INTRODUCTION

Dengue is one of the most concerned mosquito borne viral diseases in the word with the reported dengue cases increasing worldwide from 2.2 million in 2010 to 3.2 million in 2015 [1]. In 2013, estimated 9000 deaths occurred globally with a majority being reported from low and middle income countries [2]. Dengue virus which is transmitted by *Aedes Aegypti* and *Aedes Albopictus* mosquitoes can result in asymptomatic infection, dengue fever (DF) or severe forms of dengue haemorrhagic fever (DHF) and life threatening dengue shock syndrome (DSS). Although a commercial vaccine against dengue is being licensed in several countries, it is still not in use in many parts of the world which suffer from consistent dengue outbreaks [3]. Therefore, early detection and careful body fluid management remains important in treating against dengue so as to prevent a patient from moving into critical phase.

Cytokines are believed to be associated with increased vascular permeability that may lead to severe forms of dengue [4]. In this analysis Platelet activating factor (PAF), sphingosine 1- phosphate (S1P), Tumor Necrosis Factor -α (TNF-α) and Interleukin -10 (IL-10) are used as parameters. Previous studies have shown the impact that cytokines and inflammatory mediators have on determining dengue disease severity. Elevated levels are observed for IL-1β, IFN-γ, IL-4, IL-6, IL-13 and IL-7 in DHF patients than in DF patients and TNF-α is shown to be associated with thrombocytopenia [5]. Also, compared with DF patients, DHF patients have shown to have significantly lower S1P levels throughout the course of illness and above 50% of patients with DHF have shown S1P levels below 0.5 µM at some time point in their illness and only 10% of DF patients have shown S1P levels below 0.5 µM [6].

Decision trees are commonly used to handle biological problems and in this study Improved ID3 (IID3) algorithm is used to determine the impact from cytokines and inflammatory mediators. A classification and regression tree (CART) analysis performed on a cohort of Thai children analysed at 72 hours from onset of illness achieved a 97 % sensitivity in detecting patients who proceed into DSS [7]. This decision tree algorithm used white blood cell count, percent monocytes, platelet count and haematocrit to make the decisions. CART decision tree based on clinical and laboratory parameters including platelets, IL-10 and Lymphocyte resulted in a best model with an accuracy of 84.6 % for DHF and 84.0% for DF and identified IL-10 and platelet counts as the most informative parameters [8].

METHODS

Data was obtained from 36 adult patients who were admitted to the Colombo South Teaching Hospital, Sri Lanka. According to 2011 WHO guidelines, out of these, 11 patients are classified as DF while 25 are classified as DHF. These patients are admitted to the hospital at varying time points ranging from 72-144 hours from onset of illness. However, our analysis is limited to only 96, 108 and 120 hours from onset of illness as the aim is for early detection and sufficient data didn’t exist for earlier time points.

The decision tree algorithm that is used in this analysis is Improved ID3 algorithm (IID3). ID3 algorithm is one of the most widely used algorithms in decision trees. This uses information gain to determine the most suitable property for each node and the attribute with the highest information gain is selected as the attribute for that particular node. However, as ID3 algorithm tend to be biased towards selecting the attribute with many values, this is modified using an association function to overcome this drawback and the modified IID3 algorithm is developed [9].

RESULTS

IID3 decision tree algorithm is performed for 96, 108 and 120 hours from onset of illness as shown in Fig.1, Fig.2 and Fig.3 respectively. At 96 hours from onset of illness decisions are made using only the parameters TNF- α and IL-10. IL-10, TNF- α and S1P is measured in pg/ml units and PAF is measured in units of ng/ml. The decision rules are as follows:

1. If IL-10 <31.81 then categorize as a DHF patient.
2. If IL-10 >= 31.81 and TNF <8.16 then categorize as a DF patient.
3. If IL-10 >= 31.81 and TNF >= 8.16, then those patients are DHF.

At this time point 12 out of 17 (70.59%) of DHF patients are classified based only on IL-10 concentration. All four DF patients fall under second rule and this indicates that TNF-α plays a vital role in classifying DF patients.

Fig.1: Decision tree at 96 hours from onset of illness. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and ‘n’ refers to the number of patients classified under that particular decision making.

At 108 hours from onset of illness since TNF-α has the highest information gain, decision making is started with TNF-α. Decisions are made using only the parameters TNF- α and PAF. 13 out of 17 (70.59%) of DHF patients are classified based only on TNF-α values.

1. If TNF >=26.67 then categorize as a DHF patient.
2. If TNF is in the region [14.18, 26.27) then categorize as a DF patient.
3. If TNF <14.18 and PAF >= 53.06, then categorize as a DHF patient.
4. If TNF < 14.18 and PAF is in the region [11.03, 53.06), then categorize as a DF patient.
5. If TNF <14.18 and PAF < 11.03, then categorize as a DHF patient.

However, out of 16 DHF patients there’s only one DHF patient that is classified in this way. If this particular DHF patient is eliminated, the decisions can be simplified as:

1. If TNF >=26.67 then categorize as a DHF patient.
2. If TNF is in the region [14.18, 26.27) then categorize as a DF patient.
3. If TNF <14.18 and PAF >= 53.06 then categorize as a DHF patient.
4. If TNF <14.18 and PAF < 53.06 then categorize as a DF patient.

Fig.2: Decision tree at 108 hours from onset of illness. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and ‘n’ refers to the number of patients classified under that particular decision making.

At 120 hours from onset of illness the decision tree, as seen in Fig.3 fails to provide with useful rules to determine dengue severity as it results in a complexed tree with only a few patients being classified under each rule.

Fig.3: Decision tree at 120 hours from onset of illness. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and ‘n’ refers to the number of patients classified under that particular decision making.

DISCUSSION

This study is an attempt to develop a decision criteria that could be used to predict the severity level of dengue patients. IID3 decision trees are generated for 96, 108 and 120 hours from onset of illness.

At 96 hours from onset of illness, if the IL-10 concentration is less than 31.81 (pg/ml) the patients are directly categorized as DHF and thus indicates that IL-10 is an important parameter in making decisions as it was in [8]. However, according to [10], [11] IL-10 levels have shown to be higher in DHF patients than in DF patients and according to [12] DHF patients showed a median IL-10 level of 110.8 pg/ml and DF patients a median of 15.5 pg/ml. Therefore, further analysis is required to determine if the low levels of IL-10 in DHF patients is significant or whether it is specific to this data set alone. At 108 hours from onset of illness TNF-α alone has correctly classified 70.59% of DHF patients. The decision that if TNF-α >= 26.67 pg/ml the patient is DHF is compatible with previous findings where the mean TNF-α for DHF patients was 29.95, SD 39.5 pg/ml with higher TNF-α values being shown by DHF and shock patients than DF patients [13].

The study is only limited to decision trees generation and couldn’t be validated at these time points as sufficient data doesn’t exist. Data was limited to 17, 16 and 19 DHF patients respectively at 96,108 and 120 hours from onset of illness and only 4 DF patients at 96 and 108 hours and 7 DF patients at 120 hours from onset of illness existed. With a larger data set the accuracy of this tree could be evaluated by means such as k-fold cross validation, which would enable to strengthen the validity of the decision rules. Also, all the patients considered in this sample are adult patients and it is important to test the decision rules on samples which include children as well, as severe dengue and death is common among children [1].

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