Infection: Liberal versus Restrictive

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Abstract

Objective: Effective fluid management is important to achieve adequate perfusion during critical and recovery phases of severe dengue infection (SDI).

Methods: This study involved 113 patients with SDI during critical phase in the intensive care unit (ICU) and was divided into Group Liberal (GL) and Group Restrictive (GR) based on the fluid management received. Both groups were compared in terms of demographic data, organ dysfunctions, duration of ICU stay, ventilation support and mortality. Risk factors for each significant outcome within group were evaluated.

Results: Patients in GL had significantly increased incidence of cardiovascular (CVS) dysfunction (67.2 vs 46.0%), duration of ICU stay (3.8 vs 2.8 days) and mortality (12.1 vs 0.0%) when compared to GR. The risk of CVS dysfunction is increased in patients from cluster dengue area receiving liberal fluid (OR 3.56, 95% CI 1.00-12.68, p=0.043). Those in GL with blood transfusion (OR 37.50, 95% CI 3.14-448.59, p=0.001) and Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥25 (OR 66.67, 95% CI 5.57-797.49, p<0.001) was predisposed to higher mortality. The APACHE II score ≥ 25 was also a significant independent predictor of mortality (OR 53.63, 95% CI 3.31-869.68, p=0.005).

Conclusion: Liberal fluid management particularly blood transfusion and APACHE II score ≥ 25 in patients with SDI residing in cluster dengue area increases the risk of cardiovascular dysfunction, mortality and prolonged the duration of ICU stay.

Key words: Severe Dengue Infection, Intensive Care Unit, Liberal Fluid Therapy, Restrictive Fluid Therapy

INTRODUCTION

Global incidences of dengue infection mainly from the Western Pacific regions have been increasing over the past decade.[1,2] The rate of severe dengue infection was 18 folds higher in the Southeast Asian region when compared to the United States of America.[1] In Malaysia, there was a surge of deaths related to dengue infection by 19.1% in 2015.[3] The rising incidences were due to increased Aedes mosquitoes breeding sites from recent population growth and urbanization.[1,4,5] Malaysia spent an estimated 56 million USD annually on acute dengue infection management excluding prevention, control, surveillance and long-term sequelae of dengue infections.[6]

Dengue infected patients may present in a broad and complex clinical spectrum.[2,7,8] Following an incubation period, the disease may sequentially progress towards febrile, critical and recovery phases.[7,8] Increased vascular permeability and resultant plasma leak into the extravascular compartments characterises the critical phase.[7,8] Indicators of plasma leak are defervescence, haemoconcentration, relative leucopaenia and thrombocytopaenia.[2,7,8] Inadequate or delayed fluid resuscitation during early hypotension from plasma leak commonly leads to multiple organ dysfunctions (MODs).[2,7,8] Recovery phase typically follows if patients survived beyond 24 to 48 hours of plasma leak. This phase is defined by intravascular reabsorption of fluid from the extravascular compartments.[2,7,8] During this period, complications from fluid overload may arise due to judicious or prolonged fluid regimes administered during the critical phase. Patients risk problems associated with hypervolemia including cerebral oedema, congestive cardiac failure or liver congestion.[7,8]

Apart from regular objective clinical monitoring and assessments, fluid therapy remained a good core clinical practice in the management of dengue illness.[2,7] The target is to maintain adequate circulation and perfusion.[7] Timely and proportionately administered

intravenous fluids are simple management strategies to achieve these circulation goals especially during the critical and recovery phases.[2,7] Schmitz et al. (2011) emphasised the importance of guided fluid replacement to avoid positive fluid balance which was shown to worsened outcomes.[7,9] Large volumes of fluid administration were associated with increased risk of tissue oedema and clinical signs of volume overload such as ascites, pleural effusion and respiratory distress.[7,9,10] The key to prescribing appropriate parenteral fluids regimes lies in prompt and continuous assessment of patients' hydration status.[2,7,10]

Since 2013, there was a shift in our institution fluid management strategy. This is guided by local clinical practice fluid management in patients with severe dengue infection. We designed this study to compare the mortality rates and incidences of MODs in patients who received liberal versus restrictive fluid management for severe dengue infection between 2011 until 2015 in the general adult Intensive Care Unit (ICU).

MATERIALS AND METHODS

This single-centre, retrospective, cross-sectional, observational study was conducted at the Health Information Department in Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia Medical Centre (UKMMC) following approval by the Research Committee of Department of Anaesthesiology & Intensive Care, HCTM, UKMMC and the Medical Research & Ethics Committee, HCTM, UKMMC (Research Code: FF-2016-198).

A total of 113 patients admitted to ICU from January 2011 to December 2015, aged 18 years old and above with SDI in critical phase were enrolled into this study. Pregnant patients, patients with underlying chronic kidney disease and underlying congestive cardiac failure were excluded from the study.

Patients with SDI were recruited based on the guideline by Mustafa et al. (2010).[7] The critical phase was indicated by the presence of either capillary refill time > 2 seconds, heart rate > 100 beats per minute, pulse pressure ≤ 20 mmHg, postural drop of ≥ 20 mmHg in systolic blood pressure, systolic blood pressure ≤ 90 mmHg, urine output ≤ 0.5 mL/kg/hour, haematocrit > 20% from baseline or > 45% in males and > 40% in females, lactate levels > 2 mmol/L, pH < 7.0 or base excess > -5 mEq/L on arterial blood gas or clinical findings of third space fluid accumulation. Onset of the critical phase was determined by either a sudden drop in temperature (< 38°C) or downward leukopaenic trend.[7]

Patients were allocated into either Group Liberal (GL) or Group Restrictive (GR) based on the fluid management received. Patients in GL received either a fluid bolus ≥ 10 mL/kg, fluid infusion rates ≥ 3 mL/kg/hour, fluid infusion rates ≥ 1 mL/kg/hour despite having good enteral intake or using ideal body weight or fluid regimes calculated based on total body weight. Patients in GR have received either a fluid bolus <5 mL/kg, fluids infused at ≥ 3 mL/kg/hour and did not exceed beyond 2 hours, fluid infusion rates between 1-3 mL/kg/hour fluid with poor oral intake, fluid infusion rates ≤ 1 mL/kg/hour or good oral intake without intravenous drip infusion, fluid regimes calculated based on ideal body weight or adjusted body weight or intravenous fluid therapy terminated at the onset of the reabsorption phase. Onset of recovery phase was indicated either by a sudden increase in total white cell count trend, relative hypertension or urine output >2 mL/kg/hour.

Demographic data from recruited patients were recorded. This includes gender, age, race, area of residence for past 2 weeks since onset of illness which were then classified into non-dengue area or cluster dengue area according to the Ministry of Health (MOH) [11], citizenship, and actual body weight. Other information such as total blood or blood products received prior to ICU admission was recorded as well. Acute Physiology and Chronic Health Evaluation (APACHE) II scores of patients within 24 hours of ICU admission were similarly documented.

Information related to patients' MODs outcomes and mortality from fluid management were recorded as well. Central Nervous System (CNS) dysfunction was indicated by either the lowest GCS score recorded during ICU stay or presence of cerebral oedema from Computed Tomography (CT) scan of the head within 48 hours of critical phase.

Cardiovascular (CVS) dysfunction was indicated by either presence of bilateral end inspiratory lung crepitations or reduced air entry or features of fluid overload on chest radiograph such as Kerley B lines, peribronchial cuffing, perihilar consolidation, air bronchograms, pleural effusion and increased cardiac silhouette during ICU stay.

Presence of hepatic dysfunction was indicated by either right hypochondriac pain, tenderness on palpation of the area or evidence of hepatomegaly from either palpation,

ultrasonography or CT scan of the abdomen. Raised levels of serum transaminases such as alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase were taken into consideration as well.

Presence of third space compartment volume accumulation such as ascites either by palpation, ultrasonography or CT scan of the abdomen during ICU stay was documented. Mortality due to SDI, duration of ICU stay and ventilation support were recorded as well.

All data were analysed using Statistical Package for the Social Sciences (SPSS, IBM) version 23.0^{TM} software for windows. Continuous variables were compared using student's independent t-tests and presented as means ± standard deviations (SD) or median (25%-75% interquartile range [IQR]). The categorical variables were compared using the Pearson chi-square test as well as Yates Correction and presented as numbers (*n*) or proportions (%) where appropriate. The normality of distribution of continuous variables was first evaluated using Kolmogorov-Smirnov Test. Non-parametric test which is Mann-Whitney U test was used to compare continuous variables evaluated as not normally distributed. Risk factors were further tested against significant MODs between groups where the odd ratios (OR) and 95% confidence intervals were calculated. Variables associated with mortality were included in multivariate logistic regression model. Two-sided *p* value <0.05 was considered as statistically significant.

RESULTS

A total of 113 patients were included in the study. Five patients dropped out of the study due to missing documents.

Table I. Demographic data, blood and blood product transfusion with APACHE II scores. Values expressed as numbers and percentage or median and IQR in parenthesis.

	GL n=58	GR n=50	*p* value
Gender			
Male	34 (58.6)	25 (50.0)	0.370
Female	24 (41.4)	25 (50.0)	
Age	29.0 (22.0-50.2)	35.5 (26.5-52.8)	0.106
Race			
Malay	37 (63.8)	31 (62.0)	0.415
Chinese	15 (25.9)	12 (24.0)	
Indian	3 (5.2)	4 (8.0)	
Others	3 (5.2)	3 (6.0)	
Area of Residence			
Cluster Dengue Area	23 (39.7)	25 (50.0)	0.281
Non-Dengue Area	35 (60.3)	25 (50.0)	
Citizenship			
Malaysian	55 (94.8)	46 (92.0)	0.839
Others	3 (5.2)	4 (8.0)	
Actual body weight	70.0 (60.5-78.4)	70.0 (57.2-86.6)	0.863
Blood Transfusion	4 (6.9)	0 (0.0)	0.167

Blood Product Transfusion	8 (13.8)	4 (8.0)	0.339
APACHE II score	9.0 (5.0-15.0)	7.5 (5.0-13.3)	0.372

CVS dysfunction in patients who received liberal fluid was significantly higher than those who had restrictive fluid management (p = 0.026). There were no significant differences of other organs and overall dysfunction between groups.

Table II. Organ dysfunction between groups. Values expressed as numbers and percentage in parenthesis.

Organ Dysfunction	**GL n=58**	**GR n=50**	***p* value**
CNS	5 (8.6)	5 (10.0)	1.000
CVS	39 (67.2)	23 (46.0)	0.026*
Hepatic	41 (70.7)	34 (68.0)	0.762
Third space volume accumulation	8 (13.8)	5 (10.0)	0.546
Overall organ dysfunction	49 (84.5)	38 (76.0)	0.267

*Statistically significant at $p < 0.05$

The duration of ICU stay was longer in GL than in GR (p = 0.014). Median length of ICU stay in GL and GR were 3 days and 2 days respectively. The longest days spent was 27 days in GL compared to those in GR which was 7 days. There were no mortality in GR (p = 0.032).

Table III. Duration of ICU stay, ventilation support (days) and mortality between groups. Values expressed as number and percentage in parenthesis or median and IQR in parenthesis.

Outcomes	**GL (n=58)**	**GR (n=50)**	***p* value**
Duration of ICU stay (days)	3 (2.0-4.3)	2 (1.9-3.0)	0.014*
Duration of ventilation support (days)	0 (0.0-2.0)	0 (0.0-0.6)	0.142
Mortality	7 (12.1)	0 (0.0)	0.032*

*Statistically significant at $p < 0.05$

Risk of CVS dysfunction is increased in patients from cluster dengue area receiving liberal fluid. Those in GL with blood transfusion and APACHE II score ≥ 25 was predisposed to higher mortality as shown in Figure 1 and 2.

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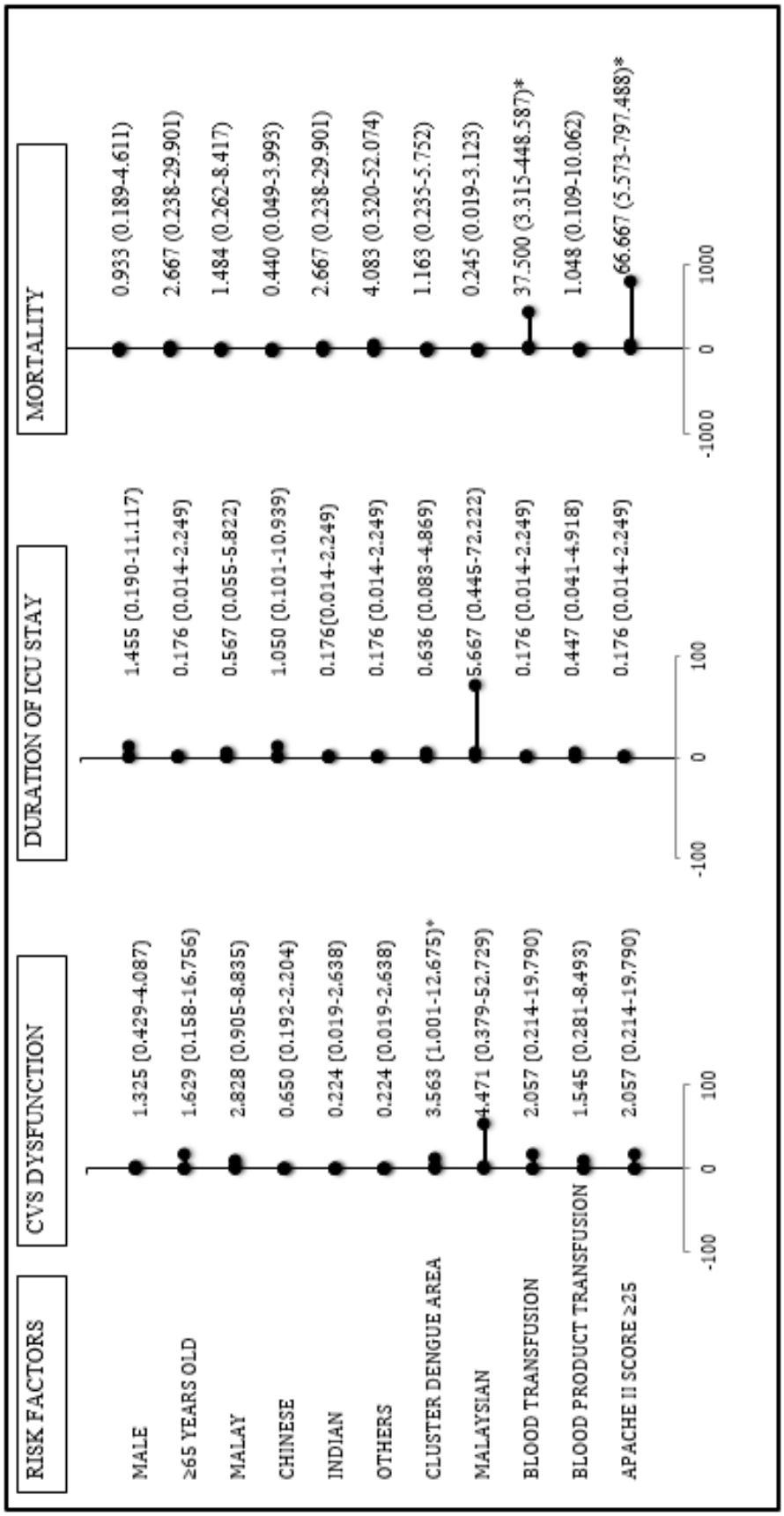

Figure 1. Risk factors associated with CVS dysfunction, duration of ICU stay and mortality in severe dengue infection patients receiving Liberal fluid management. Values expressed as OR and 95% CI.

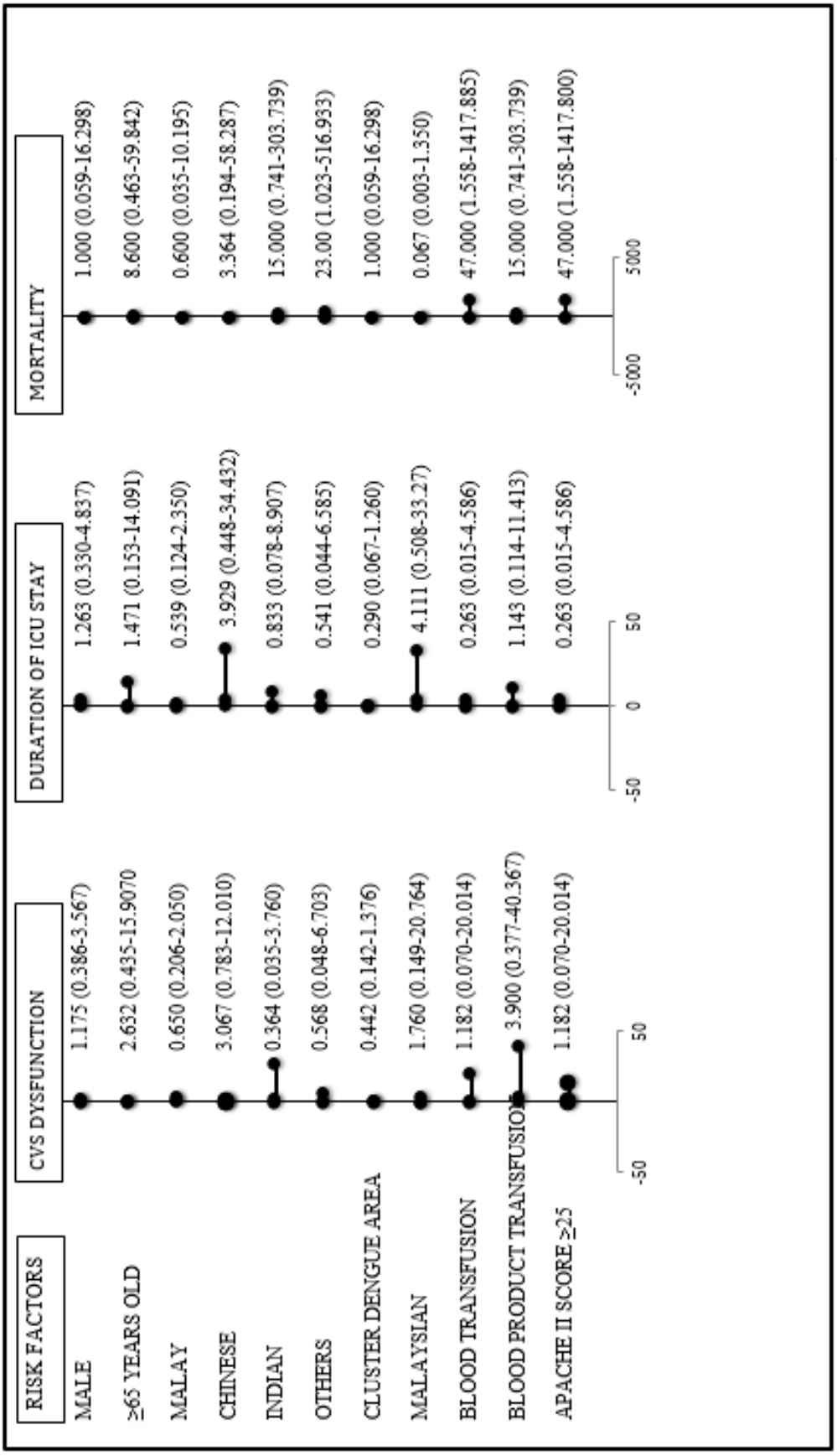

Figure 2. Risk factors associated with CVS dysfunction, duration of ICU stay and mortality in severe dengue infection patients receiving Restrictive fluid management. Values expressed as OR and 95% CI.

The APACHE II scores was an independent risk factor for mortality (p = 0.005), as shown in Table IV.

Table IV. Relationship between clinical factors and mortality. Values expressed as OR with 95% CI.

	OR	95% CI	*p* value
Blood transfusion	9.078	0.237-347.581	0.236
APACHE II score ≥ 25	53.634	3.308-869.681	0.005*

*Statistically significant at $p < 0.05$

DISCUSSION

This is one of a few studies which focuses on fluid management in patients with SDI in critical phase admitted to general adult ICU. Tight fluid management had been shown to improve pulmonary function and reduced the likelihood of prolonged ventilation support.[12,13] Cardiovascular and pulmonary dysfunction were identified as the most common organ failure besides haematological dysfunction in patients with SDI.[9] Similarly, 67.2% of patients who received judicious fluid during critical phase of SDI had higher incidences of cardiovascular and pulmonary dysfunction in this study. It was found that resting myocardial ionized calcium levels were raised following infection with dengue virus.[14] The arrhythmogenic threshold is lowered and cardiac contractility is altered due to a shift in intracellular calcium balance.[14] Endothelial cells in blood vessels are likewise affected. We postulate that the plasma leak resulting from SDI will impact the lung vasculature more significantly than other organs' microcirculation. This is due to the alteration in its natural tendency to favour reabsorption which would affect its main role in gas exchange.[15]

Not surprisingly, no ICU mortality occurred in patients with restrictive fluid regimes in this study. Respiratory distress commonly follows if the fluid delivered is beyond that required for effective perfusion.[2] According to World Health Organization's guideline for dengue infection management, over-zealous fluid administration is a leading cause of fluid overload in SDI.[2] Cardio-respiratory failure from high cumulative positive fluid balance is strongly associated with a 4-fold increased risk for mortality.[9] The duration of ICU stay is also significantly longer by one day in patients with liberal fluid management. Sequential organ failure assessment (SOFA) scores are consecutively greater in the initial 5 days of ICU admission as the number of organ dysfunction rises in those who succumbed to dengue related deaths.[9] Large volumes of fluid can indirectly lower the survival rate by acting through other mechanisms such as reperfusion injury, subclinical alteration in pulmonary vessels' compliance, myocardial function and intracranial pressure.[16]

Patients residing in cluster dengue area were found to have an odds of 3.56 for cardiovascular and pulmonary dysfunction when liberal fluid were administered (p=0.043). Progression towards more serious forms of dengue infection such as SDI is related to the succession and types of dengue virus (DENV) infecting serotypes.[17,18] The predominant geographical circulating DENV serotype changes annually between serotypes DENV 1 to 4 in a periodic manner.[7,19] Dengue endemicity and pattern of all four DENV serotypes co-circulation is strongly implicated in the risk of developing SDI.[18,19] Outbreaks in terms of number and severity is predictable when there is a sudden shift in the dominant infecting DENV serotype. The particularly susceptible population would be those who had been previously infected in a series of different DENV strains.[17,18,19] Planned city expansion and densification through overhaul urbanization in the 21st century has become a major risk for shifts in DENV serotypes.[19] This led to the subsequent dramatic rise in the incidence of dengue infection with adverse outcomes.[19] The subpopulation studied mainly originated from Klang Valley, Malaysia. It is an urban hub where

63% of the nation's total reported dengue infected cases occurred.[19]

Patients who received blood transfusion as part of their liberal fluid therapy had significantly lower survival rate. The mainstay of treatment for plasma leak in SDI remains immediate and rapid intravenous fluid resuscitation followed by timely cautious fluid therapy.[7,17,20] However, prophylactic blood transfusion notably in substandard intravenous fluid resuscitation contributes to delayed mortality. The larger volumes of blood transfusion, greater plasma transfusion volume and a faster transfusion rate increases the risk of fluid overload and MODs.[7,21,22] Transfusion related acute lung injury is not uncommon in those who did not survive.[9,20] Most literatures state a common observation of blood transfusion in patients with respiratory distress who did not survive. Therefore, until further evidence, it is imperative to ensure guided fluid therapy preferably with the use of heart echocardiogram to avoid fluid overload.

The degree of derangement of routinely measured physiological variables in APACHE II score is the best-known and widely used predictor of illness severity in the first 24 hours of ICU admission. The odds for higher mortality were significantly elevated in those who had APACHE II score ≥ 25 followed by exposure to liberal fluid management. Following multivariate analysis, the APACHE II score was also shown to be significant independent predictor of mortality. According to Bouch et al. (2008), 50% and 80% in-hospital mortality is predicted when the APACHE II scores 25 and 35 respectively.[23] It is likely that patients with higher APACHE II scores were already severely ill from SDI.[24,25,26] Hence, even an aggressive management approach and organ support is not sufficient to prevent deterioration of more severe forms of SDI.

This study has limitations. Data collection in a retrospective study depends on pre-existing documentation in medical files. Some useful and important data for analysis such as body mass index and pre-ICU fluid management were incomplete or lacking. Significant bleed related to dengue infection was not considered which could confound the studied dengue related outcomes. The scope of this research could be widened by involving multiple centres which can diversify the data and analysis of outcomes as the result generated by our single centred study may be limited by the number of patients studied.

CONCLUSION

Fluid management is the mainstay of SDI. Inappropriate fluid therapy can lead to fatal outcomes. Fluid administered liberally including inappropriate blood transfusion in patients from cluster dengue area with APACHE II score ≥ 25 predisposes to significantly higher mortality.

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