OBSERVATIONAL STUDY

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Immunocompromised Children With Acute Respiratory Distress Syndrome Possess a Distinct Circulating Inflammatory Profile

John Nguyen, BS[1]
Jill M. Thompson, MS[1]
Daniel R. Balcarcel, MD[1]
Matthew N. Alder, MD[2]
Daniel J. McKeone, MD[3]
E. Scott Halstead, MD[4]
Courtney M. Rowan, MD[5]
Robert B. Lindell, MD[1,6]
Nadir Yehya, MD[1,7]

IMPORTANCE: Immunocompromised status, with and without stem cell transplant, confers a worse prognosis in pediatric acute respiratory distress syndrome. An improved understanding of the biochemical profile of immunocompromised children with acute respiratory distress syndrome would inform whether specific pathways are targetable, or merely bystanders, in order to improve outcomes in this high-risk subgroup.

OBJECTIVES: We aimed to identify a biomarker profile of immunocompromised children, with and without stem cell transplant, independent of illness severity.

DESIGN, SETTINGS, AND PARTICIPANTS: This was a secondary analysis of a prospective cohort study of intubated children with Berlin-defined acute respiratory distress syndrome with existing biomarker measurements conducted in a large academic PICU between 2014 and 2019.

MAIN OUTCOMES AND MEASURES: Biomarker levels were compared between immunocompetent and immunocompromised children, with and without stem cell transplant, both prior to and after adjusting for severity of illness.

RESULTS: In 333 children with acute respiratory distress syndrome, 84 were immunocompromised, of whom 39 had a stem cell transplant. Circulating neutrophil levels were strongly correlated with biomarkers, with 14 of 18 measured proteins differentially expressed in patients with versus without neutropenia. In order to identify biomarker levels independent of severity of illness, acute respiratory distress syndrome etiology, and neutrophil levels, we computed predicted (log-transformed) biomarker levels after adjusting for confounders using linear regression and then compared these severity-adjusted levels between immunocompetent and immunocompromised (with and without stem cell transplant) subjects using analyses of variance and post hoc Bonferroni. After multivariable adjustment, 11 biomarkers were higher in immunocompromised subjects without stem cell transplant, relative to immunocompetent, implicating endotheliopathy (angiopoietin-2), tissue damage (procollagen type III N-terminal peptide), and innate immunity. A single biomarker, C-C motif chemokine ligand 22, was lower in immunocompromised subjects with and without stem cell transplant.

CONCLUSIONS AND RELEVANCE: Immunocompromised children with acute respiratory distress syndrome were characterized by elevations in pro-inflammatory and endothelial damage biomarkers. Our study provides insight into mechanisms underlying the molecular heterogeneity of this population and potentially identifies targetable pathways to mitigate their increased mortality risk.

KEY WORDS: acute respiratory distress syndrome; immunocompromised; pediatric; stem cell transplantation

Acute respiratory distress syndrome (ARDS) is heterogeneous, with patients having distinct inciting etiologies (1, 2), comorbidities, severity of hypoxemia (3), and coexisting organ failures. In both adults

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KEY POINTS

Question: Do plasma protein levels differ in children with acute respiratory distress syndrome (ARDS) according to immunocompromise and stem cell transplant (SCT) status?

Finding: Immunocompromised children had a distinct biomarker profile than immunocompetent, independent of severity of illness, etiology of ARDS, and absolute neutrophil count, with higher levels of inflammatory and endothelial damage biomarkers, and lower levels of C-C motif chemokine ligand 22. Immunocompromised children with SCT had average risk-adjusted biomarker levels between immunocompromised without SCT and immunocompetent children.

Meaning: Biochemical differences in immunocompromised children with ARDS can help clarify how immunocompromise status contributes to the molecular heterogeneity of ARDS and potentially can identify targetable pathways to mitigate increased mortality risk.

and pediatric ARDS, immunocompromised status and stem cell transplant (SCT) confer worse prognosis (4–7), potentially due to risks of immunosuppression or endothelial dysfunction caused by chemotherapy. A better understanding of the biochemical profile in immunocompromised subjects with ARDS may clarify mechanisms underlying higher mortality. Additionally, improved characterization of the molecular heterogeneity of ARDS as it relates to immune status is necessary for identifying whether specific pathways are targetable, or merely bystanders, to improve outcomes in this subgroup.

Therefore, leveraging a pediatric ARDS cohort with multiple biomarker measurements, we assessed for differential expression of plasma proteins according to immunocompromised status and by presence or absence of SCT. We aimed to identify a biomarker profile of immunocompromised children with and without SCT independent of severity of illness and ARDS etiology. As neutrophils are implicated in ARDS pathobiology (8–10), we specifically focused on understanding the degree to which biomarker differences could be explained by neutropenia.

METHODS

Design and Setting

This was an unplanned secondary analysis of a prospective cohort, approved by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB 13-010578; Biomarkers of Pediatric ARDS; approved July 2, 2014), conducted in accordance with the ethical standards set forth by the CHOP IRB consistent with the Helsinki Declaration of 1975. Portions of this cohort have been reported previously (11). Complete Methods are provided in the **Data Supplement** (http://links.lww.com/CCX/B125).

Participants and Definitions

Intubated children with Berlin ARDS (12) admitted to the CHOP PICU between 2014 and 2019 were included after caregivers provided informed consent. Clinical data, including WBC and absolute neutrophil count (ANC), were prospectively recorded. Oxygenation was quantified using Pao_2/Fio_2 and the oxygenation index (OI). Severity of illness was measured by Pediatric Risk of Mortality (PRISM) III score at 12 hours. Vasopressor-Inotrope Score (VIS) was calculated using a validated equation (13). Nonpulmonary organ failures were defined using 2005 Goldstein criteria for sepsis (14). ARDS etiology was identified at time of eligibility. The designation of "immunocompromised" required presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, transplant) and active immunosuppressive therapy, or presence of a congenital immunodeficiency (15). We stratified subjects with immunocompromising conditions (ICCs) according to presence (ICC + SCT) or absence (ICC no SCT) of SCT.

Biomarker Measurements

Blood was collected within 24 hours of ARDS diagnosis, and biomarkers measured using enzyme-linked immunosorbent assays. The aim of the parent study was to identify biomarker profiles associated with worse outcomes in pediatric ARDS and was not designed a priori to assess for differences between subjects with and without ICC. Candidate biomarkers were chosen based on prior literature: olfactomedin 4 (OLFM4), granzyme B, heat shock protein 70 (HSP70), interleukin (IL)-1α, IL-8, C-C motif chemokine ligand

TABLE 1.
Demographics of the Cohort

Variables	Immunocompetent (*n* = 249)	ICC No SCT (*n* = 45)	ICC + SCT (*n* = 39)	*p*
Demographics				
Age (yr)	5.2 (1.5–12.8)	6.9 (4–14.5)	6.6 (2.8–13.6)	0.094
Male/female (%/%)	138/111 (55/45)	23/22 (51/49)	23/16 (59/41)	0.765
Severity of illness				
Pediatric Risk of Mortality III at 12 hr	10 (5–17)	16 (10–21)	11 (5–17)	0.011
Vasopressor-Inotrope Score	8 (0–15)	16 (4–45)	5 (0–20)	0.011
Organ failures	1 (1–2)	2 (1–3)	2 (2–3)	< 0.001
WBC (1,000/μL)	8.8 (5.8–13.2)	1.3 (0.2–5.6)	2.9 (1.5–6.5)	< 0.001
Absolute neutrophil count (1,000/μL)	6 (3.2–11.5)	0.3 (0–2.3)	2 (0.7–4)	< 0.001
Cause of ARDS (%)				
Pneumonia	131 (53)	11 (24)	20 (51)	
Nonpulmonary sepsis	47 (19)	20 (44)	16 (41)	< 0.001
Aspiration	43 (17)	5 (11)	2 (5)	
Other	28 (11)	9 (20)	1 (3)	
Cause of ICC (%)				
Hematologic malignancy	–	24 (53)	19 (49)	0.827
Solid cancer	–	7 (16)	7 (16)	0.778
Immunodeficiency	–	2 (4)	3 (8)	0.659
Hemophagocytic lymphohistiocytosis	–	4 (9)	10 (26)	0.076
Solid organ transplant	–	7 (16)	0	0.013
High-dose chemotherapy	–	1 (2)	0	> 0.999
ARDS onset				
Pao_2/Fio_2	150 (94–226)	155 (109–216)	172 (128–230)	0.355
OI	11.3 (7.2–22.3)	9.8 (7.2–15.4)	10.1 (8.3–16)	0.552
PIP (cm H_2O)	31 (26–36)	30 (26–33)	34 (30–38)	0.004
PEEP (cm H_2O)	10 (8–12)	10 (8–12)	10 (10–14)	0.047
mPaw (cm H_2O)	18 (15–21)	16 (13–19)	19 (17–24)	0.003
24 hr of ARDS				
Pao_2/Fio_2	235 (165–307)	231 (143–283)	181 (143–261)	0.017
OI	6.5 (4.4–11.5)	6.6 (4.8–12.2)	11.0 (7.0–14.5)	0.002
PIP (cm H_2O)	27 (23–31)	26 (24–30)	33 (30–38)	< 0.001
PEEP (cm H_2O)	10 (8–12)	8 (8–10)	12 (10–14)	< 0.001
mPaw (cm H_2O)	16 (13–19)	15 (13–18)	20 (17–22)	< 0.001
Ancillary ARDS therapies used by day 3 (%)				
Corticosteroids	108 (43)	30 (67)	27 (69)	< 0.001
Neuromuscular blockade	126 (51)	18 (40)	28 (72)	0.012
Nonconventional ventilator	65 (26)	8 (18)	10 (26)	0.491
Inhaled nitric oxide	90 (36)	15 (33)	19 (49)	0.230
PICU mortality (%)	31 (12)	14 (31)	24 (62)	< 0.001

ARDS = acute respiratory distress syndrome, ICC = immunocompromising condition, mPaw = mean airway pressure, OI = oxygenation index, PEEP = positive end-expiratory pressure, PIP = peak inspiratory pressure, SCT = stem cell transplant.
Data are presented as *n* (%) or median (interquartile range).
Dashes indicate that none of the Immunocompetent children had an immunocompromising diagnosis.

TABLE 2.
Biomarker Levels (Median and Interquartile Ranges) of Subjects Stratified According to Neutropenia (Absolute Neutrophil Count < 1,000)

Biomarkers	Whole Cohort (*n* = 333)	Neutropenia With ANC < 1,000 (*n* = 54)	Non-Neutropenic With ANC ≥ 1,000 (*n* = 279)	*p*
Angiopoietin-2 (ng/mL)	5.5 (2.9–13.3)	11.6 (5.4–13.3)	4.5 (2.6–11.8)	< 0.001
Soluble receptor for advanced glycation end-products (ng/mL)	2.3 (1.1–5.5)	3.2 (1.4–10.7)	2.2 (1–5.1)	0.011
Surfactant protein D (ng/mL)	12.2 (6.5–23.6)	11.8 (6.3–21.6)	12.4 (6.5–26.2)	0.672
Procollagen type III N-terminal peptide (ng/mL)	19.2 (4.2–44.5)	43.8 (12.5–108)	17.5 (3.4–38.2)	< 0.001
Nucleosomes (AU)	0.14 (0.05–0.34)	0.19 (0.03–0.63)	0.14 (0.05–0.32)	0.458
Granzyme B	5.8 (2.9–18.9)	8.9 (4–55.7)	5.4 (2.7–16.1)	0.003
Heat shock protein 70 (ng/mL)	155 (80–353)	278 (159–1,626)	137 (74–306)	< 0.001
Tumor necrosis factor α	16 (9.5–32.6)	35.3 (22.5–73.9)	14.4 (8.5–24.1)	< 0.001
Soluble tumor necrosis factor receptor 1 (ng/mL)	2.4 (1.4–4.8)	4.6 (3.1–9.7)	2 (1.3–4.3)	< 0.001
IL-1α	0.3 (0.1–1.4)	0.7 (0.1–3.1)	0.3 (0.1–1.3)	0.015
IL-6	179 (43–919)	2,378 (422–9,714)	118 (28–569)	< 0.001
IL-8	115 (42–546)	2,214 (342–15,372)	82 (35–254)	< 0.001
Olfactomedin 4 (ng/mL)	2.4 (0.6–6.8)	3.5 (0.6–8.9)	2.3 (0.6–6.4)	0.426
CCL7	10.2 (3.3–36.8)	48.9 (14.8–117)	7.7 (2.7–26.5)	< 0.001
CCL22	500 (304–779)	357 (140–710)	517 (323–784)	0.011
MIP-1α	22.3 (14.9–43.8)	42.9 (25.8–128)	19.8 (14.5–40.4)	< 0.001
MIP-1β	42.7 (26–78.2)	79.1 (47.2–208)	37.2 (24.7–71.9)	< 0.001
Matrix metalloproteinase 8 (ng/mL)	7.9 (3–20.3)	12.7 (3.3–24.2)	7.7 (2.8–19.3)	0.334

ANC = absolute neutrophil count, AU = arbitrary units, CCL = C-C motif chemokine ligand, IL = interleukin, MIP = macrophage inflammatory protein.
All concentrations are in pg/mL unless otherwise noted.

(CCL) 3/macrophage inflammatory protein (MIP)-1α, MIP-1β, matrix metalloproteinase 8 (MMP8), CCL7, CCL22, IL-6, soluble tumor necrosis factor receptor 1 (sTNFR1), tumor necrosis factor α (TNFα), nucleosomes (Sigma-Aldrich, St. Louis, MO), procollagen type III N-terminal peptide (P3NP; Abbexa, Cambridge, United Kingdom), surfactant protein D (SPD), angiopoietin-2 (ANG2), and soluble receptor for advanced glycation end-products (sRAGE).

Statistical Analysis

We compared clinical characteristics between immunocompetent subjects, ICC no SCT and ICC + SCT. We then compared (natural)log-transformed biomarker levels between groups using analysis of variance (ANOVA) and post hoc Bonferroni. We tested whether biomarkers differed in neutropenic (ANC < 1,000/μL) versus non-neutropenic (ANC ≥ 1,000/μL) subjects and whether biomarkers differed in the immediate (within 100 d) post-SCT period relative to greater than 100 days post-SCT in ICC + SCT subjects. Our primary aim was to test whether biomarkers varied by immune status independent of illness severity by computing predicted biomarker levels after adjusting for confounders using linear regression and then comparing severity-adjusted levels between immunocompetent, ICC no SCT, and ICC + SCT (16). Confounders included age, ARDS etiology, OI at ARDS onset, VIS, and ANC. In order to assess the robustness of our findings to the choice of confounders, we performed a sensitivity analysis adjusting for a different combination of confounders: age, ARDS etiology, OI at 24 hours after ARDS onset (17), PRISM III score, and ANC. In all analyses, biomarker levels were back-transformed to

facilitate reporting. Analyses were performed in Stata 14.2 (StataCorp, College Station, TX).

RESULTS

Demographics of the Cohort

Of 333 subjects with ARDS, 84 (25%) had an ICC, of whom 39 (12%) had received SCT (Table 1; and **Supplementary Fig. 1**, http://links.lww.com/CCX/B125). In ICC + SCT subjects, median time between SCT and ARDS was 108 days (interquartile range, 32–529 d). ICC + SCT subjects had the highest PRISM III and VIS, and all ICC subjects had more nonpulmonary organ failures than immunocompetent. ICC no SCT subjects had the lowest ANC, followed by ICC + SCT, and then immunocompetent. ICC subjects were more likely to have nonpulmonary sepsis as an ARDS etiology than immunocompetent. ICC no SCT subjects had 20% of their ARDS etiology caused by "Other" (five from engineered T-cell therapy or other chemotherapy, three from trauma, and one from transfusion-associated lung injury). Hematologic malignancies were the most common ICC for both ICC no SCT and ICC + SCT. PICU mortality was highest in ICC + SCT, followed by ICC no SCT, and lowest in immunocompetent subjects.

Absolute Neutrophil Count Was Associated With Biomarker Levels

Biomarker levels for the entire cohort are provided in Table 2. ANC predicted biomarker levels, with 14 of 18 tested biomarkers differing between neutropenic and non-neutropenic subjects. Neutropenic subjects had higher ANG2, sRAGE, P3NP, granzyme B, HSP70, TNFα, sTNFR1, IL-1α, IL-6, IL-8, CCL7, MIP-1 α, and MIP-1β, relative to non-neutropenic, and lower levels of CCL22. As the first 100 days after SCT may possess a distinct biochemical profile, we explored whether biomarkers differed in the immediate post-SCT period relative to later in ICC + SCT subjects (**Supplementary Table 1**, http://links.lww.com/CCX/B125). Of the tested biomarkers, only CCL7 was higher in ICC + SCT subjects with ARDS greater than 100 days post-SCT.

Biomarker Levels Differ According to Immunocompromised Status

In unadjusted analysis (**Fig. 1**; and **Supplementary Fig. 2**, http://links.lww.com/CCX/B125), 11 biomarkers were higher in ICC no SCT subjects, relative to immunocompetent: ANG2, P3NP, HSP70, TNFα, sTNFR1, IL-6, IL-8, granzyme B, CCL7, MIP-1α, and MIP-1β. ICC + SCT subjects had elevated levels of ANG2, SPD, P3NP, nucleosomes, HSP70, TNFα, sTNFR1, IL-8, CCL7, MIP-1α, and MIP-1β, relative to immunocompetent. ICC + SCT had higher SPD, and lower IL-6, IL-8, granzyme B, CCL7, and MIP-1β, relative to ICC no SCT. A single biomarker, CCL22, was lower in both ICC no SCT and ICC + SCT, relative to immunocompetent.

After multivariable adjustment (**Fig. 2**; and **Supplementary Fig. 3**, http://links.lww.com/CCX/B125), 11 biomarkers were higher in ICC no SCT subjects: ANG2, P3NP, HSP70, TNFα, sTNFR1, IL-6, IL-8, granzyme B, CCL7, MIP-1α, and MIP-1β. ICC + SCT subjects had higher adjusted levels of P3NP, TNFα, sTNFR1, IL-8, CCL7, MIP-1α, and MIP-1β, relative to immunocompetent. All of these biomarkers were lower in ICC + SCT relative to ICC no SCT. CCL22 was lower in both ICC no SCT and ICC + SCT, relative to immunocompetent. IL-1α, sRAGE, OLFM4, and MMP8, did not differ in unadjusted or adjusted analyses (ANOVA F test $p > 0.05$). Results were similar when adjusting for a different set of severity of illness variables (**Supplementary Fig. 4**, http://links.lww.com/CCX/B125).

DISCUSSION

We identified plasma biomarkers associated with ICC or SCT independent of severity of hypoxemia, ARDS etiology, overall illness severity, or ANC. Our results suggest that immunocompromised children with ARDS are biochemically distinct, with elevations in innate immune and endothelial damage biomarkers. These biochemical differences may underlie the reasons why immunocompromised children with ARDS are at higher risk of death, clarify how ICCs contribute to the molecular heterogeneity of ARDS, and identify mechanisms to mitigate this increased mortality risk.

ICC no SCT subjects had evidence of endotheliopathy and hyperinflammation. Intriguingly, the severity-adjusted biomarker profile of ICC + SCT subjects was more similar to that of immunocompetent, despite having similar immunocompromising diagnoses as ICC no SCT and with higher mortality. ICC no SCT subjects had higher ANG2, relative to immunocompetent,

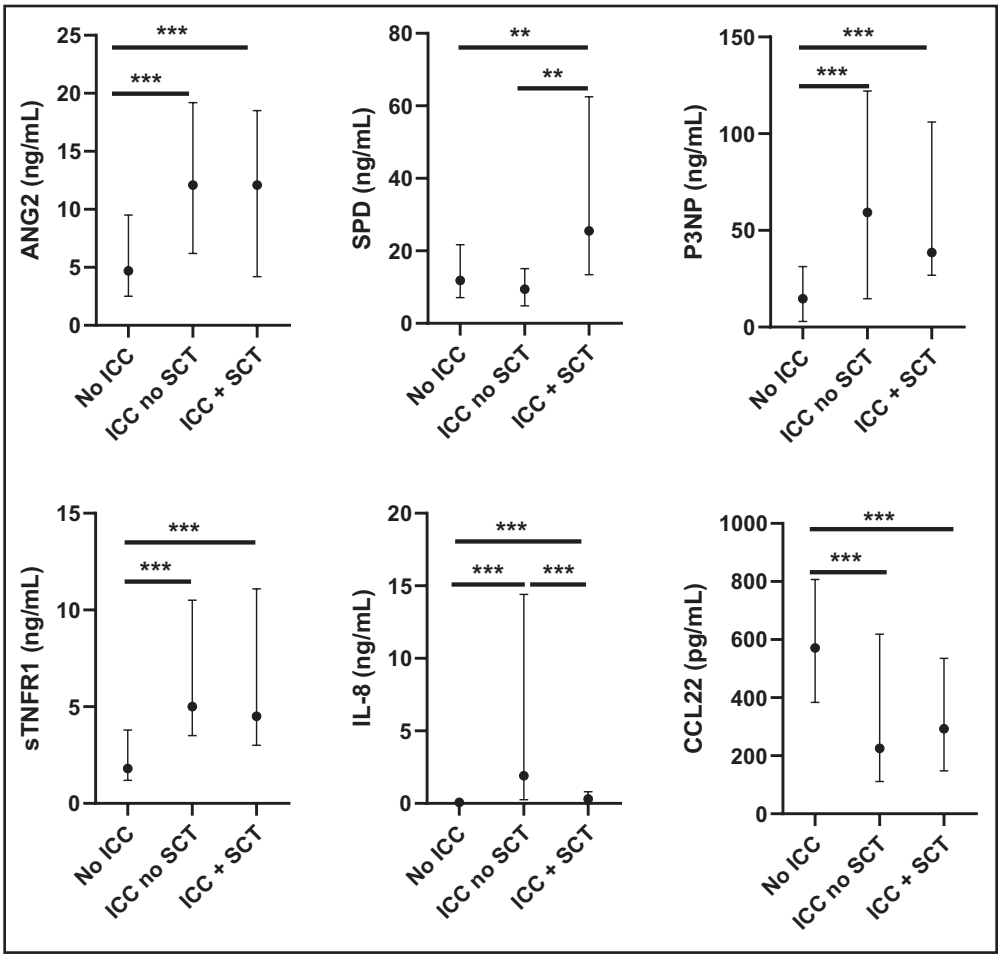

Figure 1. Selected unadjusted biomarker levels compared between immunocompetent (no immunocompromising condition [ICC]), ICC without stem cell transplant (SCT) (ICC no SCT), and ICC with SCT (ICC + SCT) subjects. Biomarkers were log-transformed and compared using analysis of variance, with post hoc Bonferroni corrections displayed (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). Data are back-transformed and presented as medians and interquartile ranges. ANG2 = angiopoietin-2, CCL22 = C-C motif chemokine ligand 22, IL-8 = interleukin-8, P3NP = procollagen type III N-terminal peptide, SPD = surfactant protein D, sTNFR1 = soluble tumor necrosis factor receptor 1.

suggesting endotheliopathy related to the underlying ICC. ANG2 was not higher in ICC + SCT, despite the well-described endothelial dysfunction in SCT (18), possibly because most subjects were not immediately post-SCT. ICC + SCT subjects with ARDS within 100 days of SCT had higher (albeit $p = 0.076$) ANG2, consistent with this possibility. ICC + SCT subjects also had WBC and ANC levels between those of ICC no SCT and immunocompetent, suggesting that differences in leukocyte levels could explain why ICC + SCT had "intermediate" ANG2.

Cytokine elevation in ICC is consistent with heightened innate inflammation. The sole biomarker with lower adjusted levels in ICC subjects was CCL22. CCL22 signals via CCR4 on regulatory T cells (T_{regs}), monocytes, and natural killer cells. CCL22 can recruit immunosuppressive T_{regs} to modulate the local immune response (19, 20), and CCL22-deficient mice have increased susceptibility to inflammatory diseases (21). Lower CCL22 in ICC + SCT raises the possibility of dysregulated T_{reg} modulation of innate immunity in these subjects, suggesting a mechanism for the increased mortality seen in patients with SCT.

Neutrophils have a central role in the pathogenesis and propagation of ARDS (22–24), and a better understanding of the clinical and molecular heterogeneity of neutropenic ARDS is needed. In our study, ANC was strongly associated with biomarker levels, and neutropenic subjects had higher levels of an endothelial damage biomarker (ANG2), tissue damage biomarkers (sRAGE, P3NP), and 10 pro-inflammatory cytokines and chemokines. Elevations in inflammatory cytokines

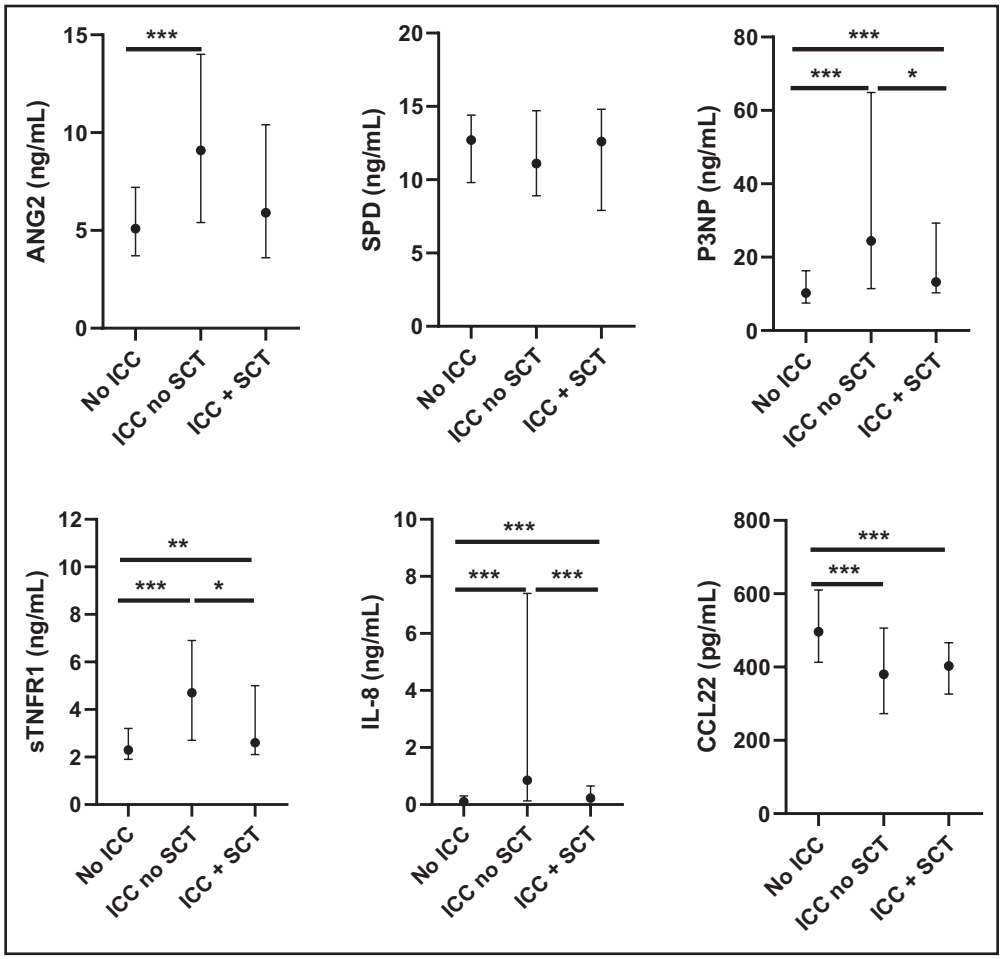

Figure 2. Selected biomarker levels adjusted for severity of illness and acute respiratory distress syndrome etiology, compared between immunocompetent (no immunocompromising condition [ICC]), ICC without stem cell transplant (SCT) (ICC no SCT), and ICC with SCT (ICC + SCT) subjects. Biomarkers were log-transformed for regression, predicted values computed, and compared between groups using analysis of variance, with post hoc Bonferroni corrections displayed (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). Data are presented as medians and interquartile ranges. ANG2 = angiopoietin-2, CCL22 = C-C motif chemokine ligand 22, IL-8 = interleukin-8, P3NP = procollagen type III N-terminal peptide, SPD = surfactant protein D, sTNFR1 = soluble tumor necrosis factor receptor 1.

are consistent with persistent signaling by damaged tissues in order to recruit neutrophils in neutropenic subjects, with no down-regulation provided by senescent neutrophils (25), resulting in persistently elevated cytokine levels (**Fig. 3**). Overall, our results suggest that the pathobiology of ARDS differs in ICC subjects and that this is partly driven by ANC. Our results also suggest that biomarker-based risk prediction tools and subphenotyping strategies may not perform consistently across populations with variable case-mixe of neutropenic or immunocompromised subjects.

Elevated biomarkers levels may point to targetable pathways in ICC subjects. Higher TNFα and IL-8 in ICC no SCT and ICC + SCT, for example, may propagate damage by preferentially recruiting younger neutrophils to lung (26). Therefore, ICC subjects may be particularly amenable to ongoing lung damage due to persistent neutrophil recruitment. Notably, two large negative trials of TNFα inhibition in sepsis excluded subjects on chemotherapy or with neutropenia (27, 28). Our data suggests that ICC and neutropenic subjects may specifically benefit from TNFα blockade. Future therapies targeting the TNFα and IL-8 pathways could be tested in ICC subjects to assess whether neutrophil recruitment to the lung can be mitigated and clinical outcomes improved.

A strength of our study is a sufficiently large sample size to permit multivariable adjustment in order to assess biomarker profiles "independent" of illness severity. For example, in unadjusted analysis, we found higher SPD in ICC + SCT, which was no longer evident after adjustment, suggesting that elevated SPD

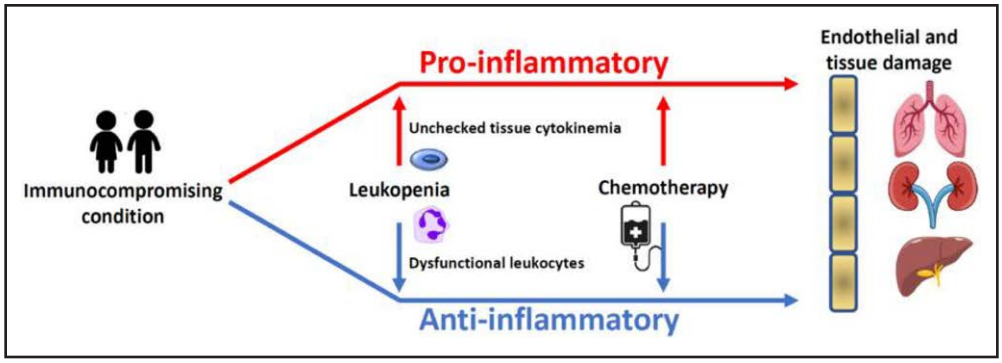

Figure 3. Proposed conceptual model demonstrating that immunocompromising conditions, partly via leukopenia, disrupt the inflammatory cytokine homeostasis in favor of unchecked hyperinflammation. Simultaneously, leukopenia and chemotherapy contribute to ongoing immune suppression. All of this contributes to endothelial and tissue damage.

in these subjects was confounded by their high prevalence of pneumonia and direct ARDS. Our study also has several limitations. Only select biomarkers were measured from a single center, precluding conclusions about generalizability. Additionally, as our cohort was initiated prior to publication of the 2015 definition of pediatric ARDS (29), we did not use the most current pediatric-specific definition, and it is possible that a cohort defined using different eligibility criteria would have disparate findings. For instance, our requirement of an arterial line likely biased our cohort to greater severity of illness and potentially greater specificity for ARDS at the expense of sensitivity. Furthermore, our severity-adjusted biomarker levels may not account for all confounding. Indeed, the greater severity of illness in ICC subjects suggests that some of our conclusions regarding differential risk-adjusted biomarker levels may actually be residual unmeasured illness severity. The retrospective nature of our study precludes firm statements about causality, and the complex interplay between an ICC diagnosis, severity of illness, use of specific therapies (e.g., corticosteroids), and eventual outcome cannot be disentangled. Specifically, it should be noted that corticosteroids have been associated with repression of adaptive immune genes (30), and despite relatively early collection of blood samples, corticosteroid exposure may have affected biomarker profiles in both immunocompetent and immunocompromised children. Finally, our study would benefit from independent replication and from longitudinal profiling, and potentially from compartments other than blood (e.g., tracheal or alveolar sapling). However, our results are the first steps in establishing a biochemical signature of ICC in pediatric ARDS and provide insight into mechanisms underlying increased mortality in this population.

CONCLUSIONS

Immunocompromised children with ARDS had a distinct biomarker profile independent of ARDS etiology, severity of illness, and ANC. ICC subjects were characterized by elevations in pro-inflammatory biomarkers and lower levels of CCL22. ICC no SCT children also had higher levels of ANG2, consistent with endotheliopathy. Our study provides insight into mechanisms underlying the molecular heterogeneity of this population and potentially identifies targetable pathways for future study.

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1 *Division of Critical Care Medicine, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA.*

2 *Division of Critical Care Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH.*

3 *Division of Pediatric Hematology and Oncology, Department of Pediatrics, Pennsylvania State University College of Medicine, Hershey, PA.*

4 *Division of Pediatric Critical Care Medicine, Department of Pediatrics, Pennsylvania State University College of Medicine, Hershey, PA.*

5 *Division of Critical Care, Department of Pediatrics, Riley Hospital for Children and Indiana University, Indianapolis, IN.*

6 *Institute for Immunology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

7 *Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA.*

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For information regarding this article, E-mail: yehyan@chop.edu

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