

Thrombocytosis - a Marker of Disease Severity in Children with Viral Respiratory Tract Infections

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January 24, 2023

Abstract

Background: Reactive thrombocytosis (Platelets $>500\text{K}/\mu\text{l}$) is estimated between 3-13% in hospitalized children and has been associated with RSV infection and younger age. We aimed to examine the clinical significance of thrombocytosis in children admitted to the hospital with an influenza-like illness (ILI). **Methods:** We performed an analysis of a database of patients evaluated at our Medical Centers with an ILI between 2009 and 2013. We included pediatric patients and examined the association between platelet count, respiratory viral infections, and admission outcomes (hospital length of stay (LOS) and admission to the pediatric intensive care unit (PICU)) using regression models adjusting for laboratory, clinical and demographic parameters. **Results:** Of 19,192 adults and children in the database, 5,171 children met inclusion criteria (median age 0.8 years (Interquartile range, 0.2-1.8), 58% male, median LOS of 3 days (Interquartile range, 2-5)). Younger age and not the type of viral infection was associated with a high platelet count ($p<0.001$). Elevated platelet count independently predicted admission outcomes, adjusted for multiple covariates ($p[?]0.006$). Furthermore, the presence of thrombocytosis was associated with an increased risk for a prolonged LOS (odds ratio=1.2 (95% Confidence interval=1.1-1.4, $p=0.003$)) and admission to the PICU (odds ratio=1.5 (95% Confidence interval =1.1-2.0, $p=0.002$)). **Conclusions:** In children admitted with an ILI, a high platelet count is associated with younger age and is an independent predictor of hospital LOS and admission to the PICU. Our results show that platelet count may be used to improve risk assessment and management decisions in these pediatric patients.

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Conflict of interest statement: No conflicts of interest or competing interests exist for the specified authors.

Funding information: The project was supported by internal departmental funds.

Ethical statement: The planning, conduct, and reporting of human research reported in this manuscript are in accordance with the Helsinki Declaration as revised in 2013. Institutional review board approved the study (HMO-16-0323).

Prior presentation of data: An abstract of this paper was presented as a poster in the European Respiratory Society international conference of August 2022. There are no other publications or submissions with any overlapping information, including studies and patients.

Author Contributions:

Dr. Sergei Elber-Dorozko – Conceptualization, formal analysis, writing – original draft preparation and reviewing and editing and visualization.

Dr. Liya Kerem – Conceptualization, investigation, formal analysis, and writing – reviewing and editing.

Prof. Dana Wolf – Investigation, and writing – reviewing and editing.

Dr. Shlomit Brodie – Conceptualization.

Prof. Yackov Berkun and Dr. Rebecca Brooks – Supervision, and writing – reviewing and editing.

Dr. Oded Breuer – Conceptualization, formal analysis, data curation, supervision, and writing – reviewing and editing.

Key words: Admission outcomes; Influenza Like Illness; Platelets; Respiratory Syncytial Virus;

Short title: Thrombocytosis in influenza like illness

Abbreviations:

CI – confidence interval

HMPV – Human metapneumovirus

ILI – Influenza like illness

IQR – Interquartile range

LOS – Length of stay

PICU – Pediatric intensive care unit

RSV -Respiratory syncytial virus

RT-PCR – Reverse transcription polymerase chain reaction

ABSTRACT

Background : Reactive thrombocytosis (Platelets >500K/ μ l) is estimated between 3-13% in hospitalized children and has been associated with RSV infection and younger age. We aimed to examine the clinical significance of thrombocytosis in children admitted to the hospital with an influenza-like illness (ILI).

Methods : We performed an analysis of a database of patients evaluated at our Medical Centers with an ILI between 2009 and 2013. We included pediatric patients and examined the association between platelet count, respiratory viral infections, and admission outcomes (hospital length of stay (LOS) and admission to the pediatric intensive care unit (PICU)) using regression models adjusting for laboratory, clinical and demographic parameters.

Results : Of 19,192 adults and children in the database, 5,171 children met inclusion criteria (median age 0.8 years (Interquartile range, 0.2-1.8), 58% male, median LOS of 3 days (Interquartile range, 2-5)). Younger age and not the type of viral infection was associated with a high platelet count ($p < 0.001$). Elevated platelet count independently predicted admission outcomes, adjusted for multiple covariates ($p[?]0.006$). Furthermore, the presence of thrombocytosis was associated with an increased risk for a prolonged LOS (odds ratio=1.2 (95% Confidence interval=1.1-1.4, $p=0.003$)) and admission to the PICU (odds ratio=1.5 (95% Confidence interval =1.1-2.0, $p=0.002$)). **Conclusions:** In children admitted with an ILI, a high platelet count is associated with younger age and is an independent predictor of hospital LOS and admission to the PICU. Our results show that platelet count may be used to improve risk assessment and management decisions in these pediatric patients.

INTRODUCTION

Influenza-like illnesses (ILIs) cause substantial morbidity worldwide with most cases occurring from December-March in the northern hemisphere¹⁻³. In the pediatric population, rates of hospitalization due to ILI vary with age and are up to tenfold higher in children younger than two years of age⁴⁻⁶ with significant healthcare and economic burden⁷⁻⁹. The most common viral etiologies for ILI are influenza viruses, respiratory syncytial virus (RSV) and rhinovirus^{10,11}.

In children admitted due to ILI, previously reported risk factors for a more severe disease course, include prematurity, young age, low birth weight, tachypnea, or apnea¹²⁻¹⁶.

Reactive thrombocytosis, (a platelet count above 500K/ μ l), is common in hospitalized pediatric patients with a prevalence of 3-13%, is more pronounced in infants, and declines with age^{17,18}. Prior studies evaluating thrombocytosis in pediatric patients with ILI have found an association with RSV and Rhino virus infections but inconclusive results regarding the association with disease severity and complications¹⁹⁻²².

The aim of this study was to assess the clinical significance of a high platelet counts in hospitalized pediatric patients with ILI, evaluating an association with admission outcomes and viral respiratory tract infections.

METHODS

Study design

We conducted an analysis of a database of patients. This database includes records of all respiratory viral-panel testing performed on nasopharyngeal samples in the clinical virology laboratory of our Medical Centers between May 2009 through July 2013 (inpatient and outpatient). The nasopharyngeal samples included in this database were obtained from patients presenting with “influenza like illness” (displaying symptoms such as cough, rhinorrhea, fever or sore throat). These samples were tested using reverse transcription polymerase chain reaction (RT-PCR) for Influenza A virus (types H3N2, H1N1), Influenza B virus, Adenovirus, RSV, Parainfluenza 1, 2 and 3 viruses and Human metapneumovirus (HMPV).

Additional information available in the database included patient demographics, laboratory blood test results, hospital length of stay (LOS) (if admitted) and the occurrence of an admission to the pediatric intensive care unit (PICU).

From this database, we included in the study all children under 16 years of age who were admitted due to an ILI to the pediatric departments at our Medical Centers. When more than one nasopharyngeal sample was collected during a single hospitalization, only the results of the first sample was included in the analysis.

To reduce the possibility of including hospital-acquired infections in the study, we excluded all children in

whom the nasopharyngeal samples were collected after more than 5 days of their admission. Furthermore, to reduce chance for disproportionate effects of uncharacteristic admissions on the study outcomes, we further excluded from the study all children in whom the hospital LOS was greater than 14 days (figure 1). The study was approved by the institutional review board (HMO-16-0323) and consent was waived due to the retrospective nature of the study.

Evaluated outcomes

The main outcomes evaluated in this study were hospital LOS and admission to the PICU, as measures of disease severity. In addition, we evaluated the association between platelet count and respiratory viral panel results.

Statistical analysis

Data were summarized by standard descriptive statistics. Differences between different viral infections (viral pathogen not detected, RSV, influenza A and B, adenovirus, HMPV and parainfluenza) were evaluated using chi square test for categorical variables and Kruskal-Wallis test for continuous variables, with the Mann–Whitney U test for multiple pairwise comparisons. A linear regression model correcting for age and sex was used to evaluate the association between different respiratory viral infections and platelet count. Linear and logistic regression models were used to evaluate the association between platelet count and the primary study outcomes (hospital LOS and admission to the PICU), correcting for demographic variables, laboratory blood test results and respiratory viral panel results. The statistical analysis was performed using STATA 15.1 (StataCorp LLC, Texas USA). For the primary outcomes, p-values of less than 0.05 were considered significant. For multiple pairwise comparisons, nominal p-values are reported and p-values of less than 0.008 were considered significant, as per the Bonferroni correction.

RESULTS

Study population

The database included 19,192, inpatient and outpatient, adults and children with an ILI who underwent a respiratory viral panel RT-PCR test. Of these patients, 5,171 children were included in the study (figure 1) (median age = 0.8 years (interquartile range (IQR)=0.2-1.8), 58% male, median LOS = 3 days (IQR=2-5)). Nasopharyngeal swab results were positive in 2595 children (58%), the most commonly detected viral pathogen was RSV (57%) followed by adenovirus (19%). The prevalence of thrombocytosis in our cohort was 22%. This decreased to 9% and 6% in children above 2 years and 5 years of age, respectively, and varied significantly with the type of viral infection (see below). Additional clinical characteristics are presented in table 1.

The association of platelet count and other clinical variables with the type of viral infection

We found significant differences in most evaluated clinical and laboratory parameters when assessing admissions according to different respiratory viruses (table 1).

The platelet count was found to be significantly higher in children in whom an RSV infection was detected (P-value < 0.008, for multiple pairwise comparisons) when compared to children in whom a respiratory virus panel was negative or other respiratory viruses were detected. Furthermore, the presence of thrombocytosis had an odds ratio of 1.3 (95% confidence interval (CI), 1.1-1.5 (P<0.001)) for the detection of an RSV infection in the respiratory viral panel analysis. However, children with an RSV infection were also found to be significantly younger (P-value < 0.001, for multiple pairwise comparisons) when compared to children in whom a respiratory virus panel was negative or other respiratory viruses were detected (table 1).

When performing a multivariate analysis, evaluating factors associated with platelet count, a younger age was independently associated with an increased platelet count (difference per year of age = -14.4; 95% CI, -16–12; P<0.001), however the detection of an RSV infection was not (difference = -2.6; 95%CI, -5.7-14.1; P=0.648) (E-Table 1 – Online supporting information). Figure 2A presents the association between platelet count and age in children with and without an RSV infection.

E-Table 1 shows additional results of multivariate models looking at the association between laboratory evaluation results and the type of viral infection corrected for demographic variables. Of note is a strong positive association between an adenoviral infection and increased inflammatory indices and a strong negative association between influenza B infection and increased inflammatory indices.

The association between platelet count and disease severity outcomes

Figure 2 (Panels B and C) shows a highly significant association between disease severity outcomes (hospital LOS and admission to the PICU) and platelet count.

A multivariate regression analysis, corrected for demographic variables, laboratory results and the type of viral respiratory infections, similarly showed that platelet count is independently associated with the disease severity outcomes evaluated in our study. Specifically, platelet count was found to be positively associated with hospital LOS (difference in LOS of = 0.11 days, 95%CI (0.1-0.2) for every 100 K/ μ l increase in platelet count, $p < 0.001$) and increased risk for admission to the PICU (odds ratio = 1.1 95%CI (1.03-1.25) for every 100K/ μ l increase in platelet count, $p = 0.006$). These findings remained significant also when evaluating young children, under 2 or 3 years of age (Table 2).

When evaluating the presence of thrombocytosis as a dichotomic variable predicting admission

outcomes, the odds ratios (corrected for age and gender) of a child with thrombocytosis to have a longer than median hospital LOS or to be admitted to the PICU were 1.2 (95%CI 1.1-1.4, $p = 0.003$) and 1.5 (95%CI 1.1-2.0, $p = 0.002$), respectively.

DISCUSSION

In this observational study, evaluating a large database of patients with an influenza like illness, we show that in hospitalized children under 16 years of age, an elevated platelet count is associated with worse admission outcomes. Our results also show that thrombocytosis in children with ILI is more prevalent in younger children and not associated with the type of viral infection. Results from our study provide information, which may improve risk assessment in children admitted to the hospital with an ILI, directing attention to children at higher risk to have a more severe disease course.

To the best of our knowledge our findings of worse disease outcomes in children with ILI and elevated platelet counts were previously examined in two retrospective studies with contradictory findings. The first, evaluating clinical data in 92 hospitalized children, did not find any association between disease outcomes and thrombocytosis²⁰. The second, evaluating medical records of 136 hospitalized infants, using multivariate logistic regression analysis, found a significant association between thrombocytosis and both hospital LOS and the duration of oxygen requirement during admission^{19,23}. Our results, evaluating a large database of admitted children provide conclusive findings, which strongly associate elevated platelet count with worse disease outcomes in children admitted with symptoms of viral lower respiratory tract infections. Unlike the above-mentioned studies^{19,23}, we did not evaluate the duration of oxygen therapy but we similarly found hospital LOS to be associated with high platelet count. We further show an increased risk of admission to the PICU in children with an elevated platelet count; with a 10% increase in risk in PICU admission for every 100 K/ μ l increase in platelet count.

Reactive or secondary thrombocytosis is a well described phenomenon seen frequently in hospitalized children^{17,24}. It is thought to be secondary to stimulation of megakaryocytic progenitor cells by circulating cytokines and hematopoietic factors, such as interleukin-3, interleukin-6, interleukin-8, interleukin-11 and thrombopoietin^{17,18}. Thus, our findings showing that increased platelet count is associated with worse disease outcome, suggest that the increased platelet count is related to an increased inflammatory response, possibly due to increased lower airway inflammation.

Furthermore, secondary thrombocytosis is thought to be an age dependent phenomenon. Young children, compared to adults, demonstrate higher circulating thrombopoietin concentrations and a higher megakaryocyte progenitor cells sensitivity to thrombopoietin^{25,26}.

Indeed, in our study as well as in numerous previous studies^{18–20,22,27,28}, the prevalence of reactive thrombocytosis was found to be higher in younger children. We further show that when evaluating multiple variables in children with an ILI, a younger age was the main factor independently associated with increased platelet count while the type of respiratory viral infection was not.

Previous studies have described an association between thrombocytosis and respiratory infection with RSV and rhinovirus^{19–21,29,30}. We also present an association between thrombocytosis and the detection of an RSV infection, but our results show, that at least in part, this association reflects a younger median age of children admitted with an RSV infection, when compared to children admitted due to other viral respiratory infections.

The main strengths of this study lie in the large number of children included in the database and the available RT-PCR results for multiple respiratory viruses, allowing a comprehensive assessment of the study aims. The main limitations of the study lie in the retrospective nature of its design, the lack of assessment for rhinovirus infection and the absence of information which has been previously shown to be associated with worse admission outcomes (i.e. prematurity, chronic cardiac or respiratory morbidity etc.). However, while this study is of retrospective nature, the relatively large cohort allows the generalization of our findings.

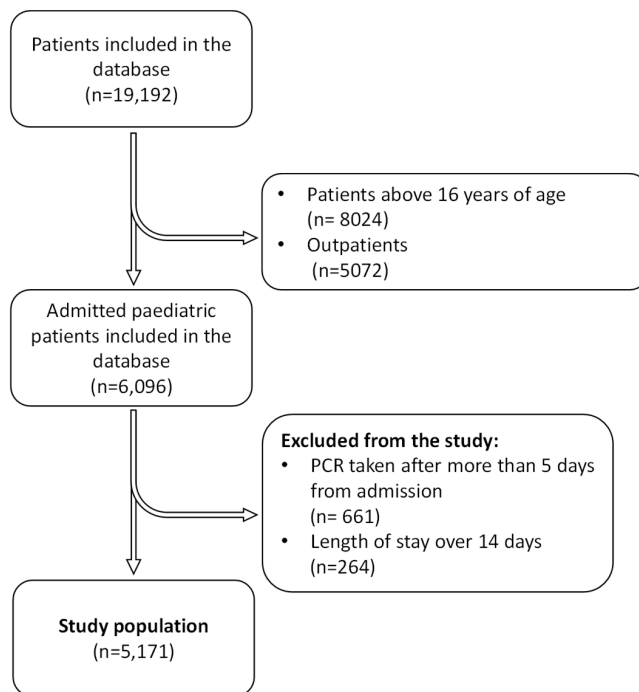
In summary, we show that elevated platelet counts in children with an influenza like illness are associated with worse admission outcomes. This finding provides data that may be used to improve emergency department and inpatient management of these children. We speculate that the increased platelet count is due to an increased inflammatory response and that platelet count may serve an indirect marker for lower airway inflammation in children with an influenza like illness.

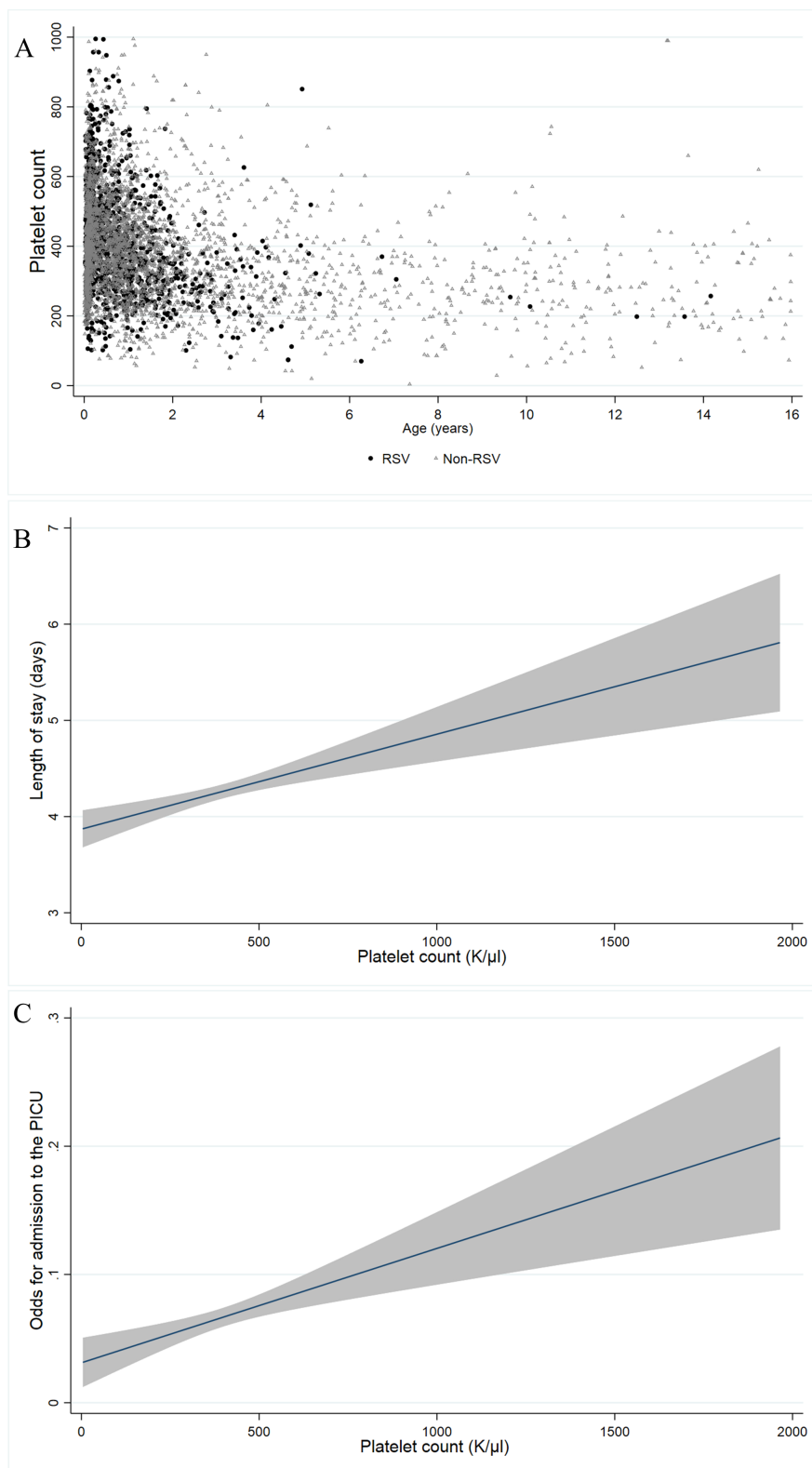
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