# Prolonged Prothrombin Time Does Not Correlate with Clinical Bleeding Symptoms in Newly Diagnosed Pediatric Leukemia Patients

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March 07, 2024

**Abstract**

Prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) are frequently seen in newly diagnosed pediatric leukemia patients (NDPLP), which can lead to delayed diagnostic and therapeutic procedures due to concern for bleeding. In this single center retrospective study of NDPLP we analyzed these parameters in 93 patients (aged 1-21 years). None had a personal history of bleeding, but 33.3% had bleeding symptoms within 30 days of presentation, predominantly mucosal bleeding (80.6%) and petechiae (64.5%). Median laboratory values at diagnosis: white blood cell count 15.7, hemoglobin 8.1, platelets 64, PT 13.2, and a PTT 31. Red blood cells were administered in 41.2%, platelets in 52.9%, FFP in 7.8%, and vitamin K in 21.6% based on institutional cut-off values for replacement or clinical symptoms. Prolonged PT was found in 54.8% of patients (factor VII 33.1% (interquartile range [IQR] 19.4-50.5), while aPTT was prolonged in 5.4%. Anemia and thrombocytopenia did not correlate with prolonged PT (p=0.73 and p=0.18 respectively), or prolonged aPTT (p=0.52 and 0.42). Leukocytosis and neutrophilia showed significant correlation with elevated PT (p<0.001 and <0.01 respectively), but not aPTT (p=0.3 and 0.5). Bleeding symptoms upon presentation did not correlate with prolonged PT (p=0.83), prolonged aPTT (p=1) or anemia (p=0.06) but had significant correlation with thrombocytopenia (p=<0.0001) and elevated AST (p=0.05). Therefore, a prolonged PT in NDPLP may not necessitate the reflexive use of blood product replacement in the absence of significant bleeding, which is likely related to leukocytosis than to a true coagulopathy.

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*Submission to:* Pediatric Blood and Cancer

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*Additional Information:*

Main text word count: 1448

Abstract word count: 244

Tables: 2

Figures: 1

Supporting files: 0

Short running title: PT does not correlate with bleeding in new leukemia

Keywords: Leukemia, Coagulation, Hemorrhage, Bleeding, Prothrombin Time, Transfusion

*Abbreviations*

| **Abbreviation** | **Full text** |
|---|---|
| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloid leukemia |
| APL | Acute promyelocytic leukemia |
| aPTT | activated partial thromboplastin time |
| CVL | central venous line |
| FFP | fresh frozen plasma |
| Pre-B ALL | pre-B cell acute lymphoblastic leukemia |
| PT | prothrombin time |
| RBCs | Red blood cells |
| T-ALL | T-cell acute lymphoblastic leukemia |

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Prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) are frequently seen in newly diagnosed pediatric leukemia patients (NDPLP), which can lead to delayed diagnostic and therapeutic procedures due to concern for bleeding. In this single center retrospective study of NDPLP we analyzed these parameters in 93 patients (aged 1-21 years). None had a personal history of bleeding, but 33.3% had bleeding symptoms within 30 days of presentation, predominantly mucosal bleeding (80.6%) and petechiae (64.5%). Median laboratory values at diagnosis: white blood cell count 15.7, hemoglobin 8.1, platelets 64, PT 13.2, and a PTT 31. Red blood cells were administered in 41.2%, platelets in 52.9%, FFP in 7.8%, and vitamin K in 21.6% based on institutional cut-off values for replacement or clinical symptoms.

Prolonged PT was found in 54.8% of patients (factor VII 33.1% (interquartile range [IQR] 19.4-50.5), while aPTT was prolonged in 5.4%.

Anemia and thrombocytopenia did not correlate with prolonged PT (p=0.73 and p=0.18 respectively), or prolonged aPTT (p=0.52 and 0.42). Leukocytosis and neutrophilia showed significant correlation with elevated PT (p<0.001 and <0.01 respectively), but not aPTT (p=0.3 and 0.5). Bleeding symptoms upon presentation did not correlate with prolonged PT (p=0.83), prolonged aPTT (p=1) or anemia (p=0.06) but had significant correlation with thrombocytopenia (p=<0.0001) and elevated AST (p=0.05). Therefore, a

prolonged PT in NDPLP may not necessitate the reflexive use of blood product replacement in the absence of significant bleeding, which is likely related to leukocytosis than to a true coagulopathy.

*Introduction*

Acute leukemia in pediatric patients can present with bleeding symptoms such as bruising, petechiae and epistaxis secondary to thrombocytopenia, endothelial cell injury, abnormal fibrinolysis, disseminated intravascular coagulation (DIC), or inherited bleeding disorders such as von Willebrand disease or clotting factor deficiencies(1). Bleeding, along with thrombosis, in acute promyelocytic leukemia (APL) has been attributed to augmented fibrinolysis via increased expression of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), leading to generation of plasmin and degradation of fibrin(2). Enhanced fibrinolysis, in addition to thrombocytopenia and DIC, leads to the bleeding diathesis seen in these patients.

Abnormal coagulation screening in pediatric patients diagnosed with leukemia include prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT), which are common at presentation. These abnormalities generally require further work up due to the need for rapid diagnostic procedures (such as a lumbar puncture and bone marrow aspirate and/or biopsy), along with central venous line (CVL) placement for initiation of chemotherapy. Abnormal coagulation screening tests requiring further work up can lead to delays in procedures due to concerns of bleeding. There is also a tendency to achieve correction of the PT/aPTT using fresh frozen plasma (FFP) and/or vitamin K, in the hope of preventing bleeding during the procedure, which is not evidence-based.

A systematic review by Liontos et al(3) did not find evidence of utility of routine pre-operative coagulation testing to predict perioperative bleeding with different types of procedures. However, given the complex interplay of factors involved in the leukemia population, it is unclear if abnormal screening coagulation tests, in the absence of significant bleeding, increase bleeding risk. Even more unclear is the utility of correcting these abnormal values using blood products to prevent peri-procedural bleeding. Therefore, the aim of this study was to assess if there was a correlation between prolonged PT/aPTT and bleeding symptoms or other laboratory parameters measured at initial leukemia diagnosis, with the goal of reassessing the need for work up of these abnormal results to justify use of blood products to correct laboratory values.

*Methods*

This single-center retrospective study of newly diagnosed pediatric leukemia patients, 1 to 21 years of age, was conducted at Cohen Children's Medical Center (New York) from January 2015 to December 2018, after appropriate institutional ethics approval. Inclusion criteria were: new diagnosis of leukemia including pre-B cell acute lymphoblastic leukemia (pre-B ALL), T-cell acute lymphoblastic leukemia (T-ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), mature B cell leukemia or biphenotypic leukemia. Exclusion criteria included: prior leukemia diagnosis, leukemia relapse, chemotherapy for leukemia at an outside institution, treatment with steroids within the month prior to presentation, previously diagnosed congenital or acquired coagulopathy (in addition to known or suspected renal or hepatic disease) and transfer to outside institution prior to undergoing procedures. Patients' relevant history, presenting symptoms (including bleeding/clotting), diagnosis and laboratory values were extracted. Exact Wilcoxon tests and Fisher's Exact tests were performed, as appropriate, to compare lab values and bleeding symptoms with PT and aPTT.

*Results*

Ninety-three patients met inclusion criteria out of 144 records reviewed during the study period. Patients were 43% female, of varied races, 21.5% had a medical history (e.g. asthma), none with a personal history of bleeding and one patient had a family member with documented bleeding history (menorrhagia) – Table 1. A third of patients had bleeding symptoms upon presentation, which were most commonly bruising (80.6%) and petechiae (64.5%).

Patients were diagnosed (via peripheral blood flow and/or bone marrow studies) predominantly with ALL

(82.7%). Of these, 82.9% had pre-B cell ALL and 17.1% had T-cell ALL. The remainder of diagnoses were AML (12.9%), APML (3.2%), biphenotypic leukemia (2.2%), and mature B cell leukemia (2.2%). All patients underwent a lumbar puncture (LP), bone marrow aspirate (and bone marrow biopsy for some patients) along with CVL placement for chemotherapy. One patient was diagnosed via fluid from a pleural effusion.

Two patients had minor bleeding (both WHO grade 2) noted at a procedure site. One patient had a bleed at the LP site (day 2 post-procedure), with normal PT/aPTT at presentation; bleeding was attributed to thrombocytopenia which resolved with a pressure bandage. The second patient had bleeding at the CVL site (day 1 post-procedure) and had presented with a PT of 13.9. This was not corrected initially, but patient was initiated on a course of vitamin K for the CVL site bleed.

Laboratory data are also presented in Table 1. The median age at diagnosis was 8 years (interquartile range [IQR] 3-12) with hematologic lab values as follows: white blood cell count (WBC) with leukocytosis (median 15.7; IQR 5.3-57.2), anemia with hemoglobin 8.1 (5.7-10.4), thrombocytopenia with platelets 64 (24-119), mildly prolonged prothrombin time (PT) at 13.2 (12.4-15.4), and normal partial thromboplastin time at 31 (27.4-33.6). Fibrinogen (343; 227-465) and D-dimer (834; 341-2869) were obtained in 37.6% and 22.5% of patients respectively, which were both elevated. Chemistries were obtained, most notably with an elevated LDH (637; 368-1218).

Prolonged PT was found in over half of patients (N=51, 54.8%) and only 5 had prolonged aPTT (5.4%). Of interest, 84.6% (11 of 13) patients with T cell leukemia had prolonged PT, along with 58.3% of patients with AML, and all 3 patients with APML. In our cohort, less than 27% of patients with prolonged PT/aPTT had factor levels obtained; of those, factor VII had the lowest activity with a median of 33.1% (19.4-50.5).

Varying blood products were administered for prophylaxis per institution guidelines prior to procedures (for hemoglobin <8 g/dL, platelets <10 K/uL, PT >15 s). Red blood cells (RBCs) were administered in 41.2% of patients, platelets in 52.9%, FFP in 7.8% and vitamin K in 21.6%.

Anemia and thrombocytopenia did not appear to correlate with prolonged PT (p=0.73 and p=0.18 respectively), nor with prolonged aPTT (p=0.52 and 0.42 respectively). Leukocytosis, however, showed significant correlation with elevated PT (p<0.001), but not aPTT (p=0.3) – Figure 1. This was also seen with elevated absolute neutrophil count with elevated PT (p<0.01), but not aPTT (p=0.5). Bleeding symptoms did not correlate with prolonged PT (p=0.83), prolonged aPTT (p=1) or anemia (p=0.06), but had significant correlation with thrombocytopenia (p=<0.0001) and elevated AST (p=0.05).

*Discussion*

In our cohort of newly diagnosed pediatric leukemia patients, a third presented with bleeding symptoms, which correlated significantly with thrombocytopenia, but not with prolonged PT or aPTT. Interestingly, over half of patients presenting with a prolonged PT had significant correlation with leukocytosis. All patients with APL presented with elevated PT (which is consistent with published literature(4), along with most patients with T-cell ALL, which has been reported in adult T-cell patients(5).

The leukemic process can lead to the unregulated production of white blood cells with increased inflammation by release of cytokines and stress hormones(6). Hepatic dysfunction can also occur due to leukemic infiltration (as noted by increased bleeding symptoms correlating with elevated AST upon presentation), leading to deficiencies in coagulation factors synthesized by the liver. Factor VII was most notably affected due to its short half-life(7), contributing to a prolonged PT. However, bleeding in newly diagnosed leukemia patients is most likely related to thrombocytopenia as noted in our study, and not a prolonged PT. Thrombocytopenia is common in hematologic malignancies(8), with a platelet count below 10 K/uL leading to increased risk of hemorrhage(9).

Use of products such as FFP and vitamin-K prior to procedures in those with a prolonged PT is routinely practiced. With the finding of low factor VII levels in pediatric leukemia patients upon initial presentation, the use of targeted therapy with factor VII concentrate may be appropriate for major procedures such as lumbar punctures, to avoid administration of FFP with its complications such as fluid overload and allergic

reactions. In inherited FVII deficiency, significant bleeding occurs with levels <10%, and whether this can be applied to acquired FVII deficiency is debated. Furthermore, the automated use of product replacement may not be indicated in the absence of significant bleeding associated with a prolonged PT and low FVII levels, which are likely related to leukocytosis than to a true coagulopathy. A previous study from our institution observed that low FVII levels do not predict peri-op bleeding even in the absence of intervention(10). In an adult study by Benlakhal et al(11), they recommended a FVII cut off of 10% in considering replacement therapy, irrespective of bleeding phenotype, for major surgeries (sensitivity of 87% and negative predictive value of 94% for 7% cutoff).

The limitations to this study are its retrospective design (with reliance on documentation for patient history) and incomplete patient workup in relation to abnormal laboratory values (such as prolonged PT and factor deficiencies). Nonetheless, the findings in our patients may enable tailoring the use of blood products based on significant bleeding symptoms and avoiding treating abnormal values in the absence of clinical bleeding.

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