1.0 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 can 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 than DF patients [6].

Immune parameters used in the study are dengue NS1 antigen levels, dengue IgG antibody levels, platelet counts and lymphocyte counts. NS1 positivity is found to be associated with severe dengue, especially on day 5-6 after illness. Also, it is found to be inversely correlated with lymphocyte count [7]. During a secondary dengue infection IgG is present in high values even in the acute phase and thus IgG/IgM antibody ratios are used to distinguish between primary and secondary infection [8]. Thrombocytopenia is believed to be a resultant of bone marrow suppression and peripheral destruction of platelets [9].

This study is an extension of the studies in [10] and [11] in which fuzzy based decision models are developed separately for inflammatory mediators [10] and immune parameters [11]. The objective of this study is to develop a decision tree informed fuzzy decision system that can detect dengue severity at an early stage. Thus, this model focuses on detection at 96 hours from onset of illness rather than at 108 or 120 hours from onset of illness as was the case in the previous models. This model is a combination of the previous two models and is targeted at determining disease severity at an early stage. The combined interaction of inflammatory mediators together with immune parameters is of interest to study as, previous studies have shown that S1P levels are significantly correlated with platelet counts in DHF patients [12] and IL-10 levels are significantly and inversely correlated with lymphocyte counts [13]. Furthermore, this model targets at reducing the number of parameters that are required for decision making.

Fuzzy logic is commonly used in models involving medicine as it has the ability to handle the imprecision and uncertainty associated in medical decision making. Decision trees are commonly used to handle biological problems and in this study, Improved ID3 (IID3) algorithm is used to determine the effect that inflammatory mediators and immune parameters have on detecting disease severity. 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 proceeded into DSS [14]. This decision tree algorithm used white blood cell count, percent monocytes, platelet count and haematocrit to make decisions. CART decision tree based on clinical and laboratory parameters including platelets, IL-10 and lymphocyte resulted in a 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 [15].

2.0 METHODS

2.1 Data

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 hours from onset of illness as the aim is for early detection and sufficient data didn't exist for earlier time points. There are 17 DHF and 4 DF patients who are admitted at 96 hours from onset of illness.

2.2 Decision Tree

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 [16].

2.3 Theoretical Framework

Fuzzy set

Elements of a fuzzy set are mapped using a membership function $\mu: A \rightarrow [0,1]$ which measures the degree to which an element belongs to the set [17].

Hamacher Operator

$$\mu_H(x) = \begin{cases} 0 & \text{if } \mu_A(x) = \mu_B(y) = 0 \\ \frac{\mu_A(x) * \mu_B(y)}{\mu_A(x) + \mu_B(y) - \mu_A(x) * \mu_B(y)} & \text{otherwise,} \end{cases} \quad (1)$$

where $\mu_A(x)$, $\mu_B(x)$ are the membership function values of the fuzzy sets A and B respectively.

Ordered Weighted Aggregation (OWA) Operator

OWA operator is defined as,

$$OWA(a_1, a_2, \ldots., a_n) = \sum_{j=1}^{n} w_j\, b_j \qquad (2)$$

where b_j is the j[th] largest element of the collection of aggregated objects $a_1, a_2, \ldots, a_n$ and $\sum_{j=1}^{n} w_j = 1$ and $w_j \in [0,1]$.

Yager [18] [19]suggests a way to determine the weights of OWA operator by,

$$w_i = Q\left(\frac{i}{n}\right) - Q\left(\frac{i-1}{n}\right) \qquad ; i = 1,2,, \ldots, n$$

and the non-decreasing quantifier Q is defined by Zadeh [20] as,

$$Q = \begin{cases} 0 & ; if\ r < l \\ \frac{r-l}{b-m} & ; if\ l \le r \le m \\ 1 & ;\ if\ r > m \end{cases}$$

where $l, m, r \in [0,1]$.

'Orness measure' which measures the degree to which the aggregation operation is like an 'OR' operation is defined by Yager [19] as

$$orness(w) = \frac{1}{(n-1)} \sum_{i=1}^{n} (n-i) w_i$$

which lies in the interval [0,1].

2.4 Model Development

The parameters to be used in the model are determined through the IID3 decision tree algorithm evaluated at 96 hours from onset of illness. The fuzzy membership functions are developed according to the previous studies [10] and [11].

The membership functions for the inflammatory mediators are obtained from [10].

$$\mu_{10}(x) = \begin{cases} 1 & ; x \le 20 \\ \frac{110-x}{90} & ; 20 < x < 110 \\ 0 & ; x \ge 110 \end{cases} \qquad (3)$$

$$\mu_{\alpha}(x) = \begin{cases} 1 & ; x \le 15 \\ \frac{30-x}{15} & ; 15 < x < 30 \\ 0 & ; x \ge 30 \end{cases} \qquad (4)$$

$$\mu_{PA}(x) = \begin{cases} 1 & ; x \le 10 \\ \frac{100-x}{90} & ; 10 < x < 100 \\ 0 & ; x \ge 100 \end{cases} \qquad (5)$$

$$\mu_S(x) = \begin{cases} 0 & ; x \leq 0.5 \\ x - 0.5 & ; 0.5 < x < 1.5 \\ 1 & ; x \geq 1.5 \end{cases} \quad (6)$$

The membership functions for IL-10, TNF- α, PAF and S1P are given by the equations (3), (4), (5) and (6) respectively.

The membership functions for the immune parameters are obtained from [11].

$$\mu_P(x_p) = \begin{cases} 0 & \text{if } x_p \leq 25 \\ 2\left(\frac{x-25}{125}\right)^2 & \text{if } 25 < x_p \leq 87.5 \\ 1 - 2\left(\frac{x-150}{125}\right)^2 & \text{if } 87.5 < x_p \leq 150 \\ 1 & \text{if } x_p > 150 \end{cases} \quad (7)$$

$$\mu_N(x_N) = \begin{cases} 1 & \text{if } x_N = 0 \\ 1 - 2\left(\frac{x}{75}\right)^2 & \text{if } 0 < x_N \leq 37.5 \\ 2\left(\frac{x-75}{75}\right)^2 & \text{if } 37.5 < x_N \leq 75 \\ 0 & \text{if } x_N > 75 \end{cases} \quad (8)$$

$$\mu_L(x_L) = \begin{cases} \frac{x}{14000} - \frac{1}{140} & \text{if } 100 < x_L \leq 1500 \\ 0.9 * \frac{x}{4500} - 0.2 & \text{if } 1500 < x_L \leq 6000 \\ 1 & \text{if } x_L > 6000 \end{cases} \quad (9)$$

$$\mu_I(x_I) = \begin{cases} \frac{-x}{36} + 1 & \text{if } x_I < 18 \\ 0.5 & \text{if } 18 < x_I \leq 22 \\ \frac{-x}{156} + \frac{25}{39} & \text{if } 22 < x_I \leq 100 \\ 0 & \text{if } x_I > 100 \end{cases} \quad (10)$$

The membership functions for platelet, dengue NS1 antigen, lymphocyte and dengue IgG antibody levels are given in equations (7), (8), (9) and (10) respectively.

The combined effect of parameters is obtained through the Hamacher operator in (1) and the parameters are concentrated or diluted to give prominence to the most important parameters. The OWA operator given in (2) combines the Hamacher products and outputs a model value that could be used to determine disease severity level. Depending on the model results a second fuzzy decision criteria is evaluated for the required patients.

The ambiguous region, which is the region in which it is impossible to clearly distinguish between DF and DHF patients is obtained as in [10] and [11]. As the model measures the unfavourability to attain severe dengue, region above the upper limit of the ambiguous region is considered as the non-severe (DF) region and the region below the lower limit of the ambiguous region is the severe (DHF) region.

3.0 RESULTS

IID3 decision tree algorithm is evaluated for 96 hours from onset of illness for the two sets of parameters, one including cytokines and the other including immune parameters. The decision tree for cytokines is shown in Fig.1. At 96 hours from onset of illness decisions are made using only the parameters TNF- α and IL-10 and the parameters PAF and S1P are not used in the decision process. At this time point 12 out of 17 (70.59%) of DHF patients are classified based only on the IL-10 concentration. All four DF patients are categorized by the decision criteria IL-10 >= 31.81(pg/ml) and TNF <8.16 (pg/ml).

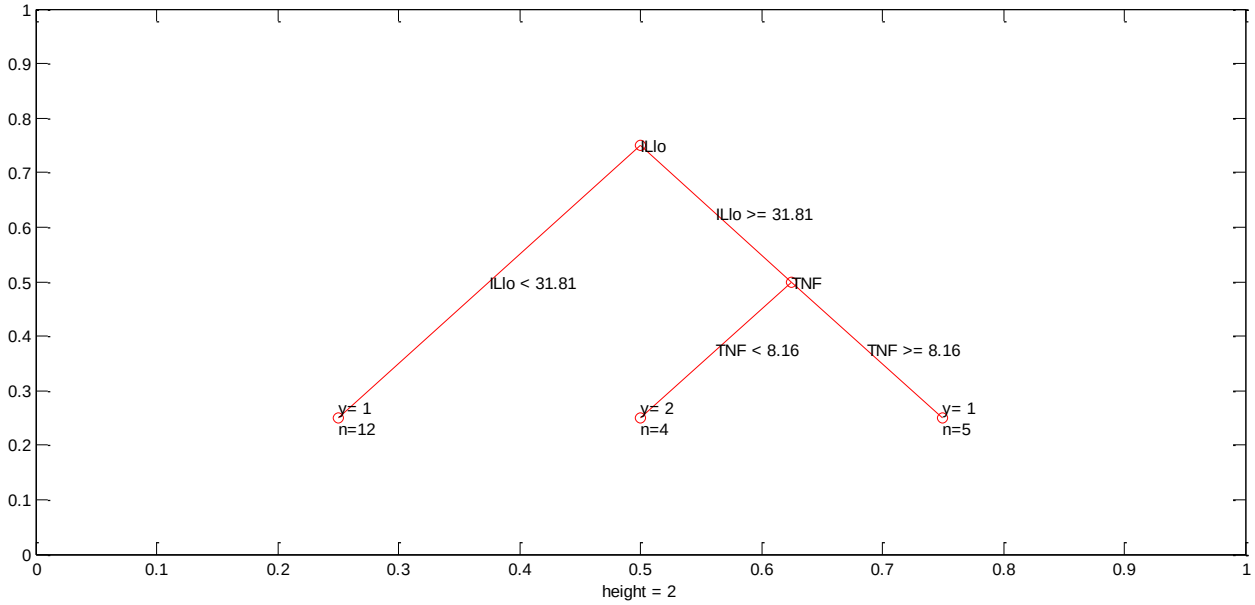

Fig.1: Decision tree at 96 hours from onset of illness for cytokines. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and 'n' refers to the number of patients classified under that particular decision making.

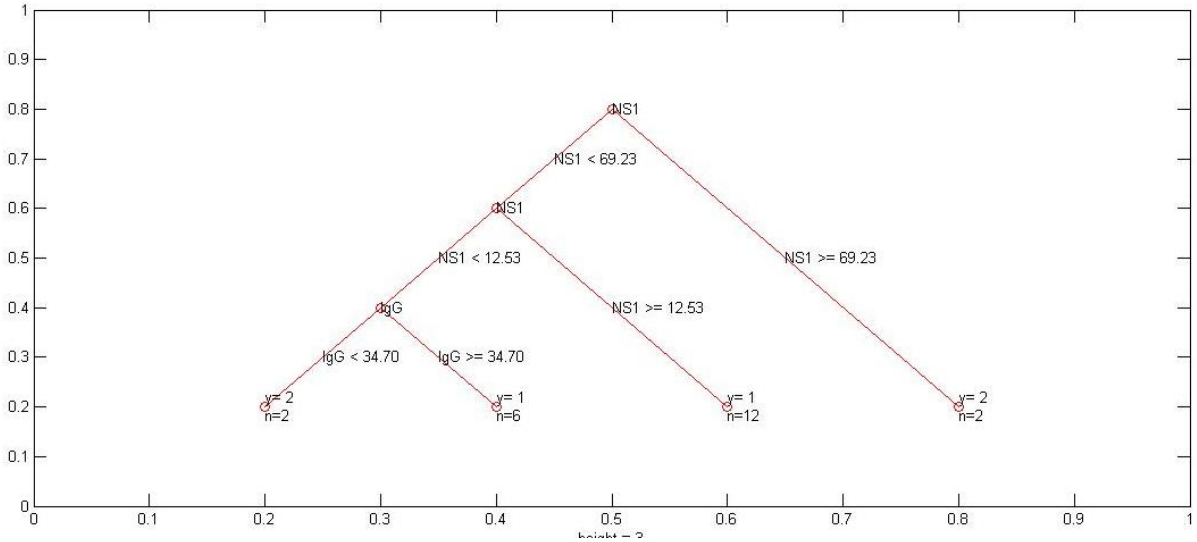

Fig.2: Decision tree at 96 hours from onset of illness for immune parameters. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and 'n' refers to the number of patients classified under that particular decision making.

The decision tree for immune parameters evaluated at 96 hours from onset of illness is shown in Fig.2. At 96 hours from onset of illness decisions are made using only the parameters dengue NS1 antigen and dengue IgG antibody, indicating these parameters to be informative at 96 hours from onset of illness. The parameters platelet and lymphocyte counts are not used in the decision process.

Since, at 96 hours from onset of illness, the decision tree based on inflammatory mediators outputs the results based only on the parameters TNF-α and IL-10 and the immune parameters based decision tree outputs the results based only on the parameters NS1 and IgG, the initial fuzzy decision model is developed using only these four parameters. In order to account for the combined effect from the parameters the Hamacher operator is performed on the parameters as described in equations (11) and (12). The fuzzy concentration and dilution of the parameters is performed as in [10] and [11].

$$\mathrm{H1} = \frac{\mu_\alpha(x)^{1.1} * \mu_{10}(x)^{1.1}}{\mu_\alpha(x)^{1.1} + \mu_{10}(x)^{1.1} - \mu_\alpha(x)^{1.1} * \mu_{10}(x)^{1.1}} \quad (11)$$

where $\mu_\alpha(x), \mu_{10}(x)$ are the membership values of TNF-α and IL-10 respectively and both are concentrated by 1.1 as in [10].

$$\mathrm{H2} = \frac{\mu_N(x)^{0.2} * \mu_I(x)^{1.1}}{\mu_N(x)^{0.2} + \mu_I(x)^{1.1} - \mu_N(x)^{0.2} * \mu_I(x)^{1.1}} \quad (12)$$

where $\mu_N(x), \mu_I(x)$ are the membership values of NS1 and IgG respectively and NS1 is diluted by 0.2 and IgG is concentrated by 1.1 as in [11].

The Hamacher results in (11) and (12) are then combined using the Ordered Weighted Aggregation Operator (OWA) as in (13).

$$\mathrm{OWA} = 0.4 * \mathrm{maximum}\{\mathrm{H1}, \mathrm{H2}\} + 0.6 * \mathrm{minimum}\{\mathrm{H1}, \mathrm{H2}\} \quad (13)$$

The weights of the OWA operator are determined from [10].

The ambiguous region of this fuzzy model is constructed using the concepts in [10] and [11]. According to this fuzzy implementation the ambiguous region lies in between the values 0.4413 and 0.5727. Thus, values above 0.5727 indicate the region with DF patients (non-severe) whereas the region with DHF patients (severe) is shown for values less than 0.4413.

The model validation results of the fuzzy model for patients with 96 hours from onset of illness are shown in Table 1.

Table 1: Model validation results at 96 hours from onset of illness.

Patient severity level	Percentage in severe region	Percentage in ambiguous region	Percentage in non-severe region
DHF	58.8%	11.8%	29.4%
DF	25%	50%	25%

Form the results in Table 1, it can be seen that at 96 hours from onset of illness this model performs better in classifying DHF patients and has a much lower percentage of misclassifications than the models in [10] and [11]. However, this model misclassifies five DHF patients. This is a costly error as, by classifying a patient as DF who indeed should be

classified as a DHF patient, the patient may not receive proper attention and thus the patient can easily proceed into critical stage without being detected.

Therefore, the existing model is further improved by using information from the decision trees evaluated at 108 hours from onset of illness (Fig.3 and Fig.4). As it can be seen from Fig.3 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.

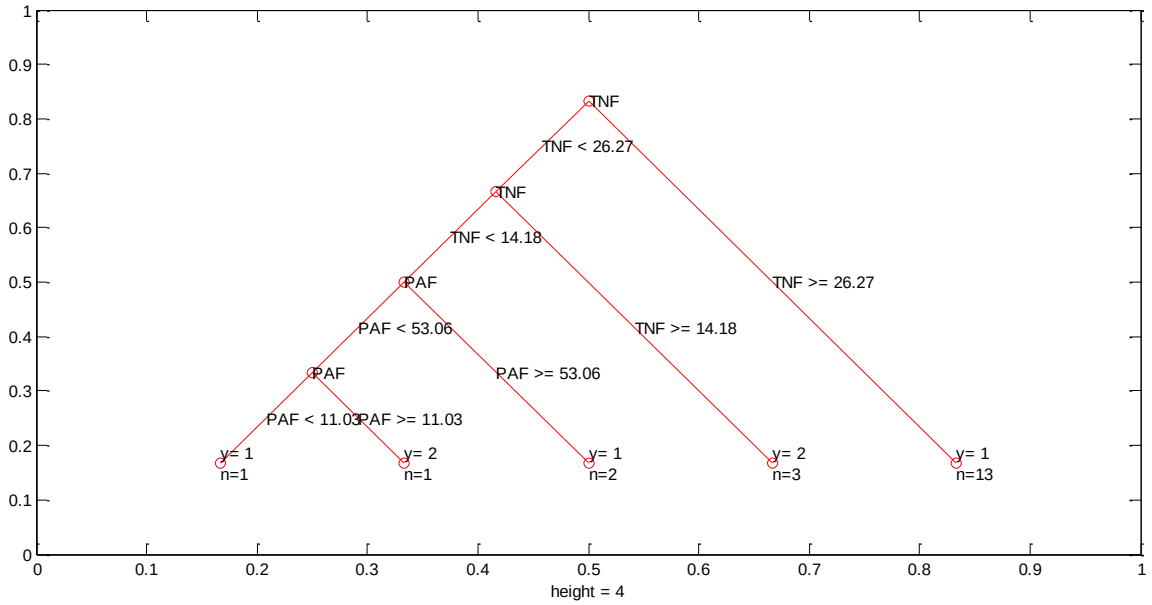

Fig.3: Decision tree at 108 hours from onset of illness for inflammatory mediators. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and 'n' refers to the number of patients classified under that particular decision making.

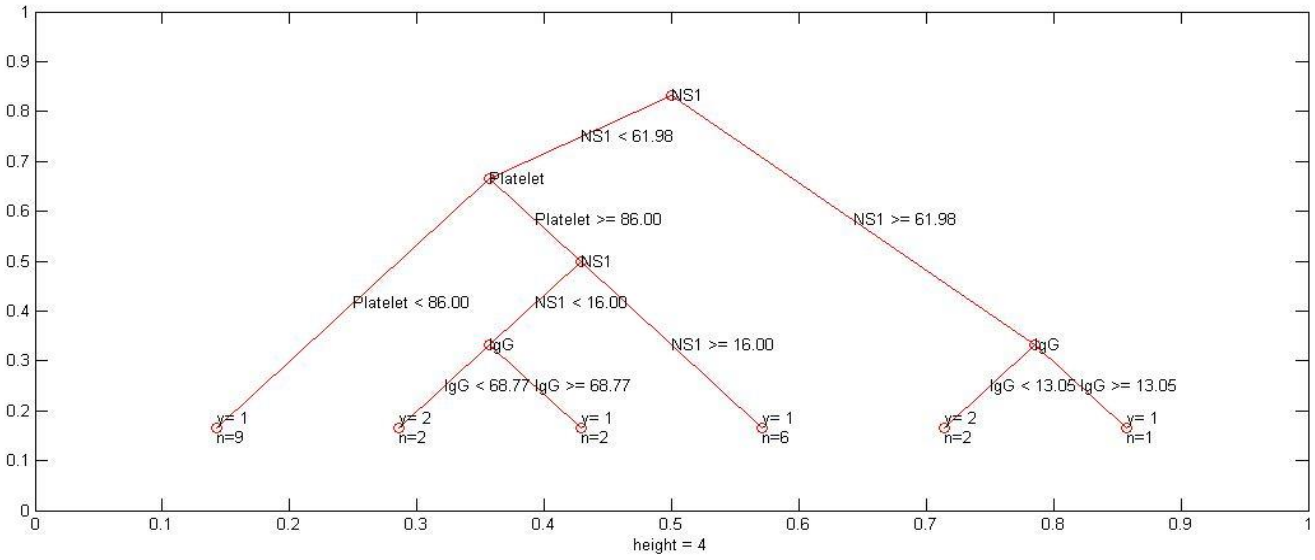

Fig.4: Decision tree at 108 hours from onset of illness for immune parameters. In the figure y=1 refers to DHF patients and y=2 refers to DF patients and 'n' refers to the number of patients classified under that particular decision making.

As it can be seen from Fig.4 at 108 hours from onset of illness since NS1 has the highest information gain, decision making is started with it. Decisions are made using only the parameters NS1, IgG and platelet count but the lymphocyte count is not taken for consideration.

Therefore, the fuzzy model is further improved to include the effect from the parameters PAF and Platelet count. Since the model misclassifies DHF patients into non-severe region, the patients with initial model operator values above 0.4413 are subjected to second fuzzy decision making which includes PAF and Platelet count as in equation (14).

$$\mathrm{H3} = \frac{\mu_P(x)^4 * \mu_{PA}(x)^4}{\mu_P(x)^4 + \mu_{PA}(x)^4 - \mu_P(x)^4 * \mu_{PA}(x)^4} \quad (14)$$

where $\mu_P(x), \mu_{PA}(x)$ are the membership values of Platelet and PAF respectively and both are concentrated by 4.

For these patients, after going through the second decision criteria, the final model output result is obtained through equation (15).

$$\mathrm{OWA}_{new} = 0.4 * \mathrm{maximum}\{\mathrm{OWA}, \mathrm{H3}\} + 0.6 * \mathrm{minimum}\{\mathrm{OWA}, \mathrm{H3}\} \quad (15)$$

The model validation results when performed including second testing with PAF and platelet count is given in Table 2.

Table 2: Model validation results at 96 hours from onset of illness after second test.

Patient severity level	Percentage in severe region	Percentage in ambiguous region	Percentage in non-severe region
DHF	82.3%	5.93%	11.76%
DF	75%	0%	25%

Compared with Table 1 results, from Table 2 it can be seen that the model output results have improved for DHF patients. Without testing for PAF and Platelet counts five DHF patients were misclassified and two were in the ambiguous region. However, after considering their PAF and platelet counts there were only two misclassifications of DHF patients and only one DHF patient fell into the ambiguous region.

The accuracy of this fuzzy model is calculated using equation

$$Accuracy = \frac{correctly\ classified\ DHF\ +\ correctly\ classified\ DF}{Total\ number\ of\ patients} \quad (16)$$

At 96 hours from onset of illness, the final model performed with an accuracy of 76.19%. This improved fuzzy model implemented using decision tree results performs with much higher accuracy than the individual models developed in [10] and [11].

Sensitivity analysis is performed to see how the model outcomes would be affected when the degrees of fuzziness are changed. Fig. 5 denotes the change in the ambiguous region when the lower and upper boundary of the membership functions are changed over a small range. It can

be seen that as the boundary values of the membership functions are changed the ambiguous region does not change in a way that could affect the classification of the patients.

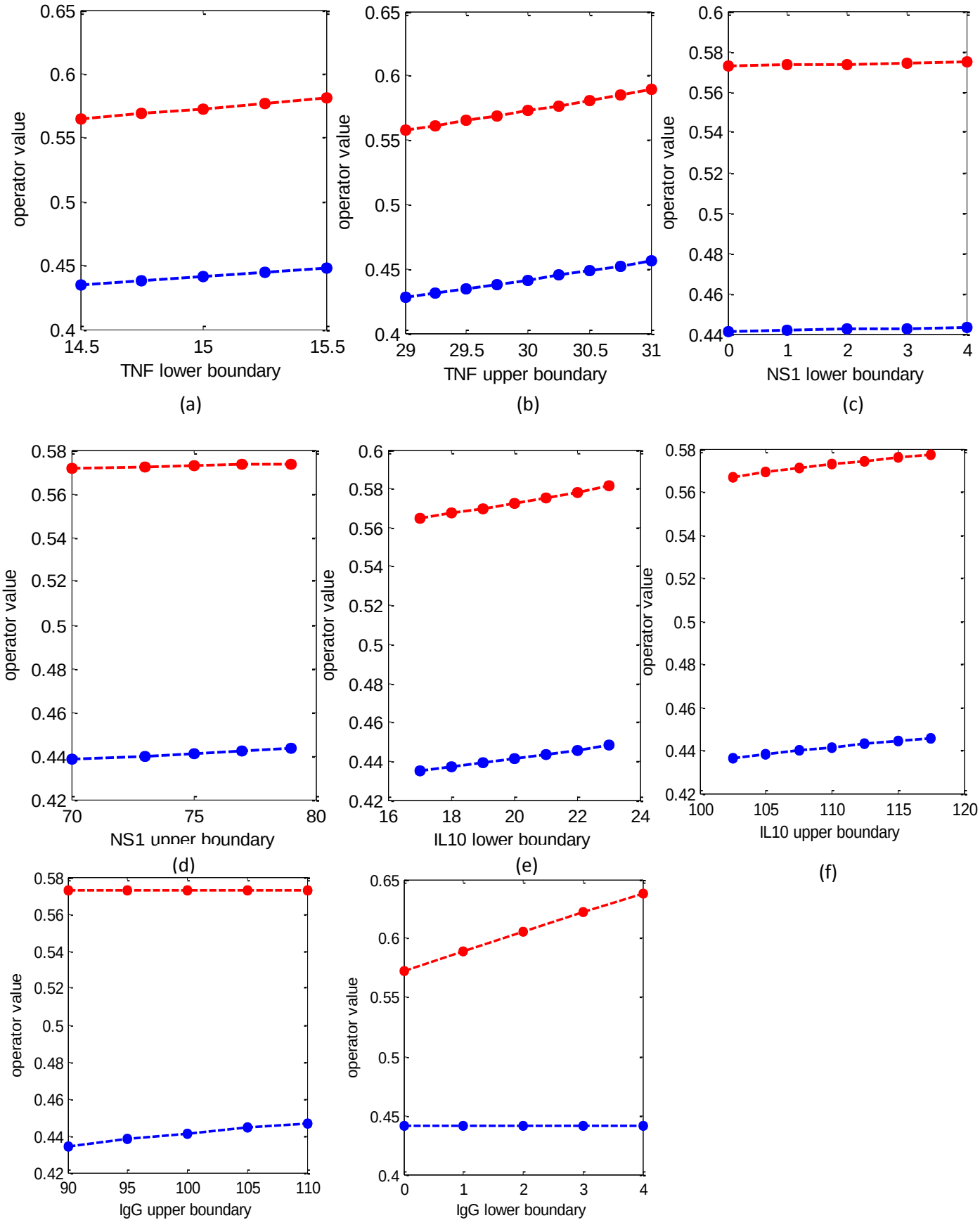

Fig.5: Behaviour of the ambiguous region when the lower cut off value and the upper cut off value of the membership function is changed for the parameters TNF (a, b), NS1 (c, d), IL-10 (e, f), IgG (g, h).

Fig.6 denotes the change in the ambiguous region when the amounts of concentration and dilution are changed.

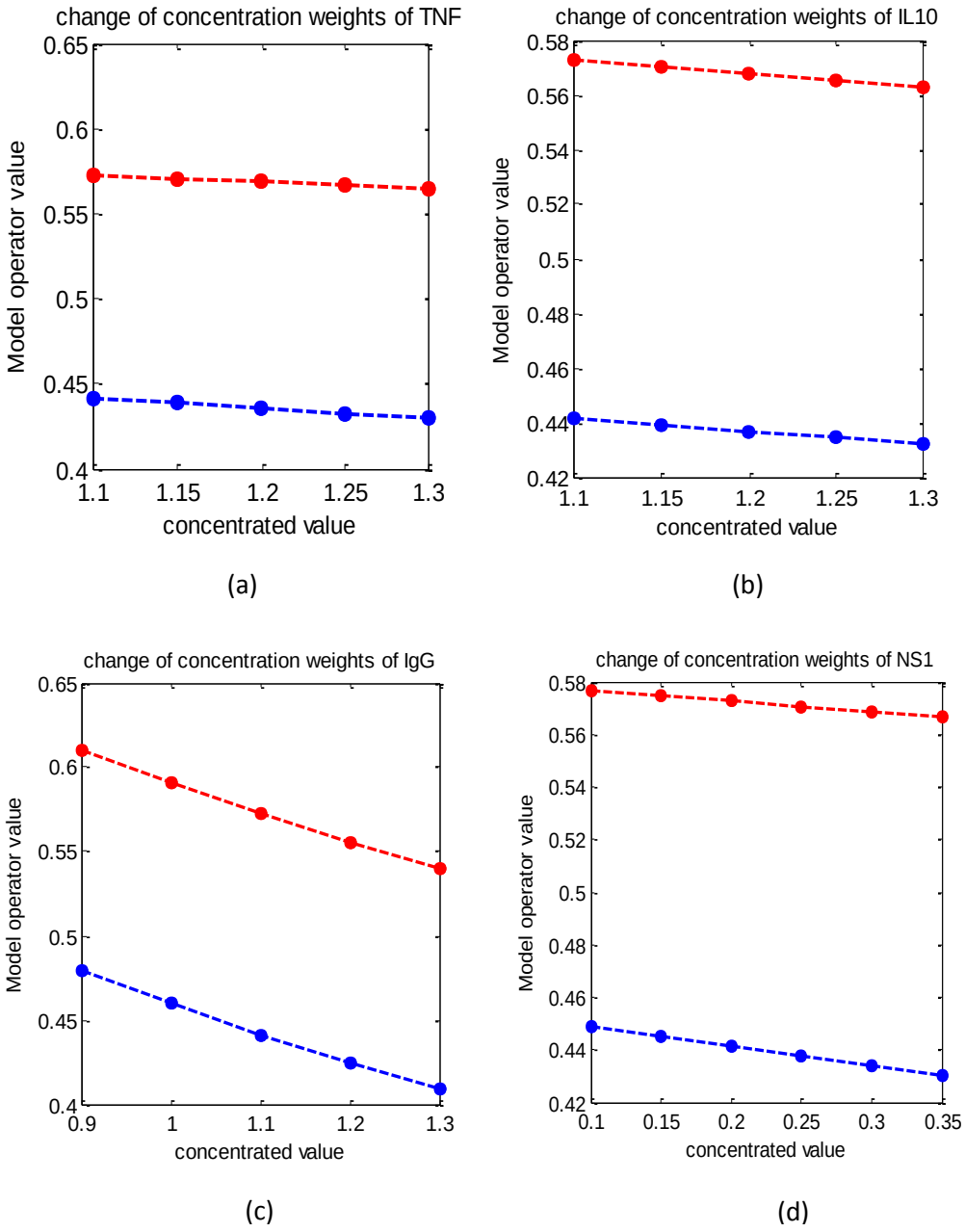

Fig.6: Behaviour of ambiguous region for a change in concentration weights for TNF (a), IL-10 (b), IgG (c), NS1 (d).

It can be seen that when the parameter concentration and dilutions are varied over a small range the model outcomes remain unchanged as the ambiguous region remains relatively unchanged. Therefore, Fig. 5 and Fig.6 indicate that the model is robust.

4.0 DISCUSSION

This study is an attempt to develop a fuzzy decision model to predict the severity level of dengue patients. IID3 decision trees are used to determine which inflammatory mediators and immune parameters should be used in constructing the fuzzy model.

In Fig. 1 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 [15]. However, according to [21], [12] IL-10 levels have shown to be higher in DHF patients than in DF patients and according to [22] 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 (Fig.3). 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 $\pm$ 39.5 pg/ml with higher TNF-α values being shown by DHF and shock patients than DF patients [23].

This model uses a reduced number of parameters than the previous studies [10] and [11]. The cytokines IL-1β and S1P and the immune parameter lymphocyte count are not used in this model. This makes it a relatively cost effective model as well. The accuracy of this fuzzy model at 96 hours from onset of illness is highly improved than the models [10] and [11]. This indicate that the model with combined interactions between inflammatory mediators and immune parameters performs well than when they are used individually to measure dengue severity and that decision trees play a vital role in making decisions about parameter selection for fuzzy model.

Early detection of dengue and management is essential to reduce dengue mortality [8]. As the model performed with an accuracy of 76.19% at 96 hours from onset of illness, this robust model can be reliably used for early decision making.

The drawback of this model is it tend to overestimate the risk of DF patients. In the final model 3 out of 4 DF patients were misclassified into severe region. However, more data on DF patients is needed to accurately measure their behaviour with the model and the data limitation on DF patients contributes to the model being biased towards severe level. 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].

5.0 CONCLUSIONS

This is a fuzzy logic based mathematical model which uses information gained from IID3 decision tree algorithms for model construction. This study attempts to develop a model that can be used as an early detection tool to determine dengue severity.

The model makes decisions mainly based on the parameters NS1, IgG, TNF-α and IL-10. Second decision criteria is made using PAF and platelet counts. Unlike in [10] this model uses only three inflammatory mediators for the decision making and this can be economically beneficial. This model can be considered as an improved decision maker than the individual models in [10] and [11]. Although the model tends to overestimate the risk of DF patients, this

model reduces the more serious risk of incorrectly classifying DHF patients as DF patients. The model validation results for patients at 96 hours from onset of illness achieved an accuracy of 76.19% and only 2 DHF patients (out of 17) were misclassified. The sensitivity analysis indicated the model to be robust. Therefore this model will be useful as an early indicator to detect dengue severity.

The model needs to be further validated on larger data sets which includes more DF patients and children.

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