Analyzing Electronic Medical Records to Predict Risk of DIT (Death, Intubation, or Transfer to ICU) in Pediatric Respiratory Failure or Related Conditions

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Abstract

Large volumes of data are generated in hospital settings, including clinical and physiological data generated during the course of patient care. Our goal, as proof of concept, was to identify early clinical factors or traits useful for predicting the outcome, of death, intubation, or transfer to ICU, for children with pediatric respiratory failure. We implemented both supervised and unsupervised methods to extend our understanding on statistical relationships in clinical and physiological data. As a supervised learning method, we use binary logistic regression to predict the risk of developing DIT outcome. Next, we implemented unsupervised k-means algorithm on principal components of clinical and physiological data to further explore the contribution of clinical and physiological data on developing DIT outcome. Our results show that early signals of DIT can be detected in physiological data, and two risk factors, blood pressure and oxygen level, are the most important determinant of developing DIT.

Introduction

In the healthcare industry, a considerable amount of data is generated through routine clinical practice, including data for patient blood pressure, oxygen level, respiratory rate, heart rate, hemoglobin and hematocrit, and blood electrolytes. While these data are used primarily to monitor patient clinical status, their use in the field of predictive analytics – for the purpose of predicting upcoming clinical deterioration - has been relatively limited. Healthcare institutions are increasingly joining the ranks of other major industries in using numerous data mining techniques to identify trends and hidden relationships in these large and complex data sets1, 2. Structured record data has been used to extract phenotype information from free-text records to produce fine-grained disease correlations and patient stratification3. Such data has also been used to create similarity ranking (or matrices) between pairs of patients with rare diseases4. Data mining techniques have been widely employed in the fields of clinical informatics and genomics5. Bayesian models are among the most widely applied techniques in medical applications, and are used to classify data into supervised learning classes6. For free-text documents, latent semantic indexing has been widely used to produce a concept vector space in which query vectors and term-document are projected7. For example, latent semantic indexing techniques have facilitated the extraction of gene function data from peer-reviewed scientific abstracts, which contributes to the understanding of high-throughput genomic studies8.

Mining data from medical information systems has been useful for predictive modeling, for example, to guide preventive care or to inform the healthcare team of critical patient signs indicative of disease or acute clinical crises. Symbolic time series approaches have been used to study physiological data; using symbolic time series analysis techniques, heart rate variability dynamics have been shown to distinguish healthy subjects from patients with cardiac problems9. Using features extracted from symbolic series and time-frequency indices of heart rate variability, Aziz et al. (2004) suggests that the use of new features based on symbolic series, coupled with classic time-frequency and clinical indices, is a good predictor of death in patient with Chagas disease. Symbolic time series analyses have also been applied to heart period (RR) and QT variability, and can improve separation between ischemic dilated cardiomyopathy patients and a healthy control group10.

Current research has successfully developed an early detection signaling system capable of identifying young adolescents at high risk for sepsis11, and has also allowed for the rapid identification of patients with possible septic shock in order to enroll them into a time sensitive clinical study12. Other examples of successful applications of data mining techniques to complex healthcare data include its use to guide hypertension management13, and to identify...
factors contributing to preterm birth\textsuperscript{14}. Previously, we studied pediatric asthma patients by mining data from electronic medical records\textsuperscript{15} using low-rank matrix decomposition (LRMD) in vector space models\textsuperscript{16}. LRMD techniques were applied to the parse All Patient Refined Diagnosis Related Group (APR-DRG) datasets for asthma, allowing for the extraction of dominant features and the prediction of outcomes.

Asthma and acute lower respiratory tract infections are the single most common causes of hospitalization annually at Le Bonheur Children’s Hospital (LBCH; a large referral hospital in Memphis, TN), and account for the majority of hospitalization during the winter months\textsuperscript{17}. Children hospitalized with asthma or lower respiratory tract infections that have persistent episodes of hypoxemia (or require increasing fraction of inspired oxygen (FiO\textsubscript{2})) are more likely to require ICU transfer or need mechanical ventilation. A system that enables early recognition of declining respiratory function could affect real change in a clinical setting, and in turn may help improve medical outcomes.

Methods

Setting & Participants

We used data from all patients admitted to LBCH with a diagnosis of asthma or related pulmonary conditions (such as wheezing and bronchiolitis) from January 2013 to April 2013. All data used for this study was extracted from the LBCH ‘Cerner’ Electronic Medical Records. The total number of observations included in our study includes 745 encounters from 563 distinct patients. Of these 563 patients, 60\% were African American, 28\% Caucasian, <1\% were Asian American, and 12\% were ‘other’ race; 53\% were male, and 28\% were between 1 and 4 years old. Of the study cohort, 10.5\% (n=59) required ICU transfer, approximately 2\% (n=11) required mechanical ventilation and 0.1\% (n=1) died. The UTHSC Institutional Review Board (IRB) approved this study for exempt status.

Variable Selection & Model Building Process

In data mining, the selection of the set of explanatory variables (or predictors) is typically part of the analysis. For our approach, we used an automatic variable selection procedure, stepwise regression based on Akaike Information Criteria\textsuperscript{18, 19}. We used Beta or standardized coefficients after converting all variables to z-scores prior to the variable selection process. Standardized coefficients allow a comparison of the relative importance of the risk or predictor variables. Since the outcome of ‘death, intubation, or transfer to the ICU’ was dichotomous in nature (DIT=No, DIT=Yes), we used binary logistic regression to support the evaluation of multiple risk factors\textsuperscript{20, 21}.

Unlike age and gender, some variables such as FiO\textsubscript{2}, SpO\textsubscript{2}, BP, MCV and respiratory rate consist of multiple measurements over time for each patient. In order to handle the multiple measurements obtained within one hospitalization for these potential risk factors, we converted the multiple measurements into a single value, based on the selection criteria outlined in Table 1. This approach was used to minimize data loss associated with converting to descriptive statistics (for example, mean or median). To study the time window effect on DIT, we used Table 1 in processing variables with multiple measurements in two different ways; 48 and 12 hours prior to DIT. Therefore, we created two separate logistic predicting the risk of developing DIT using the variables in Table 1. This allows us to explore both whether there were different variables associated with DIT at different time windows before the occurrence of DIT and whether the variables associated with DIT had different strengths of association when measured in these different time windows prior to DIT.

Table 1. Potential Risk Factors

| Potential Risk Factor                | Selection Criteria                                      |
|--------------------------------------|--------------------------------------------------------|
| Fraction of Inspired Oxygen (FiO\textsubscript{2})\textsuperscript{†} | Number of times FiO\textsubscript{2} > 0.5             |
| Oxygen Saturation (SpO\textsubscript{2}) \textsuperscript{‡}         | Number of times SpO\textsubscript{2} < 90              |
| Mean Corpuscular Volume of Blood Cell (MCV) | First value measured after admission                     |
| Mean Corpuscular Hemoglobin Concentration in blood (MCHC)           | First value measured after admission                     |
| Respiratory rate\textsuperscript{§}                                 | Number of times respiratory rate less than or above normal age-specific range |
| Blood pressure (Systolic)\textsuperscript{§}                        | Number of times blood pressure less than or above the normal age-specific range |
Table 1. Potential Risk Factors (continued)

| Sodium     | First value measured after admission |
|------------|--------------------------------------|
| Potassium  | First value measured after admission |
| Gender     | Male/Female                          |
| Race       | African American, White, Asian, others |
| Age        | Between 1 and 18 years old           |

† = FiO₂ is typically maintained below 0.5 even with mechanical ventilation (to avoid oxygen toxicity); ‡ = Normal pulse oximeter readings usually range from 95 to 100 percent. SpO₂ values under 90 percent are considered low and usually indicate the need for supplemental oxygen; § = we used the standard primary vital signs that are provided by American College of Emergency Physicians²²

Further, we applied principal component analysis (PCA) on explanatory variables to reduce the dimension and to examine which clinical factors are most strongly correlated with each principal component. In our case, a correlation value above 0.5 magnitudes in either positive or negative direction is deemed important. Next, we carried out k-means clustering algorithm²³ on selected principle components to find patterns between the risk factors and DIT.

Results

Our logistic regression analysis results for the data organized for 48 hours prior to DIT are shown in Table 2. Our results suggest that among all variables collected, FiO₂ is most strongly associated with the outcome, followed by MCV, respiratory rate, and the subject’s race (Table 2). Figure 1 shows the receiver operating curve for our final model, presenting the true positive rate versus false positive rate; the area under the curve (AUC; the c-index or c-statistic) is 0.875.

Table 2. Multivariable logistic regression (48 hours prior to DIT outcomes).

| Parameter     | Parameter Estimate | Standard Error | p Value | Odds Ratio | CI Lower Limit | CI Upper Limit |
|---------------|--------------------|----------------|---------|------------|----------------|----------------|
| Age           | -0.026             | 0.082          | 0.752   | 0.974      | 0.825          | 1.149          |
| Gender        |                    |                |         |            |                |                |
| Male          | 0.541              | 0.471          | 0.251   | 1.716      | 0.687          | 4.407          |
| Race*         |                    |                |         |            |                |                |
| African American | 1.492            | 0.679          | 0.028   | 4.445      | 1.245          | 18.463         |
| Other         | 2.089              | 0.883          | 0.018   | 8.078      | 1.478          | 4.957          |
| SpO₂*         | -0.025             | 0.027          | 0.347   | 0.975      | 0.921          | 1.029          |
| BP systolic   | 0.056              | 0.034          | 0.096   | 1.057      | 0.993          | 1.134          |
| Respiratory rate* | 0.057           | 0.022          | 0.008   | 1.059      | 1.016          | 1.108          |
| MCHC          | -0.219             | 0.199          | 0.271   | 0.803      | 0.534          | 1.176          |
| MCV*          | 0.099              | 0.034          | 0.003   | 1.105      | 1.038          | 1.186          |
| Potassium     | -0.082             | 0.357          | 0.819   | 0.922      | 0.451          | 1.858          |
| Sodium        | -0.112             | 0.068          | 0.098   | 0.894      | 0.776          | 1.019          |
| FiO₂*         | 0.257              | 0.074          | < 0.001 | 1.293      | 1.145          | 1.529          |

The five variables most strongly associated with Death, Intubation and ICU Transfer are shown in bold. * = The odds ratios for these variables (with 95% confidence intervals) are significant at the 0.05 level.
Figure 1. Receiver Operating Curve (true positive vs. false positive).

Our second logistic regression model using the data organized for 12 hours prior to DIT is shown in Table 3. Among variables measured 12 hours prior to DIT, blood pressure was significantly associated with DIT, along with race and FiO₂, but MCV and respiratory rate were not found to be strongly associated with DIT at this time point.

Table 3 Multivariable logistic regression (less than 12 hours prior to DIT outcomes)

| Parameter                 | Estimate | Standard Error | p Value | Odds Ratio | CI Lower Limit | CI Upper Limit |
|---------------------------|----------|----------------|---------|------------|----------------|----------------|
| Age                       | 0.045    | 0.127          | 0.724   | 1.046      | 0.821          | 1.357          |
| Gender                    |          |                |         |            |                |                |
| Male                      | 0.055    | 0.785          | 0.944   | 1.056      | 0.209          | 4.939          |
| Race*                     |          |                |         |            |                |                |
| African American          | 3.224    | 1.153          | **0.005** | 25.143    | 3.168          | 318.144        |
| Other                     | 1.974    | 1.527          | 0.196   | 7.205      | 0.409          | 182.855        |
| SpO₂                      | 0.001    | 0.007          | 0.945   | 1.001      | 0.987          | 1.013          |
| BP systolic*              | 0.029    | 0.006          | <**0.001** | 1.029    | 1.019          | 1.044          |
| Respiratory rate          | -0.004   | 0.006          | 0.556   | 0.996      | 0.983          | 1.008          |
| MCHC                      | -0.027   | 0.314          | 0.930   | 0.973      | 0.524          | 1.809          |
| MCV                       | 0.448    | 0.049          | 0.367   | 1.046      | 0.951          | 1.158          |
| Potassium                 | 0.101    | 0.676          | 0.882   | 1.106      | 0.288          | 4.327          |
| Sodium                    | -0.233   | 0.144          | 0.106   | 0.792      | 0.583          | 1.029          |
| FiO₂*                     | 0.549    | 0.171          | **0.001** | 1.732    | 1.283          | 2.522          |

The three variables most strongly associated with Death, Intubation and ICU Transfer are shown in bold. * = The odds ratios for these variables (with 95% confidence intervals) are significant at the 0.05 level.

We applied a PCA technique to simplify our data set into a lower dimensional space to allow for visualization of associations in the data. Figure 2 shows a plot of variances (y-axis) associated with principal components (x-axis). We selected the first 3 components for our analysis, based on the variability in the data using the “elbow” method of scree plot (Figure 2).
Figure 2. The plot of variances (y-axis) that is associated with each principal component using PCA. The “elbow” is shown by the red circle.

A correlation value of magnitude 0.5 was assumed as significant. We found that the first principal component is highly correlated with BP systolic (correlation co-efficient of -0.547), while SpO₂ (0.565) is correlated with the second component. Age (-0.686) and MCV (-0.596) are correlated with the third principal component. To examine patterns in the data with respect to DIT, we applied an unsupervised machine learning technique, k-means clustering analysis, using the first three principal components. To determine the number of clusters, we looked at the within groups sum of squares and selected the “elbow” in the plot. We can see that the “elbow” in the scree plot is at $k = 3$ (Figure 3) so we applied the k-mean clustering with $k = 3$.

Figure 3. Number of clusters vs. within groups sum of squares using the “nstart = 25” and “iter.max = 1000” in R version 3.2.3. The “elbow” is shown by the red circle.

Figure 4. Applied k-mean clustering with $k = 3$ to the first three principal components (PC1, PC2, and PC3).
We then applied the $k$-mean clustering with $k = 3$ using the first three principal components (Figure 4). In each box, principal components are compared and are either commingled (mixture of blue and red dots) or clustered separately (blue cluster and red cluster). Outliers can be clearly identified, and are shown in green. Figure 4 shows separation between PC1 and PC2 clusters, therefore we focused on BP systolic and SpO$_2$ as we previously identified these variables as highly correlated with the first two principal components. Despite this result, SpO$_2$ was not one of the statistically significant predictors of DIT in our logistic regression models in Table 2 and Table 3. Also, BP systolic was significant when we analyzed our data for 12 hours prior to DIT, but not at 48 hours prior to DIT (see Table 3). Therefore, we studied these two variables’ associations to DIT by projecting the $k$-mean clustering results with $k = 3$ on these two variables (Figure 5).

**Figure 5.** Count of the number of times that BP systolic values reach less than normal values or above normal values (adjusted for the patient’s age) (freq_bpsystolic) versus the number of times SpO$_2$ values reach less than 90 (freq_spo2). 0 = patient without DIT outcomes (red dot); 1 = patient with DIT outcomes (blue dot).

Plotting abnormal fluctuations in BP systolic versus SpO$_2$ revealed clustering of DIT (blue dot) and non-DIT (red dot) based on BP systolic, indicating that BP systolic is a promising variable for predicting our outcome. We did not observe a similar clustering pattern for SpO$_2$. To visualize the relationship between three clusters (from Figure 3) and the variables BP systolic and SpO$_2$, we used a $k$-mean algorithm to project BP systolic and SpO$_2$ variables onto three clusters (Figure 6). The count of the number of times BP systolic was less than or above the normal values is the main indicators assigning cases into these three clusters (Figure 6). The result of $k$-mean clustering analysis applied to BP systolic yielded promising results among patients who later progressed to DIT (i.e., transitioning from C$k_1$ to C$k_2$) and distinguished them from patients who remained healthy (i.e., transitioning from C$k_1$ to C$k_3$).

**Figure 6.** $k$-mean clustering results for $k = 3$; 1 = cluster number 1 (blue dot) with the centroid of “freq_bpsystolic” = 56.35 (or C$k_1$ = 56.35); 2 = cluster number 2 (red dot) with the centroid of “freq_bpsystolic” = 151.51 (or C$k_2$ = 151.51); 3 = cluster number 3 (green dot) with the centroid of “freq_bpsystolic” = 309.52 (or C$k_3$ = 309.52); “freq_bpsystolic” = the number of times BP systolic is less than or above the normal values (adjusted for patient age).
Discussion

In this study, we found that race, respiratory rate, MCV and FiO₂ were significantly associated with impending respiratory failure - defined in this study as intubation, transfer to the ICU, or death. Interestingly, the strongest predictor of impending DIT is MCV. An abnormal MCV was associated with risk for respiratory deterioration 48 hours prior to DIT. MCV, along with MCH and MCHC, are part of red blood cell count indices and represent size, content, and hemoglobin concentration, but the biologic explanation for its association with DIT is not clear. In addition, we found that systolic BP was a key clinical factor predictive of DIT, especially in the time window 12 hours prior to DIT.

We found some evidence that predictive risk factors differ in their association with respiratory failure depending on the timing of these events. For example, abnormalities in some risk factors may be detected 48 hours before DIT, such as respiratory rate, MCV and FiO₂, while abnormalities in BP readings are significant for DIT in the following 12 hours. Since some of these traits, such as blood pressure, may also be evaluated in the context of a series of observations in a specific time interval, our future work will investigate the optimal time lag to be used for characterizing pattern transition behaviors like a Markov chain or Hidden Markov Model (HMM) to further identify specific patterns of time series among patients at particularly high risk for DIT. While our study did not use information downloaded directly from the cardiorespiratory monitors for time series data and these values were 2-3 hourly averages calculated and entered by the bedside nurse in the Electronic Medical Records, we believe that our analyses are suitable to apply to information downloaded directly from the cardiorespiratory monitors, which will allow for real-time monitoring in the future.

Study Limitations

One challenge to predictive modeling is that of generalizability. Because our study was relatively small, we elected against using split samples to validate our models. Therefore, our future plans will focus on verifying that our predictive models are robust and generalizable beyond just the data in hand. We will apply our predictive model to larger datasets such as the Pediatric Health Information System (PHIS) database, which consists of data from 44 leading children’s hospital.

Conclusion

Analyzing Electronic Medical Records by applying data mining and clustering analysis techniques facilitates the possibility of discovering unexpected relationships and trends to gain new insights. Indeed, we hope that results from this study will advance progress toward the goal of identifying patients at high risk for respiratory failure. We believe our techniques can be expanded to encompass other diseases amendable to such modeling.

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Author Contributions

TV conceived and drafted the manuscript with contributions from BD and OA.

Conflicts of Interest

The authors declare no conflict of interest.

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