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MAJOR ARTICLE

Impact of SARS-CoV-2 Infection on the Association Between Laboratory Tests and Severe Outcomes Among Hospitalized Children

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Background. To assist clinicians with identifying children at risk of severe outcomes, we assessed the association between laboratory findings and severe outcomes among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–infected children and determined if SARS-CoV-2 test result status modified the associations.

Methods. We conducted a cross-sectional analysis of participants tested for SARS-CoV-2 infection in 41 pediatric emergency departments in 10 countries. Participants were hospitalized, had laboratory testing performed, and completed 14-day follow-up. The primary objective was to assess the associations between laboratory findings and severe outcomes. The secondary objective was to determine if the SARS-CoV-2 test result modified the associations.

Results. We included 1817 participants; 522 (28.7%) SARS-CoV-2 test-positive and 1295 (71.3%) test-negative. Seventy-five (14.4%) test-positive and 174 (13.4%) test-negative children experienced severe outcomes. In regression analysis, we found that among SARS-CoV-2-positive children, procalcitonin ≥0.5 ng/mL (adjusted odds ratio [aOR], 9.14; 95% CI, 2.90–28.80), ferritin >500 ng/mL (aOR, 7.95; 95% CI, 1.89–33.44), D-dimer ≥1500 ng/mL (aOR, 4.57; 95% CI, 1.12–18.68), serum glucose ≥120 mg/dL (aOR, 2.01; 95% CI, 1.06–3.81), lymphocyte count $<1.0 \times 10^9$/L (aOR, 3.21; 95% CI, 1.34–7.69), and platelet count $<150 \times 10^9$/L (aOR, 2.82; 95% CI, 1.31–6.07) were associated with severe outcomes. Evaluation of the interaction term revealed that a positive SARS-CoV-2 result increased the associations with severe outcomes for elevated procalcitonin, C-reactive protein (CRP), D-dimer, and for reduced lymphocyte and platelet counts.

Conclusions. Specific laboratory parameters are associated with severe outcomes in SARS-CoV-2-infected children, and elevated serum procalcitonin, CRP, and D-dimer and low absolute lymphocyte and platelet counts were more strongly associated with severe outcomes in children testing positive compared with those testing negative.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be a global public health threat, accounting for 16 100 deaths among children as of November of 2022 [1]. While most SARS-CoV-2-infected children are at low risk of experiencing adverse outcomes such as critical illness or death [2, 3], the ability to risk-stratify children by employing objective laboratory tests could assist with decision-making, particularly among hospitalized children.

Prior research has identified several routinely available biomarkers associated with severe disease in adults with coronavirus disease 2019 (COVID-19), including reduced lymphocyte count and elevated C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase, troponin, and creatinine phosphokinase [4–11]. However, few studies have evaluated these biomarkers in large cohorts of children with COVID-19 of varying degrees of severity, and varying results have been reported [12, 13]. Thus, we sought to assess the association between laboratory findings and severe outcomes among SARS-CoV-2-hospitalized and -infected children. Furthermore, to aid in clinical decision-making, we sought to evaluate if the associations between laboratory parameters and severe outcomes differ in children with SARS-CoV-2 infections vs those with other similar clinical presentations but who are SARS-CoV-2 test negative (ie, positive vs negative). We also sought to determine if, among all participants tested for SARS-CoV-2 infection, test result status (ie, positive vs negative) modified the associations with severe outcomes.

METHODS

Study Design and Setting

Participants were recruited in 41 pediatric emergency departments (EDs) in 10 countries (Argentina, Australia, Canada, Costa Rica, Italy, New Zealand, Paraguay, Singapore, Spain, and the United States) that participated in the Pediatric Emergency Research Network [14] (PERN)–COVID-19 prospective cohort study [15].

Patient Consent

All participating sites had local research ethics review board approval. The legal guardians of all participants provided informed consent, and children provided assent, as appropriate.

Participants and Recruitment

Eligible participants presented for care between March 18, 2020, and June 15, 2021, were <18 years old, and had any of the following symptoms potentially attributable to SARS-CoV-2 infection: fever, chills, malaise, myalgia, runny or stuffy nose, sore throat, cough, difficulty breathing or shortness of breath, nausea or diarrhea, or loss or altered sense of taste/smell. Eligible participants were evaluated for SARS-CoV-2 infection with nucleic acid testing, had bloodwork performed, and were hospitalized at the index ED visit or in the subsequent 14 days. Patients diagnosed with multisystem inflammatory syndrome in children (MIS-C) or Kawasaki disease on 14-day medical record review were excluded as these inflammatory conditions could exert disproportionate effects on associations between laboratory parameter and severe outcomes [16]. In addition, participants were excluded if none of the laboratory tests being evaluated were performed.

Initially, potentially eligible participants were approached for participation consecutively, regardless of SARS-CoV-2 test result, up to a maximum of 5 enrollments per day per site. However, in regions with low prevalence, this led to overenrollment of SARS-CoV-2-negative participants. Therefore, in September of 2020, sites began to consecutively enroll as many SARS-CoV-2-positive participants as possible, along with two consecutive SARS-CoV-2-negative participants for every positive participant enrolled. Testing indications varied by institution and country and were modified as the pandemic evolved.

Objectives

The primary study objective was to evaluate the associations between laboratory findings and severe outcomes among SARS-CoV-2-hospitalized and -infected children. Furthermore, to aid in clinical decision-making, our secondary objective was to determine if the associations between laboratory parameters and severe outcomes differ in children with SARS-CoV-2 infections vs those with other similar clinical presentations but who are SARS-CoV-2 test negative (ie, positive vs negative). The latter was determined through evaluating if there were statistical interactions between SARS-CoV-2 test result status and the laboratory parameters.

Data Collection

Demographic (eg, age, sex, chronic conditions) and clinical symptom (eg, duration of symptoms) data were collected during or as soon as possible after the index ED visit via interviews with participants' caregivers; additional data (eg, severe outcomes, diagnoses, interventions, laboratory parameters) were extracted from a medical record review. To collect outcome data (eg, severe outcomes—diagnoses and interventions) that may have occurred after the index ED visit and hospitalization, 14-day telephone follow-up surveys were conducted along with medical record reviews. Participants were considered lost to follow-up if 5 follow-up telephone attempts were unsuccessful. All data were collected using standardized case report forms and stored in an electronic database.

Laboratory testing was performed at the discretion of treating physicians. We recorded the following first available laboratory results: (1) complete blood count: absolute neutrophil count

(ANC), lymphocyte count, hemoglobin, hematocrit, platelet count; (2) coagulation tests: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), D-dimer; (3) renal function: creatinine, blood urea nitrogen (BUN); (4) liver enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT); (5) inflammation biomarkers: ferritin, erythrocyte sedimentation rate (ESR), procalcitonin, CRP; and (6) other tests: serum lactate, glucose, and sodium. Laboratory parameters were categorized using standard high and low ranges as normal/abnormal and for age, if applicable (Supplementary Text 1) [17]. The cutoff values for lymphocyte count ($<1.0 \times 10^9$/L), platelet count ($<150 \times 10^9$/L), serum sodium (<135 mmol/L and >145 mmol/L), serum glucose (<40 mg/dL and ≥120 mg/dL), PTT (>45 seconds), INR (>1.1), lactic acid (>2.2 mmol/L), procalcitonin (≥0.5 ng/mL), ferritin (>500 ng/mL), ESR (>25 mm/h), and D-dimer (≥1500 ng/mL) were chosen based on clinical relevance and the available COVID-19 literature [7, 8, 18–23].

SARS-CoV-2 Testing

This pragmatic observational study did not specify the approach to SARS-CoV-2 detection as local SARS-CoV-2 specimen acquisition and testing procedures evolved over time based on access to swabs, reagents, regional epidemiology, and scientific advances. Local practices and illness severity dictated investigation, treatment, and hospitalization decisions.

Definitions

SARS-CoV-2 status was classified as "positive" if a nucleic acid test performed on a swab from the nares, nasopharynx, or oral cavity collected at the index ED visit or during the subsequent 14 days was positive. A participant's hospitalization and illness severity outcome status was evaluated up to 14 days following the index ED visit. The primary outcome was a composite measure of severe illness, defined by the occurrence of any of the following events: cardiovascular (cardiac arrest, cardiac ischemia, congestive heart failure, endocarditis, myocarditis, pericarditis, stroke), infectious (disseminated intravascular coagulation, mastoiditis, sepsis with bacteremia, septic shock, toxic shock syndrome), neurologic (encephalitis, meningitis), respiratory (acute respiratory distress syndrome, empyema, necrotizing or cryptogenic organizing pneumonia, pleural effusion or pneumothorax or pneumomediastinum requiring drainage, respiratory failure), and death; or interventions representing a severe outcome: chest drainage, extracorporeal membrane oxygenation, inotropic support, high-flow oxygen by nasal cannula, mechanical ventilation, and renal replacement therapy [3].

Sample Size

As this was a secondary analysis of the parent PERN-COVID-19 prospective study, the available sample size was predetermined. The sample size specification for the parent study included the recruitment of up to 12 500 participants to enroll ≥50 COVID-positive children who experienced the study's primary outcome [3, 15]. When this target number of events was achieved, recruitment was terminated. During the planning of the parent study, we anticipated that the achieved sample size would enable this study to achieve its objectives, including exploration of effect modification (Supplementary Text 2).

Statistical Analysis

Laboratory parameters were summarized with medians and interquartile ranges (IQRs) or frequencies and percentages as appropriate. Among SARS-CoV-2-positive children, we compared laboratory parameters between those with and without the severe outcome, using chi-square and Mann-Whitney *U* tests for categorical and continuous variables, respectively.

To assess associations between laboratory parameters and severe outcomes among SARS-CoV-2-positive and -negative subgroups and to assess whether SARS-CoV-2 modified these associations, we conducted multivariable logistic regression analyses fitted with generalized estimating equations (GEEs) for each laboratory parameter. Each model included the severe outcome dependent variable (yes vs no) and the following independent variables: the categorized laboratory parameter, SARS-CoV-2 test result (positive vs negative), age, sex, baseline duration of symptom, presence of a chronic condition, and an adjustment term for the correlation within study site. We also included an interaction term between the laboratory parameters and the SARS-CoV-2 test result to evaluate whether the associations between the laboratory parameters and the outcome (ie, severe outcome) depend on SARS-CoV-2 status (ie, positive or negative). This approach allowed us to estimate adjusted associations of the laboratory test that depend on SARS-CoV-2 status while also providing a rigorous test to determine if the effects were significantly different based on SARS-CoV-2 status along with adjustment for the common effects of the covariates, two advantages not readily available from a stratified analysis. Collinearity was checked using variance inflation factor. We calculated the adjusted odds ratio (aOR) of the laboratory parameter on severity among the SARS-CoV-2-positive and -negative subgroups, respectively, and compared them for significance using the interaction terms.

We used a complete case analysis approach as only 0.4% of participants lacked primary outcome data and there were no missing baseline demographic data. We did not impute missing laboratory variables as the assumption of missing at random required for multiple imputation was not met as missing laboratory results were likely due to true missingness (ie, not performed based on clinical assessment). Statistical significance was set at .05 for all tests. *P* values were corrected for multiple comparisons using the Benjamini-Hochberg method. All analyses were two-tailed and conducted using SPSS 25.0 (IBM Corp., Armonk, New York, NY, USA).

RESULTS

Between March 18, 2020, and June 15, 2021, 10 558 eligible children were enrolled in the parent study; 20.5% (n = 1817) met study eligibility criteria, including 522 (28.7%) SARS-CoV-2-test-positive and 1295 (71.3%) test-negative children (Figure 1). The median (IQR) age of SARS-CoV-2-positive participants was 3.0 (0.7–12.0) years, and 54.8% were male. Among SARS-CoV-2-positive children, those who experienced a severe outcome were older (median [IQR], 8.0 [2.0–15.0] vs 3.0 [0.5–11.0] years; $P = .002$) (Table 1]. Seventy-five (14.4%) of the SARS-CoV-2-positive and 174 (13.4%) of the SARS-CoV-2-negative children experienced severe outcomes during the 14-day study period (Table 2). Among SARS-CoV-2-positive patients, those who were excluded due to the absence of laboratory testing results, compared with those who were included, revealed no clinically meaningful differences in clinical characteristics (Supplementary Table 1).

Laboratory Parameters and Severe Outcomes Among SARS-CoV-2-Positive Children

In bivariable analyses, the proportions of participants with a lymphocyte count $<1.0 \times 10^9$/L (34.8% vs 13.5%; $P < .001$) and a platelet count $<150 \times 10^9$/L (18.1% vs 5.7%; $P = .002$) were higher among those with severe outcomes. Inflammatory markers differed between the 2 groups—those who experienced severe outcomes were more likely to have elevated procalcitonin (66.7% vs 26.2%; $P = .001$), ferritin (34.6% vs 7.9%; $P = .04$), and CRP (75.4% vs 53.2%; $P = .01$) values than those without. In addition, a greater proportion of children with severe outcomes,

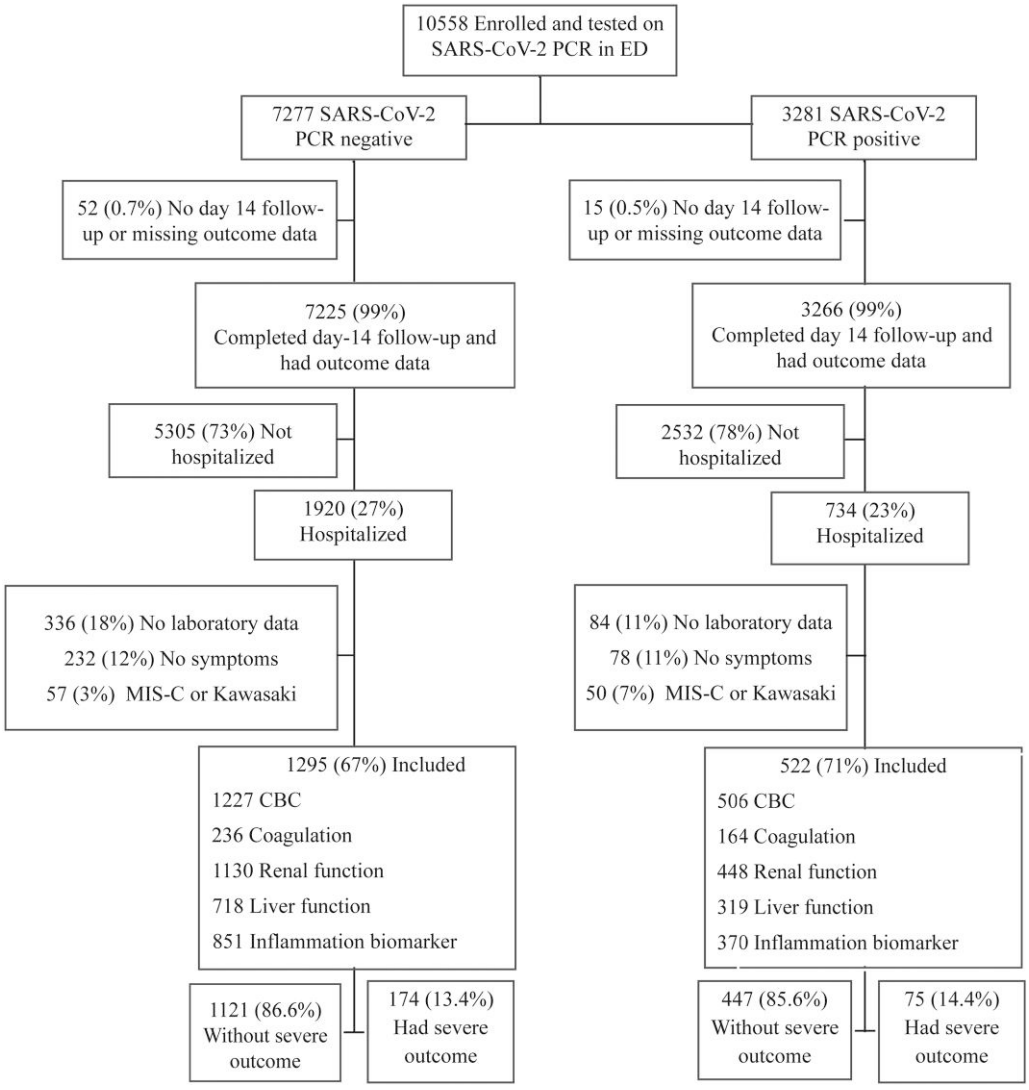

Figure 1. Study participants, SARS-CoV-2 test result, hospitalization status, laboratory tests performed, and occurrence of severe outcomes. Abbreviations: CBC, complete blood count; ED, emergency department; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Demographics, Baseline Clinical Characteristics, and Outcomes of the Hospitalized Patients, Stratified by SARS-CoV-2 PCR Status and Presence of Severe Outcomes

Characteristics	SARS-CoV-2 Positive				SARS-CoV-2 Negative			
	Subtotal (n = 522)	Without Severe Outcomes (n = 447)	Had Severe Outcomes (n = 75)	Adjusted *P* Value[a]	Subtotal (n = 1295)	Without Severe Outcomes (n = 1121)	Had Severe Outcomes (n = 174)	Adjusted *P* Value[b]
Age, median (IQR), y	3.0 (0.7–12.0)	3.0 (0.5–11.0)	8.0 (2.0–15.0)	.002	4.0 (1.0–11.0)	4.0 (1.0–11.0)	2.0 (0.7–8.0)	.04
Age group, No. (%)				.002				.08
<1 y	158 (30.3)	145 (32.4)	13 (17.3)		287 (22.2)	234 (20.9)	53 (30.5)	
1–<5 y	122 (23.4)	103 (23.0)	19 (25.3)		381 (29.4)	334 (29.8)	47 (27.0)	
5–<12 y	105 (20.1)	95 (21.3)	10 (13.3)		342 (26.4)	301 (26.9)	41 (23.6)	
≥12 y	137 (26.2)	104 (23.3)	33 (44.0)		285 (22.0)	252 (22.5)	33 (19.0)	
Sex, male, No. (%)	284 (54.4)	242 (54.1)	42 (56.0)	.80	711 (54.9)	597 (53.3)	114 (65.5)	.01
Country, No. (%)				.08				.20
United States	313 (60.0)	256 (57.3)	57 (76.0)		886 (68.4)	758 (67.6)	128 (73.6)	
Australia	0 (0)	0 (0)	0 (0)		26 (2.0)	25 (2.2)	1 (0.6)	
New Zealand	0 (0)	0 (0)	0 (0)		8 (0.6)	8 (0.7)	0 (0)	
Canada	35 (6.7)	33 (7.4)	2 (2.7)		151 (11.7)	135 (12.0)	16 (9.2)	
Spain	40 (7.7)	37 (8.3)	3 (4.0)		94 (7.3)	88 (7.9)	6 (3.4)	
Argentina	6 (1.1)	6 (1.3)	0 (0)		15 (1.2)	13 (1.2)	2 (1.1)	
Paraguay	10 (1.9)	8 (1.8)	2 (2.7)		12 (0.9)	9 (0.8)	3 (1.7)	
Costa Rica	94 (18)	83 (18.6)	11 (14.7)		100 (7.7)	82 (7.3)	18 (10.3)	
Singapore	16 (3.1)	16 (3.6)	0 (0)		2 (0.2)	2 (0.2)	0 (0)	
Italy	8 (1.5)	8 (1.8)	0 (0)		1 (0.1)	1 (0.1)	0 (0)	
Chronic condition, No. (%)	163 (31.2)	132 (29.5)	31 (41.3)	.06	485 (37.5)	398 (35.5)	87 (50.0)	.002
Duration of presenting symptom, median (IQR), d	2.0 (0.5–5.0)	2.0 (0.5–5.0)	3.0 (1.0–6.0)	.05	2.0 (0.5–5.0)	2.0 (0.5–5.0)	2.0 (0.5–4.0)	.29
Duration of presenting symptom, No. (%)				.05				.63
<4 d	340 (65.1)	301 (67.3)	39 (52.0)		837 (64.6)	719 (64.1)	118 (67.8)	
4–7 d	121 (23.2)	95 (21.3)	26 (34.7)		268 (20.7)	236 (21.1)	32 (18.4)	
>7 d	61 (11.7)	51 (11.4)	10 (13.3)		190 (14.7)	166 (14.8)	24 (13.8)	

Abbreviations: IQR, interquartile range; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Comparisons between the severe and nonsevere groups in the SARS-COV-2-positive participants using the Mann-Whitney *U* test, chi-square test, and Fisher exact test, as appropriate; *P* values reported were adjusted *P* values by Benjamini-Hochberg method for multiple comparisons within sets of tests.

[b]Comparisons between the severe and nonsevere groups in the SARS-COV-2-negative participants using the Mann-Whitney *U* test, chi-square test, and Fisher exact test, as appropriate; *P* values reported were adjusted *P* values by Benjamini-Hochberg method for multiple comparisons within the set of tests.

than those without, had elevated AST and serum glucose concentrations (Table 3; Supplementary Table 1 and Supplementary Figure 1). In multivariable regression analyses, laboratory parameters associated with severe outcomes included ferritin >500 ng/mL, procalcitonin ≥0.5 ng/mL, D-dimer ≥1500 ng/mL, lymphocyte count $<1.0 \times 10^9$/L, platelet count $<150 \times 10^9$/L, serum glucose ≥120 mg/dL, and ANC $<1.0 \times 10^9$/L (Table 4).

Interaction Between Laboratory Parameters and SARS-CoV-2 Test Status on Severe Outcomes

When we compared the associations between laboratory parameters and severe outcomes among the SARS-CoV-2-positive vs -negative groups, certain laboratory parameters were associated with severe outcomes among SARS-CoV-2-positive children but not among test-negative children in stratified analysis. These included lymphocyte count $<1 \times 10^9$/L, D-dimer ≥1500 ng/mL, platelet count $<150 \times 10^9$/L, ferritin >500 ng/dL, and procalcitonin ≥0.5 ng/mL. Meanwhile, ANC > upper limit of normal, INR >1.1, ALT > upper limit of normal for age, and serum sodium >145 mmol/L were associated with severe outcomes among SARS-CoV-2-negative children. The interaction analysis revealed that the effect differed significantly based on SARS-CoV-2 test status, with an increased odds of severe outcomes for SARS-CoV-2 test-positive children for the following laboratory findings: platelet count $<150 \times 10^9$/L ($P = .005$), procalcitonin ≥0.5 ng/mL ($P < .001$), CRP > upper limit of normal ($P = .02$), D-dimer ≥1500 ng/mL ($P = .04$), and lymphocyte count $<1.0 \times 10^9$/L ($P = .05$) (Table 4).

DISCUSSION

As COVID-19 continues to be an important, prevalent condition and severe outcomes continue to occur in children, understanding the associations between readily accessible laboratory parameters and the occurrence of severe outcomes in SARS-CoV-2-infected patients is needed to guide clinical care. We found that elevated procalcitonin, CRP, ferritin, D-dimer, and glucose and low lymphocyte and platelet counts

Table 2. Presence of Severe Outcomes of the Hospitalized Patients, Stratified by SARS-CoV-2 Test Result Status

	SARS-CoV-2 Positive (n = 522)	SARS-CoV-2 Negative (n = 1295)	Adjusted *P* Value[b]
Any severe outcome,[a] No. (%)	75 (14.4)	174 (13.4)	.92
Cardiac or cardiovascular	4 (0.8)	13 (1.0)	.99
Endocarditis/myocarditis/pericarditis	2 (0.4)	5 (0.4)	>.99
Congestive heart failure	2 (0.4)	3 (0.2)	.92
Cardiac arrest	0 (0)	4 (0.3)	.92
Stroke	1 (0.2)	1 (0.1)	>.99
Cardiac ischemia	0 (0)	0 (0)	n/a
Infectious	7 (1.3)	22 (1.7)	.92
Septic shock	5 (1.0)	11 (0.9)	>.99
Sepsis with bacteremia	1 (0.2)	7 (0.5)	.92
Toxic shock syndrome	1 (0.2)	1 (0.1)	>.99
Disseminated intravascular coagulation	0 (0)	2 (0.2)	.92
Mastoiditis	0 (0)	1 (0.1)	>.99
Neurologic	5 (1.0)	17 (1.3)	.92
Encephalitis/meningitis	5 (1.0)	17 (1.3)	.92
Respiratory	38 (7.3)	60 (4.6)	.37
Respiratory failure	28 (5.4)	43 (3.3)	.44
Acute respiratory distress syndrome (severity not specified)	12 (2.3)	7 (0.5)	.06
Pleural effusion or pneumothorax or pneumomediastinum requiring drainage	3 (0.6)	4 (0.3)	.92
Mild acute respiratory distress syndrome	3 (0.6)	3 (0.2)	.92
Moderate acute respiratory distress syndrome	0 (0)	2 (0.2)	.92
Empyema	0 (0)	2 (0.2)	.92
Severe acute respiratory distress syndrome	1 (0.2)	0 (0)	.92
Necrotizing or cryptogenic organizing pneumonia	0 (0)	1 (0.1)	>.99
Interventions representing a severe outcome	41 (7.9)	92 (7.1)	.92
Mechanical ventilation	30 (5.7)	62 (4.8)	.92
Inotropic support	16 (3.1)	24 (1.9)	.87
Renal replacement therapy	2 (0.4)	13 (1.0)	.92
Chest drainage	3 (0.6)	4 (0.3)	.92
Extracorporeal membrane oxygenation	0 (0)	2 (0.2)	.92
High-flow oxygen by nasal cannula	24 (4.6)	45 (3.5)	.92
Death	1 (0.2)	1 (0.1)	.99

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Comparisons between groups using chi-square test or Fisher exact test, as appropriate.

[b]*P* values reported were adjusted *P* values by Benjamini-Hochberg method for multiple comparisons within sets of tests.

were associated with severe outcomes among hospitalized children with SARS-CoV-2 infections. Furthermore, elevated procalcitonin, CRP, and D-dimer and low lymphocyte and platelet counts had significantly stronger associations with severe outcomes among SARS-CoV-2-positive participants than among those who were test-negative.

Inflammatory mechanisms play a principal role in COVID-19-related organ dysfunction and mortality [16, 24], and patients with COVID-19 typically have increases in inflammatory cytokines such as interleukin-6 and tumor necrosis factor–α [25, 26]. SARS-CoV-2 infections may trigger MIS-C [27–30], a serious and life-threatening illness. Typical laboratory hyperinflammatory manifestations in laboratory findings in MIS-C include elevation in neutrophils, procalcitonin, CRP, ESR, ferritin, D-dimer, INR, ALT, BUN, and creatinine, and decrease in hemoglobin, platelet count, and lymphocyte count. Our findings add to the literature by demonstrating that elevated levels of serologic indicators of inflammation are associated with severe outcomes in children with COVID-19, even those who do not have MIS-C. Furthermore, we found interactions between several markers and positive SARS-CoV-2 testing on the occurrence of severe outcomes. This finding suggests that SARS-CoV-2 infection affects the pediatric immune system in a manner that differs from other common pediatric illnesses that can also lead to severe outcomes.

In our study, SARS-CoV-2-positive children with elevated procalcitonin ≥0.5 ng/mL were at a 9-fold increase in odds of experiencing a severe outcome compared with children with lower procalcitonin levels. Previous pediatric COVID-19 studies did not identify significant differences in procalcitonin levels between those with and those without severe outcomes [12, 31]. However, in adults with COVID-19, a meta-analysis that included 4 studies reported that a procalcitonin level ≥0.5 ng/mL was associated with a nearly 5-fold increased odds of severe

Table 3. First Available Laboratory Test Results Among SARS-CoV-2-Positive Hospitalized Patients Stratified by Outcome Severity; All Data Presented Are Count (%)

	Without Severe Outcomes (n = 447)		Had Severe Outcomes (n = 75)		Adjusted *P* Value[a]
Complete blood count					
White blood cell, $\times 10^9$/L	433	8.6 (5.7–13.4)	73	8.8 (5.8–12.7)	.99
ANC $<1.0 \times 10^9$/L	417	42 (10.1)	70	3 (4.3)	.39
ANC > upper normal limit[b]	417	95 (22.8)	70	20 (28.6)	.58
Lymphocytes $<1.0 \times 10^9$/L	377	51 (13.5)	66	23 (34.8)	<.001
Hemoglobin < normal lower limit[b]	432	118 (27.3)	73	25 (34.2)	.45
Platelet count $<150 \times 10^9$/L	424	24 (5.7)	72	13 (18.1)	.002
Hematocrit < normal lower limit[b]	427	147 (34.4)	73	22 (30.1)	.67
Hematocrit > normal upper limit[b]	427	17 (4.0)	73	6 (8.2)	.34
Inflammatory biomarkers					
Procalcitonin ≥0.5 ng/mL	65	17 (26.2)	21	14 (66.7)	.001
ESR >25 mm/h	69	32 (46.6)	21	10 (47.6)	.99
Ferritin >500 ng/mL	38	3 (7.9)	26	9 (34.6)	.04
CRP > normal upper limit,[b] mg/dL	284	151 (53.2)	57	43 (75.4)	.01
Coagulation					
PTT >45 s	100	3 (3.0)	37	3 (8.1)	.58
INR >1.1	102	40 (39.2)	38	18 (47.4)	.58
D-dimer ≥1500 ng/mL	45	8 (17.8)	26	8 (30.8)	.45
Other					
Lactic acid >2.2 mmol/L	59	24 (40.7)	24	11 (45.8)	.84
Serum sodium <135 mmol/L	377	86 (22.8)	71	16 (22.5)	.99
Serum sodium >145 mmol/L	377	3 (0.8)	71	2 (2.8)	.39
BUN > normal upper limit,[b] mg/dL	345	39 (11.3)	70	9 (12.9)	.99
Creatinine > normal upper limit [6]	374	29 (7.8)	70	7 (10.0)	.70
ALT > normal upper limit[b]	256	32 (12.5)	61	14 (23.0)	.11
AST > normal upper limit[b]	247	54 (21.9)	60	23 (38.3)	.04
Glucose <40 mg/dL	360	2 (0.6)	69	0 (0)	>.99
Glucose ≥120 mg/dL	360	63 (17.5)	69	21 (30.4)	.05

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophils count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

[a]Comparisons between the severe and nonsevere groups in the SARS-COV-2-positive participants using the Mann-Whitney *U* test, chi-square test, or Fisher exact test, as appropriate; *P* values reported were adjusted *P* values by Benjamini-Hochberg method for multiple comparisons.

[b]Age-adjusted ranges of normal laboratory values are provided in Supplementary Text 1.

SARS-CoV-2 disease [22]. In addition, we found that a positive SARS-CoV-2 test significantly increased the magnitude of the associations between elevated CRP and procalcitonin levels and the occurrence of severe outcomes. Thus, among children with COVID-19 who are sufficiently ill to be hospitalized, baseline CRP and procalcitonin levels should be obtained.

Although the association between lymphopenia and severe illness among adults with COVID-19 is well established [6–8, 32], this association in children is less well characterized. In a meta-analysis of 398 children with COVID-19, the incidence of lymphopenia was 16% (97% CI, 7%–32%) [33]. In a study of 171 mild and severe pediatric SARS-CoV-2 cases in Wuhan, China, 3.5% had a lymphocyte count $<1.2 \times 10^9$/L [34]. However, in these studies, no associations between lymphopenia and severe outcomes were established. In another study that included 36 children in China, 47% (9/19) of the moderate SARS-CoV-2 cases had decreased lymphocyte counts [23].

Lymphopenia is believed to occur because lymphocytes express high levels of angiotensin-converting enzyme 2 (ACE2) receptors, and the SARS-CoV-2 virus has a predilection for these receptors. Once lymphocyte infection occurs, cell lysis follows [35, 36]. In adults with severe COVID-19, the proportion with lymphopenia exceeds 90%, and individuals with lymphopenia are at a 4-fold increased odds of developing severe relative to moderate disease [37]. In this study, we found that 23% of children with severe outcomes had lymphocyte counts $<1 \times 10^9$/L. Lymphopenia was associated with severe outcomes, and the magnitude of the association between lymphopenia and severe outcomes was increased among SARS-CoV-2-positive children.

A meta-analysis including 9 studies and 1779 COVID-19 adult patients revealed that platelet count was significantly lower in patients with more severe illness [38]. Moreover, in a subgroup analysis, low platelet count (<150 or 100×10^9/L) was associated with a 5-fold increased risk of severe

Table 4. Summary of Multivariable Analysis of Associations Between Laboratory Features and Severe Outcomes Including an Interaction Term for the Association Between SARS-CoV-2 Nucleic Acid Test Status and Laboratory Features on Severe Outcomes

	Association With Severe Outcome				Interaction Between Laboratory Feature and SARS-CoV-2	
	SARS-CoV-2 Negative		SARS-CoV-2 Positive			
Laboratory Parameters	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
ANC						
ANC <1.0 k/mcl	1.13 (0.47–2.70)	.79	0.37 (0.15–0.92)	.03	0.33 (0.09–1.17)	.09
ANC > upper limit[a]	1.68 (1.05–2.67)	.03	1.45 (0.88–2.40)	.14	0.87 (0.42–1.80)	.70
ANC >1.0 k/mcl and < normal upper limit	Reference		Reference			
Lymphocyte count <1.0 k/mcl	1.29 (0.71–2.37)	.41	3.21 (1.34–7.69)	.009	2.49 (1.01–6.12)	.05
Hemoglobin < lower limit[a]	1.02 (0.76–1.38)	.89	1.24 (0.78–1.98)	.36	1.22 (0.70–2.12)	.49
HCT, %						
HCT < lower limit[a]	1.31 (0.89–1.93)	.18	0.79 (0.48–1.30)	.35	0.60 (0.34–1.07)	.08
HCT > upper limit[a]	1.98 (0.99–3.94)	.05	1.85 (0.85–4.02)	.12	0.93 (0.41–2.11)	.87
HCT within normal limit	Reference		Reference			
Platelet count $<150 \times 10^9$/L	0.77 (0.42–1.42)	.40	2.82 (1.31–6.07)	.008	3.66 (1.47–9.09)	.005
PTT >45 s	2.83 (0.40–19.79)	.30	3.45 (0.40–29.94)	.26	1.22 (0.07–21.09)	.89
INR >1.1	1.93 (1.10–3.37)	.02	1.53 (0.69–3.36)	.29	0.90 (0.37–2.20)	.82
D-dimer ≥1500 ng/mL	0.71 (0.26–1.93)	.50	4.57 (1.12–18.68)	.03	6.45 (1.13–36.98)	.04
Creatinine > normal upper limit [4]	1.32 (0.72–2.45)	.37	1.27 (0.50–3.25)	.61	0.96 (0.35–2.67)	.94
BUN > normal upper limit[a]	0.99 (0.54–1.83)	.97	1.09 (0.63–1.90)	.76	1.10 (0.55–2.21)	.79
AST > upper limit[a]	1.27 (0.74–2.18)	.38	1.97 (0.84–4.66)	.12	1.55 (0.53–4.51)	.42
ALT > upper limit[a]	1.80 (1.03–3.14)	.04	1.83 (0.85–3.92)	.12	1.02 (0.33–3.10)	.98
Serum lactate >2.2 mmol/L	0.76 (0.43–1.36)	.36	1.05 (0.32–3.48)	.93	1.38 (0.43–4.42)	.59
Ferritin >500 ng/mL	0.79 (0.06–10.02)	.86	7.95 (1.89–33.44)	.005	10.03 (0.45–224.85)	.15
ESR >25 mm/h	1.24 (0.60–2.57)	.57	0.83 (0.30–2.29)	.72	0.67 (0.16–2.81)	.58
Procalcitonin ≥0.5 ng/mL	0.97 (0.54–1.77)	.93	9.14 (2.90–28.80)	<.001	9.38 (3.24–27.12)	<.001
CRP > normal upper limit,[a] mg/dL	0.72 (0.46–1.13)	.15	2.43 (0.95–6.17)	.06	3.36 (1.2–9.39)	.02
Serum glucose ≥120 mg/dL	1.62 (1.10–2.38)	.02	2.01 (1.06–3.81)	.03	1.24 (0.52–2.95)	.63
Serum sodium						
Serum sodium >145 mmol/L	3.87 (1.55–9.68)	.004	3.40 (0.82–14.19)	.09	0.88 (0.15–5.15)	.89
Serum sodium <135 mmol/L	0.70 (0.45–1.10)	.12	1.01 (0.47–2.14)	.99	1.44 (0.72–2.84)	.30
Serum sodium 135–145 mmol/L	Reference		Reference			

A regression analysis was conducted for each of the laboratory parameters using multivariable logistic regression models, with the dependent variable being severe outcomes (yes vs no), fitted with the generalized estimating equation method to estimate the adjusted odds ratios of the categorical laboratory features and the interaction between the laboratory feature and SARS-CoV-2 test result status. Models included the laboratory test result, SARS-CoV-2 test result (positive vs negative), and the following a priori defined covariates: age, sex, illness duration at the time of the index ED visit, presence of a chronic condition, and an adjustment term for the correlation within study site.

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate; HCT, hematocrit; INR, international normalized ratio; OR, odds ratio; PCR, polymerase chain reaction; PTT, partial thromboplastin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Age-adjusted ranges of normal laboratory values are provided in Supplementary Text 1.

COVID-19. While no reports have evaluated platelet count in relation to severe outcome in children with COVID-19, we found that among SARS-CoV-2-infected children, those with platelet counts $<150 \times 10^9$/L had an increased odds of experiencing severe outcomes compared with those with higher platelet counts. Additionally, SARS-CoV-2 test positivity was associated with a greater association between thrombocytopenia and severe outcomes. This may be due to direct infection of hematopoietic stem cells, megakaryocytes, and platelets, inducing growth inhibition and apoptosis [39].

Previous reports have found that elevated D-dimer levels in SARS-CoV-2-infected children are associated with intensive care unit admission and length of stay [40]. Moreover, among hospitalized adults with COVID-19, elevated D-dimer levels are associated with mortality [9]. Our study sheds additional light on the importance of D-dimer in hospitalized children with SARS-CoV-2 infection. Those with values ≥1500 ng/mL had a 4-fold increase in the odds of experiencing a severe outcome; no association was found among children who were SARS-CoV-2 negative. Additionally, SARS-CoV-2 positivity increased the magnitude of the association between elevated D-dimer values and severe outcomes.

Our study has limitations. We only collected the first available laboratory test result, and thus we were unable to analyze the evolution of laboratory parameters over time. Nonetheless, as most children with COVID-19 are managed as outpatients, the first laboratory tests, commonly performed in an ED, can

provide crucial information to inform clinical decision-making and the need for hospitalization. Additionally, we could not correlate the timing of the occurrence of severe outcomes in relation to laboratory test performance, and participants experienced these events at varying stages of their illnesses.

While we categorized laboratory variables to ensure that the assumption of linearity of log odds was met in our regression model and to simplify data interpretation and integration into practice, such an approach reduces power, and although based on previous literature, it was performed without certainty that the selected cut-points were the most appropriate for this study. Although we excluded patients who were not hospitalized because they were deemed to be clinically well and we have previously demonstrated that such children rarely have severe outcomes [3], their exclusion precludes generalizing our results to nonhospitalized children. There is the possibility that bias was introduced by not including individuals who declined consent/assent to study participation, those who declined to be tested, and those who were not tested by the responsible physician. However, these events were uncommon, and it is unlikely that the interaction between their laboratory parameters and SARS-CoV-2 status differs from those that were included.

Although we excluded patients who did not have laboratory data available, we found no meaningful differences between included and excluded children. Our multivariable analysis could not include all laboratory parameters in a single model because very few patients had all the laboratory blood tests performed, which is required when such an approach is used. While our multivariable analyses adjusted for symptom duration, given the aforementioned limitations, we did not evaluate the laboratory parameters as predictors of severe outcomes; rather, we report the strength of the association.

We did not collect data on reasons for hospitalization and thus cannot be certain that all participants were hospitalized due to their infectious symptoms. However, we minimized potential differences between SARS-CoV-2-positive and -negative children by limiting eligibility to children with symptoms potentially associated with COVID-19 infection. As most participants did not undergo testing for other respiratory viruses, we could not perform analyses related to the effect of coinfection. Finally, participants were recruited during the first two COVID-19 pandemic waves; as variants of concern evolve over time, the associations between laboratory parameters and severe outcomes may not be constant.

Our findings have implications for clinicians, who must always evaluate the importance of abnormal laboratory findings. However, when the laboratory parameters we identified that interact positively with SARS-CoV-2 test status are present, they have even greater importance in this population than among children who are ill from other etiologies. Thus, extra care should be taken when present; this may include additional monitoring, admission to a step-down unit, or transfer to a pediatric tertiary care institution.

In conclusion, in this large multicenter, multinational study, we identified laboratory parameters associated with severe outcomes in hospitalized children with SARS-CoV-2 infections. As laboratory testing interacted with SARS-CoV-2 status, elevated serum procalcitonin, CRP, and D-dimer and low absolute lymphocyte and platelet counts were more strongly associated with severe outcomes in children testing positive compared with those testing negative for SARS-CoV-2 infection. These readily available biomarkers may assist clinicians providing care to children hospitalized with SARS-CoV-2 infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Data access, responsibility, and analysis. Drs. Jianling Xie and Stephen Freedman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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