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Predicting Deep Venous Thrombosis and Evaluating Factors Associated with Length of Stay in Children Hospitalized with *Staphylococcus Aureus* Osteomyelitis

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Predicting Deep Venous Thrombosis and Evaluating Factors Associated with Length of Stay in Children Hospitalized with *Staphylococcus Aureus* Osteomyelitis

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Abstract

Predicting Deep Venous Thrombosis and Evaluating Factors Associated with Length of Stay in Children Hospitalized with *Staphylococcus Aureus* Osteomyelitis

By
Kavita N. Patel

Background: Deep venous thrombosis (DVT) has been reported to be a frequent complication occurring in children admitted to the hospital with *Staphylococcus aureus* osteomyelitis (OM). Increased length of hospital stay has been reported in children who have both *S. aureus* OM and DVT. In review of the literature, there is no published model to help predict which children are at increased risk of developing DVT and if DVT is associated with increased length of stay in children hospitalized with *S. aureus* OM.

Methods: A retrospective cohort study consisting of children aged 0-18 years with *S. aureus* OM were identified at Texas Children's Hospital and Children's Healthcare of Atlanta from 2005-2010. Statistical methods included use of Student's t-test, Wilcoxon rank sum test, Chi Square, simple and multivariable logistic, linear, and Cox regression analyses using SAS v9.4 (SAS Institute INC., Cary, NC).

Results: S. aureus OM was identified in 382 children; 47 (12.3%) had deep venous thrombosis (DVT). Overall in-hospital survival was 99.6%. A predictive model was developed containing the following factors: presence of bacteremia, C - reactive protein (CRP) level >24mg/dl and platelet count <200 platelets/microliter and male gender predicted DVT with moderate sensitivity and specificity (area under curve (AUC) of 0.85, sensitivity 86% and 71%). Median length of stay was 20 days vs. 8 days (p=<0.0001) in those with and without DVT, respectively. DVT was associated with 65% increase in length of stay compared to those without DVT using linear regression analysis and a hazard ratio of 0.47 (95% confidence interval 0.34-0.67) with regards to time to hospital discharge in those with DVT compared to those without DVT. Additional factors associated with length of hospital stay were pediatric intensive care admission, methicillin resistant *S. aureus* infection, the presence of bacteremia, multiple sites of osteomyelitis infection, and location of cohort.

Conclusions: Bacteremia, CRP >24mg/dl, platelet count <200 platelets/microliter, and male gender predicted DVT and the presence of DVT was associated with a longer hospital in children hospitalized with *S. aureus* OM.

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INTRODUCTION

Children who develop thrombosis have increased morbidity and mortality compared to healthy children (1, 2). A subset of children who are suspected to be at increased risk of development of thrombosis is children with community acquired *Staphylococcus aureus* osteomyelitis. Numerous observational studies have shown that these children have increased frequency of deep venous thrombosis (DVT) and these DVTs are not always present nor found upon presentation to the hospital (3-7). The reported percentages of children with *S. aureus* osteomyelitis who develop DVT while hospitalized have been reported to be between 5-30% and can occur between hospital days 0 to prior to discharge (6-9). Length of stay has been reported to be increased in children who develop DVT (4, 6, 8). A notable limitation of these observational (regardless if prospective or retrospective) studies is that no child was routinely screened for DVT and that only one study thus far has evaluated any measure of associations for factors associated with length of hospital stay. Symptoms of DVTs such as pain and swelling mimic the symptoms seen in osteomyelitis and as result DVT may not be suspected when a child presents to the hospital or even during the course of hospitalization. This overlap of symptoms makes it difficult for physicians and other healthcare providers caring for these patients to correctly identify who is at risk for DVT and if or when they should be screened for DVT. As a result there is a gap in knowledge regarding the true burden of thrombosis in children with osteomyelitis and defining the subset of children who are at high risk of DVT and may benefit from DVT screening. Also, it is not known to

what degree the occurrence of DVT is associated with hospital length of stay and what other factors may influence length of stay in this patient population.

The focus of this work will be to develop a model that predicts the subset of children with *S. aureus* osteomyelitis are at risk of DVT at time of admission to the hospital and to evaluate the association between DVT and hospital length of stay.

BACKGROUND

Infections with *Staphylococcus Aureus* are rising as are the rates of venous thrombosis in pediatrics

Children who develop thrombosis, particularly deep venous thrombosis, have increased morbidity and mortality compared to children without DVT based on nationally reported rates of death in children (from all causes) (1, 2, 10, 11). In addition to pre-existing conditions such as prior episode of thrombosis, cancer, and genetic predisposition, the presence of an infection increases the risk for developing thrombosis (12-14). Infections in the bone, known as osteomyelitis, have been shown to be associated with DVT(15). In the last decade infections with *Staphylococcus aureus* have been increasingly recognized and reported as a predisposition for the development of thrombosis in previously healthy children though case reports and case series have reported this phenomenon since 1971(7, 15-21). In the last decade, the incidence of community acquired *S. aureus* infections in children have risen (22). As a result of the rising incidence of community acquired *S. aureus* infections, the risk of DVT may also be on the rise.

In 2006, the largest case series up to that time was published by Gonzalez et al. from Texas Children's Hospital showing a relationship between the presence of venous thrombosis and *S. aureus* osteomyelitis compared to other types of osteomyelitis. At the time of their report, only 15 cases had been published. In the interim, DVT associated with osteomyelitis due to *S. aureus* infections have been increasingly recognized as a predisposition for the development of thrombosis in previously healthy children (3-9, 16, 17, 19, 23-25). Children with *S. aureus* osteomyelitis and

DVTs are being seen throughout the US at all major children's hospitals (personal communication). The limitations of these observational studies include that no children were routinely screened for DVT, small sample sizes, and that most studies were retrospective.

Diagnostic Challenges

Osteomyelitis can be diagnosed with imaging including bone scintigraphy, x-ray, or MRI as well as using bone biopsy or with a combination of those modalities (26-28). Of the imaging modalities, MRI can often detect DVTs in children but the sensitivity and specificity without dedicated MRV is lacking (29). Additionally, DVT can be present at diagnosis or found up to weeks later (7, 8). The prevalence of DVT in *S. aureus* osteomyelitis is estimated to be between 5-30%, with an average of 9-10% across all studies (6). DVTs in children with osteomyelitis are not routinely screened for and thus are often found incidentally when imaging is performed for diagnosis of osteomyelitis or if patient develps symptoms of DVT during hospitalization that prompt the healthcare provider to screen for DVT. The median time to diagnosis of DVT from admission to hospitalization has been reported to be between 2-6 days (7, 8). One possible reason for the variablilty in the time to diagnosis of DVT is that symptoms of DVT such as pain and swelling mimic those symptoms seen in patients with osteomyelitis. A second reason for the variability in time to diagnosis is that not all DVTs have occurred when these children present to the hopsital. As a result of variable time to diagnosis leading to a potenital delay in the time to start anticoagulation treatment, part of the infection may become localized within the thrombus, potentially prolonging bacteremia, lengthening hospitalization, and

increasing risk of developing sepsis or respiratory failure due to septic pulmonary emboli.

Screening studies and prediction models have increased the diagnosis of venous thrombosis

In adults, it is well established that prediction models (not specific to any one population except for adults in general), such as the Well's criteria for pulmonary embolism risk and use of d-dimer for DVT risk and recurrence, have been paradigm shifting (30-32). There a very few studies of predicting DVT in pediatrics (33-36). Studies trying to extrapolate these adult findings into the pediatric population have not proven successful (37). Novel prediction models are needed because when studies are performed to screen for DVT in children, thrombosis is several fold more prevalent than would be found by symptomatology alone(38, 39). Thus far in the review of the literature, no prediction model for DVT risk in children with *S. aureus* OM has been developed.

Establishing a clinically relevant DVT risk prediction model has potential to improve diagnosis of disease, morbidity and potentially mortality

Children with *S. aureus* osteomyelitis with DVT have been reported to have worse outcomes including prolonged length of hospital stay, need for ICU admissions, increased utilization of hospital resources, and mortality (5-9, 24, 25). Clinical prediction models may help physicians and other healthcare providers determine the risk of DVT and therefore assist in clinical decision making, particularly with regards to surveillance for DVT or perhaps in employing DVT prophylaxis strategies.

METHODS

Research Objectives

The first research objective was to develop a DVT risk prediction model for children hospitalized with *S. aureus* osteomyelitis based upon factors identified at time of hospital admission or early in admission (<24-48 hours). The second research objective was to test the hypothesis that the occurrence of DVT during admission for osteomyelitis due to *S. aureus* was increases the length of hospital stay.

Study Design

For research objective one, a model was developed to predict DVT utilizing routinely collected demographic, clinical and laboratory factors in a retrospective cohort of children aged 0-18 years who were admitted to the hospital with *S. aureus* osteomyelitis. For the second research objective, the same cohort of children was used to estimate the association between DVT and hospital length of stay. The study population was derived from a cohort of children from Texas Children's Hospital in Houston, Texas and Children's Healthcare of Atlanta in Atlanta, Georgia.

Cohort Criteria

Children eligible for inclusion in this retrospective cohort analysis were between 0-18 years of age admitted to Texas Children's Hospital in Houston, Texas and Children's Healthcare of Atlanta in Atlanta, Georgia between January 1, 2005, and December 31, 2010 (n=226). The subjects in the Texas cohort were identified using a database maintained by the Infectious Disease service at Texas Children's Hospital

as part of an ongoing bio-repository and clinical database of community acquired S. aureus infections and was approved by the Institutional Review Board (IRB) at Baylor College of Medicine. The definitions of "community acquired" have been outlined previously (40). The patients in the Georgia cohort were identified by using any ICD-9 codes that included osteomyelitis as well as electronic medical record database searching for the term osteomyelitis. The ICD-9 codes utilized included: 730.00, 730.01, 730.02, 730.03, 730.04, 730.05, 730.06, 730.07,730.08, 730.09, 730.10, 730.11, 730.12, 730.13, 730.14, 730.15, 730.16, 730.17, 730.18, 730.19, 730.20, 730.21, 730.22, 730.23, 730.24, 730.25, 730.26, 730.27, 730.28, 730.29, 730.30, 730.31, 730.32, 730.33, 730.34, 730.35, 730.36, 730.37, 730.38, 730.39, 730.70, 730.71, 730.72, 730.73, 730.74, 730.75, 730.76,730.77, 730.78, 730.79, 730.80, 730.81, 730.82, 730.83, 730.84, 730.85, 730.86, 730.87, 730.88, 730.89, 730.90, 730.91, 730.92, 730.93, 730.94, 730.95, 730.96, 730.97, 730.98, 730.99. Time zero for the cohort was defined as date of admission. Osteomyelitis diagnosis was confirmed by MRI, bone scan, or bone culture proven infection. *S. aureus* infection was confirmed by blood culture or bone culture.

Exclusion criteria included diagnosis of DVT prior to admission, chronic osteomyelitis, and osteomyelitis of hand, foot, or cranium since these locations have not previously been shown to be associated with DVT in children with osteomyelitis due to *S. aureus*.

Data Collection and Measurements

After obtaining approval from the respective IRBs of each institution, medical charts were then reviewed for demographic, clinical, and laboratory information. Data collection was performed by a trained individual and the primary investigator (KP). Outcomes of presence of DVT and hospital length of stay were also collected. Demographic data included age at diagnosis of OM, gender, date of birth, date of death (if applicable). Clinical data recorded included date of admission, date of discharge, date of diagnosis of OM, location of OM, diagnostic method of determining if OM present, date of first and last positive blood culture, susceptibility to methicillin, admission to ICU, presence of septic pulmonary emboli, date of diagnosis of DVT, location of DVT, presence of DVT on OM diagnostic imaging, whether any anticoagulants used to treat DVT, date of anticoagulation initiation, date of anticoagulation discontinuation, resolution of DVT (complete, partial, or no change). Laboratory data collected included white blood cell count, hemoglobin, platelet count, C-reactive protein which we performed no later than 48 hours from admission. Additional labs collected were prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, d-dimer, factor 8 activity at time of admission or initiation of anticoagulation(+/-48 hours). For this study, the bones with osteomyelitis were categorized as belonging to one of the following categories: proximal upper extremity (humerus), distal upper extremity (radius, ulna), proximal lower extremity (femur), distal lower extremity (tibia, fibula), pelvic (iliac, ischium, pubis, sacrum), and other (clavicle, scapula, patella, vertebrae). Relevant radiographs were also reviewed. Additionally for analytic purposes, OM sites were

categorized as follows: proximal included the proximal upper extremity, proximal lower extremity and pelvic sites; all other sites were considered distal sites (due to lack of proximity to deep veins). Missing data was only seen for the laboratory variable, C-reactive protein, missing n=26, 6.8%.

Statistical Plan

Descriptive analyses involved calculation of proportions (frequencies) for categorical data, mean and standard deviation for normally distributed continuous data, median for non-normally distributed data and odds ratios as measure of association of risk. Student's t-test and Wilcoxon Rank Sum Test were used to compare continuous normally and non-normally distributed variables, respectively in children with and without DVT.

For the predictive model building for the first objective, logistic regression was utilized. Crude analyses were initially performed between a given potential predictors and the outcome variable (DVT). To simplify interpretation by clinicians in future studies, the significant continuous variables (hemoglobin, platelet count, C - reactive protein) found in the crude analyses were then dichotomized by utilizing interquartile values. When the direction of the relationship was in the negative, the lower 25^{th} percentile was utilized (e.g. platelet count and hemoglobin) and when positive relationship, then the upper 25^{th} percentile (i.e. 75^{th}) was utilized (e.g. CRP). The entire cohort was randomly partitioned using SAS into a training and validation data sets (70% and 30% split, respectively) such that they were mutually exclusive data sets. A predictive model was developed using logistic regression on the training

data set. Potential variables included for consideration for the model were chosen based on prior literature search and if they were factors that could be ascertained at time of admission or within 24-48 of admission. Additionally, factors (potential predictors) from the univariate analyses were included if the respective p value was <0.1. Product terms were created amongst the predictors that were significant in initial main effects model based on the crude analyses. The main effects model was then developed using automated selection methods (forward, backward, and stepwise were all evaluated to determine if the model was the same regardless of selection method). The final predictive model included variables with significance at $p<0.05$. The final main effects predictive model was then evaluated for goodness of fit using the Hosmer-Lemeshow test, calibration plots, and for predictability using the Receiver Operating Curve (ROC) to determine the area under the curve (AUC). The model performance was evaluated using the validation data set and reassessed for predictability using the Receiver Operating Curve to determine the AUC. From the training data set a classification rule using a cut point based on the predicted probability that yielded the best sensitivity and specificity was developed. Then using the cut point from the training data set, the sensitivity and specificity of the model was re-calculated in the validation data set. As a sensitivity analysis to assess whether any predictors of DVT were influenced by the cohort location (Texas versus Georgia) a model was evaluated in which final model plus cohort and its respective product terms were assessed for significance.

For the second objective, estimation of measure of association between DVT and length of hospital stay, first crude analyses (Simple linear regression, Wilcoxon Rank

Sum tests, etc…) were initially performed between a given potential variable and the outcome variable (length of stay). The model was developed using potential variables identified based on prior literature search and if they were factors that were significant in the crude analyses. Subsequently, multivariable linear regression was performed for the main effects model. Interaction terms were also assessed. Regression diagnostics (such as evaluation of outliers and collinearity analyses (correlation, variance inflation factors and tolerance)) were performed for the multivariable linear regression analyses. In the linear regression analyses, non-normally distributed variables were log transformed to become normal and to linearize the relationships, for those variables with values of 0 that were log transformed 0.01 was added to allow for transformation.

Additionally, Cox regression was used to compute the hazard ratio (HR) with accompanying 95% confidence intervals (CI) as measures of relative risk for the endpoint analyses (hospital length of stay which was measured in days from admission to the hospital until discharge home) with main exposure variable of DVT and covariates found significant in the crude analyses. This method was also assessed since Cox regression is a semi-parametric model and no transformation of the variables was needed and there was time to event data for each subject in the dataset thus providing a second method to answer the research question 2. The risk of hospital discharge while alive was modeled with a Cox regression model with in-hospital death was considered a competing event. Because the number of deaths in the dataset was very small relative to the number of patients discharged while alive,

a cause specific hazard approach was used in which the times of occurrence of competing risk (death) were represented by censored times. There was no loss of follow up with regards to hospital length of stay since this was recorded for all patients.

All statistical analyses were performed using SAS® software v9.4 (SAS Institute INC., Cary, NC).

RESULTS

Characteristics of the children admitted with community acquired S. aureus osteomyelitis

Three hundred and eighty children with a mean age of 8.1 years (std. dev 4.7, median 8.1, minimum-maximum: 0.04-18.3 years) were identified as having community acquired *S. aureus* osteomyelitis during the study period. Within the entire study cohort, there were a higher proportion of males compared to females (58.9% vs. 41.1%). Predominant locations of osteomyelitis in order of frequency were the proximal lower extremity, distal lower extremity, pelvic sites, proximal upper extremity, other sites (such vertebrae, scapula, etc.) followed lastly by the distal upper extremity. There were similar numbers of osteomyelitis cases due to Methicillin resistant *S. aureus* (MRSA, 51.6%) compared to Methicillin sensitive *S. aureus* (MSSA, 48.4). There were a total of 47(12.3%) children diagnosed with deep venous thrombosis in the combined cohort, with higher proportion of cases in Texas vs. Georgia (13.7% vs. 10.3%, p=0.001). Overall (in the combined cohort) the median length of hospital stay was 8 days (min-max: 1-73 days). The children who were diagnosed with DVT had a median length of stay of 20 days (min-max: 4-63 days, interquartile range (IQR: 13-35 days) and those without DVT had median length of stay of 8 days (min-max: 1-73 days, IQR: 6-11 days) (p=<0.0001). A comparison of the demographic, osteomyelitis-related and clinical characteristics, and outcomes within each cohort (Texas and Georgia) are outlined in Table 1. The populations were generally similar with the exception of pelvic infections which had a higher frequency of occurrence in the Georgia cohort.

Comparison of demographic and clinical characteristics and laboratory values of children with and without DVT

There was minimal difference in the mean age, in the number of bones affected (single vs. multiple), sex, or mean white blood cell count of children with and without DVT (Table 2). Location of the cohort, location of osteomyelitis, presence of bacteremia, hemoglobin <11 g/dl, platelet count <200 platelets/microliter, and C - reactive protein >24 mg/dl were associated with presence of DVT (Table 2).

Model Development: Training Data Set Predictor Variable Selection

Based on the bivariate analysis as shown in Table 2 as well as performing univariate logistic regression analysis of the possible predictors from the training data set (i.e. 70% of the randomly partitioned full dataset), the factors included in the model development included location of cohort, bacteremia, hemoglobin <11 g/dl, platelet count <200 platelets/microliter, and C-reactive protein <24mg/dl. Given prior scientific knowledge of an increased risk of male predisposition to thrombosis as well as p value with borderline significance, male sex was also included in the multivariable model (Table 3) (6). Ultimately, the final prediction model was found to include the factors bacteremia, platelet count, C-reactive protein, and male gender. Hemoglobin (either as continuous or categorical variable) did not remain significant in the final model (i.e. improve the predictability or significance regardless of the model selection method utilized). Furthermore inclusion back into the model did not improve the predictability of the model. Evaluation of all possible product term variables following hierarchical principles was also examined and no product terms were found to be significant for inclusion in the final model. As a

sensitivity analysis, the effect of cohort location was also assessed on the main effects model (Table 4). The main effects model did not vary significantly despite inclusion of the cohort location. The final estimated main effects model is shown below.

$$\hat{p} = \frac{\exp\left(-2.4357 - X_1(0.8099) + X_2(0.9687) + X_3(0.9566) + X_4(0.1929)\right)}{1 + \exp\left(-2.4357 - X_1(0.8099) + X_2(0.9687) + X_3(0.9566) + X_4(0.1929)\right)}$$

Where

- p= probability of deep venous thrombosis
- X_1= Bacteremia (if present =yes (1))
- X_2= Platelets (if <200 /microliter =yes (1))
- X_3= C-reactive protein (if >24mg/dl =yes (1))
- X_4= Male sex (yes=1)

Model Development: Training Data Set Predictive Model Calibration/ Assessment

Several methods were used to assess model performance including Goodness of Fit testing using the Hosmer-Lemeshow test, performing calibration plots as well as evaluation of the ROC. The goodness of fit test statistic was not significant (p=0.67) thus the null hypothesis that the model fits the training data set was accepted. The calibration plot (Figure 1) demonstrates that the predicted vs. observed proportions within each of the groups is similar (falls close to the 45 degree line) indicating good

model fit. Evaluation of the predictability of the model using receiver operating curve (Figure 2) produced and AUC of 0.85.

Model Validation: Validation Data Set Predictive Model Calibration/Assessment

Using the validation data set, the predictive model was assessed using an independent data set (the 30% of the randomly partitioned cohort). The receiver operating curve produced an AUC of 0.8 (Figure 3).

Derivation of the classification rule, sensitivity and specificity of the final model

A cut point for the predicted probability was based upon the highest combination of sensitivity and specificity. In the training data set, this cut point was for the predicted probability > 0.11 which yielded at sensitivity of 85.7% with specificity of 70.6% (Table 5A). Using the same cut point in the validation data set yielded a sensitivity of 58% and specificity of 79% (Table 5B). The classification rule using the final estimated model (shown above) is when estimated p value is greater than 0.11, then patient is a risk of developing DVT while hospitalized with *S. aureus* osteomyelitis.

Crude analyses of factors associated with length of stay

There were statistically significant differences in the demographic, clinical characteristics/diagnoses and laboratory values with regards to median length of

stay (gender, location of cohort, proximal location of osteomyelitis, presence of multiple bones infected, DVT diagnosis, admission to the ICU, presence of MRSA and if bacteremia was diagnosed (Table 6). Those factors with the greatest difference in median length of stay were presence of DVT and ICU admission (difference of 12 and 14 days, respectively if DVT or ICU admission occurred vs. did not occur). Simple linear regression analysis showed that age at diagnosis and sex were not significantly associated with length of stay (Table 7).

Multivariable analysis of factors associated with length of stay

In multivariable linear regression analysis our exposure variable, DVT, and covariates, ICU admission, presence of MRSA, bacteremia, multiple sites of OM, and location of the cohort, remained associated with the median length of stay (Table 8). The other factors from crude analyses were placed back in the model to assess confounding of the exposure variable of interest, DVT, and there was no change of the beta estimate (for DVT) of more than 2% so no potential confounding variables were not put back in the model. Regression diagnostics for the evaluation of interaction terms, outliers, collinearity, etc. were performed. There were no interaction terms that were significant. Additionally, there were no significant outliers needed to be excluded nor was there evidence of collinearity. The final model for association of DVT and other clinically relevant factors and median length of stay is as follows.

$$\ln(y) = \mathrm{B0} + B1\,(DVT) + B2\,(ICU) + B3\,(MRSA) + B4\,(Bacteremia) +$$

$$B5\,(MultipleOM) + B6\,(Location)$$

Where y = length of stay

Since the outcome of length of stay was not normally distributed and was log transformed comparison of presence vs. absence of the factor of interest with regards to the outcome becomes a multiplicative model. The main result of these analyses showed in comparing 2 children, one with DVT vs. one without DVT controlling for ICU admission, MRSA, bacteremia, and multiple sites of osteomyelitis statuses as well as location, the hospital length of stay was increased by 65% or an estimated factor of 1.65.

Multivariable Cox regression analysis of factors associated with time to discharge (hospital length of stay)

Multivariable Cox regression analysis revealed the same factors that were significant in the linear regression model (Tables 8 (linear regression model) and 9 (Cox model)). The children with *S. aureus* osteomyelitis who developed DVT were shown to have one half of the hazard of those without DVT of being discharged home (i.e. have longer length of hospital stay), with a hazard ratio of 0.46 (95% CI, .82–1.09) after adjusting for ICU admission, methicillin sensitivity, bacteremia status, number of sites of OM (single/multiple) and location of cohort. Other factors found to be significantly associated with decreased risk of discharge home were ICU admission, methicillin sensitivity, bacteremia status, and number of sites of OM (single/multiple) (table 9). Location of the cohort, specifically the Texas Children's Hospital cohort, was the only factor that had increased risk of prolonged stay with a HR (1.3, 95% CI 1.06-1.59).

DISCUSSION/CONCLUSIONS

DVT in children is a relatively rare occurrence in hospitalized children with estimated incidence between 58-70/10000 hospital admissions (41, 42). The occurrence of DVT during hospital admission has been associated with increased length of stay, increased costs, increased morbidity and mortality (43). In adults who have increased prevalence of DVT compared to children, thromboprophylaxis strategies are often very broad and able to be implemented on more generalizable scale (44-46). In pediatrics, the implementation of broad thromboprophylaxis or even screening for DVT is not cost effective and has potential for parental and patient anxiety. This research study sought to 1) develop a predictive model based on demographic attributes, clinical characteristics, and/or laboratory values obtained early in admission to identify which children with *S. aureus* osteomyelitis are at risk of being diagnosed with DVT and 2) further refine the measure of association between children with *S. aureus* osteomyelitis who develop DVT and length of hospital stay as well as to estimate the role of other potential clinical factors in this patient population with regards to length of hospital stay.

The contribution of this work primarily is that the predictive model provides a framework to determine a subset of children with *S. aureus* osteomyelitis who may develop DVT and could be potentially targeted for earlier screening for DVT or receive DVT prophylaxis from early in their hospital stay. If DVTs in this population of children could be prevented, there could be potential to shorten length of hospital stay which in turn could decrease healthcare costs as well as decrease morbidity

from long term sequela of DVT. The key findings of this study were to show that a simple predictive model could be developed for identifying children with osteomyelitis due to *S. aureus* with increased risk of developing DVT while admitted to the hospital. The specific predictors included having bacteremia, a platelet count of < 200 platelets per microliter, C - reactive protein of > 24 mg/dl at time or within 24 hours of admission, and male gender.

The second key finding of this study was to show that DVT was also associated with length of stay. Two methods, linear regression and Cox regression modeling, demonstrated the association between DVT and length of hospital stay. Notably, the linear regression model demonstrated a 65% increased length of stay in children with S. aureus osteomyelitis with DVT compared to those without DVT. Using Cox regression, the discharge rate in children with DVT was half that of children without DVT (i.e. those with DVTs had a longer length of stay). The additional factors found to be associated with increased length of hospital stay in this population of children type of infection (those with MRSA more likely to have longer length of stay), ICU admission, presence of bacteremia, multiple (versus single site of osteomyelitis) and location of cohort (Texas versus Georgia).

Over the last decade, the link between osteomyelitis due to Staphylococcal infections and deep venous thrombosis has been described. Numerous case reports and case series have described this association. Several groups have tried to further characterize the association, however have been limited by the retrospective nature of the data collection. There have been a few prospective cohorts that have

attempted to differentiate between children who developed DVT and those that did not develop DVT however were limited by their small sample sizes (7, 9). To date this study represents the largest cohort of children with community acquired *S. aureus*. The proportion of children with deep venous thrombosis in our cohort (12.7%) was similar to other reports though on the lower to middle of the reported range of 6-30% (7-9). Mortality in this cohort is lower than reported by others with a survival of >99% (8, 9, 11). Additionally, research to date using multivariable modeling in looking at factors associated with length of stay or specifically estimating the measure of association between DVT and length of hospital stay has not been performed in this patient population with the exception of one study (4). This study provides further evidence that DVT increases hospital length of stay and provides justification for further investigation of prevention and/or early identification of DVT to reduce hospital length of stay.

Limitations of the study include differences in the cohorts in terms of capturing of all eligible subjects. The Texas cohort was identified as part of a prospective study while the Georgia cohort was collected using ICD-9 coding with its known biases (47, 48). Despite the prospective identification of the *S. aureus* patients and entry into a registry in the Texas Children's Hospital cohort, not all data of interest in this study was prospectively collected and lead to some missing data. Overall there was little missing data (<10% in 1 of the variables of interest, no other missing data) since these variables were selected because they are generally considered standard of care testing when osteomyelitis is suspected.

In developing the model, one limitation could include small number of events of the outcome of interest. However there were enough events per (predictive) variables utilized per published literature focused on risk prediction model development (49, 50). The sensitivity and specificity of the predictive model were moderate and could be improved if additional variables could be identified or potentially if sample size was larger to have a larger number of the outcome of interest (DVT). The predictive value of a model depends on disease prevalence (51) and though several studies have reported the prevalence and/or incidence of DVT ranging from 10-30% no study has prospectively screened patients for DVT and in this largest cohort of patients the prevalence was approximately 12%. The robustness of such a prediction model cannot be assessed in single cohort, especially given the challenges and limitation with retrospective data. External validation in a prospective cohort is needed to assess the true performance of risk prediction model in a standardized way (51, 52). Another potential predictor that was not able to be studied, which could be different between the geographical cohorts, was race. There is a distinct racial diversity between the Texas vs. Georgia cohort but race was not routinely collected in the Texas cohort and as such could not be evaluated in this study.

Future directions based upon this research include validating the model by performing a pilot prospective observational study using the risk prediction model and performing screening Doppler ultrasounds on all patients with *S. aureus* OM. This would be a novel model in pediatrics and validation is an important undertaking prior to disseminating this model to the general pediatrics population. Additional prospectively collected variables (including race, family/personal history

of DVT, etc…) could be collected and the predictive model could be further refined. Ultimately based upon this research and the pilot study, a multi-center randomized clinical trial could be developed to compare the use of prophylactic anticoagulation vs. standard of care in children predicted to be at high risk of DVT for the outcome of hospital length of stay.

In conclusion, a simple model for predicting deep venous thrombosis in children with community acquired *S. aureus* osteomyelitis was developed with moderate sensitivity and specificity. The predictors in this model included presence of bacteremia, elevated levels of C- reactive protein (>24mg/dl), platelet counts on lower end of normal (<200 platelets per microliter), and male sex. Additionally, children with *S. aureus* osteomyelitis associated DVT have significantly increased length of hospital stay compared to those without DVT (specifically increased length of stay by 65% using a linear regression model or approximately double using a Cox regression model). Additional factors associated with increased length stay also included the presence of methicillin resistance *S. aureus*, ICU admission, bacteremia, multiple infected bones, and location of cohort.

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TABLE 1. Demographic, clinical characteristics, and outcomes of children with *S. Aureus* osteomyelitis admitted to TCH (n=226) and CHOA (n=156) from 2005-2010 (n=382)

	TCH Number of subjects (%)	**CHOA Number of subjects (%)**
Demographic		
Male	140 (62)	86 (55)
Age (years, mean, SD)	8.4 (4.9)	7.7 (4.5)
Osteomyelitis Related Factors		
Location		
Upper Extremity		
Proximal	24 (10.5)	14 (9)
Distal	7 (3)	7 (4.5)
Lower Extremity		
Proximal	90 (40)	57 (36.5)
Distal	70 (31)	47 (30)
Pelvis	24 (10.5)	27 (17.4)
Other	11 (5)	4 (2.6)
MRSA	116 (51)	69 (44)
Clinical Data		
Bacteremia	140 (62)	101 (64)
Septic Pulmonary Emboli	22 (9)	18 (12)
Outcomes		
Deep Venous Thrombosis	31 (14)	16 (10)
ICU admission	33 (15)	21 (14)
Length of Stay days, median (min-max)	9 (1-73)	8 (3-63)
Survival	225 (99.6)	156 (100)

TCH-Texas Children's Hospital, CHOA- Children's Healthcare of Atlanta
SD- standard deviation
MRSA- Methicillin Resistant *S. Aureus*
ICU- Intensive Care Unit

TABLE 2. Measures of association between demographic, osteomyelitis related, and laboratory factors and presence of DVT

Factors	**Deep Venous Thrombosis (n)** *		**P value**
	Present	**Absent**	
Age (years, mean)	8	8.1	0.88
Gender			
Male	33	192	0.1
Female	14	143	
Location of cohort			
Texas	31	195	**0.001**
Georgia	16	140	
Location of Osteomyelitis ^			
Proximal	36	200	**0.03**
Distal	11	135	
Number of Bones			
Multiple	6	25	0.22
Single	41	310	
Bacteremia			
Present	40	201	**0.002**
Absent	7	134	
Laboratory Related#			
WBC	11.8	12	0.11
Hemoglobin			
Low (<11)	21	90	**0.01**
Normal (≥11)	26	245	
Platelet			
Low (<200)	29	81	**<0.0001**
Normal (≥200)	18	254	
C- Reactive Protein			
> 24 mg/dl	20	278	**<0.0001**
≤ 24 md/dl	27	62	

* For the entire cohort of 382 subjects

^ Location of osteomyelitis, proximal: proximal upper and lower extremity and pelvis, distal= all other locations

WBC= white blood cell count normal range ~5-15K WBC per microliter, Hemoglobin normal range ~11.5-16 g/dl, Platelet count normal range 150-450,000 platelets/microliter

TABLE 3. Model development: evaluation of predictors

Factors	**Univariate Association Training data set Odds Ratio (CI)***	**Multivariable Association Training data set Odds Ratio (CI)**
Age (years, mean)	1 (0.92-1.09)	-
Gender		
Male	1.24 (0.55-2.8)	1.5 (0.6-3.8)
Female	reference	
Location of cohort		
Texas	0.63(0.28-1.45)	-
Georgia	reference	
Location of Osteomyelitis^		
Proximal	1.61 (0.68-3.8)	-
Distal	reference	
Number of Bones		
Multiple	0.82 (0.18-3.7)	-
Single	reference	
Bacteremia		
Present	**7.95 (1.86-34.3)**	**5.1 (1.1-23.4)**
Absent	reference	
Laboratory Related#		
WBC	1.03 (0.97- 1.1)	-
Hemoglobin		
Low (<11)	2.12 (0.95-4.73)	Not significant
Normal (≥11)	reference	
Platelet		
Low (<200)	**5.94 (2.59-13.6)**	**6.94 (2.74-17.6)**
Normal (≥200)	reference	
C- Reactive Protein		
> 24 mg/dl	**7.02 (3.1-16.15)**	**6.77 (2.67-17.2)**
≤ 24 md/dl	reference	

CI: 95% confidence interval

* If variable significant at p< 0.1 with crude analyses then used in the multivariable model or if previously shown to be related to the outcome in literature

^ Location of osteomyelitis, proximal: proximal upper and lower extremity and pelvis, distal= all other locations

For model development also categorized the significant continuous variables in the model to assist in a clinically relevant manner, used the upper or lowed 25% quartile based on direction of association

Figure 1. Calibration plot used in assessing the final predictive model for study question 1

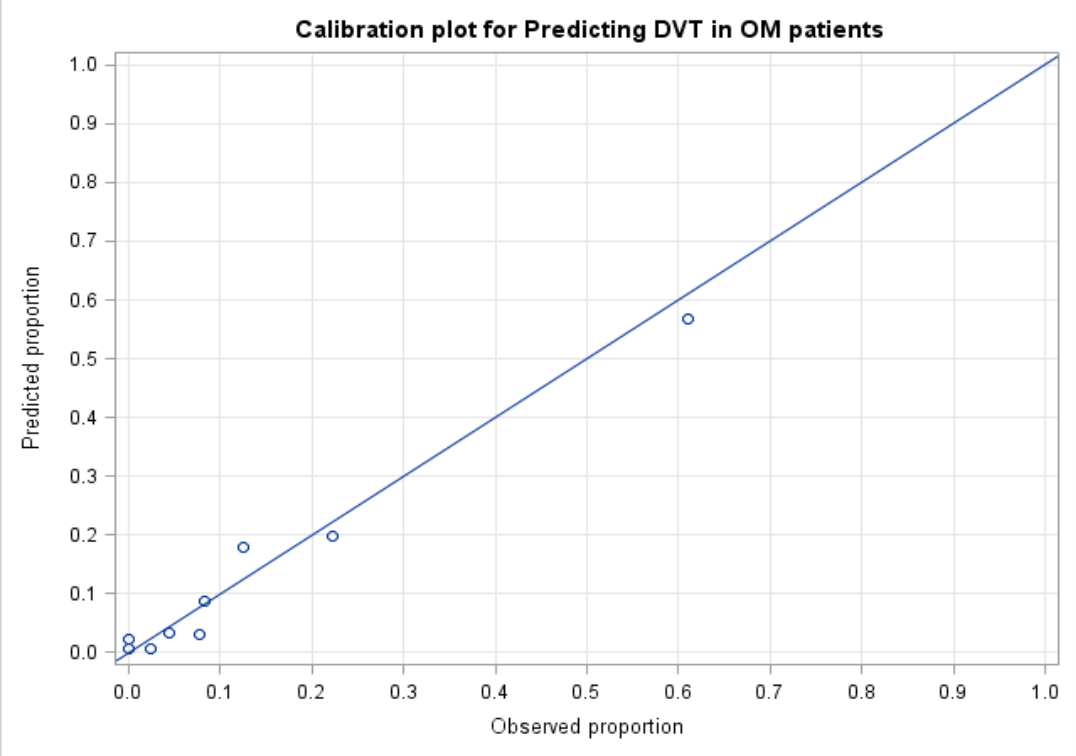
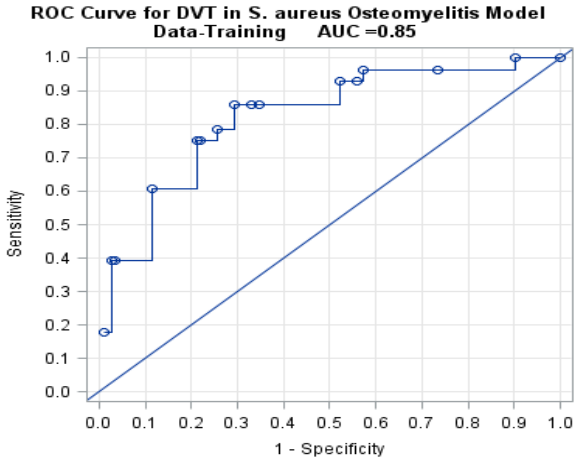
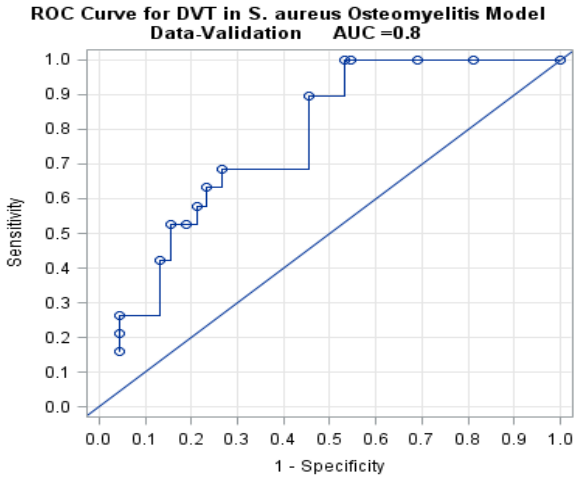


Figure 2. Receiver Operating Curves for the predication model for the training data set (Panel A, AUC 0.85), validation data set (Panel B, AUC 0.8) and a comparison graph of the training and validation data sets ROC curves (Panel C)

A.



B.



C.

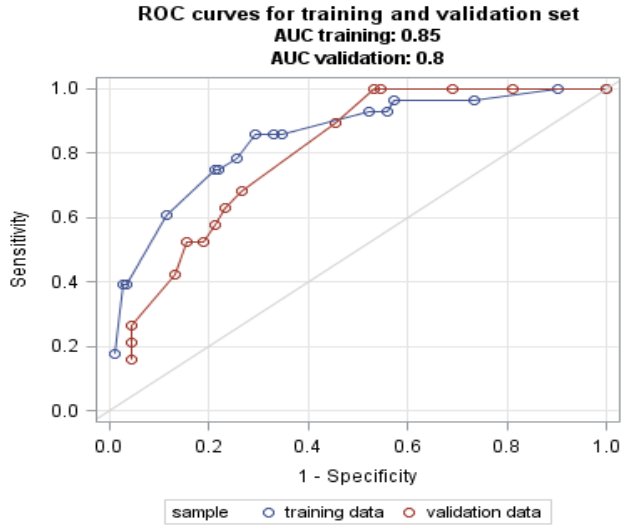


TABLE 4. Sensitivity analysis: evaluation of significant predictors by cohort location

Factors	**β estimate (SE)**	**P value**
Male sex (female= reference)	0.21 (0.25)	0.4
Location of cohort		
Texas	0.09 (0.4)	0.82
Georgia	Reference	
Bacteremia		
Present	0.76(0.39)	0.04
Absent	Reference	
Laboratory Related#		
Platelet		
Low (<200)	0.95 (0.25)	0.0001
Normal (≥200)	Reference	
C- Reactive Protein		
> 24 mg/dl	0.93(0.25)	0.0002
≤ 24 md/dl	Reference	
Location * bacteremia	-0.27(0.39)	0.5
Location * platelet	-0.14(0.25)	0.57
Location * c-reactive protein	-0.14(0.25)	0.58

SE: standard error

TABLE 5. Sensitivity and specificity of the final predictive model. Table 4A. Classification table using a cut point predicted probability /classification rule of 0.11 from our training data yields 85.7% sensitivity and 70.6% specificity. Table 4B. Classification table using the same cut point of 0.11 from our training data set yields 58% sensitivity and 79% specificity in our validation data set.

A.

	Observed DVT Absent	**Observed DVT Present**	**Total**
Predicted DVT Absent	173	4	177
Predicted DVT Present	72	24	96
Total	245	28	273

B.

	Observed DVT Absent	**Observed DVT Present**	**Total**
Predicted DVT Absent	71	8	79
Predicted DVT Present	19	11	30
Total	90	19	109

TABLE 6. Crude analysis of factors related to hospital length of stay

	Median Length of Stay (days)	P value
Gender		
Male	9	**0.04**
Female	8	
Location of cohort		
Texas	9	**0.002**
Georgia	8	
Osteomyelitis Related		
Bone Location*		
Proximal	9	**0.0006**
Distal	7	
Multiple bones	14	**<0.0001**
Single bone	8	
Clinical Factors		
Deep Venous Thrombosis		
Present	20	**<0.0001**
Absent	8	
ICU Admission		
Yes	22	**<0.0001**
No	8	
MRSA		
Yes	11	**<0.0001**
No	7	
Bacteremia		
Yes	10	**<0.0001**
No	6	

* Location of osteomyelitis, proximal: proximal upper and lower extremity and pelvis, distal= all other locations
ICU- Intensive Care Unit
MRSA- Methicillin Resistant *S. Aureus*

Table 7. Simple linear regression evaluating association between ln length of stay and DVT and other relevant variables

	β Estimate	**Standard Error**	**$e^{\hat{}\beta}$**	**P value**
Demographic				
Age	0.002	0.007	1.002	0.78
Male sex (ref = female)	0.14	0.07	1.15	0.05
Location of cohort: Georgia (ref = Texas)	-0.18	0.07	0.84	**0.01**
Osteomyelitis Related				
Proximal Bone Location (ref = distal)	0.21	0.06	1.23	**0.002**
Multiple bones involved (ref = single)	0.53	0.12	1.7	**<0.001**
Clinical Factors				
Deep Venous Thrombosis (ref= absent)	0.93	0.09	2.53	**<0.001**
ICU Admission (ref = no)	0.94	0.08	2.56	**<0.001**
MRSA (ref = MSSA)	0.43	0.06	1.54	**<0.001**
Bacteremia (ref =no)	0.45	0.07	1.57	**<0.001**

Ref= reference category
ICU- Intensive Care Unit
MRSA- Methicillin Resistant *S. Aureus*
MSSA- Methicillin Sensitive *S. Aureus*

Table 8. Multivariable linear regression evaluating association between ln length of stay and DVT and other relevant variables

Factors	**β Estimate (95% CI)**	**$e^{\hat{\beta}}$**	**Partial R^2**	**P value**
DVT (ref= no)	0.5 (0.32-069)	1.65	0.05	<0.0001
ICU admission (ref= no)	0.52 (0.34-0.7)	1.68	0.24	<0.0001
MRSA (ref= MSSA)	0.25 (0.15-0.36)	1.28	0.06	<0.0001
Bacteremia(ref= no)	0.23(0.12-0.34)	1.26	0.03	<0.0001
Multiple sites of OM (ref= single)	0.35 (0.16-0.54)	1.42	0.02	<0.0001
Location of cohort (ref= Texas)	-0.14 (-0.24- -0.03)	0.87	0.01	<0.0001

CI- Confidence Interval
DVT- Deep Venous Thrombosis
ICU- Intensive Care Unit
MRSA- Methicillin Resistant *S. Aureus*
OM- Osteomyelitis

Table 9. Cox regression analysis with factor specific hazard ratios adjusted for all of the other factors listed and time to discharge home (i.e. hospital length of stay)

Factors*	**Hazard Ratio (95% CI)**	**P value**
DVT (ref= no)	0.47 (0.34-0.67)	<0.0001
ICU admission (ref= no)	0.47 (0.33-0.66)	<0.0001
MRSA (ref=MSSA)	0.61 (0.49-0.75)	<0.0001
Bacteremia (ref=no)	0.63(0.51-0.79)	<0.0001
Multiple sites of OM (ref=single)	0.59 (0.4-0.86)	0.007
Location of cohort (ref=Texas)	1.3 (1.06-1.59)	0.01

* Ref= reference categories
CI- 95% Confidence Interval
DVT- Deep Venous Thrombosis
ICU- Intensive Care Unit
MRSA- Methicillin Resistant *S. Aureus*
OM- Osteomyelitis