



Evaluation of Risk Factors for Prolonged Invasive Mechanical Ventilation in Paediatric Intensive Care Unit (PICU)

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ABSTRACT

Prolonged mechanical ventilation (PMV) is associated with increase in mortality and resource utilisation as well as hospitalisation costs. This study evaluates the risk factors of PMV. A retrospective study was conducted involving 890 paediatric patients comprising 237 neonates, 306 infants, 223 of pre-school age and 124 who are of school going age. The data mining decision trees algorithms and logistic regression was employed to develop predictive models for each age category. The independent variables were classified into four categories, that is, demographic data, admission factors, medical factors and score factors. The dependent variable is the duration of ventilation where it is categorized 0 denoting non-PMV and 1 denoting PMV. The performances of three decision tree models (CHAID, CART and C5.0) and logistic regression were compared to determine the best model. The results indicated that the decision tree outperformed the logistic regression model for all age categories, given its good accuracy rate for testing dataset. Decision trees results identified length of stay and inotropes as significant risk factors in all age categories. PRISM 12 hours and principal diagnosis were identified as significant risk factors for infants.

Keywords: Mechanical ventilation, prolonged mechanical ventilation, paediatric, logistic regression, decision tree

INTRODUCTION

The Paediatric Intensive Care Unit (PICU) provides care for infants, children and adolescents who are critically ill or injured. There are several conditions that usually cause critical illness such as severe infection, poisoning, drug overdose, trauma, extensive

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surgery, congenital anomalies and immunological disorders. The first PICU was developed in 1955 in Gothenburg, Sweden to provide intensive care for polio patients, new-borns diagnosed with respiratory distress syndrome (RDS), postoperative children and severe pneumonia (Lin and Hsieh, 2009). In the United States, it was reported that 276 PICUs were established in 1989, 306 PICUs in 1995 and 349 in 2001 (Randolph et al., 2003).

The first PICU in Malaysia was established in University Hospital Kuala Lumpur (now known as University Malaya Medical Centre) in 1980. The PICU in University Malaya Medical Centre has the capacity to ventilate 10 patients with 24-hour Paediatric Intensivist coverage. This ten-bed multidisciplinary unit provides care for patients with hepatobiliary-gastrointestinal, haemato-oncology, cardiology, respiratory, genetic & metabolic, general surgery, otolaryngology, ophthalmology subspecialties and those undergoing bone marrow transplant.

Mechanical ventilation (MV) is usually used for a few days to help patients with acute serious illness. It can be applied as negative pressure on the outside of the thorax. Mostly, mechanical ventilation is applied as positive pressure to the airway where positive pressure ventilation can be invasive and non-invasive. The use of MV with positive pressure in PICU has increased [3]. Invasive ventilation is delivered via endotracheal tube or tracheostomy while non-invasive ventilation helps the patients to breathe with the help of a face mask.

Several previous studies found that children who require mechanical ventilation have increased. Farias et al., (2004) found that 35% of children or 659 out of 1893 patients were ventilated for 12 hours while Traiber et al., (2009) reported that the proportion of children in three Brazilian paediatric intensive care unit (PICU) who required mechanical ventilation for > 21 days was 2.5% or 192 of 7598 admissions. In a study by Payen et al. (2012), they found nearly similar results whereby 30% for all PICU admissions (315 patients) were ventilated for 12 hours and 2.9% for at least 21 days.

The use of mechanical ventilation can result in several complications such as airways, barotrauma, and nosocomial infections. Complications arising from the use of mechanical ventilation may cause prolonged mechanical ventilation (PMV), and lead to an increase in length of hospitalization and mortality rates (Kipps et al., 2011). A study by Chelluri et al., (2004) revealed that mortality rate for patients who received mechanical ventilation > 48 hours increased with age and number of comorbidities. Tracheostomy in children results in higher mortality and complication rates (Putra et al., 2006). There are several complications that may arise from PMV such as pneumothorax, airway injury, alveolar damage, and ventilator-associated pneumonia. According to Lum et al., (2011), invasive mechanical ventilation is associated with ventilator-induced and ventilator-associated pneumonia where a tracheal tube may cause subglottic and tracheal injury and ineffective clearance of secretions.

This study focuses on developing models for predicting duration of invasive mechanical ventilation and determining risk factors associated with PMV for patients in a PICU in Malaysia.

METHODS

Data Source

A retrospective study was conducted with e data retrieved from clinical records of paediatric patients admitted at Paediatric Intensive Care Unit (PICU) in a local hospital in Kuala Lumpur, Malaysia from August 2008 to June 2012. The data was extracted from the patients' forms which recorded information on demography, admissions, information on mechanical ventilation, patient related procedure, patient related therapy surgery, ICU acquired infection and death. The patients' forms were filled by the nurses at the unit.

Population and Sample of Study

All patients who were below 18 years old and requiring invasive mechanical ventilation were included in this study. A total of 1931 patients were admitted to PICU from August 2008 to June 2012. Of 1931 patients, 994 of them required invasive ventilation. This study only focuses on patients who needed invasive ventilation. Among the 916 patients included in this study, 447 needed ventilation ≥ 72 hours (PMV) and 496 patients required < 72 hours (non-PMV). Since there are only 26 adolescents, these adolescents were not included in the process of building the predictive models.

Theoretical Framework. The variables were classified into four categories (demographic data, admission factors, medical factors and score factors). The theoretical framework proposed in this study is presented in Figure 1. There are 4 continuous predictors (age, weight, length of stay and PRISM III-12) and the remaining predictors are categorical. The predictors involve (Age, Gender, Ethnicity and Weight, Admission source (Elective, Non-Elective), Admission type (Emergency, Ward, Referral), Surgery (Yes/No), VAP (Yes/No), BSI(Yes/No), Inotropes (Yes/No), Shock(Yes/No), Principal Diagnosis (respiratory, cardiovascular, gastroenterology, neurology and others), length of stay and PRISM III-12. The Paediatric Risk of Mortality (PRISM) is physiology-based predictor for PICU patients. This composite score use the death rate as an outcome measure. Using for evaluation within 24 hours after admission, PRISM III is a score between 0-38 where it comprises of 17 physiological data. The 17 physiological data consist of 5 clinical parameters which are systolic blood pressure, heart rate, Glasgow Coma Scale, papillary reflexes and temperature and the other 12 variables are acid-base status (pH, CO₂, PCO₂, and PaO₂), chemistry tests (glucose, potassium, creatinine, blood urea nitrogen) and haematology tests (white blood cell count, platelet count, prothrombin time and partial thromboplastin time). The dependent variable is Duration of Ventilation. If duration of ventilation is ≥ 72 hours it is coded as 1 (PMV) while 0 (Non- PMV) represents ventilation < 72 hours.

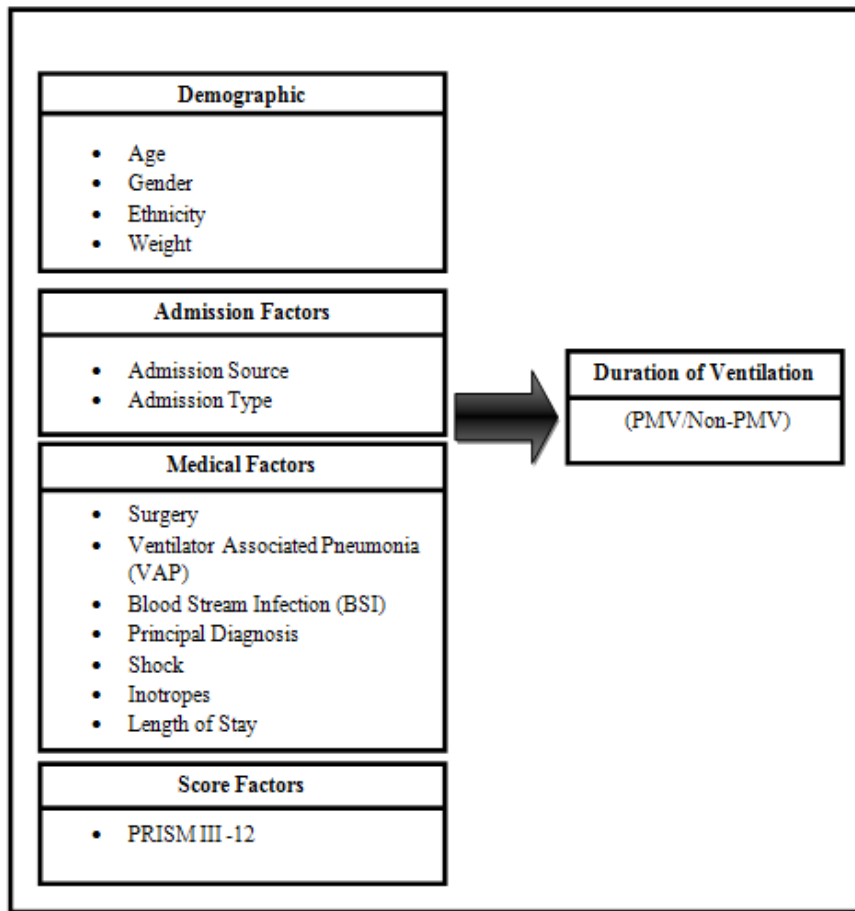


Figure 1. Theoretical Framework

Statistical Analysis

The analysis was carried out for four different age categories. Table 1 presents the age range for each age category. The predictive models include logistic regression and decision trees.

Table 1
Age Category

Age Category	Age Range
Neonate	0 -30 days
Infant	1 - 12 months
Pre-School Age	1 - 5 years
School-Age	6 - 12 years

Logistic Regression

Logistic regression is widely used in modelling a dichotomous dependent variable (Hair et al., 1998). The use of logistic regression is appropriate for predicting disease state (diseased/healthy) and decision making (yes/no) (Bagley et al., 2001). Due to its ability to model binary outcomes, it is widely implemented in health sciences study and for determining risk factors in medical studies (Lin et al., 2011; Camdeviren et al., 2007). The logistic regression model is developed based on the values of a set of predictor variables. The predictor variables in logistic regression can be either continuous, categorical or combination of both. For the purpose of developing logistic regression equation, the maximum-likelihood estimation was employed and Wald's statistic was used to determine the significance of the variables (Hosmer & Lemeshow, 2000). Logistic regression may be thought of as an approach that is similar to that of multiple linear regression but the difference is the dependent variable in logistic regression is categorical. The odds-ratio in logistic regression model provides important information on the effect of the risk factors.

The logistic regression model is written as follows:

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \dots + \beta_k X_{ik} \quad (1)$$

where $p_i = P(Y_i = 1)$.

In this study, Y is the dependent variable (duration of ventilation) which is categorized as ventilation ≥ 72 hours (PMV) and ventilation < 72 hours (non-PMV).

Thus, by solving the logit in Equation (1), the probability of event $Y=1$ is obtained as follows:

$$P(Y_i = 1) = \frac{1}{1 + e^{-z}} \quad (2)$$

In this study, $P(Y_i = 1)$ is defined as the probability of requiring PMV, $z = \beta_0 + \beta_1 X_{i1} + \dots + \beta_k X_{ik}$.

β_0 = the constant of the equation

β_{ik} = the coefficient for predictor variable

x_{ik} = the predictor variable

β_0 is a constant and $\beta_1, \beta_2, \dots, \beta_k$ are the regression coefficients of the independent variables X_1, X_2, \dots, X_k . where the regression coefficient explains the size of contribution of the predictor variables to the outcome (Ayer et al., 2010). The criterion that is commonly used in measuring and testing statistical significance of the coefficients of the variables is Wald's statistics with $p \leq 0.05$.

Decision Tree

Decision tree is a powerful classification algorithm and widely used in classification problems. This non-linear discrimination method is used to split sample into smaller segments where the process of splitting is based on a set of independent variable (Ture et al, 2005). Decision tree has become a popular method for the purpose of classification and prediction by implementing a sequence of simple rules (Ibrahim et al., 2008). This machine learning technique recursively

splits the sample in branches or segments in order to develop a tree in a process known as recursive partitioning. Quinlan’s ID3, C4.5, C5 and Breinman et al.’s CART are some of the popular decision tree algorithms.

In this study, three commonly used algorithm constructing decision trees that is Chi-Square Automatic Interaction Detector (CHAID), Classification and Regression Tree (CART), and C5.0 were performed. As the dependent variable is a binary categorical variable, the decision trees generated in this study are called a classification tree.

CHAID will select the predictor that is the most significant with the smallest p-value to perform the first split. The process of constructing CHAID tree is done by repeatedly splitting subsets into two or more child nodes. CHAID has an ability to handle large number of predictors and appropriate to be employed when non-linear or complex relationship exists.

The construction of CART begins with the entire data set and repeatedly split subsets of the data based on independent variables to develop two child nodes (Ture et al., 2005). The selection of best predictor in CART can be done using several impurity measures such as Gini, twoing, ordered twoing and least-squared deviation (Kurt et al., 2008). In this study, Gini impurity measure was employed where Gini impurity can be applied for categorical dependent variable.

C5.0 algorithm is the improved version of C4.5 and ID3 algorithm where it is the most recent version of a machine learning program. It uses entropy as a measure of impurity when splitting subsets of observations into child nodes. The process of splitting the subsets repeats until the subsets cannot be split further. At the final stage, the lowest-level splits are reviewed and those that do not contribute significantly to the value of model are removed.

Model Performance Evaluation

The data was partitioned into 70% training and 30% validation samples. The evaluation was based on levels of accuracy, sensitivity, and specificity. The best decision tree model was then compared with logistic regression model. Sensitivity is defined as the proportion of patients who received ventilation ≥72 hours (PMV) correctly predicted by the model. Specificity is defined as the proportion of patients with ventilation < 72 hours (non-PMV) correctly predicted by the model. Classification accuracy, sensitivity and specificity are calculated by referring to the confusion table.

Table 2
Confusion Matrix

		Predicted		Total
		PMV	Non-PMV	
Actual	PMV	TP (True Positives)	FN (False Negatives)	TP + FN
	Non-PMV	FP (False Positives)	TN (True Negatives)	FP + TN
Total		TP + FN	FN + TN	TN+FP+FN+TP

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN}, \quad \text{Sensitivity} = \frac{TP}{TP+FN}, \quad \text{Specificity} = \frac{TN}{TN+FP}$$

RESULTS

Table 3 presents some descriptive statistics for each group.

Logistic Regression Analysis

This section discusses the result of logistic regression where ENTER, FORWARD, BACKWARD was used as selection methods in developing the models. The logistic models obtained were employed to identify risk factors associated with PMV.

Table 3
Descriptive Statistics

Age Category	Variable Name	Mean \pm Standard Deviation
Neonates	Weight(Kilogram)*	2.82 \pm 0.62
	Length of Stay(Days)	13.70 \pm 30.54
	PRISM III 12 hours	7.54 \pm 5.54
Infants	Weight(Kilogram)*	5.18 \pm 2.10
	Length of Stay(Days)	12.25 \pm 24.73
Pre -School Age	PRISM 12 hours	5.2 \pm 5.05
	Weight(Kilogram)*	11.85 \pm 24.59
	Length of Stay(Days)	9.69 \pm 17.73
	PRISM 12 hours	4.96 \pm 4.94
School Age	Weight(Kilogram)*	27.80 \pm 12.30
	Length of Stay(Days)	9.41 \pm 19.12
	PRISM 12 hours	5.67 \pm 5.82

Note: PRISM- Paediatric Risk of Mortality

* Data for weight was questionable and thus excluded in predictive modelling analysis.

Table 4 presents the summary of logistic regression results which includes the accuracy rate, sensitivity and specificity values. The logistic regression with ENTER selection method were chosen as the best model for all age categories.

Table 4
Performance of Logistic Regression Models

Age Category	Model	Training Set			Testing Set		
		Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Neonate	ENTER	76.40	73.26	80.00	68.42	65.42	72.41
	FORWARD	73.91	69.77	78.67	67.11	59.57	79.31
	BACKWARD	73.91	69.77	78.67	67.11	59.57	79.31
Infant	ENTER	77.99	70.48	85.58	77.32	66.67	87.76
	FORWARD	77.99	69.52	86.54	75.26	58.33	91.84
	BACKWARD	77.99	69.52	86.54	75.26	58.33	91.84
Pre-School Age	ENTER	77.63	59.70	91.76	71.83	71.43	72.22
	FORWARD	76.32	53.73	94.12	77.46	68.57	86.11
	BACKWARD	76.32	53.73	94.12	77.46	68.57	86.11
School Age	ENTER	84.09	75.76	89.09	66.67	47.06	84.21
	FORWARD	78.41	60.61	89.10	72.22	47.06	94.74
	BACKWARD	78.41	60.61	89.10	72.22	47.06	94.74

The significant risk factors found in the best logistic regression model for each age categories are summarized in Table 5.

Table 5
Significant Variables

NEONATE (ENTER)	INFANT (ENTER)	PRE-SCHOOL AGE (ENTER)	SCHOOL AGE (ENTER)
<ul style="list-style-type: none"> • PRISM III-12 • Admission Source = Ward • Inotropes = Yes 	<ul style="list-style-type: none"> • Length of Stay 	<ul style="list-style-type: none"> • PRISM III-12 • Inotropes = Yes • Principal Diagnosis = Cardio 	<ul style="list-style-type: none"> • Length of Stay • Inotropes = Yes

Table 6 presents the interpretation of the odds ratio for significant variables found in the logistic regression results.

Table 6
Interpretation of Odds Ratio

NEONATE	PRE-SCHOOL AGE
<ul style="list-style-type: none"> • PRISM 12 Hours (OR = 1.155) Neonates with higher PRISM III-12 score are more likely to receive PMV. • Admission Source (OR = 0.260) Neonates who admitted to PICU from ward are less likely to receive PMV compared to neonates admitted from referrals. • Inotropes (OR = 4. 223) Neonates who required inotropes are 4 times more likely to receive PMV compared to neonates who do not require inotropes. 	<ul style="list-style-type: none"> • PRISM III 12 Hours (OR = 1.135) Pre-school age patients with higher PRISM III-12 score are more likely to receive PMV. • Inotropes (OR = 11.508) Pre-school age patients who required inotropes are 12 times more likely to receive PMV compared to those who do not require inotropes. • Principal Diagnosis = Cardiovascular (OR = 5.964) Pre-school age patients diagnosed with cardiovascular are 6 times more likely to receive PMV compared to those who were diagnosed with other principal diagnosis.
INFANT	SCHOOL AGE
<ul style="list-style-type: none"> • Length of Stay (OR = 1.188) Infants with longer length of stay are more likely to receive PMV. 	<ul style="list-style-type: none"> • Length of Stay (OR = 1.071) School age patients with longer length of stay are more likely to receive PMV. • Inotropes (OR = 9.675) School age patients who required inotropes are 10 times more likely to receive PMV compared to those who do not require inotropes.

Decision Tree Analysis

In this study, three algorithms were used to generate decision tree CHAID, CART and C5.0. Table 7 compares the accuracy, sensitivity and specificity for training and testing dataset of decision tree models. Below are results for each age categories.

Table 7
Decision Tree Performance

Age Category	Model	Training Set			Testing Set		
		Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Neonate	CHAID	85.09	94.19	74.67	85.53	91.49	75.86
	CART	85.09	94.19	77.33	85.53	91.49	79.31
	C5.0	85.09	94.19	74.67	85.53	91.49	75.86
Infant	CHAID	84.69	89.52	79.81	80.41	70.83	89.80
	CART	82.30	77.14	87.50	72.16	52.08	91.84
	C5.0	79.90	82.86	76.92	79.38	70.83	87.76
Pre-School Age	CHAID	84.87	88.06	82.35	81.69	91.43	72.22
	CART	86.84	92.54	82.35	78.87	94.29	63.89
	C5.0	86.18	94.03	80.00	80.28	97.14	63.89
School Age	CHAID	88.64	69.70	100.00	75.00	52.94	94.73
	CART	90.91	78.79	98.18	80.56	70.59	89.47
	C5.0	88.64	78.79	94.55	83.33	76.47	89.47

For neonate, all three decision tree models gave same accuracy rate and sensitivity rate for both datasets. CART gave the best specificity rate for both datasets. While CHAID produced the best accuracy and sensitivity rate for training and testing sets for infants. For pre-school age patients, CART produce the best accuracy rate for training set while the best accuracy rate in testing set was given by CHAID. CART gave the best accuracy in training dataset for school age patients. C5.0 gave the best accuracy and sensitivity rate for testing dataset for pre-school age.

CART and C5.0 are chosen as the best decision tree model for neonate and school age patients respectively. While, for infant and pre-school age patients, CHAID is chosen as the best model due to slightly higher accuracy rate in testing dataset.

The interpretation of the best decision tree model for each category is presented in Table 8 respectively.

Table 8
Decision Tree Rules

NEONATE (CART)

- If neonates had length of stay for more than 4 days AND did not require inotropes, THEN these neonates received ventilation ≥ 72 hours (PMV).
- If neonates had length of stay for more than 4 days AND required inotropes, THEN these neonates received ventilation ≥ 72 hours (PMV).
- If neonates had length of stay for less or equal to 4 days AND did not require inotropes, THEN these neonates received ventilation < 72 hours (non- PMV).

Table 8 (continue)

INFANT (CHAID)
<ul style="list-style-type: none"> • If infants had length of stay for more than 10 days AND had PRISM 12 hours score of more than 0, THEN these infants received ventilation \geq 72 hours (PMV). • If infants had length of stay for more than 4 days and less or equal to 10 days AND had principal diagnosis of respiratory OR cardiovascular OR neurology OR gastroenterology, THEN these infants received ventilation \geq 72 hours (PMV). • If infants had length of stay more than 10 days AND had PRISM 12 hours score of 0, THEN these infants received ventilation $<$ 72 hours (non- PMV). • If infants had length of stay for more than 4 days and less or equal to 10 days AND had principal diagnosis except of respiratory, cardiovascular, neurology and gastroenterology, THEN these infants received ventilation $<$ 72 hours (non-PMV). • If infants had length of stay for more than 3 days and less or equal to 4 days, THEN these infants received ventilation $<$ 72 hours (non-PMV). • If infants had length of stay for less or equal to 3 days, THEN these infants received ventilation $<$ 72 hours (non-PMV).
PRE-SCHOOL (CHAID)
<ul style="list-style-type: none"> • If pre-school age patients had length of stay more than 6 days AND required inotropes, THEN these school age patients received ventilation \geq 72 hours (PMV). • If pre-school age patients had length of stay more than 4 days and less or equal to 6 days, THEN these school age patients received ventilation \geq 72 hours (PMV). • If pre-school age patients had length of stay more than 2 days and less or equal to 4 days, THEN these school age patients received ventilation $<$ 72 hours (non-PMV). • If pre-school age patients had length of stay less than 2 days, THEN these school age patients received ventilation $<$ 72 hours (non-PMV). • If pre-school age patients had length of stay more than 6 days AND did not require inotropes, THEN these school age patients received ventilation $<$ 72 hours (non-PMV).
SCHOOL AGE (C5.0)
<ul style="list-style-type: none"> • If school age patients had length of stay less or equal 4days AND required inotropes, THEN these school age patients received ventilation \geq 72 hours (PMV). • If school age patients had length of stay more than 4 days, THEN these school age patients received ventilation \geq 72 hours (PMV). • If school age patients had length of stay less or equal 4days AND did not required inotropes, THEN these school age patients received ventilation $<$ 72 hours (non-PMV).

Model Comparison

The performance of logistic model and the best models resulted from decision tree analysis is summarized in Table 9. For all age categories, the decision tree models outperformed the logistic regression model in which the decision tree models had better accuracy, sensitivity and specificity rate for testing set. Thus, decision tree models were found to be better predictive models compared to the traditional statistical technique, logistic regression in predicting risk factors for PMV.

Table 9
Model Evaluation

Age Category	Model	Training Set			Testing Set		
		Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Neonate	Logistic Regression (ENTER)	76.40	73.26	80.00	68.42	65.96	72.41
	CART	85.09	94.19	77.33	85.53	91.49	79.31
Infant	Logistic Regression (ENTER)	77.99	70.48	85.58	77.32	66.67	87.76
	CHAID	84.69	89.52	79.81	80.41	70.83	89.80
Pre-School Age	Logistic Regression (ENTER)	77.63	59.70	91.76	71.83	71.43	72.22
	CHAID	84.87	88.06	82.35	81.69	91.43	72.22
School Age	Logistic Regression (ENTER)	84.09	75.76	89.09	66.67	47.06	84.21
	C5.0	88.64	78.79	94.55	83.33	76.47	89.47

CONCLUSION AND RECOMMENDATION

This study found that five out of twelve potential risk factors examined in logistic regression analysis are significantly associated with PMV for all age categories. The five significant risk factors include PRISM III 12 hours, inotropes, length of stay, admission source, and principal diagnosis. Four significant risk factors (PRISM III 12 hours, inotropes, length of stay and principal diagnosis) were also found to be significant in decision tree making it better than logistic regression model. The predictive models developed in this study show the potential of the decision tree model in medical research.

Future study could consider potential risk factors such as Paediatric Index Mortality (PIM) and PRISM III 24 hours. A larger sample size is also recommended in order to validate the results of this study. Other data mining classification technique can be employed such as Artificial Neural Network (ANN) and Support Vector Machine (SVM).

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