Published in final edited form as:

Pediatr Crit Care Med. 2015 July ; 16(6): 497–504. doi:10.1097/PCC.0000000000000409.

FACTOR VIII MAY PREDICT CATHETER-RELATED THROMBOSIS IN CRITICALLY ILL CHILDREN: A PRELIMINARY STUDY

Edward Vincent S. Faustino, MD, MHS¹, Simon Li, MD, MPH², Cicero T. Silva, MD³, Matthew G. Pinto, MD², Li Qin, PhD⁴, Joana A. Tala, MD⁵, Henry M. Rinder, MD^{6,7}, Gary M. Kupfer, MD^{1,8}, and Eugene D. Shapiro^{1,9,10} for the Northeast Pediatric Critical Care Research Consortium

¹Department of Pediatrics, Yale School of Medicine

²Pediatric Intensive Care Unit, Maria Fareri Children's Hospital

³Department of Diagnostic Radiology, Yale School of Medicine

⁴Yale Center for Analytical Sciences, Yale School of Public Health

⁵Pediatric Intensive Care Unit, Yale-New Haven Hospital

⁶Department of Laboratory Medicine, Yale School of Medicine

⁷Department of Internal Medicine, Yale School of Medicine

⁸Department of Pathology, Yale School of Medicine

⁹Department of Epidemiology of Microbial Diseases, Yale School of Public Health

¹⁰Department of Investigative Medicine, Yale Graduate School of Arts and Sciences

Abstract

OBJECTIVE—If we can identify critically ill children at high risk for central venous catheter-related thrombosis, then we could target them for pharmacologic thromboprophylaxis. We determined whether factor VIII activity or G value was associated with catheter-related thrombosis in critically ill children.

DESIGN—Prospective cohort study

SETTING—Two tertiary academic centers

Reprint request author: Edward Vincent S. Faustino, MD, MHS; 333 Cedar Street, New Haven, CT, USA 06520; vince.faustino@yale.edu; (v) 203-785-4651; (f) 203-785-7194. No reprints will be ordered..

Northeast Pediatric Critical Care Research Consortium Investigators: Lee A. Polikoff, MD, Department of Pediatrics, Yale School of Medicine; Kenneth Baker, MD, Department of Diagnostic Radiology, Yale School of Medicine; Ann Bisland, RN, Department of Pediatrics, Yale School of Medicine; Adele R. Brudnicki, MD, Department of Radiology, Maria Fareri Children's Hospital; Michelle Kim, BS, Pediatric Intensive Care Unit, Maria Fareri Children's Hospital

Institutions where work was performed: Yale-New Haven Children's Hospital and Maria Fareri Children's Hospital

The other authors do not have any real or perceived conflicts of interest.

PATIENTS—We enrolled children <18 years old who were admitted to the pediatric intensive care unit within 24 hours after insertion of a central venous catheter. We excluded children with a recently diagnosed thrombotic event or those anticipated to receive anticoagulation. Children with thrombosis diagnosed with surveillance ultrasonography on the day of enrollment were classified as having prevalent thrombosis. Those who developed catheter-related thrombosis thereafter were classified as having incident thrombosis.

INTERVENTIONS—None

MEASUREMENTS AND MAIN RESULTS—We enrolled 85 children in the study. Once enrolled, we measured factor VIII activity with one-stage clotting assay and determined G value with thromboelastography. Of those enrolled, 25 had incident and 12 had prevalent thromboses. The odds ratio for incident thrombosis per standard deviation increase in factor VIII activity was 1.98 (95% confidence interval: 1.10-3.55). The area under the receiver operating characteristic curve was 0.66 (95% confidence interval: 0.52-0.79). At factor VIII activity >100 IU/dL, which was the optimal threshold identified using Youden index, sensitivity and specificity were 92.0% and 41.3%, respectively. The association between factor VIII activity and incident thrombosis remained significant after adjusting for important clinical predictors of thrombosis (odds ratio: 1.93; 95% confidence interval: 1.10-3.39). G value was associated with prevalent but not with incident thrombosis.

CONCLUSION—Factor VIII activity may be used to stratify critically ill children based on their risk for catheter-related thrombosis.

Keywords

biomarker; clotting factor; intensive care unit; platelet; thromboelastography; venous thromboembolism

INTRODUCTION

Deep venous thrombosis (DVT) is a significant problem in critically ill children. The most important risk factor for DVT is the presence of a central venous catheter (CVC). DVT develops in approximately 17.5% of critically ill children with CVC (1). The risk for CVC-related DVT is low within 24 hours after insertion of the CVC but significantly increases thereafter (2). Although routinely used in critically ill adults, pharmacologic thromboprophylaxis is not recommended in children with CVC due to paucity of studies to support this practice (3, 4). It would be ideal to provide thromboprophylaxis only to critically ill children at high risk for CVC-related DVT. At present, we do not have any tests to identify these children.

CVC, specifically the nontunneled type, is usually inserted when children are critically ill and likely hypercoagulable (5, 6). Coagulation factors, particularly factor VIII, increase during critical illness (7). Factor VIII activity >150 IU/dL is associated with 2.6 to 4.8-fold odds of developing DVT in adults (8). Overall clot strength (*i.e.*, G value), as measured with thromboelastography (TEG), reflects platelet activity (9, 10). G value >12.4 kdyn/cm² is associated with 30-fold odds of developing DVT in adults admitted to the surgical intensive care unit (ICU) (9).

We hypothesized that factor VIII activity or G value, when measured soon after insertion of a nontunneled CVC, could be used to stratify critically ill children based on their risk for CVC-related DVT so that in the future, we may target those at high risk for thromboprophylaxis. To test this hypothesis, we determined whether either of these biomarkers was associated with a future or incident CVC-related DVT in critically ill children. *Post-hoc*, we explored whether either of them was associated with a current or prevalent DVT to determine whether they could be used to screen critically ill children who would need further testing to diagnose DVT.

MATERIALS AND METHODS

Study Design

We conducted a prospective cohort study from October 2012 to November 2013 in which we enrolled critically ill children admitted to the pediatric ICUs at Yale-New Haven Children's Hospital (YNHCH), New Haven, CT and New York Medical College-Maria Fareri Children's Hospital, Valhalla, NY. The institutional review boards at both institutions approved the study.

Study Subjects

Children <18 years old with a nontunneled CVC inserted within the previous 24 hours were eligible. We excluded children with documented thromboembolic event within the past 3 months. We also excluded children who were expected to receive anticoagulants (except for unfractionated heparin at doses to maintain the patency of the CVC), recombinant factor VIIa or factor VIII; on comfort measures only; or, scheduled for discharge from the ICU on the day of screening (1, 11). We did not exclude children who were expected to receive other hemostasis support, particularly fresh frozen plasma or cryoprecipitate, because this was not associated with CVC-related DVT in our prior study (1).

Study Procedures

After obtaining consent, citrated venous blood was drawn from the CVC and centrifuged at 4°C for 10 minutes at 3000 g to obtain platelet-poor plasma, which was frozen at -70°C until assayed. Factor VIII activity was measured with a one-stage clotting assay (Actin® FSL, Dade Behring, Marburg, Germany) at the Department of Laboratory Medicine at YNHCH (12). As a standard procedure, heparin contamination was confirmed to be absent by baseline partial thromboplastin time prior to measurement of factor VIII activity. Kaolin-activated TEG with and without heparinase was performed locally on citrated whole blood using a TEG® 5000 Thromboelastograph® Hemostasis Analyzer (Haemonetics Corporation, Braintree, MA) according to the manufacturer's recommendations, which had been described elsewhere (9, 10). Trained research personnel from each ICU processed all samples at 37°C within 2 hours of collection. Aside from G value, TEG also evaluates reaction time, kinetics time, angle, maximum amplitude and coagulation index that correspond to different aspects of coagulation (10). We tested all subjects for factor V Leiden and prothrombin G20210A mutations, the 2 most common inherited thrombophilias (13).

On the day of enrollment, we performed ultrasonography on the central vein where the CVC was inserted and on both lower extremities, the most common sites of non-CVC-related DVT (4, 14). We repeated the ultrasonography on the site of insertion of the CVC within 24 hours of its removal or of the subject's discharge from the ICU, at 28 days after insertion of the CVC (if the CVC had not been removed by that time and the subject remained in the ICU), when the clinical team suspected CVC-related DVT, when an anticoagulant was started, or when the subject was unlikely to survive for the next 24 hours. Blinded, certified radiology technicians at each hospital performed the ultrasonography using Philips® iU22® Ultrasound Imaging Platform (Universal Diagnostics Solution, Oceanside, CA) with 7-15 MHz linear transducers.

DVT was diagnosed based on the presence of at least 2 of the following: intravenous echogenic material, inability to compress the vein, and abnormal Doppler pattern (1, 2). Certified pediatric radiologists reviewed all ultrasonographic images blindly, independently and in duplicate. A 3rd pediatric radiologist arbitrated differences in readings. Consistent with studies in critically ill adults, we classified subjects with DVT detected on the day of enrollment as having prevalent DVT (15). Those who did not have DVT on the day of enrollment but developed DVT thereafter were classified as having incident DVT.

Statistical Analysis

Differences between groups were determined using chi-square or Fisher exact test for categorical variables and Mann-Whitney test for continuous variables. To determine the association between incident CVC-related DVT and the biomarkers, we excluded subjects with prevalent DVT in the analysis. We performed logistic regression to calculate the odds ratio (OR) associated with factor VIII activity and with G value for incident DVT. To determine the performance of each biomarker, we calculated the area under the receiver operating characteristic curves (AUC) and its 95% confidence interval (CI). We compared the AUC of the biomarkers alone with the AUC of their combination using the method of DeLong, DeLong and Clarke-Pearson (16). We estimated the sensitivity and specificity of each biomarker at their optimal thresholds identified using Youden index and at previously reported thresholds (17). Youden index is a summary measure that represents the maximum potential effectiveness of a biomarker. We adjusted the association for age, center effect, recent surgery within 3 months prior to enrollment and characteristics of the subject or of the CVC that were different at $p < 0.05$ between children with and without incident DVT (15). Subjects' ages were categorized into <1 year old, 1-13 years old and >13 years old to reflect the age-related distribution of DVT (1). Center effect would account for differences in practice related to the care of the CVC between ICUs that might affect the risk for DVT. We conducted similar analyses between subjects with and without prevalent DVT. All statistical analyses were conducted using Stata 13 (StataCorp, College Station, TX). A 2-sided p value <0.05 was considered statistically significant.

Based on prior studies, we determined that with 85 children we would have 90% power to detect a change corresponding to an OR of at least 2.5 for every standard deviation (SD) increase in factor VIII activity or G value (1, 9, 18). We stopped the study after enrolling 85

subjects (Figure 1). At that point, the frequency of incident DVT (25/71; 35.2%) was double the frequency of 17.5% that we used to calculate the sample size (1).

RESULTS

We enrolled 85 of 121 eligible children. Overall, 37 subjects had DVT of which 25 were incident and 12 were prevalent (Figure 1). Of the prevalent DVT, one was in the lower extremity unrelated to a CVC. Two subjects did not have repeat ultrasonography because of unexpected discharge from the hospital. The agreement in the readings between radiologists was 93.9%. We did not find any difference in the characteristics of the subjects and of the CVC, co-interventions and laboratory results between subjects with and without incident DVT (Table 1). In contrast, subjects with prevalent DVT were older and had bigger CVCs than those without DVT (Table 2). The frequency of factor V Leiden and prothrombin G20210A mutations were not different between those with and without incident or prevalent DVT. Factor VIII activity was measured in all 85 subjects except for one who had incident DVT whose specimen clotted. G value and other TEG parameters were measured in all subjects. Because the values measured with and without heparinase were not significantly different, we presented those measured without heparinase. The average time from insertion of the CVC to blood draw was 19.8 ± 8.4 hours (mean $\pm$ SD).

Association of Factor VIII Activity, G Value and Incident DVT

Factor VIII activity was associated with incident CVC-related DVT. For every SD increase in factor VIII activity measured in the study population, the OR for incident DVT was 1.98 (95% CI: 1.10-3.55) (Figure 2A). The AUC of factor VIII activity was 0.66 (95% CI: 0.52-0.79) (Figure 3A). Combining factor VIII activity and G value did not significantly change the AUC (0.67, 95% CI: 0.54-0.80; $p=0.58$). At the optimal threshold of >100 IU/dL, the sensitivity of factor VIII activity was 92.0% (95% CI: 74.0%-99.0%) while its specificity was 41.3% (95% CI: 27.0%-56.8%). The sensitivity and specificity of factor VIII activity at the previously reported threshold of >150 IU/dL were 36.0% (95% CI: 18.0%-56.5%) and 80.4% (95% CI: 66.1%-90.6%), respectively. When adjusted for age, center effect and recent surgery, the association remained significant (OR: 1.93; 95% CI: 1.10-3.39). The OR for incident DVT also remained significant when the 2 subjects with no exit ultrasonography were analyzed as having (OR: 1.93, 95% CI: 1.08-3.43) or not having (OR: 1.96, 95% CI: 1.11-3.47) incident DVT. G value and the other TEG parameters were not associated with incident DVT (Figure 2A and 3B).

Association of Factor VIII Activity, G Value and Prevalent DVT

Unlike with incident DVT, factor VIII activity was not associated with prevalent DVT (Figure 2B and 3C). G value, on the other hand, was associated with prevalent DVT. For every SD increase in G value measured in the study population, the OR for prevalent DVT was 2.21 (95% CI: 1.19-4.10) (Figure 2B). The AUC was 0.68 (95% CI: 0.504-0.87) (Figure 3D). Combining G value and factor VIII activity did not significantly change the AUC (0.69, 95% CI: 0.51-0.88; $p=0.46$). The sensitivity of G value at the optimal threshold of >11.0 kdyn/cm² was 50.0% (95% CI: 21.1%-78.9%) with a specificity of 87.7% (95% CI: 77.9%-94.2%). The sensitivity and specificity of G value at the previously reported

threshold of >12.4 kdyn/cm² were 33.3% (95% CI: 9.9%-65.1%) and 94.5% (95% CI: 86.6%-98.5%), respectively. When adjusted for age, center effect, recent surgery and size of the CVC, the OR for prevalent DVT was 2.46 (95% CI: 1.18-5.13). The other TEG parameters were not associated with prevalent DVT (Figure 2B).

DISCUSSION

Our preliminary study is the first to evaluate biomarkers in predicting CVC-related DVT in critically ill children. Previous studies investigated the association of CVC-related DVT and inherited thrombophilias (13, 19). We found that factor VIII activity is associated with incident CVC-related DVT while G value is associated with prevalent DVT. The associations remained significant after adjusting for important predictors of CVC-related DVT. These findings are important because we may have found a test to stratify critically ill children based on their risk for CVC-related DVT. Currently, we do not have any tests to stratify these children. We may be able to use factor VIII activity, at a threshold of >100 IU/dL, to identify critically ill children who would or would not need pharmacologic thromboprophylaxis.

The relationship between factor VIII activity, platelet activity and DVT is well described in adults with spinal cord injury (20). Factor VIII activity increases early in the course after injury while platelet activity does not increase until before DVT is detected (20, 21). Consistent with these reports, we showed that factor VIII activity was elevated in critically ill children on the day of enrollment when they did not have a DVT and before the incident DVT developed. On the other hand, G value, which is a measure of platelet activity, is elevated in those with prevalent DVT (10, 20). Based on our study design, we cannot determine whether the elevation in G value was a cause or a consequence of the DVT. However, in adults with spinal cord injury, increased platelet activity precedes the DVT (20). In contrast to our findings, some studies in adults and children report that factor VIII activity is elevated in those with prevalent DVT (8, 11, 22). These studies, however, measured factor VIII activity later in the course of illness. It is our conjecture that some form of consumptive coagulopathy might have occurred in our subjects with prevalent DVT that led to a reduction in factor VIII activity (23). D-dimer levels might have provided evidence of consumption but we did not measure them because they did not predict DVT in critically ill adults (14). Kashuk *et al* reported in a retrospective study that elevated G value predicted DVT in critically ill adults admitted to the surgical ICU, which is contrary to our results (9). They analyzed the maximum G value at any time before DVT was diagnosed. This approach would not be useful when trying to predict DVT prospectively in clinical practice.

The most basic requirement for a biomarker is that it should be able to discriminate between patients with and without the outcome of interest (24). The significant associations between factor VIII activity and incident DVT, and between G value and prevalent DVT support the discriminatory ability of these biomarkers. In addition, the AUC of both biomarkers were better than 0.50, which corresponds to random chance (25). Their performances are likely better than those of inherited thrombophilias. Except for factor V Leiden and prothrombin G20210A mutations, which may be associated with CVC-related DVT, none of the inherited

thrombophilias have been shown to increase the risk for CVC-related DVT in children (13, 19). Factor V Leiden and prothrombin G20210A mutations were not associated with DVT in our study partly because of inadequate statistical power. The performances of factor VIII activity and G value on their own are modest and slightly below the suggested minimum clinically acceptable AUC of 0.70 (25). Combining the biomarkers did not improve their performance.

The optimal thresholds for factor VIII activity and G value identified using Youden index were both lower than previously reported thresholds (9, 13). At the optimal threshold of >100 IU/dL, factor VIII activity was more sensitive (92.0% vs. 33.3%) but less specific (41.3% vs. 80.4%) than the previously reported threshold of >150 IU/dL (13). This suggests that factor VIII activity at the optimal threshold may be used as a screening test for incident DVT. Factor VIII >100 IU/dL may identify critically ill children who are at low risk for CVC-related DVT and would not need thromboprophylaxis. Because the normal values of factor VIII activity range from 50 to 150 IU/dL, our finding suggests that in critically ill children with CVC, factor VIII activity in the upper normal range may be sufficient to increase the risk for DVT. This is probably because these children have various degrees of inflammation, which is intricately intertwined with coagulation, that predispose them to DVT (23). In addition, factor VIII activity may need to be reduced to at most low normal values, such as with monoclonal antibody against factor VIII, to reduce the risk for CVC-related DVT (26). These hypotheses need to be tested in future studies. The sensitivity of G value using the optimal threshold of >11.0 kdyn/cm² was better than the previously reported threshold of >12.4 kdyn/cm² (50.0% vs. 33.3%), although its specificity was lower (87.7% vs. 94.5%) (9). Because G value at either threshold is more specific than sensitive, it may be useful as a confirmatory, but not as a screening, test for prevalent DVT. The clinical application of this finding is limited because most cases of DVT can easily be confirmed with ultrasonography (4).

Another requirement for a biomarker is that it should be able to incrementally improve our ability to predict the outcome of interest above the predicted risk from established clinical predictors alone (24). This would justify the burden of measuring the biomarker. The appropriate method to evaluate this is to compare the AUC of a risk prediction model with and without the biomarker added to the model (24). Currently, there are no risk prediction models for CVC-related DVT in children. In its absence, we adjusted the associations between factor VIII activity and incident DVT for age, center effect and recent surgery, and between G value and prevalent DVT for age, center effect, recent surgery and size of the CVC. The associations between the biomarkers and DVT remained significant after adjusting for these predictors suggesting that the biomarkers may incrementally improve our ability to identify CVC-related DVT in critically ill children (24).

Our study has several strengths. We obtained consistent results when we evaluated the performance of the biomarkers using different measures. We actively surveilled all subjects ultrasonographically and detected both clinically apparent and asymptomatic CVC-related DVT. DVT is associated with adverse sequelae, such as pulmonary embolism, paradoxical embolic stroke and loss of venous access, whether it is clinically apparent or not (4). We ascertained the diagnosis of incident DVT by screening for prevalent DVT on enrollment.

We imaged the lower extremities to detect prevalent non-CVC-related DVT and excluded them in the analysis of incident DVT. All images were centrally adjudicated to minimize misclassification bias. We systematically tested for the most common inherited thrombophilias. We did not test for less common thrombophilias because they are not associated with CVC-related DVT (13, 19). We also did not test for D-dimer, protein C, protein S and antithrombin because they did not predict DVT in critically ill adults (14).

There were limitations to our study. We did not investigate the mechanisms underlying the association between the biomarkers and CVC-related DVT (7, 22). The goal of prognostic research, such as our study, is to predict the outcome as accurately as possible and not to explain causality or pathophysiology, as is true for etiological research (27). Although elevated factor VIII may increase the risk for DVT, it may simply be a marker for other acute phase responses (7). We measured each biomarker once per subject. It would have been ideal to enroll children during the time of insertion of the CVC, obtain baseline study as soon as the CVC was inserted, then measure the biomarkers serially within 24 hours after insertion of the CVC when the incidence of CVC-related DVT is low and when the result might affect the decision to provide thromboprophylaxis (2). This was not feasible because CVCs were inserted emergently when the children were acutely ill. This also when parents were overwhelmed to provide consent. The average time from insertion of the CVC to obtain consent and draw blood was 19.8 hours. The performances of the biomarkers on their own and when combined are modest. Other biomarkers that are downstream to the activation of factor VIII (*e.g.*, thrombin-antithrombin complex), biomarkers of platelet activation (*e.g.*, platelet microparticles) or biomarkers of inflammation (*e.g.*, interleukins) may be useful, and should also be tested. Because this was the first study to determine the performance of factor VIII activity and G value in predicting CVC-related DVT, the study was not designed to assess the performance of these biomarkers at specific thresholds. We plan to validate these thresholds in future studies. Lastly, we only enrolled children from 2 pediatric ICUs. Practices related to the care of the CVC, and patient characteristics that may affect the risk for DVT may be different in other ICUs. Differences in patient characteristics may explain the difference in the frequency of DVT between our studies (1).

CONCLUSIONS

Our preliminary study shows that we may have found a test to stratify critically ill children based on their risk for CVC-related DVT. Factor VIII activity is associated with incident DVT and its overall performance is modest. Further studies of factor VIII activity as a biomarker for DVT may be warranted (24). G value is associated with prevalent DVT. However, its use to screen for critically ill children who would need further testing to diagnose DVT is likely limited.

Acknowledgments

This publication was made possible by CTSA Grants Numbers UL1 TR000142 and KL2 TR000140 from the National Center for Research Resources and the National Center for Advancing Translational Science, components of the National Institutes of Health (NIH), and NIH roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH. Haemonetics Corporation loaned equipment and provided supplies but did not have any role in the design or analysis of the study.

References

1. Faustino EV, Spinella PC, Li S, et al. Incidence and acute complications of asymptomatic central venous catheter-related deep venous thrombosis in critically ill children. *J Pediatr*. 2013; 162(2): 387–391. [PubMed: 22883418]
2. Beck C, Dubois J, Grignon A, et al. Incidence and risk factors of catheter-related deep vein thrombosis in a pediatric intensive care unit: A prospective study. *J Pediatr*. 1998; 133(2):237–241. [PubMed: 9709712]
3. Alhazzani W, Lim W, Jaeschke RZ, et al. Heparin thromboprophylaxis in medical-surgical critically ill patients: A systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2013; 41(9):2088–2098. [PubMed: 23782973]
4. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 suppl):e737S–801S. [PubMed: 22315277]
5. Faustino EV, Lawson KA, Northrup V, et al. Mortality-adjusted duration of mechanical ventilation in critically ill children with symptomatic central venous line-related deep venous thrombosis. *Crit Care Med*. 2011; 39(5):1151–1156. [PubMed: 21336130]
6. Ryan ML, Van Haren RM, Thorson CM, et al. Trauma induced hypercoagulability in pediatric patients. *J Pediatr Surg*. 2014; 49(8):1295–1299. [PubMed: 25092093]
7. Tichelaar V, Mulder A, Kluin-Nelemans H, et al. The acute phase reaction explains only a part of initially elevated factor VIII:C levels: A prospective cohort study in patients with venous thrombosis. *Thromb Res*. 2012; 129(2):183–186. [PubMed: 21992898]
8. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol*. 2007; 44(2): 62–69. [PubMed: 17433897]
9. Kashuk JL, Moore EE, Sabel A, et al. Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery*. 2009; 146(4): 764–772. [PubMed: 19789037]
10. Raffini L, Schwed A, Zheng XL, et al. Thromboelastography of patients after Fontan compared with healthy children. *Pediatr Cardiol*. 2009; 30(6):771–776. [PubMed: 19357907]
11. Vormittag R, Simanek R, Ay C, et al. High factor VIII levels independently predict venous thromboembolism in cancer patients: The cancer and thrombosis study. *Arterioscler Thromb Vasc Biol*. 2009; 29(12):2176–2181. [PubMed: 19778945]
12. Mackie I, Cooper P, Lawrie A, et al. Guidelines on the laboratory aspects of assays used in haemostasis and thrombosis. *Int J Lab Hematol*. 2013; 35(1):1–13. [PubMed: 22978493]
13. Raffini L, Thornburg C. Testing children for inherited thrombophilia: More questions than answers. *Br J Haematol*. 2009; 147(3):277–288. [PubMed: 19656153]
14. Crowther MA, Cook DJ, Griffith LE, et al. Neither baseline tests of molecular hypercoagulability nor D-dimer levels predict deep venous thrombosis in critically ill medical-surgical patients. *Intensive Care Med*. 2005; 31(1):48–55. [PubMed: 15592816]
15. Cook D, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical critically ill patients: Prevalence, incidence, and risk factors. *Crit Care Med*. 2005; 33(7):1565–1571. [PubMed: 16003063]
16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics*. 1988; 44(3):837–845. [PubMed: 3203132]
17. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950; 3(1):32–35. [PubMed: 15405679]
18. O'Donnell J, Laffan M. Elevated plasma factor VIII levels - A novel risk factor for venous thromboembolism. *Clin Lab*. 2001; 47(1-2):1–6. [PubMed: 11214218]
19. Thom K, Male C, Mannhalter C, et al. No impact of endogenous prothrombotic conditions on the risk of central venous line-related thrombotic events in children: Results of the KIDCAT study (KIDs with Catheter Associated Thrombosis). *J Thromb Haemost*. 2014; 12(10):1610–1615. [PubMed: 25131188]

20. Rossi EC, Green D, Rosen JS, et al. Sequential changes in factor VIII and platelets preceding deep vein thrombosis in patients with spinal cord injury. *Br J Haematol.* 1980; 45(1):143–151. [PubMed: 6769466]
21. Myllynen P, Kammonen M, Rokkanen P, et al. The blood F VIII:Ag/F VIII:C ratio as an early indicator of deep venous thrombosis during post-traumatic immobilization. *J Trauma.* 1987; 27(3): 287–290. [PubMed: 3104622]
22. Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *N Engl J Med.* 2004; 351(11):1081–1088. [PubMed: 15356305]
23. Levi M. The coagulant response in sepsis and inflammation. *Hamostaseologie.* 2010; 30(1):10–12. 14–16. [PubMed: 20162247]
24. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: A scientific statement from the American Heart Association. *Circulation.* 2009; 119(17):2408–2416. [PubMed: 19364974]
25. Hosmer, DW.; Lemeshow, S.; Sturdivant, RX. *Applied Logistic Regression.* 3. New York, NY: John Wiley & Sons; 2013.
26. Verhamme P, Gunn S, Sonesson E, et al. Single-dose TB-402 or rivaroxaban for the prevention of venous thromboembolism after total hip replacement. A randomised, controlled trial. *Thromb Haemost.* 2013; 109(6):1091–1098. [PubMed: 23615791]
27. Moons KG, Royston P, Vergouwe Y, et al. Prognosis and prognostic research: What, why, and how? *BMJ.* 2009; 338:b375. [PubMed: 19237405]

Figure 1.
Distribution of subjects with and without deep venous thrombosis (DVT)

A. Incident DVT **B. Prevalent DVT** **Figure 2.**

Association between incident and prevalent deep venous thrombosis (DVT) and factor VIII activity and thromboelastography parameters. Coagulation index, a global measure of coagulation, is a combination of reaction time, kinetics time, angle and maximum amplitude.

Figure 3. Receiver operating characteristic curves showing the performance of factor VIII activity and G value, expressed as area under the curve (AUC), in identifying incident and prevalent deep venous thrombosis (DVT)

Table 1Characteristics of subjects with and without incident deep venous thrombosis (DVT)^a

Characteristics	With Incident DVT n=25	Without Incident DVT n=46	<i>p</i> value
Subject characteristics			
Center			0.10
Yale-New Haven Children's Hospital	64.0%	43.5%	
Maria Fareri Children's Hospital	36.0%	56.5%	
Age category			0.66
<1 year old	36.0%	41.3%	
1-13 years old	52.0%	41.3%	
>13 years old	12.0%	17.4%	
Pediatric Index of Mortality 2 score ^b	0.05 ± 0.13	0.04 ± 0.05	0.37
Diagnoses			
Congenital heart disease	28.0%	43.5%	0.20
Cancer	0%	2.2%	0.46
Trauma	12.0%	15.2%	0.71
Infection	32.0%	30.4%	0.89
Recent surgery	48.0%	67.4%	0.11
Personal history of DVT	4.0%	0%	0.17
Co-Interventions			
Mechanical ventilation	76.0%	84.8%	0.36
Vasopressor	64.0%	54.4%	0.43
Mechanical thromboprophylaxis	16.0%	26.1%	0.33
Laboratory Results			
Factor V Leiden mutation	0%	0%	–
Prothrombin mutation	8.0%	2.2%	0.24
Central Venous Catheter Characteristics			
Location			0.58
Internal jugular	44.0%	32.6%	
Femoral	40.0%	43.5%	
Subclavian	16.0%	23.9%	
Size			0.44
< 5 French	32.0%	41.3%	
5 French	68.0%	58.7%	

^aThere were no statistically significant differences between groups in gender, race and ethnicity, blood product transfusion, total parenteral nutrition, platelet count, prothrombin time, activated partial thromboplastin time, laterality of insertion of the catheter and number of catheter days.

^bExpressed as probability of mortality in mean ± standard deviation.

Table 2Characteristics of subjects with and without prevalent deep venous thrombosis (DVT)^a

Characteristics	With Prevalent DVT n=12	Without Prevalent DVT n=73	<i>p</i> value
Subject characteristics			
Center			0.27
Yale-New Haven Children's Hospital	66.7%	49.3%	
Maria Fareri Children's Hospital	33.3%	50.7%	
Age category			0.003
<1 year old	25.0%	39.7%	
1-13 years old	16.7%	45.2%	
>13 years old	58.3%	15.1%	
Pediatric Index of Mortality 2 score ^b	0.11 ± 0.20	0.05 ± 0.09	0.69
Diagnoses			
Congenital heart disease	25.0%	38.4%	0.37
Cancer	0%	1.4%	0.68
Trauma	0%	13.7%	0.17
Infection	41.7%	30.1%	0.43
Recent surgery	33.3%	60.3%	0.08
Personal history of DVT	0%	1.4%	0.68
Co-Interventions			
Mechanical ventilation	83.3%	82.2%	0.92
Vasopressor	83.3%	58.9%	0.11
Mechanical thromboprophylaxis	25.0%	21.9%	0.81
Laboratory Results			
Factor V Leiden mutation	0%	0%	—
Prothrombin mutation	0%	4.2%	0.47
Central Venous Catheter Characteristics			
Location			0.15
Internal jugular	33.3%	37.0%	
Femoral	66.7%	42.5%	
Subclavian	0%	20.6%	
Size			0.04
< 5 French	8.3%	38.4%	
5 French	91.7%	61.6%	

^aThere were no statistically significant differences between groups in gender, race and ethnicity, blood product transfusion, total parenteral nutrition, platelet count, prothrombin time, activated partial thromboplastin time, laterality of insertion of the catheter and number of catheter days.

^bExpressed as probability of mortality in mean ± standard deviation.