~ CHAPTER 6 ~

THE CLASSIFICATION OF CLINICAL DENGUE CASES

6.1 Introduction

In this chapter, the primary objective is to classify the clinical dengue cases into DF and the more acute DHF by means of the same approach in Chapter 5. Acknowledging the symptomatic differences between children and adult dengue patients, these two groups of patient are analyzed separately. For each group, the chapter follows through the process of developing a logistic regression equation comprises a set of variables that will best discriminate between the two classifications – DF and DHF (dependent variable is *Clinical Diagnosis 2*). It begins with the usual univariable examination of logistic relationship for each independent variable for the purpose of selecting potential candidates for inclusion in the logistic model. Then, using stepwise procedure, the logistic regression model is estimated, following which its classification accuracy is discussed and assessed. Age, gender and ethnicity of patients were not analyzed here since literature does not recognize them as the criteria of dengue infection.

6.2 Classification of the Clinical Diagnosis for Dengue Infection

In this study, there were three main clinical diagnosis of dengue infection, namely DF, DHF and DSS. Acknowledging that there were only seven DSS cases (six children and one adult) and that the WHO (1997a) guidelines basically regard DSS as the more severe form of DHF (DHF grade III and IV), the said DSS cases were regrouped into DHF for further analysis, resulting in only two groups – DF and DHF. The resultant independent variable (*Clinical Diagnosis_2*) was coded as 0 for DF and 1 for DHF.

Separate logistic regression models are developed for child and adult patients due to the earlier-mentioned symptomatic differences. The primary objective is to pick up predictor variables that have significant contribution to the classification of patients into DF and DHF. Depending on the final model, the short-listed independent variables may provide insights into the consistency and compliance of the clinical diagnosis of dengue infection as to whether it abides by the prescribed recommendation of dengue classification. In other words, if the clinical diagnosis follows the WHO guidelines, then it is reasonable to expect symptoms explicitly related to thrombocytopenia and haemoconcentration to be in the multivariate logistic model or the univariate model at the very least since they are the consistent indicators of DHF.

6.2.1 Clinical Classification of Dengue in Child Patients

For the case of pediatric patients, the univariate likelihood ratio test in Table 6.1 reveals a large number of independent variables significant in explaining the outcome variable (with at least 25% level of significance). *Hepatomegaly, hematocrit change, platelet count at admission, thrombocytopenia_100, thrombocytopenia_50, haemoconcentration_20, abdominal pain, bleeding* and *vomit* are all significant at 1% in explaining the outcome. *Dehydration, haemoconcentration_50* and *shock evidence* are significant at 5% while giddiness at 10% level of significance.

Referring to the odds ratios in Table 6.1, those with thrombocytopenia, haemoconcentration, abdominal pain or bleeding are about 5 times more likely (except *thrombocytopenia_50* which has higher odds of about 7 times) to be diagnosed as having DHF. Children with hepatomegaly are about 12 times more likely to be classified as

DHF while those with evidence of shock are about 7.5 times. Cases with vomiting, dehydration and giddiness are about 4, 3 and 2 times more likely to be treated as DHF respectively.

Table 6.1: Likelihood ratio test[a] and odd ratio for the clinical dengue classification of child patients

Variable	Likelihood Ratio Test Statistic [b c]	Odds Ratio	95% Confidence Interval
Fever	N/A	N/A	N/A
Fever duration	0.044	1.018	(0.861, 1.204)
Vomit	10.899****	3.835	(1.630, 9.023)
Giddiness	3.714**	2.182	(1.000, 4.762)
Headache	0.289	1.688	(0.251, 11.336)
Skin Rash	0.649	0.455	(0.067, 3.094)
Eye Pain	0.171	1.857	(0.100, 34.439)
Muscle & Joint Pain	0.061	0.800	(0.135, 4.745)
Bleeding	12.533****	4.511	(1.986, 10.248)
Shock Evidence	4.567***	7.500	(1.039, 54.116)
Hepatomegaly	28.645****	12.351	(4.787, 31.864)
Rash / Petechiae	0.413	1.875	(0.266, 13.202)
Abdominal Pain	14.689****	4.586	(2.101, 10.009)
Dehydration	6.488***	2.647	(1.240, 5.652)
Haemoconcentration_20	16.108****	4.889	(2.237, 10.684)
Haemoconcentration_50	4.857***	4.533	(1.234, 16.653)
Thrombocytopenia_50	18.322****	6.750	(2,834, 16.076)
Thrombocytopenia_100	18.544****	5.455	(2.413, 12.330)
Platelet count at admission	20.907****	0.987	(0.980, 0.994)
Heart rate per minute	0.530	1.006	(0.989, 1.024)
Hematocrit change	22.607****	1.047	(1.024, 1.071)

[a] For comparing the based model with a constant only to the univariate logistic model. Independent variable is *Clinical diagnosis 2.*

[b] It is the change in the -2 log-likelihood from the based model to the univariate logistic model and is distributed as χ^2 with 1 degree of freedom under the hypothesis that the coefficient for the independent variable is zero.

[c] Critical Value, $\chi^2_{(1)}$:

1.323	25%	*
2.706	10%	**
3.841	5%	***
6.635	1%	****

Computation is not available for *Fever* due to a zero cell in the contingency table.

As recommended by Hosmer and Lemeshow (2000), these potential predictor variables in Table 6.1 with significance of 25% or less were included as candidates in the subsequent stepwise estimation of the logistic model. The final logistic model for classifying the disease into DF and DHF is summarized in Table 6.2.

Referring to Table 6.2, the significant predictor variables for classifying dengue infection among the pediatric patients are hepatomegaly, bleeding, thrombocytopenia of 50,000 platelet cells per mm^3 or less, abdominal pain and haemoconcentration with hematocrit changes of 20% or more. The latter two symptoms are borderline significant at 5% while the others (including the constant) are significant at 5% as shown by the respective Wald statistics. It is noted that the two WHO criteria – thrombocytopenia_100 and haemoconcentration_20 – that provide the basis for the clinical diagnosis of DHF are in the final logistic model, suggesting that the clinical diagnosis of DF/DHF among the pediatric patients is consistent with the said guidelines.

Table 6.2: Estimated logistic regression model for the clinical dengue classification in child patients

Variable		β	Std. Error	Wald	Sig.
X_1	Hepatomegaly	2.135	0.590	13.108	0.000
X_2	Bleeding	1.402	0.534	6.899	0.009
X_3	Thrombocytopenia_50	1.449	0.616	5.534	0.019
X_4	Abdominal Pain	0.964	0.502	3.686	0.055
X_5	Haemoconcentration_20	1.077	0.565	3.634	0.057
Constant		-3.370	0.477	49.922	0.000

Y = Clinical Diagnosis_2 (Code 1 = DHF; 0 = DF)
N = 173 child cases

Thrombocytopenia_50 and *thrombocytopenia_100* were derived from *platelet count at admission* and hence, due to collinearity only one variable with the highest association with the outcome variable was retained in the model. The same explanation goes for *haemoconcentration_20* and *haemoncentration_50* which were dichotomized from *hematocrit change*.

Due to the lack of scientific basis on the possible pair-wise interactions among the main effects (X_1 to X_5) and the fact that inclusion of interactions in the model produces inappropriate coefficients and at times, renders the main effect insignificant, no interaction term is incorporated in the final model.

The fitted logistic model (from Table 6.2) can be represented as:

$$\hat{P}(Y=1|X) = \left[1+e^{-(-3.370+2.135X_1+1.402X_2+1.449X_3+0.964X_4+1.077X_5)} \right]^{-1}$$

which computes the probability of child patients being diagnosed as DHF, given the predictor variables, X_1 to X_5.

The adjusted odds ratios in Table 6.3 provide the relative risk estimate in relation to the predictor variables in the model. Holding other effect constant, children with hepatomegaly or enlarged liver are about 8.5 times more likely to be categorized as DHF compared with those without such symptom. Those with episodes of bleeding have about 4 times the odds of being diagnosed as DHF in contrast with those without such

condition, ceteris paribus. Children with platelet count of 50,000 cells per mm^3 or lower are about 4 times more likely to be classified as DHF as opposed to those with higher count. Those suffering abdominal pain have almost 3 times the odds of being defined as DHF. Similarly, those with haemoconcentration of 20% or less have about the same odds of being classified as DHF. Yet, the 95% confidence intervals for the odds ratios of *abdominal pain* and haemoconcentration_20 contain the value of one, suggesting that children may possibly have no relative risk of being diagnosed as DHF even if such symptoms prevail.

Table 6.3: Adjusted odds ratio and 95% confidence intervals for the estimated logistic model in Table 6.2

			95% Confidence Interval	
		e^{β}	Lower	Upper
X_1	Hepatomegaly	8.460	2.663	26.877
X_2	Bleeding	4.063	1.427	11.568
X_3	Thrombocytopenia_50	4.260	1.274	14.250
X_4	Abdominal Pain	2.623	0.980	7.021
X_5	Haemoconcentration_20	2.935	0.970	8.880

The classification performance of the model is good for DF where 94.2% of these cases are correctly classified (specificity) at the cut-point of 0.50 (Table 6.4). Performance with regards to DHF is rather mediocre with slightly more than half (55.9%) of the cases correctly classified (sensitivity). The overall classification accuracy is 86.7%. Measuring this hit ratio against the maximum chance criterion of 80.3% and proportional chance criterion of 68.4% (Table 6.5), it shows that at 86.7%, the classification performance of the logistic model is acceptable. Furthermore, the significance of the Press's Q statistic suggests that the prediction is better than chance.

Table 6.4: Classification performance of the estimated logistic model in Table 6.2

		Observed		
		DHF	DF	Total
Classified	DHF	19	8	27
	DF	15	131	146
Total		34	139	173

Cut point is 0.50
Sensitivity = 55.9% (19 / 34)
Specificity = 94.2% (131 / 139)
Overall accuracy = 86.7% ((19 + 131) / 173)

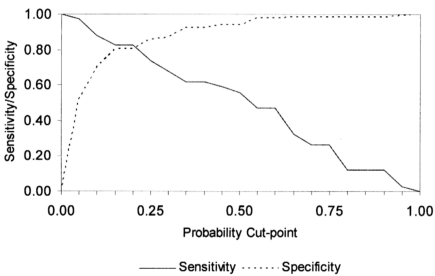
Table 6.5: Measures of classification accuracy for the estimated logistic model in Table 6.2

Measures	Value / Statistic
Maximum Chance Criterion	80.3%
Proportional Chance Criterion	68.4%
Press's Q Statistic	93.23 [a]

[a] Critical value $\chi^2_{0.01\,(1)} = 6.635$

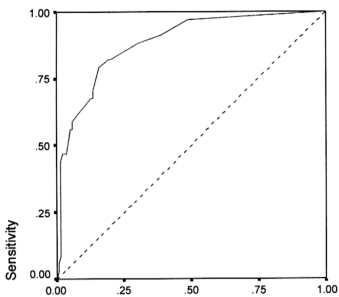
For the objective of classification, the optimal cut-point which maximizes both sensitivity and specificity can be obtained via the graph of sensitivity and specificity for all possible cut-points (Hosmer and Lemeshow, 2000) as in Figure 6.1. The optimal cut-point where both curves cross is approximately 0.21 (lower than 0.50) with sensitivity of 79.4% and specificity of 84.2%.

Figure 6.1: Plot of sensitivity and specificity for all possible cut-points using the estimated logistic model in Table 6.2



In classifying the clinical pediatric dengue cases into DF and DHF, the area under the ROC curve is 0.885 as in Figure 6.2. This is considered excellent discrimination according to Hosmer and Lemeshow (2000). The area under the curve is essentially the proportion of observed clinical DHF children with higher probability of being diagnosed as DHF than children with clinical DF.

Figure 6.2: Receiver Operating Characteristic (ROC) Curve for the estimated logistic model in Table 6.2



Note: Area under the curve is 0.885

The non-significance of the Hosmer and Lemeshow test (Chi-square of 4.591 with p-value of 0.597) implies no difference in the distribution of the actual and predicted outcome. The reduction in the -2 log-likelihood of about 57.97 (from 171.463 of the base model to 113.497) is greater than the critical Chi-Square value of 11.071 (at 5% with 5 degrees of freedom) which indicates that the overall model is significant. The low values of the Cox & Snell R-square and Nagelkerke R-square at 28.5% and 45.3% respectively indicate much of the unexplained variability in the outcome variable that may be attributed to the fact that the in this study, DHF is compared to DF, instead of a healthy subject which would otherwise capture more predictor variables in the model and produce a higher R-square.

6.2.2 Clinical Classification of Dengue in Adult Patients

The univariate likelihood ratio tests in Table 6.6 reveal 8 potential predictor variables significant in the discrimination of DHF from DF. These variables are *hematocrit change* and *shock evidence,* both significant at 5%, followed by *haemoconcentration_50* and *abdominal pain* at 10%. In addition, *haemoconcentration_20, dehydration, giddiness* and *vomit* are all significant at 25% in predicting DHF. It is noted that none of the variables associated with platelet count is significant in the prediction of DHF. This simply implies that platelet count was not consistently regarded as a factor in the clinical diagnosis of adult DHF.

The odds ratio shows that adults with evidence of shock are highly likely (about 74.5 times) to be diagnosed as DHF than those without shock. Those exhibiting *haemoconcentration_50* are about 11 times more likely to be classified as DHF. Adult patients experiencing symptoms such as vomiting, giddiness, general abdominal pain, dehydration or haemoconcentration_20 are about 2 to 3 times more likely than those without such symptoms.

In estimating the logistic regression model for classifying the clinical dengue disease among the adult patients, the above significant variables (with 25% level of significance or less) were included as candidates in the stepwise procedure. The final model in Table 6.7 was obtained.

Table 6.6: Likelihood ratio test[a] and odds ratio for clinical dengue classification of adult patients

Variable	Likelihood Ratio Test Statistic [b c]	Odds Ratio	95% Confidence Interval
Fever	N/A	N/A	N/A
Fever duration	0.248	1.091	(0.779, 1.528)
Vomit	2.159*	2.587	(0.678, 9.873)
Giddiness	1.565*	2.350	(0.660, 8.042)
Headache	0.021	1.227	(0.075, 19.997)
Skin Rash	0.402	0.468	(0.041, 5.268)
Eye Pain	N/A	N/A	N/A
Muscle & Joint Pain	N/A	N/A	N/A
Bleeding	N/A	N/A	N/A
Shock Evidence	5.489***	74.500	(3.346, 1658.9)
Hepatomegaly	N/A	N/A	N/A
Rash / Petechiae	0.347	0.493	(0.044, 5.559)
Abdominal Pain	3.337**	3.227	(0.964, 10.803)
Dehydration	2.488*	2.643	(0.794, 8.804)
Haemoconcentration_20	2.588*	3.433	(0.879, 13.405)
Haemoconcentration_50	2.774**	11.400	(1.167, 111.356)
Thrombocytopenia_50	1.118	2.011	(0.577, 7.009)
Thrombocytopenia_100	0.054	1.158	(0.334, 4.013)
Platelet count at admission	0.323	0.997	(0.987, 1.007)
Heart rate per minute	1.446	1.027	(0.985, 1.071)
Hematocrit change	6.027***	1.046	(1.014, 1.080)

[a] For comparing the based model with a constant only to the univariate logistic model. Independent variable is *Clinical diagnosis 2*.

[b] It is the change in the -2 log-likelihood from the based model to the univariate logistic model and is distributed as χ^2 with 1 degree of freedom under the hypothesis that the coefficient for the independent variable is zero.

[c] Critical Value, $\chi^2_{(1)}$: 1.323 25% *
2.706 10% **
3.841 5% ***
6.635 1% ****

Computation is not available for some variables due to zero cells in the contingency table.

The final logistic model contains only one predictor variable – *hematocrit change*. The Wald statistics are significant for both *hematocrit change* and the constant. The result suggests that hematocrit change in adult patients was the only significant predictor of DHF in adult patients. Although thrombocytopenia should be the concurrent symptom in diagnosing clinical DHF, it is not captured in the final model (not even at the univariate level), suggesting that the clinical diagnosis of DF/DHF for the adult patients at UMMC in this study might not be consistent in adhering to the prescribed guidelines by WHO.

Table 6.7: Estimated logistic regression model for the clinical dengue classification in adult patients

Variable	B	Std. Error	Wald	Sig.
X_1 Hematocrit change	0.0451	0.016	7.816	0.005
Constant	-4.3495	0.423	105.581	0.000

Y = Clinical Diagnosis_2 (Code 1 = DHF; 0 = DF)
N = 468

The estimated logistic model can be fitted as the following:

$$\hat{P}(Y=1|X_1)=\left[\ 1+e^{-(-4.3495+0.0451X_1)}\ \right]^{-1}$$

which provides the probability of the adult patient being diagnosed as DHF, given his or her hematocrit percentage change.

Due to the scaling of the continuous variable, the computed odds ratio (Table 6.8) for hematocrit change is very close to the value of one (1.046), suggesting possible triviality of a small change in the said effect. However, for every 10% increase in the

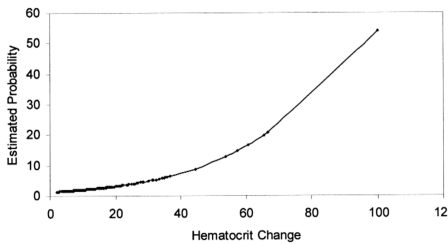
hematocrit of adult patients, the risk of being diagnosed as clinical DHF increases about 1.6 times ($e^{(10 * \beta)}$, where β is 0.0451), assuming linearity in the logit[4].

Table 6.8: Adjusted odds ratio and 95% confidence interval for the estimated logistic model in Table 6.7

			95% Confidence Interval	
		e^{β}	Lower	Upper
X_1	Hematocrit change	1.046	1.014	1.080

The graph in Figure 6.3 shows that the estimated probability for DHF is below 50% for most of the time, up to a point where the percentage change of hematocrit in adult patients surpasses approximately 96%. If a cut-point of 50% is used, majority of the adults would be classified as clinical DF despite having hematocrit changes of 20% or more – a WHO criterion for establishing DHF besides thrombocytopenia.

Figure 6.3: Estimated probability for the hematocrit change in adult patients for the classification of clinical dengue cases



[4] The plot of lowess smoothed univariable logit versus hematocrit change supports treating the latter continuous variable as linear in the logit. This method of determining whether the model is linear in the logit for continuous variable is discussed by Hosmer and Lemeshow (2000).

Overall classification performance of the model is high at 97.3%. Nevertheless, it has very low sensitivity (9.1%) with only 1 correct classification out of 11 observed DHF cases. Specificity is perfect at 100% with all observed DF cases correctly classified. It must be noted that between the two groups (DF and DHF), DF is relatively larger. Hosmer and Lemeshow (2000) point out that classification is sensitive to the relative sizes of the two groups and often favours classification into the larger group, independent of the fit of the model. If one were to simply group all 468 cases as DF, the accuracy rate is 97.6% (457/468, known as the maximum chance criterion as in Table 6.10), marginally higher than the current hit ratio of 97.3% as obtained by the model. However, proportional chance criterion and the Press's Q statistic imply better-than-chance prediction.

Table 6.9: Classification performance of the estimated logistic model in Table 6.7

		Observed		
		DHF	DF	Total
Classified	DHF	1	0	1
	DF	10	457	467
Total		11	457	468

Cut point is 0.50
Sensitivity = 9.1% (1 / 11)
Specificity = 100.0% (457 / 457)
Overall accuracy = 97.9% ((1+457) / 468)

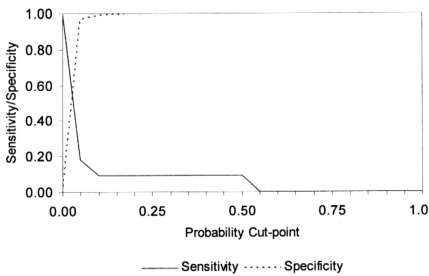
Table 6.10: Measures of classification accuracy for the estimated logistic model in Table 6.7

Measures	Value / Statistic
Maximum Chance Criterion	97.6%
Proportional Chance Criterion	95.4%
Press's Q Statistic	428.85[a]

[a] Critical value $\chi^2_{0.01\,(1)} = 6.635$

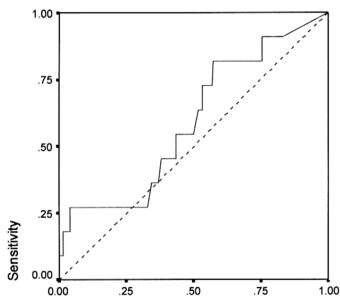
Figure 6.4 shows that the optimal cut-point for the purpose of classification is lower than 0.50. Referring to Figure 6.4, the optimal cut-point which maximizes sensitivity and specificity is given by the intersection of the curves at about 0.04. This optimal cut-point yields a sensitivity of 27.4% and specificity of 95.2%.

Figure 6.4: Plot of sensitivity and specificity for all possible cut-points using the estimated logistic model in Table 6.7



To further understand the classification accuracy of the logistic model in Table 6.7, the ROC curve in Figure 6.5 is examined. The area under the ROC curve is low at 0.592, denoting poor discriminative capability of the model. This translates to the low likelihood that adults clinically observed as DHF will have higher probability of being classified as DHF than those who were observed as DF.

Figure 6.5: Receiver Operating Characteristic (ROC) Curve for the estimated logistic model in Table 6.7



Note: Area under the curve is 0.592

The Hosmer and Lemeshow test reveals nothing untoward (Chi-square of 7.162 and p-value of 0.412) which implies good fit and the reduction in the -2 log-likelihood value of about 6.027 (critical Chi-square value of 3.841 at 5% with 1 degree of freedom) indicates overall model significance. The low Cox & Snell R-square and the Nagelkerke R-square (1.3% and 6.4% respectively) can be accounted to the same reason as explain previously.

Recall that the primary objective of the above logistic models (for both children and adults) is to correctly classify subjects into DF and DHF. While model diagnostic measures may provide insights into possible improvements of the said models, they are of little use here given the low number of misclassification in both models (Hair et al., 1998).

6.4 Concluding Remarks

This chapter presented two logistic models; one for the children and one for the adults suspected of dengue infection at UMMC. The logistic model for pediatric patients showed reasonable classification accuracy and acceptable fit in categorizing the disease into clinical DF and DHF. On the other hand, the model for adult patients has weak discriminative ability as shown by the small area under the ROC curve which is slightly better than flipping a coin. For the pediatric patients, all the predictors in the final model are consistent with literature. It is important to note that thrombocytopenia and haemoconcentration are both significant at explaining the outcome of DHF (likewise can be seen at the univariate level), implying that the initial clinical diagnosis of DF/DHF for

children did adhere to the prescribed case definition of DHF by WHO. On the contrary, the clinical diagnosis of DF/DHF for adult patients did not seem to follow the proposed classification. The resulted model for adults relies on only one predictor – hematocrit change – to classify the disease. Even then, it was shown that the cut-off in the change of hematocrit was higher than the recommended 20% before an adult patient is classified as DHF. The fact that no variable related to thrombocytopenia was shown to be significant in the prediction of adult DHF, not even at the univariate level, and the fact that an adult's hematocrit change has to be sky-high before he or she is being treated as DHF, indicate that the clinical diagnosis of adult DHF has departed from the guideline of DHF diagnosis to some extent. This puts forth the needs to ensure better consistency and conformity to the diagnosis protocol for better management of adult dengue patients.