Outcome of AIDS Patients Requiring Mechanical Ventilation Predicted by Recursive Partitioning*

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Mechanical ventilatory support (VS) is often required for patients with AIDS. Patients and/or their surrogates often ask the likely outcome of this intervention. To answer this question, we have developed a classification tree using clinical data from 71 patients with AIDS identified from the discharge abstracts of two hospitals between January 1990 and September 1994. These data were obtained at the time of hospital admission prior to any treatment and before VS was initiated. Survival was defined as discharge from the hospital that occurred in 13 of 72 admissions reviewed. A classification tree was developed by binary recursive partitioning. The output of the resulting tree was adjusted to produce a positive predictive value for death of 100% (95% confidence interval [95% CI], 94 to 100%) and a sensitivity and specificity of 98% (95% CI, 91 to 100%) and 100% (95% CI, 74 to 100%), respectively. The negative predictive value was 92% (95% CI, 64 to 100%). The tree predicted that patients with lactate dehydrogenase (LDH) levels less than 1,176 IU/L survived until hospital discharge, unless they had a positive blood culture, active tuberculosis prior to VS, a blood CD4 count less than 12 cells per cubic millimeter, or creatinine and hemoglobin values that were either above 2.4 mg/dL or less than 8.5 mg/dL, respectively. The remainder of the patients with an LDH level above 1,176 IU/L in this study died before hospital discharge. The classification tree requires prospective validation before it can be used as a predictive instrument. Nevertheless, this approach can be used to develop a concise summary of the local outcome experience of this circumstance in a manner that could be conveyed to patients and/or their surrogates. *(CHEST 1996; 109:1584-90)*

Key words: AIDS; classification trees; logistic regression; mechanical ventilation; outcome

Abbreviations: CART=classification and regression tree; CL=confidence limits; DNR=do not resuscitate; ICD-9=International Classification of Diseases, ninth edition; LDH=lactate dehydrogenase; MAI=*Mycobacterium avium-intracellulare*; PCP=*Pneumocystis carinii* pneumonia; VS=mechanical ventilatory support

It is estimated that more than 1 million Americans carry the HIV at the present time,[1] the majority of whom are destined to develop AIDS at some point in the coming years. In the absence of curative therapy and dwindling intensive care resources, difficult clinical and ethical questions concerning prognosis and cost benefit analysis of life-sustaining therapy in AIDS patients have started to surface in the medical literature. Patients and families often approach the physician requesting an assessment of the patient's condition and prognosis before initiating, withdrawing, or withholding life support measures. Prognostic estimates of patient survival have been shown to vary widely among physicians because of differences in interpretations of physiologic data,[2] social environment, and lack of general consensus of the predictive variables. The prediction of outcome in complicated situations has always been difficult in clinical practice. Prognostic estimates based on well-validated statistical systems are often more reliable than those predicted by clinical judgment.[3,4]

Data regarding outcome from respiratory failure in AIDS patients have focused mainly on predictors of mortality in AIDS-related *Pneumocystis carinii* pneumonia (PCP);[5-9] however, this approach has provided a limited perspective into the prognosis of AIDS patients requiring mechanical ventilation. Several series estimated the mortality rates of AIDS patients with acute respiratory failure to range from 80 to 100%.[10-12] A simple and valid prognostic scheme that provides AIDS patients and/or their families with an adequate assessment of the patient's prognosis at the time of initiation of mechanical ventilation will be of great assistance in daily ICU decision making. This retrospective chart review was conducted at two major hospitals in a metropolitan area to assist in elucidating the predictive outcome of AIDS patients who require me-

chanical ventilatory support (VS) using a decision tree analysis. The classification and regression tree (CART),[13] a statistical approach developed over the past 20 years, is utilized in this study. It has the advantage of having statistical validity which is often lacking in decisions based on clinical experience or expert opinion.

MATERIALS AND METHODS

Data Collection

A retrospective medical record review was conducted involving patients who were admitted to two hospitals between January 1, 1990 to September 30, 1994. Both hospitals (Erie County Medical Center and Buffalo General Hospital) are affiliated with the State University of New York at Buffalo. Patients who had AIDS (*International Classification of Diseases, ninth Edition [ICD-9]* codes 42.0 to 42.9) and required mechanical ventilation (*ICD-9* codes 96.71 and 96.72) were identified from the hospital discharge abstracts. The diagnosis of AIDS was made using the Centers for Disease Control surveillance criteria.[14] The source of the study group consisted of patients from the two hospitals listed above and included inpatient transfers and outpatient admissions seen initially in an HIV clinic or the emergency department. Two patients who required VS (one for an operative procedure and one patient with hemophilia) were excluded from further analysis because they did not meet our inclusion criteria of (1) patients with AIDS but without hemophilia, and (2) requiring VS for medical reasons.

Potential predictors of survival on initiation of mechanical ventilation were recorded at the time of initial evaluation in the emergency department or outpatient clinic prior to any specific therapeutic intervention. The data included social, demographic, and risk factors for AIDS: age, gender, race, and history of IV drug abuse or homosexual activity. The hospital length of stay, the time from the date of hospital admission to the time of assisted ventialtion, and the ultimate outcome were also calculated.

The reason for mechanical ventilation was classified into respiratory failure, cardiac failure, or other (airway protection in unconscious patients or hyperventilation for increased intracranial pressure). Data concerning AIDS-related opportunistic infections (past or a recent history) of PCP, mycobacterial infections, disseminated cryptococcosis, or cerebral toxoplasmosis were also collected. Kaposi's sarcoma and non-Hodgkin's lymphoma were recorded whenever the diagnosis was confirmed by pathologic analysis. Mental status at the time of hospital admission was categorized to be either alert and oriented, or altered. The results of laboratory studies from hospital admission were reviewed and included the CBC count, blood lymphocyte CD4 count, serum creatinine, serum lactate dehydrogenase (LDH), and albumin levels. The hospital admission chest radiograph and CT of the head (if done) were reviewed and categorized as normal or abnormal (excluding cerebral atrophy). Blood culture results, whenever available, were included only if drawn at the time of hospital admission. Patients were classified as survivors and nonsurvivors. Survivors were defined as those patients who were able to be weaned off mechanical ventilation and ultimately discharged from the hospital. Nonsurvivors were those who died during their hospitalization.

Statistical Analysis

Descriptive statistics for continuous variables were expressed as mean±1 SD. Difference in mean values was assessed using Student's two tailed t test. Significant value indicates a value of $p<0.05$. Commercially available software was used for classification trees and logistic regression (S-Plus; Statsci; Seattle, Wash), and also for confidence limit (CL) analysis (CIA; *British Medical Journal*; London, England).

A classification tree was developed with binary recursive partitioning[13] to predict the outcome of AIDS patients requiring mechanical ventilation. This method has been described in detail elsewhere.[15] In brief, the method uses the input data that consist of either continuous variables such as the LDH level, or nominal variables such as the presence or absence of opportunistic infection. Nominal variables are coded as 1 for yes, -1 for no, and NA for uncertain or missing data. Continuous data are entered as the actual values or as missing data. The output or dependent variable is the outcome that was coded as 1 for dead and 0 for alive. First, the root of the tree is determined by the probability of survival based on the prevalence in the data set. Next, each variable is selected in turn to determine which one produces the most accurate classification into survivors and nonsurvivors. The data at this first node are then separated into two branches. At the end of each branch, a new node is developed and the input variables are retested to determine the best "separator" of the data into the correct classification. This process of recursive binary partitioning is continued until there is no further improvement in the accuracy of classification. The resulting tree is then tested to determine if the tree is overfitting the data.[16]

Overfitting is avoided by introducing a weighting factor at each node that reduces the influence of the parent branch on its offshoots. This process is termed "shrinking the tree." By shrinking the tree, the optimal size of the tree can be determined from the effective size of the tree at which the mean deviance is a minimum. Deviance is a measure of the ability of the model to predict the data compared with a model that has a perfectly correct prediction. A minimum occurs because the model becomes a more accurate predictor for the new data set on which a new tree is developed. However, the model becomes less precise because it is less able to predict a new data set with the same degree of accuracy. This balance between accuracy and precision has been called the bias-variance tradeoff.

A tenfold cross-validation is used to determine this minimum. The data are divided randomly into ten mutually exclusive subsets. In this case, there are about seven patients in each set. Nine of the subsets are used to grow a new tree; the remaining subset is withheld from development of the tree and is used to test the accuracy of the tree in predicting the outcome of this subset. The process is repeated on nine further occasions using a different test set on each occasion. The combined results from all ten trials are used to estimate the optimal size of the tree. The original tree developed from the entire database is then pruned to optimal size. This process is designed to produce a tree that has good predictive ability when tested with completely new data, in this case, a new patient. Finally, we used a logistic regression built with the same clinical factors described in the CART analysis, and compared its predictive abilities with that of the classification tree.

RESULTS

Study Population

Seventy-seven patients satisfied the inclusion criteria for the study. Five patients were excluded because of missing data from the medical record. One patient was excluded because of hemophilia. Seventy-one patients were evaluated for a total of 72 episodes of mechanical ventilation. Table 1 describes the demographic characteristics of the 71 patients included in the study. All patients carried the diagnosis of AIDS according to the Centers for Disease Control definition criteria of AIDS.[14] Fifty-nine (82%) died in the ICU.

Table 1—*Demographic Characteristics of the 72 AIDS Patients in the Study*

	Value
Age, yr, mean±SD	38.1±8.6
Sex, No. (%)	
Male	61 (84.7)
Female	11 (15.3)
Race/ethnicity, No. (%)	
White	23 (32)
African-American	40 (56)
Hispanic	9 (13)
Risk factor, No. (%)	
IVDA*	43 (60)
Homosexual	21 (29)
Unknown	8 (11)

*IVDA=IV drug abuse.

Thirteen (18%) were extubated successfully and survived to be discharged from the hospital.

Forty-seven patients (65%) had at least one prior or present opportunistic infection at the time of intubation. *Pneumocystis carinii* was the predominant opportunistic infection in both the survivors and the nonsurvivors. Thirty-six patients (53%) in the nonsurvivors had been diagnosed as having PCP at the time of initiation of mechanical ventilation, as compared to 5 patients (7%) in those who were discharged alive from the ICU. Overall, less than half of the patients had active PCP at the time of initiation of VS (33 of 72 patients). The diagnosis of PCP was based in either group on the result of BAL, transbronchial biopsy specimen, or induced sputum. All patients had either been treated or were receiving treatment on entry in the study.

Disseminated *Mycobacterium avium-intracellulare* (MAI) was the second most common cause of opportunistic infections. Ten patients (15%) had MAI iso-

Table 2—*CD4 of AIDS Patients With Positive Blood Culture on Hospital Admission*

Staphylococcus aureus	9
Klebsiella pneumonia	20
Streptococcus pneumoniae	13
Pseudomonas aeruginosa	24
S pneumoniae	NA*
S aureus	10
Aspergillis fumigatus	60
Bacteroides fragilis	NA
Candida albicans	4
C neoformans	9
S aureus	NA
C neoformans	18
S aureus	10
Mycobacterium avium	9
P aeruginosa	8
S aureus	10

*NA=not available.

lated either from blood cultures or from tissue biopsy specimens prior to endotracheal intubation. All of these patients died in the ICU. Two (20%) of the ten patients were receiving a combination of ciprofloxacin, ethambutol, rifampin, and clofazimine. Two others (20%) were being treated with rifabutin alone. The other opportunistic infections considered in this study included cerebral toxoplasmosis and disseminated *Cryptococcus neoformans*. Both of these infections occurred in a total of six patients (9%). None of these survived their hospital stay. Thirteen patients (18%) had been diagnosed as having a malignancy. Eight (61%) of the 13 patients had non-Hodgkin's lymphoma. None of these had received chemotherapy prior to intubation. All eight patients died in the ICU. The rest (39%) had Kaposi's sarcoma. One patient had both non-Hodgkin's lymphoma and Kaposi's sarcoma.

Respiratory failure was the major reason of intubation in 60 patients (83%). Cardiogenic respiratory failure and airway protection accounted for the remainder of the indications for VS. Fifty-two (88%) of 59 nonsurvivors, compared to 8 (61%) of 13 survivors, required mechanical ventilation for respiratory failure. PCP was identified as the most common cause of respiratory failure in the survivors and nonsurvivors, as it occurred in 37% and 25%, respectively.

The second most common reason for respiratory failure was bacterial pneumonia. Eleven (21%) of 52 nonsurvivors were diagnosed as having bacterial pneumonia as a cause of respiratory failure, compared to 2 (25%) of 8 survivors. Other causes of respiratory failure in nonsurvivors included active pulmonary tuberculosis (6%), disseminated MAI (6%), Kaposi's sarcoma (4%), lymphoma (4%), and Strongyloides (2%). Severe asthma (37%) accounted for the balance of respiratory failure in the survivors group.

Positive blood cultures obtained at the time of hospital admission were found to correlate positively with inhospital mortality following VS. Of the 16 patients who had positive blood cultures on hospital admission, none survived to be discharged from the hospital. Table 2 lists the different pathogens isolated from these patients, along with their CD4 lymphocyte counts. Of particular interest, the mean CD4 count of nonsurvivors with positive blood culture and those with negative blood culture was 17.5 and 24.9 cells/mm^3 respectively; this difference in CD4 lymphocyte count was not statistically significant (p>0.2). A similar trend was seen in patients recently diagnosed as having active tuberculosis. Seven patients were either receiving treatment or were found to have active tuberculosis by sputum or tissue biopsy specimen prior to initiation of mechanical ventilation. All seven patients were among the nonsurvivors.

We assessed the mental status of the 71 patients on presentation, and we separated them into 2 categories: normal and altered mental status. Nonsurvivors were more likely to present as either lethargic, confused, or unresponsive, (22/59 or 37%) compared with survivors (1/13 or 8%) following mechanical ventilation. CT scans of the head revealed an abnormality in 10 (43%) of 23 patients with altered mental status. The most common abnormality reported was single or multiple areas of hypodensity with or without ring enhancing lesion(s). There were no discerning characteristic findings of the chest radiograph at the time of initiation of mechanical ventilation among the survivors and nonsurvivors. Diffuse interstitial infiltrates and lobar consolidation were the most reported abnormalities.

Laboratory data were available on hospital admission for most patients. All of the diagnostic variables and biologic specimens were obtained at the time of hospital admission before any therapeutic interventions were initiated by the emergency department physician or the admitting medical team. As a result, no interventions were included that could have modified these predictors, such as blood transfusion or renal dialysis.

A comparison of the characteristics of these diagnostic variables in the survivors and nonsurvivors is shown in Table 3. Survivors had significantly higher CD4 and lower serum creatinine and LDH levels on hospital admission. Similarly, hemoglobin and albumin levels were higher in the survivors than the nonsurvivors, although the difference did not attain statistical significance. The total WBC and platelet counts were also not significantly different between the two groups. Survivors and nonsurvivors did not differ with regard to the total length of stay, or the time from hospital admission to intubation.

None of the patients at the entry of the study had a "Do Not Resuscitate" (DNR) order. Two patients had limitation of treatment requested by their families: one patient had widespread lymphoma, and the other developed disseminated cryptococcosis 24 h prior to his death.

Classification Tree

The classification tree was grown by binary recursive partitioning and was shrunk to determine its optimal size using tenfold cross-validation; it was pruned accordingly to avoid overfitting.

The resulting tree was developed to produce a positive predictive value of 100%; the 95% CIs were 92 to 100%. Positive predictive value in this context is defined as the proportion of patients who were predicted to die and ended up dying during that admission. The positive predictive value of 100% was obtained at the expense of a negative predictive value

Table 3—Characteristic of Clinical Diagnostic Variables in Survivors and Nonsurvivors

Clinical Variables	Survivors, Mean±SD	Nonsurvivors Mean±SD	p Value
Age, yr	37.3±6.2	38.2±9.1	NS*
LOS, d	17.7±13.3	19.4±16.4	NS
CD4, cells/mm³	70.4±55.4	22.3±15.4	<0.05
Creatinine, mg/dL	0.8±0.4	22.5±2.7	<0.05
Hemoglobin, g/dL	11.0±1.5	10.1±2.7	<0.1
Platelet count, cells/mm³	213.3±80.4	180.5±122.8	NS
LDH, IU/L	645.3±209.6	1,904.6±1,786.7	<0.05
WBC count, cells/mm³	6.8±2.7	6.2±4.3	NS
Albumin, g/dL	3.0±0.6	2.6±1.0	<0.1

*NS=not significant.

of 92% (95% CL, 64 to 100). The negative predictive value is defined as the proportion of patients who were predicted to live and ended up living during that admission. Any error in predicting outcome should be made in erroneously predicting survival because an erroneous prediction of death could lead to unwarranted withdrawal of therapy.

The variables used in the construction of the tree comprised a single or combination of factors that had demonstrated a discriminative power in predicting outcome (Fig 1). The tree predicted that all patients with LDH level above 1,176 IU/L are more likely to die of their illness if they require VS during their hospitalization. A similar outcome is predicted for those patients with LDH level less than 1,176 IU/L who are found to have positive blood culture on admission or who have recently been diagnosed as having active tuberculosis. Those patients with LDH level less than 1,176 IU/L are more likely to survive if they had no history of opportunistic infections or malignancy at the time of initiation of mechanical ventilation. Among patients with history of opportunistic infections or malignancy, those with CD4 less than 12 cells/mm³ are unlikely to be discharged from the hospital, whereas in those with CD4 above 12 cells/mm³, the tree used the combination of serum creatinine and hemoglobin concentrations to predict outcome. In this node, the tree predicted that those patients with creatinine concentration greater than 2.4 mg/dL or hemoglobin level less than 8.5 g/dL are not expected to survive their hospitalization. The probability of death was specified at each node of the decision tree. This probability ranged from 0 to 1. Since the tree was selected to produce a positive predictive value for death of 100% and a sensitivity and specificity of 98% and 100%, all terminal nodes but one carried a probability of outcome of either 0 or 1. A misclassification occurred in one patient of the 72 entries that yielded a probability of death of 0.2 at one of the terminal nodes. The tree projected that the patient in question was ex-
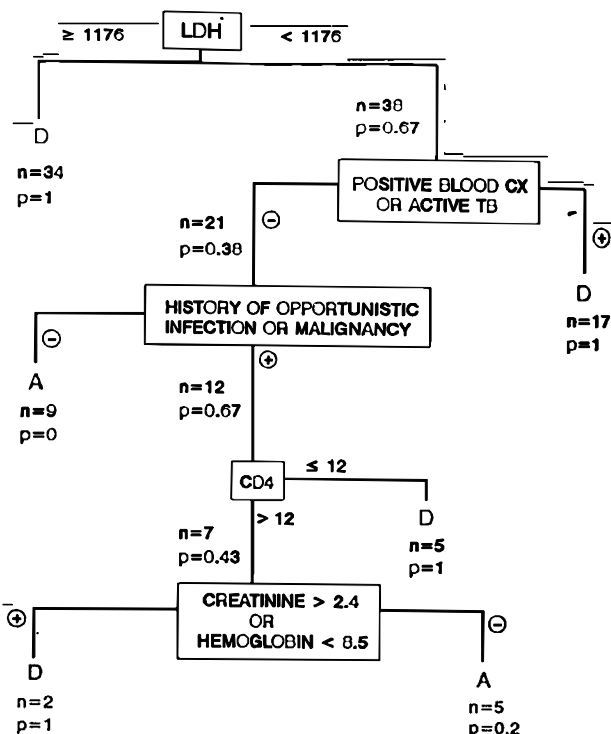
FIGURE 1. Classification tree predicting the outcome of patients in our dataset. LDH is expressed international units per liter. CX=culture. CD4 count is expressed as cells per cubic millimeter. Serum creatinine and hemoglobin concentration are expressed as milligrams per deciliter and grams per deciliter, respectively. D and A=dead and alive, respectively.

pected to survive hospitalization, while in reality he died in the ICU.

Logistic Regression

The same variables used in the CART were used in a logistic regression model. The only variables that achieved statistical significance were LDH, CD4 count, and a history of opportunistic infection or malignancy. To avoid instability in the model, a natural logarithmic transformation of LDH levels was used. The coefficients for the logistic regression model were -19.76 ± 7.46 for the intercept, -0.03661 ± 0.01459 for CD4 count, 3.316 ± 1.1771 for the log of the LDH level, and 1.823 ± 0.7244 for the history of opportunistic infection or malignancy. As with the CART, the model prediction was adjusted to provide a specificity of 100%. Under these circumstances, there were 16 patients who died that logistic regression model predicted would survive. This result differs significantly from the CART, which had only one misclassification ($p < 0.01$). Of these 59 deaths, there were 7 patients for whom prediction was unavailable from the logistic regression model because of missing data. This occurrence is significantly greater than the CART where this circumstance did not occur ($p < 0.05$).

This study has tried to determine the predictors of outcome in AIDS patients admitted to medical ICUs who require VS. Our data included a total of 72 episodes of mechanical ventilation, with an overall mortality of 82%. Although recent surveys have documented an improved survival in AIDS patients with PCP and respiratory failure,[17-20] the overall prognosis of AIDS patients with acute respiratory failure remains poor.[10-12,21-23] Previous studies were not able to achieve an accurate prognostic model to assist physicians in clinical decision making concerning withdrawing or withholding life support measures. This analysis attempted to identify a model that would accurately predict survival or mortality before initiation of mechanical ventilation based on readily available clinical variables.

The advantage of the indexes chosen in the development of the decision tree presented in this report comes from their availability in a routine history, physical examination, and laboratory data at the time of hospital admission. The indexes used in the construction of the decision tree included LDH, positive blood culture or active tuberculosis, history of opportunistic infections or malignancy, CD4 count, creatinine, and hemoglobin values. Three of the four laboratory variables (LDH, creatinine, and CD4 count) have been found to vary significantly between the survivors and nonsurvivors as shown in Table 3. Previous studies from predictors of PCP-related mortality and prognostic staging systems in AIDS have identified similar variables, particularly low CD4 count, elevated LDH, decreased hemoglobin, and elevated creatinine values as important predictors of increased mortality.[7,24,25] The similarity of these prognostic variables to previously published models suggests that the results of this study could be generalized to other institutions. The important feature identified in this study is the sequence of applying a combination of known factors that enhanced the predictive ability of the model. The standard logistic regression model had lower predictive capacity and it was more susceptible to missing data than the CART. Furthermore, the strength or weakness of a prediction using the CART is readily apparent from the number of patients at the terminal branch. This information is not apparent in the logistic regression model.

Another advantage of the indicators used in the decision tree presented herein is their versatility. They are not limited to a disease-specific entity. Most of the previously published prognostic indexes have been limited to HIV-related PCP. Although PCP remains the most common cause of respiratory failure in AIDS patients requiring mechanical ventilation, disease-specific systems usually focus only on one aspect of the

wide range of circumstances of patients with AIDS who require VS, so that the results cannot be generalized to other disease states and are invalid in multisystem disorders.[26]

The limitations of the present study include a relatively small number of patients obtained from two inner-city hospitals that could possibly reflect a subset of AIDS population with low socioeconomic status. Therefore, there is some uncertainty as to the extent to which our classification tree can be generalized, particularly because socioeconomic factors have been shown to play a role in AIDS survival time.[27]

Another source of limitation stems from the fact that our data are based on a retrospective review of patient records. Missing data are a major drawback in such kind of analyses, and this was encountered in seven patients; four of those happened at the root of the decision tree-LDH node. Nevertheless, this problem was minimized by the fact that the proposed decision tree reallocated those patients with missing LDH values to those with a value less than 1,176 IU/L, and thus were not eliminated from the decision-making process, and therefore from a more intensive treatment. Another three cases with missing data were classified into a terminal branch by virtue of other characteristics so that the missing data were not required to determine their prediction. A potential limitation of the decision tree is the arbitrary but relevant cutoff value assigned to continuous variables. The binary nature of the classification tree requires a level to be selected so that patients can be separated into two groups. The particular cutoff value is selected because it optimizes the predictive properties of the model. This approach of using empirical cutoff levels is not uncommon in clinical practice such as defining the serum drug level between toxic and therapeutic range, as in the case of digoxin or theophylline.

Despite these limitations, the CART did provide more accurate predictions than logistic regression. First, there were 16 misclassifications among the 59 deaths of patients who were predicted to live according to logistic regression compared with 1 for the CART (p<0.01). Second, there were 7 of the 59 patients who died who could not be assigned a prediction because of missing data. In contrast, this circumstance did not arise with the CART (p<0.05). Overall, the CART predictions were 98.6% correct in these patients compared with accurate predictions in only 76% for logistic regression (p<0.01). The performance of the logistic regression model was not improved when the model was recast in precisely the same terms as used for the CART or when substitutions were made for missing data. The primary reason for the differences between the CART and logistic regression for this particular dataset is the manner in which missing data are handled rather than any intrinsic mathematical properties.

Although a DNR order is limited to cardiopulmonary resuscitation, it could have led to an unrecognized limitation of other medical treatment. In this event, it could introduce bias in the outcome of AIDS patients toward a lower survival. In fact, none of the patients at the entry of the study had a DNR order. Treatment was not withheld unless there was a specific instruction by the patient or the family for limitation of treatment. In the cases reviewed herein, only two patients had limitation of treatment apart from a DNR order. Finally, an inescapable limitation of any prognostic model is the dynamic nature of the system that makes the predicted outcome vulnerable to change in response to new treatment modalities or a change of the pattern of the natural disease process or its progression.

This tree needs to be validated in a prospective study so that it can be used as a prognostic tool to guide health-care providers and their families in clinical decision making that minimizes both patient suffering and unnecessary health-care expenditure. Such information could lead to changes in clinical decision making that could optimize the use of ICU facilities, enhance patient satisfaction, and guide the rational allocation of health-care resources. Without validation, the classification tree can be easily developed using patient data to summarize local experience.

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