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Immature platelet fraction as a biomarker for disease severity in pediatric respiratory coronavirus disease 2019

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In this retrospective single-institution cohort study of 113 hospitalized pediatric patients with respiratory coronavirus disease 2019, those admitted to the intensive care unit or requiring mechanical ventilation had significantly higher immature platelet fractions than those who did not require intensive care unit–level care or ventilation. Immature platelet fraction may be an accessible biomarker for disease severity in pediatric respiratory coronavirus disease 2019. *(J Pediatr 2022; ■:1-3).*

During the pandemic, over 12 million children nationwide have been infected with severe acute respiratory syndrome–related coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19).[1] With cases surging and limited intensive care unit (ICU) beds, there is a need to identify biomarkers that can predict disease severity, specifically targetable inflammatory biomarkers. Numerous inflammatory biomarkers have been evaluated, including D-dimer, absolute lymphocyte count, absolute platelet count, and C-reactive protein with inconsistent results.[2] There have been limited biomarker studies in pediatric patients with COVID-19, with studies pooling patients with respiratory COVID-19 and multisystem inflammatory disease in children due to small patient numbers.[3,4] One study demonstrated that increased white blood cell count was associated with ICU admission.[3]

SARS-CoV-2–mediated inflammation is partly driven by interleukin-6 (IL-6), and targeting this pathway has reduced mortality.[5] IL-6–mediated inflammation is a strong stimulator of thrombopoiesis,[6] highlighting a potential role of thrombopoiesis in COVID-19. Biomarkers of thrombopoiesis, such as immature platelet fraction (IPF%, expressed as a percentage of the total platelet count),[6] have been useful predictive biomarkers in inflammatory states, including sepsis,[7] graft vs host disease,[8] and major adverse cardiovascular events.[9] Recently, we showed an elevated IPF% at initial presentation is predictive of ICU admission in adult patients with COVID-19.[10] This study examines the relationship between pediatric respiratory COVID-19 clinical outcomes and IPF%.

Methods

This study describes patients positive for SARS-CoV-2 admitted at Children's Medical Center in Dallas, Texas, from July 2020 to January 2022. Patients were included if they had an IPF% value, which was introduced into our institutional protocol during the SARS-CoV-2 delta wave. Only initial immature platelet counts were considered. Patients were excluded if they received intravenous immunoglobulin to treat multisystem inflammatory syndrome in children. Variables included age, sex, race, medical comorbidities, length of hospitalization, platelet count, and IPF%. This study was approved by the UT Southwestern Institutional Review Board.

IPF% was determined using a Sysmex XN-9100 automated hematology analyzer (Sysmex America), utilizing polymethine and oxazine fluorescent dyes that bind and stain RNA, enabling separation of RNA-rich immature platelets and mature platelets.[10] Immature platelet fraction is expressed as a percentage (reference range: 1.1%-6.1%) of immature platelets to total platelet count. Immature platelet count (units 10^9/L) was determined by multiplying IPF% by the total platelet count.

Normality of IPF%, D-dimer, fibrinogen, and platelet was conducted using Python JupyterLab. Two-tailed, parametric unpaired *t* test with Welch's correction were used to compare ICU vs non-ICU and ventilator vs nonventilator groups using GraphPad Prism 9.

Results

There were 113 patients included in the study with a mean age of 9.93 years (range: 10 days to 18.5 years; **Table I**). Over one-half of the cohort was male (52.2%) and were identified as non-Hispanic (51.3%). Twenty-one patients

COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
IL-6	Interleukin 6
IPF%	Immature platelet fraction

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Table I. Patient demographics and clinical characteristics

Characteristics	Total
Age, y, mean (SD)	9.93 (0.58)
Sex, N (%)	
Male	59 (52.2)
Female	54 (47.8)
BMI, mean (SD)	25.62 (1.03)
Height, cm, mean (SD)	132.00 (3.71)
Weight, kg, mean (SD)	54.26 (4.03)
Ethnicity, N (%)	
Hispanic	55 (48.7)
Non-Hispanic	58 (51.3)
Race, N (%)	
American Indian	1 (0.9)
Asian	4 (3.5)
Black	28 (24.8)
Hispanic	5 (4.4)
Pacific Islander	1 (0.9)
Other	18 (15.9)
White	56 (49.6)
Bed status, N (%)	
Ward	92 (81.4)
ICU	21 (18.6)
Ventilation, N (%)	
Nonmechanical	98 (86.7)
Mechanical	15 (13.3)
WBC, mean (SD)	8.58 (0.48)
Platelet, mean (SD)	260.16 (12.83)
D-dimer, mean (SD)	1.62 (0.25)
Fibrinogen, mean (SD)	413.85 (16.96)
IPF%, mean (SD)	4.60 (0.31)
IPC, mean (SD)	10.59 (9.71)

BMI, body mass index; *IPC*, immature platelet count; *N*, number of patients; *WBC*, white blood cell count.

(18.6%) were admitted to the ICU with 71% of those patients (n = 15) requiring ventilation; all patients were admitted to the pediatric ICU during their hospitalization; one patient was admitted to the neonatal ICU and was later transferred to the pediatric intensive care unit.

When grouped by severity outcomes, ICU admission, and ventilation, the platelet counts were similar between the groups (ICU: 236 vs non-ICU 262, $P = .81$; ventilator: 286 vs non-ventilated: 257, $P = .51$), and there was no significant difference in D-dimer, fibrinogen, or white blood cell count (Table II). The immature platelet count was significantly higher in ventilated patients (ventilator: 17.1 vs non-ventilator: 9.7, $P = .02$) and trended toward significance in patients admitted to the ICU (ICU: 16.3 vs non-ICU: 9.3, $P = .07$). The IPF% was significantly higher in patients both admitted to the ICU (ICU: 7.3 vs non-ICU: 4, $P = .006$) and patients placed on ventilation (ventilator: 7.1 vs non-ventilator: 4.2, $P = .01$).

Discussion

Inflammatory biomarkers predicting pediatric respiratory COVID-19 severity have been limited. Higher IPF%, reflecting increased thrombopoiesis, correlated with active and severe inflammatory conditions in our prior studies.[8,10] We found that higher initial IPF% values were significantly associated with severe outcomes: ICU admission and ventilator

Table II. IPF %, D-dimer, fibrinogen platelets, and WBC counts by severity outcomes (intensive care unit and ventilation) by Welch's t test at 95% confidence levels

Laboratory variables	Admitted to ICU among hospitalized					Ventilator use among hospitalized				
	Yes (mean ± SD) (n)	No (mean ± SD) (n)	P*	Welch-corrected t, df	95% CI	Yes (mean ± SD) (n)	No (mean ± SD) (n)	P*	Welch-corrected t, df	95% CI
IPF(%) at initial presentation	7.29 ± 4.84 (21)	3.99 ± 2.40 (92)	.0060*	3.035, 22.30	1.046-5.545	7.05 ± 3.70 (15)	4.23 ± 3.02 (98)	.0118*	2.819, 16.98	0.7106-4.941
IPC (x10(9)/L) at initial presentation	16.28 ± 16.19 (21)	9.27 ± 7.01(91)	.0654	1.941, 21.76	−0.48 to 14.49	17.05 ± 10.11 (14)	9.66 ± 9.37 (98)	.0199*	2.579, 16.36	−13.44 to −1.325
D-dimer at initial presentation	1.45 ± 1.28 (21)	1.66 ± 2.77 (86)	.6040	0.5210, 70.47	−1.027 to 0.6014	1.61 ± 1.54 (15)	1.62 ± 2.68 (92)	.9921	0.0099, 30.01	−0.9974 to 0.9877
Fibrinogen at initial presentation	428.10 ± 193.04 (20)	409.53 ± 146.23 (66)	.6946	0.3971, 25.95	−77.57 to 114.7	408.46 ± 172.16 (13)	414.81 ± 155.77 (73)	.9028	0.1242, 15.70	−114.9 to 102.2
Platelet count (x10(9)/L) at initial presentation	235.95 ± 137.35 (21)	261.59 ± 136.17 (91)	.8195	0.2302, 29.76	−75.46 to 60.18	285.71 ± 154.09 (14)	256.51 ± 133.47 (98)	.5100	0.6740, 15.91	−62.70 to 121.1
WBC	9.94 ± 4.64 (21)	8.27 ± 5.16 (92)	.1539	1.460, 32.35	−0.6599 to 4.006	9.75 ± 2.83 (15)	8.40 ± 5.34 (98)	.1450	1.494, 32.01	−0.4933 to 3.208

*P value < .01.
WBC, white blood cell.

requirement. Although IPF% was the only significant laboratory test with OR >1 in a multivariable logistic regression for ICU admission and ventilation, a larger data set for validation is recommended to confirm this observation. Although we do not demonstrate an association between elevated IPF% and hospital length of stay or mortality as was demonstrated in our adult data, this may be due to the milder phenotype of pediatric respiratory COVID-19, resulting in fewer admissions, less morbidity, and lower mortality, which reduces both the sample size and event rate.

IL-6 is an important cytokine in the inflammatory response that mediates COVID-19 pneumonia and the associated acute respiratory distress syndrome.[11] In fact, IL-6 receptor monoclonal antibodies improve mortality in adult patients.[5] Thus, given that IL-6 promotes thrombopoiesis, IPF% may be a simple, reliable, and widely available surrogate for IL-6 levels that are associated with COVID-19 severity. Additionally, the concept of IL-6–mediated inflammation may provide an explanation for why IPF% is elevated in patients with severe respiratory COVID-19 while total platelet counts are normal. If patients with more severe inflammation are at higher risk for decompensation and ICU admission, those patients would also have elevated IPF % due to ongoing inflammation-mediated thrombopoiesis regardless of baseline platelet count rather than previous hypotheses based on adult data that postulated thrombopoiesis was related to thrombocytopenia.[8,12]

IPF% is an advantageous biomarker because it can be obtained with the complete blood count with minimal cost or technician involvement[13] and can be obtained up to 24 hours after serum sample collection allowing for easier implementation and faster results, accelerating patient triage and care. Further studies are needed to validate our findings and perform a multivariable regression in a larger, external cohort of pediatric patients. ■

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