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FEATURE ARTICLE

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Parsimonious Subphenotyping Algorithms Perform Differently in Patients With Sepsis and Hematologic Malignancy

Lukas Ronner, MD, MSCR[1]
Heather M. Giannini, MD, MS[2]
Todd A. Miano, PhD, PharmD[3]
Caroline A. G. Ittner, PhD[2]
Alexandra P. Turner, BS[2]
Thomas G. Dunn, BA[2]
Roseline S. Agyekum, BS[2]
Anushka Dasgupta[2]
Kirstin West, BA[2]
Tiffanie K. Jones, MD, MPH, MSCE[2,3]
Michael G. S. Shashaty, MD, MSCE[2]
John P. Reilly, MD, MSCE[2]
Nuala J. Meyer, MD, MS[2]

OBJECTIVES: Latent class assignment-derived subphenotyping algorithms may identify treatment-responsive subgroups of critically ill patients with sepsis and acute respiratory distress syndrome. It is unclear if these algorithms are generalizable to patients with comorbid malignancy, a state which may perturb influential inflammatory biomarkers. This study aimed to test whether malignancy or neutropenia modified the effect of subphenotype assignment by two algorithms as applied to a prospective cohort enriched for ICU patients with active malignancy.

DESIGN: Prospective cohort study at a single U.S. quaternary referral center.

SETTING/PATIENTS: ICU patients older than 18 admitted to an ICU with a primary admission indication of sepsis.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We applied two published subphenotyping algorithms utilizing either interleukin (IL)-6 or IL-8 (in addition to soluble tumor necrosis factor receptor 1 and bicarbonate) to our cohort of 930 patients with sepsis, 396 (42%) of whom had active malignancy. A greater proportion of hematologic malignancy patients were assigned the "hyperinflammatory" subphenotype by the IL-8-utilizing algorithm than the IL-6 algorithm (58% vs. 32%). Patients with leukemia and neutropenia were overrepresented among those classified as hyperinflammatory by IL-8 algorithm. We constructed Cox proportional hazards models to assess for interaction between the presence of solid malignancy, hematologic malignancy, and severe neutropenia and the subphenotype/mortality association. Hematologic malignancy uniquely appeared to attenuate the associated mortality of the IL-6-assigned hyperinflammatory subphenotype (interaction; $p = 0.037$), but not the IL-8-assigned hyperinflammatory subphenotype (interaction; $p = 0.260$), which retained an independent association with mortality in hematologic malignancy subjects (hazard ratio, 1.50; 95% CI, 1.08–2.07; $p = 0.014$).

CONCLUSIONS: As subphenotyping algorithms are being tested as point-of-care prognostic tools, it is important to understand their generalizability to patients with comorbid malignancy, which constitute an increasing proportion of ICU patients. The differential behavior of these algorithms in patients with hematologic malignancy suggests a need for independent derivation and validation in this specific population.

KEYWORDS: critical illness subphenotyping; hematologic malignancy; oncologic intensive care unit; sepsis

Two subphenotypes have been reliably identified using unsupervised clustering and latent class assignment (LCA) algorithms in patients with acute respiratory distress syndrome (ARDS) or with sepsis and "at-risk" for ARDS (1–11). A "hyperinflammatory" subphenotype—characterized

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KEY POINTS

Question: Do sepsis and acute respiratory distress syndrome subphenotyping algorithms generalize to ICU patients with active malignancy?

Findings: Two "parsimonious" subphenotyping algorithms, which yield comparable subphenotype/mortality associations when applied to patients without malignancy, appear to behave differently when applied to patients with active hematologic malignancy.

Meaning: Independent derivation and validation of subphenotyping algorithms in ICU patients with hematologic malignancy may be necessary if these patients are to be included in future attempts at subphenotype-directed ICU care.

by higher levels of circulating pro-inflammatory biomarkers and poorer survival—was retroactively shown in trial data from the ARDS network to derive a mortality benefit from high positive-end expiratory pressure, simvastatin, and a liberal fluid management strategy. The corresponding "hypoinflammatory" subphenotype did not benefit from these interventions (1, 12–14). Point-of-care identification of these subphenotypes follows as a key step toward assessing the clinical value of subphenotype-directed care in the ICU (15, 16). To this end, several "parsimonious" subphenotype assignment algorithms were developed and validated against the original LCA analyses (12). Two of these parsimonious algorithms reliably infer LCA subphenotype: an interleukin (IL)-8/soluble tumor necrosis factor receptor 1 (sTNFR1)/bicarbonate-utilizing algorithm ("IL-8 algorithm"), and an IL-6/sTNFR1/bicarbonate-utilizing algorithm ("IL-6 algorithm") (previously reported area under the curves: IL-8, 0.95; 95% CI, 0.93–0.96; IL-6, 0.94; 95% CI, 0.92–0.95) (12). The "Clinical Evaluation of a Point of Care assay to identify PHenotypes IN the Acute Respiratory Distress Syndrome" (PHIND) prospective study is currently deploying this same IL-6 algorithm into the clinical research setting (17).

However, it remains unknown if these subphenotyping algorithms are generalizable to patients with cancer. The contribution of malignancy to the pathophysiologic and immunologic heterogeneity of critical illness is incompletely understood, although there is strong rationale to suspect that host response to infection is perturbed in its presence (18–21). Murine models of sepsis in the context of subcutaneously implanted lung or pancreatic tumor suggest significant differences in T-cell activation, apoptosis, and response to immunomodulation (22–24). A prospective analysis of neutropenic sepsis patients observed higher plasma concentrations of IL-6 and IL-8 relative to nonneutropenic patients with sepsis, as well as higher risk for acute kidney injury (AKI) (25). These observations question whether subphenotyping algorithms that rely on inflammatory biomarkers and derived in a primarily nononcologic population can be extended to patients with comorbid malignancy. Patients with a predicted 6-month mortality rate of 50% or those with bone marrow transplantation were excluded from ARDS network trials, and the original LCA derivation datasets contain an unreported but presumably low proportion with cancer (13, 26, 27). As the real-world proportion of patients admitted to ICUs globally with comorbid malignancy approaches 20%, and as subphenotype-directed therapy in the ICU moves toward clinical use, we felt that patients with cancer should be included in the effort to test these approaches (19, 28, 29).

To this end, we used a prospectively enrolled cohort study of critically ill patients with sepsis at a quaternary referral center with a large cancer center to assess whether two described parsimonious subphenotyping algorithms behave consistently and contain similar prognostic information in patients with active malignancy compared with those without. We hypothesized that the association between subphenotype assignment and mortality would be independently modified by the presence of solid malignancy, liquid malignancy, or severe neutropenia. We additionally hypothesized that these modifications would be present and comparable across the two algorithms tested, one relying on measurement of IL-6, and the other on IL-8.

MATERIALS AND METHODS

Patients

We constructed a nested cohort from patients enrolled in the Molecular Epidemiology of SepsiS in the ICU (MESSI) cohort study between 2008 and 2019. The study was approved by the University of Pennsylvania

Institutional Review Board and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki (Protocol 808542: "Molecular Epidemiology of SepsiS in the Intensive Care Unit," initially approved August 5, 2008). Patients were approached for enrollment if their primary ICU indication was infection-associated organ dysfunction in accordance with Sepsis-2 criteria before 2016 and Sepsis-3 criteria from 2016 onward (30, 31). We retrospectively confirmed that all pre-2016 participants demonstrated a change in Sequential Organ Failure Assessment score greater than or equal to 2. Patients were excluded if they declined participation, desired exclusively palliative measures at ICU admission, or were admitted from a long-term acute care facility. "Active" hematologic malignancy was defined as explicit documentation of the diagnosis in emergency department, floor, or ICU admission notes. Active solid malignancy was additionally defined by documentation of either metastatic disease or a current chemotherapeutic plan at time of admission. These definitions followed the Acute Physiology and Chronic Health Evaluation (APACHE) foundations user guide (rev 1.0, September 2010).

Cytokine and Biomarker Measurement

Plasma from study subjects was collected into citrated vacutainers on the day of ICU admission (± 12 hr). Blood was centrifuged within 30 minutes of blood draw and kept at 4°C for 12–48 hours and then frozen at −80°C until analysis. Electrochemiluminescence (MesoScaleDiscovery, Meso Scale Diagnostics, Rockville, MD) was used to measure plasma IL-8, IL-6, and sTNFR1 in multiplex (32). Bicarbonate and absolute neutrophil count (ANC) were abstracted from the electronic medical record (EMR). Day 0 values were taken from the day of ICU admission if available, otherwise day 1 was used. If the patient had multiple laboratory values available for day 0, the mean was used.

Subphenotype Assignment

Two parsimonious algorithms utilizing sTNFR1, serum bicarbonate, and either IL-8 or IL-6 as published by Sinha et al (12) were applied to generate probabilities of hyperinflammatory subphenotype assignment for every patient (formulas are reproduced in the accompanying Rscript/txt file). These algorithms are logistic regression equations, which predict LCA-subphenotype utilizing a limited set of the biomarkers previously deemed to be most influential in the original LCA derivation. Patients with a probability greater than 0.5 were designated as "hyperinflammatory," whereas patients with probability less than or equal to 0.5 were designated "hypoinflammatory" (12). These two algorithms were selected on the basis of excellent performance in the original derivation and validation cohorts (receiver operating characteristic: IL-8, 0.95; IL-6, 0.94), the availability of cytokine measurements within our cohort, and previously published work showing substantial increases in plasma IL-8 and IL-6 measurements within our hematologic malignancy cohort (12, 25).

Statistical Analysis

Differences in baseline characteristics by malignancy status were characterized by standardized mean difference (SMD), considering values greater than or equal to 0.2 as meaningfully indicative of imbalance, and warranting consideration for inclusion in multivariable modeling (33–35). The use of SMDs over univariate hypothesis testing for comparison of baseline covariates is preferable in observational research as it preserves descriptive information regarding the magnitude of covariate imbalance, allows for relative comparison of imbalance across indices with different units, and may provide a more reliable assessment of imbalances with small *n* (33). Cox proportional hazards models were built controlling for either IL-8 or IL-6-assigned subphenotype, presence and type of malignancy (as a categorical variable with levels: "no malignancy," "solid malignancy," and "hematologic malignancy"), age, sex, race (White vs. nonwhite), severe neutropenia (ANC < 500 cells/μL), history of congestive heart failure, history of chronic kidney disease (CKD), and history of solid organ or bone marrow transplant, in order to estimate the independent association between subphenotype assignment and survival. These covariates were rationally selected as potentially influencing subphenotype-assignment, mortality, or both (25, 36). Although APACHE III scores were available for all subjects, they were not included in multivariable modeling due to concern over collinearity with malignancy status and neutropenia. Survival

functions were plotted using both the Kaplan-Meier and the average covariate method. Although inclusion in MESSI requires primary suspicion for infection, we additionally retroactively queried the EMRs of our subjects for billing codes for potential sepsis-mimicking conditions that are more common with hematologic malignancy, including hemophagocytic lymphohistiocytosis (HLH, *International Classification of Diseases*, 10th revision D76.1), receipt of chimeric antigen receptor T-cell (CAR-T) therapy, and receipt of tocilizumab associated with the encounter. As a sensitivity analysis, we reconstructed our primary analysis with identified patients removed. We also constructed a sensitivity analysis assessing for interactions between subphenotype and immunosuppression (as defined by the APACHE user guide), which included those with baseline corticosteroid use, other immunosuppressive medication use, history of solid organ or bone marrow transplantation, hematologic malignancy, solid malignancy with recent chemo or radiotherapy, or metastatic solid malignancy. We finally conducted a sensitivity analysis, assessing for interactions between subphenotype and antecedent steroid use alone. For all survival analyses, patients continued to be followed after hospital discharge via medical record review of subsequent encounters and are censored at date of last contact with the health system.

Hypothesizing that the presence and type of malignancy or severe neutropenia (agnostic of malignancy) would alter the phenotype/mortality association of either assignment algorithm, models containing relevant interaction terms were constructed. If significant interaction was detected (considering $p \leq 0.05$ significant), we followed with stratified models to compare the differences in these associations across subgroups.

During initial descriptive analysis, we observed that a high proportion of patients with hematologic malignancy were being categorized as hyperinflammatory by IL-8 algorithm but not IL-6 algorithm. In a post hoc analysis, we compared these "discordantly" subphenotyped hematologic malignancy patients with those assigned a "concordant" subphenotype by both algorithms, reasoning that differences between these groups might highlight factors driving discordant assignment in these patients. We again considered factors with SMD greater than or equal to 0.2 to be meaningful in these comparisons.

All analyses were conducted in R (Version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) using package survminer (Version 0.4.9) for Cox model construction, and package tableone (Version 0.13.2) for SMD calculations. An abridged dataset and Rscript file (also available in .txt format) containing all elements needed to replicate the primary analysis are available as Supplemental Material (https://links.lww.com/CCM/H749).

RESULTS

MESSI prospectively enrolled 2491 patients between 2008 and 2019 (37, 38). Of these, 930 had measured IL-8, IL-6, sTNFR1, and serum bicarbonate and were therefore included in our analysis (**Fig. 1**). The baseline characteristics of the cohort, grouped by malignancy status, are summarized in **Table 1** (an expanded table is provided as **Table S1**, https://links.lww.com/CCM/H749). Patients without malignancy were more likely to be nonwhite and have CKD. Patients with hematologic malignancy had a higher frequency of severe neutropenia, bloodstream infections, and higher APACHE III scores. IL-8 and IL-6 algorithms assigned 40% and 32% of patients without malignancy to the hyperinflammatory subphenotype. However, a large difference was noted in hyperinflammatory assignment by IL-8 algorithm vs. IL-6 algorithm among hematologic malignancy patients (58% vs. 32%), reflecting a significant difference in the median IL-8 serum concentration in this group. Patients with severe neutropenia, of whom 62% had a diagnosis of acute leukemia, had significantly higher median serum concentrations of both IL-6 and IL-8 (**Table S3**, https://links.lww.com/CCM/H749).

Ninety percent of our patient cohort had complete follow-up through 90 days post-ICU admission, whereas 10% were discharged from the hospital and were censored at time of last contact with the health system before 90 days. In the full cohort, IL-8 hyperinflammatory subphenotype was associated with increased mortality (hazard ratio [HR], 1.66; 95% CI, 1.40–1.97; $p < 0.001$). The association between subphenotype and survival was not modified by the presence of solid malignancy, hematologic malignancy, or severe neutropenia. IL-6 hyperinflammatory subphenotype was comparably associated with mortality in the full cohort (HR, 1.40; 95% CI, 1.18–1.67; $p < 0.001$). However, this association was significantly modified by the presence of hematologic malignancy

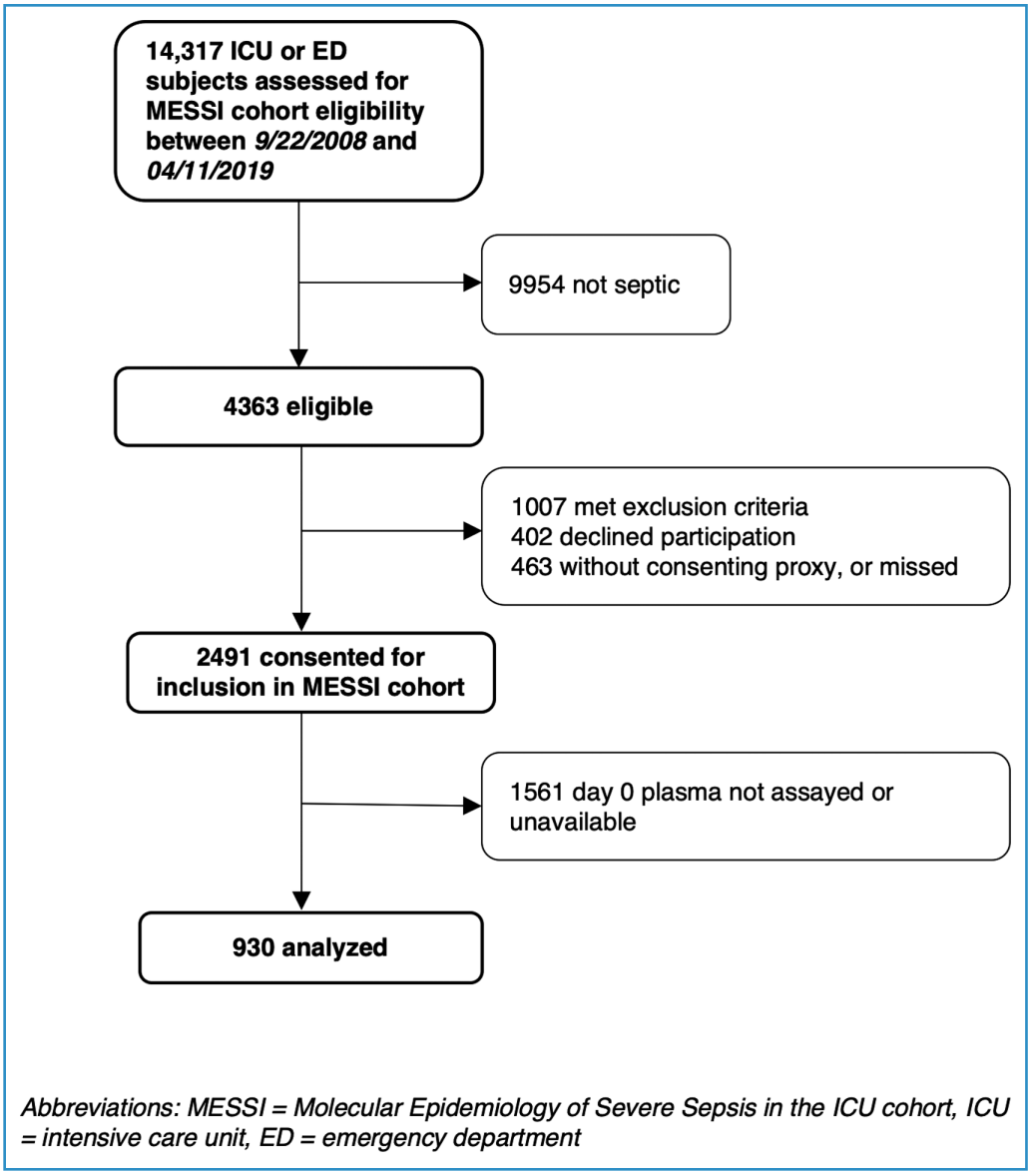

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram depicting inclusion into Molecular Epidemiology of SepsiS in the ICU (MESSI) cohort and selection of phenotyping subcohort. ED = emergency department.

(interaction; $p = 0.037$), but not solid malignancy (interaction; $p = 0.260$) or neutropenia ($p = 0.221$). We proceeded to build stratified models to compare the phenotype/mortality associations between patients with hematologic malignancy and those without malignancy. In patients with hematologic malignancy, a significant association between IL-6 hyperinflammatory subphenotype and higher mortality was no longer detected (HR, 1.10; 95% CI, 0.80–1.51; $p = 0.578$), whereas it remained significantly associated with mortality in patients without malignancy (HR, 1.68; 95% CI, 1.32–2.14; $p < 0.001$). For comparison, stratified models using the IL-8 algorithm were also constructed, where the hyperinflammatory phenotype remained strongly associated with higher mortality in both subgroups (heme malignancy: HR, 1.48; 95% CI, 1.08–2.05; $p = 0.015$; no malignancy: IL-8—HR, 1.75; 95% CI, 1.39–2.21; $p < 0.001$). These results are depicted in **Figure 2** both as unadjusted Kaplan-Meier plots and adjusted using the average covariate method. Adjusted survival curves representing patients with solid malignancy can be viewed in **Figure S1** (https://links.lww.com/CCM/H749). Our retrospective query of the EMR revealed that six patients, none of whom had hematologic malignancy, had a billing code for HLH-associated with their encounter. Two patients received CAR-T therapy within the month before ICU admission. Six patients received tocilizumab, although all received it following their initial ICU-admission blood draw. We reconstructed our primary analysis with these patients removed, with unchanged results. We additionally assessed for an interaction between the subphenotype-mortality association and APACHE-defined immunocompromised status. Again, no interactions were detected. Similar results were seen in an assessment for interaction with baseline corticosteroid use. These analyses are discussed in the Supplemental Material, **Section 1** (https://links.lww.com/CCM/H749).

Of 235 patients with hematologic malignancy, 69 (29%) were classified as hyperinflammatory by the

TABLE 1.
Baseline Characteristics of Patient Cohort Stratified by Malignancy Status

Characteristic	All	No Malignancy	Solid Malignancy[a]	Hematologic Malignancy[b]	Standardized Mean Difference[c]
Patients, *n* (% total)	**930**	**533 (57.3)**	**162 (17.4)**	**235 (25.3)**	Not applicable
Age at ICU admission, median (IQR)	61 (51–70)	60 (48–70)	64 (56–72)	62 (53–69)	**0.224**
Sex, male, *n* (%)	554 (59.6)	307 (57.6)	100 (61.7)	147 (62.6)	0.068
Self-identified race, *n* (%)					
White	577 (62.0)	284 (53.3)	47 (29.0)	178 (75.7)	**0.321**
Black	290 (31.2)	218 (40.9)	125 (77.2)	35 (14.9)	**0.402**
Asian	33 (3.5)	17 (3.2)	7 (4.3)	9 (3.8)	0.040
Pacific Islander	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0.041
Native American	2 (0.2)	0 (0.0)	1 (0.6)	1 (0.4)	0.077
Other/not available	27 (2.9)	13 (2.4)	2 (1.2)	12 (5.1)	0.151
Acute Physiology and Chronic Health Evaluation III, median (IQR)	97 (72–129)	93 (67–123)	97.5 (75.5–129.5)	112 (82–142.5)	**0.274**
History of congestive heart failure, *n* (%)	132 (14.2)	91 (17.1)	16 (9.9)	25 (10.6)	0.141
History of kidney disease, *n* (%)	138 (14.9)	109 (20.5)	11 (6.8)	18 (7.7)	**0.272**
History of solid organ transplant	97 (10.4)	68 (12.8)	2 (1.2)	27 (11.5)	**0.311**
History of bone marrow transplant	30 (3.2)	4[d] (0.8)	0 (0.0)	26 (11.1)	**0.357**
ANC (cells/μL), median (IQR)	9.26 (3.65–14.40)	10.69 (6.25–14.82)	11.00 (5.66–17.97)	1.50 (0.00–7.56)	**0.580**
ANC < 500, *n* (%)	112 (12.8)	23 (4.6)	7 (4.6)	96 (43.2)	**0.678**
Cytokine measurements, median (IQR)					
IL-6 (pg/mL)	148.6 (42.9–793.0)	143.9 (42.1–794.3)	117.55 (39.8–545.9)	207.7 (55.9–1112.2)	0.156
IL-8 (pg/mL)	80.8 (25.1–400.5)	60.0 (19.8–217.6)	75.9 (25.7–270.7)	284.7 (49.7–1292.2)	**0.288**
Soluble tumor necrosis factor receptor (pg/mL)	5685.3 (3054.6–10405.3)	5596.9 (2970.9–10458.0)	5685.3 (2889.2–10197.4)	5994.7 (3532.4–10450.4)	0.046
Bicarbonate (mmol/L)	21.0 (18.0–24.3)	21.0 (18.0–24.5)	21.0 (18.0–25.0)	21.0 (17.9–24.0)	0.080
Subphenotype assignment:					
Hyperinflammatory by IL-8	426 (45.8)	215 (40.3)	74 (45.7)	137 (58.3)	**0.243**
Hyperinflammatory by IL-6	297 (31.9)	172 (32.3)	50 (30.9)	75 (31.9)	0.020
Discordant assignment[e]	191 (20.5)	65 (12.2)	26 (16.0)	69 (29.3)	**0.253**

(*Continued*)

TABLE 1. (*Continued*)

Baseline Characteristics of Patient Cohort Stratified by Malignancy Status

Characteristic	All	No Malignancy	Solid Malignancy[a]	Hematologic Malignancy[b]	Standardized Mean Difference[c]
Developed acute respiratory distress syndrome, *n* (%)	489 (53.2)	281 (53.4)	66 (40.7)	142 (61.2)	**0.277**
Mild	46 (5.0)	27 (5.1)	4 (2.5)	15 (6.5)	0.130
Moderate	134 (14.6)	68 (12.9)	27 (16.7)	39 (16.8)	0.073
Severe	309 (33.6)	186 (35.4)	35 (21.6)	88 (37.9)	**0.242**
Developed acute kidney injury, *n* (%)	603 (65.5)	358 (67.8)	87 (54.7)	158 (67.5)	0.181
KDIGO stage 1	165 (17.9)	103 (19.5)	24 (15.1)	38 (16.2)	0.078
KDIGO stage 2	133 (14.4)	69 (13.1)	24 (15.1)	40 (17.1)	0.075
KDIGO stage 3	305 (33.1)	186 (35.2)	39 (24.5)	80 (34.2)	0.157
30-d mortality, *n* (%)	394 (42.4)	193 (36.2)	76 (46.9)	125 (53.2)	**0.230**

ANC = absolute neutrophil count, IL = interleukin, IQR = interquartile range, KDIGO = Kidney Disease: Improving Global Outcomes (consensus guidelines).

[a]Solid malignancies: 31 lung, 20 pancreatic, 14 gastrointestinal, 10 hepatic, nine prostate, six breast, four CNS, three bladder, three gynecologic, two unknown primary, one renal, one thyroid, one melanoma, 11 "other," and 46 primary not available.

[b]Hematologic malignancies: 137 leukemia, 73 lymphoma, and 25 myeloma (note that three patients are reported as having coincident lymphoma and two coincident myeloma; these patients are included in the leukemia total).

[c]Standardized mean difference is an expression of the difference in the mean of a covariate between two groups divided by that covariate's estimated SD and is reported in units of SD. Higher values indicate a greater degree of imbalance, and the relative magnitude of imbalance can be compared between covariates of different scales. It has been suggested that values > 0.2 indicate a meaningful degree of imbalance (bolded), values < 0.2 but > 0.1 indicate a small but potentially meaningful degree of imbalance, and values < 0.1 indicate a negligible degree of imbalance (32).

[d]Two of these patients had a remote history of allogenic bone marrow transplant (BMT) in childhood, one for acute lymphocytic leukemic and one for acute erythroblastic leukemia. Two had allogenic BMT in adulthood and were known to be in complete remission at time of ICU admission (one acute myelocytic leukemia and one myelodysplastic syndrome).

[e]Hyperinflammatory by one algorithm but not both.

Boldface values indicate meaningful difference.

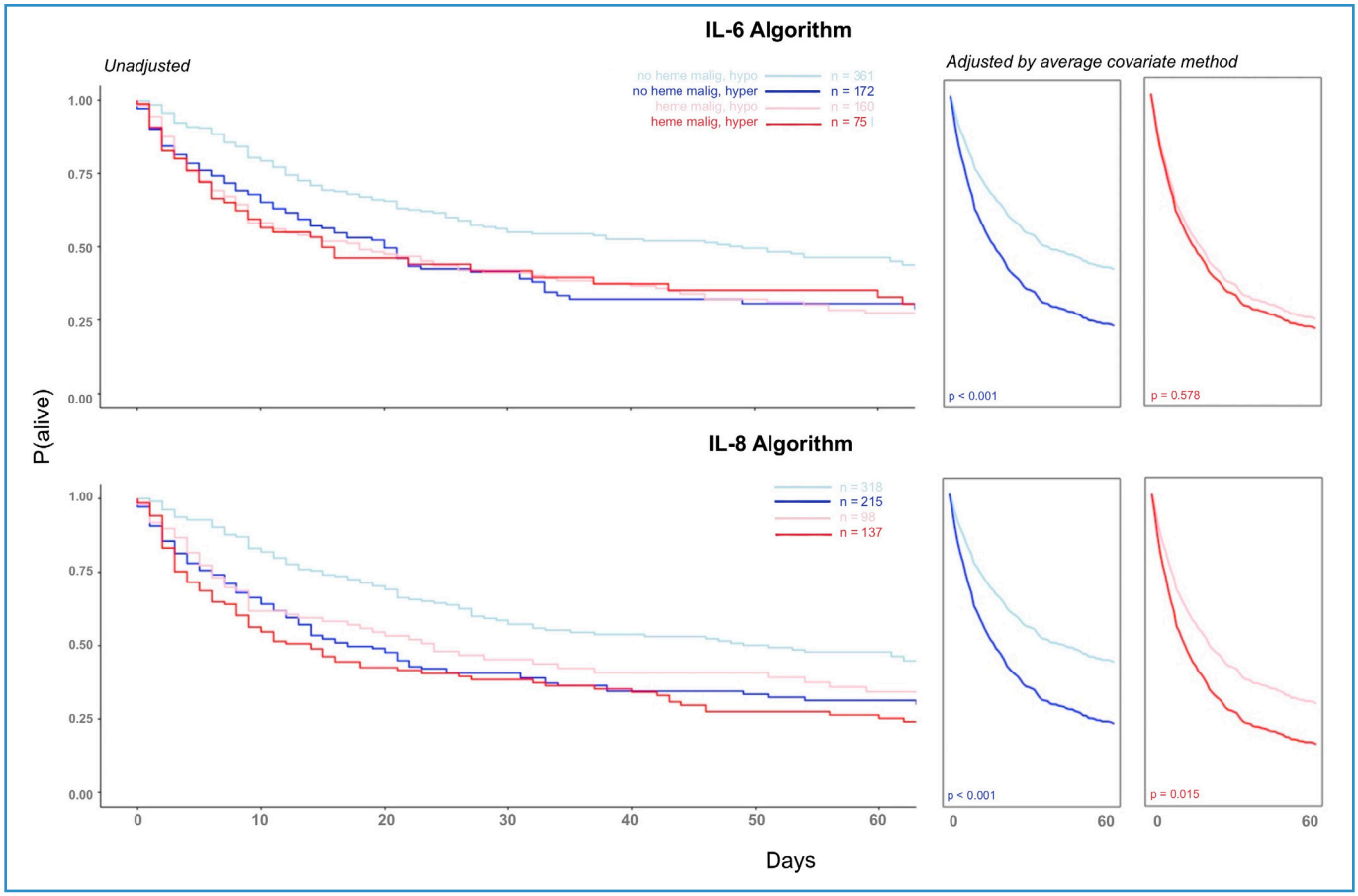

Figure 2. Survival of sepsis patients stratified by subphenotype and presence of hematologic malignancy. IL = interleukin.

IL-8 algorithm but not IL-6. Hematologic malignancy patients were nearly twice as likely to be "IL-8 discordantly" subphenotyped as patients with solid malignancy (16%) or no malignancy (12%). We therefore compared these hematologic malignancy patients to their concordant hyperinflammatory and hypoinflammatory counterparts to identify factors associated with the IL-8 algorithm's apparent propensity toward hyperinflammatory assignment in this subgroup.

Compared with the patients assigned concordant hyperinflammatory subphenotype, the IL-8 discordant patients (IL-8 hyperinflammatory, IL-6 hypoinflammatory) were less likely to be severely neutropenic (52% vs. 69%), had lower APACHE III scores (median, 109 vs. 134), and appeared less likely to develop positive blood cultures within 7 days of ICU admission (44% vs. 65%). There did not appear to be meaningful differences in development of ARDS or 30-day mortality, although a smaller proportion of IL-8 discordant patients developed AKI (74% vs. 82%). Patients with leukemia comprised a high proportion of both IL-8 discordant and concordant hyperinflammatory groups (67% and 71%).

The IL-8 discordant patients stood in greater contrast to the hypoinflammatory concordant patients across several relevant characteristics. APACHE III scores were higher (median, 109 vs. 84), perhaps in part related to the increased frequency of severe neutropenia (52% vs. 17%), as was blood culture positivity (44% vs. 15%). There were meaningful differences in the development of ARDS (65% vs. 48%) and AKI (74% vs. 51%), although 30-day mortality was comparable. Patients with leukemia comprised a larger proportion of the IL-8 discordant subgroup (67% vs. 43%), whereas lymphoma was less prevalent (22% vs. 44%). These results are summarized in **Table 2** (an expanded table is provided as **Table S2**, https://links.lww.com/CCM/H749). Kaplan-Meier survival curves comparing the IL-8 discordant group to to concordant groups can be viewed in **Figure S2** (https://links.lww.com/CCM/H749).

DISCUSSION

Two previously validated parsimonious algorithms utilizing sTNFR1, bicarbonate, and either IL-8 or

TABLE 2.

Comparison of Concordantly Subphenotyped to Discordantly Subphenotyped Interleukin-8 Hyperinflammatory Hematologic Malignancy Patients

Characteristic	Concordant Hypoinflammatory[a]	Discordant Interleukin-8 Hyperinflammatory[b]	Concordant Hyperinflammatory[c]	SMD[d]	SMD[e]
Patients, *n*	91	69	68	NA	*NA*
Age at ICU admission, median (IQR)	63 (57–72)	60 (47–68)	*60 (52–67)*	**0.422**	*0.043*
Acute Physiology and Chronic Health Evaluation III, median (IQR)	86 (66–123.5)	109 (85–142)	*134 (112–162.5)*	**0.446**	***0.593***
Hematologic malignancy, *n* (%)					
Leukemia	39 (43.3)	46 (66.7)	*48 (70.6)*	**0.482**	*0.085*
Lymphoma	40 (44.4)	15 (21.7)	*12 (17.6)*	**0.497**	*0.103*
Plasma cell dyscrasia	11 (12.1)	8 (11.6)	*8 (11.8)*	0.015	*0.005*
Transplant history, *n* (%)					
Solid organ	10 (11.0)	10 (14.5)	*6 (8.8)*	0.105	*0.177*
Bone marrow	13 (14.3)	4 (5.8)	*9 (13.2)*	**0.285**	***0.256***
Timing of cytokine sample collection relative to electronic medical record-logged ICU admission minutes, median (IQR)	+20 (−172 to +289)	−13 (−114 to +231)	*36 (−219 to +294)*	0.144	***0.256***
ANC cells/μL (IQR)	5.65 (1.92–12.00)	0.09 (0.00–3.96)	*0.12 (0.00–1.14)*	**0.797**	*0.065*
ANC < 500, *n* (%)	14 (16.5)	34 (52.3)	*45 (69.2)*	**0.815**	***0.320***
Immunosuppressive medications, *n* (%)					
Low-dose glucocorticoid[f]	13 (14.4)	9 (13.2)	*12 (17.6)*	0.035	*0.122*
High-dose glucocorticoid[g]	2 (3.2)	3 (8.8)	*2 (4.4)*	**0.237**	*0.177*
Chemotherapy	48 (53.3)	48 (72.2)	*51 (76.1)*	**0.410**	*0.078*
Other immunosuppressant	8 (12.9)	4 (11.8)	*4 (8.9)*	0.035	*0.095*
Primary infectious source, *n* (%)					
Genitourinary	7 (7.7)	5 (7.4)	*1 (1.5)*	0.013	***0.289***
Abdominal	10 (11.0)	12 (17.6)	*19 (27.9)*	0.191	***0.247***
Pulmonary	50 (54.9)	27 (39.7)	*23 (33.8)*	**0.309**	*0.122*
Head/neck	0 (0.0)	1 (1.5)	*2 (2.9)*	0.173	*0.100*
Bloodstream	11 (12.1)	13 (19.1)	*16 (23.5)*	0.195	*0.108*
Skin/soft tissue	5 (5.5)	1 (1.5)	*1 (1.5)*	**0.221**	*< 0.001*
Unknown/undocumented	8 (8.8)	10 (14.5)	*6 (8.8)*	0.178	*0.177*

(*Continued*)

TABLE 2. (*Continued*)

Comparison of Concordantly Subphenotyped to Discordantly Subphenotyped Interleukin-8 Hyperinflammatory Hematologic Malignancy Patients

Characteristic	Concordant Hypoinflammatory[a]	Discordant Interleukin-8 Hyperinflammatory[b]	Concordant Hyperinflammatory[c]	SMD[d]	SMD[e]
(+) blood culture, *n* (%)	14 (15.4)	30 (43.5)	*44 (64.7)*	**0.648**	***0.436***
Developed acute respiratory distress syndrome, *n* (%)	42 (47.7)	45 (65.2)	*50 (73.5)*	**0.358**	*0.181*
Mild	3 (3.4)	5 (7.2)	*7 (10.3)*	0.171	*0.108*
Moderate	9 (10.2)	13 (18.8)	*16 (23.5)*	**0.246**	*0.115*
Severe	30 (34.1)	27 (39.1)	*27 (39.7)*	0.105	*0.012*
Developed acute kidney injury, *n* (%)	46 (50.5)	50 (73.5)	*56 (82.4)*	**0.487**	***0.214***
KDIGO stage 1	12 (13.2)	10 (14.7)	*13 (19.1)*	0.044	*0.118*
KDIGO stage 2	12 (13.2)	10 (14.7)	*17 (25.0)*	0.044	***0.260***
KDIGO stage 3	22 (24.2)	30 (44.1)	*26 (38.2)*	**0.430**	*0.120*
30-d mortality, *n* (%)	43 (47.3)	42 (60.9)	*36 (52.9)*	**0.276**	*0.161*

ANC = absolute neutrophil count, IQR = interquartile range, KDIGO = Kidney Disease: Improving Global Outcomes (consensus guidelines), NA = not applicable, SMD = standardized mean difference.

[a]Patients classified as hypoinflammatory by both interleukin (IL)-6 and IL-8 algorithm.

[b]Patients classified as hyperinflammatory by IL-8 algorithm alone.

[c]Patients classified as hyperinflammatory by both IL-6 and IL-8 algorithm.

[d]SMDs represent comparisons between concordant hypoinflammatory and IL-8 divergent hematologic malignancy patients.

[e]SMDs represent comparisons between concordant hyperinflammatory and IL-8 divergent hematologic malignancy patients (italicized).

[f]Between 5 and 40 mg of prednisone (or prednisone equivalents) daily.

[g]Greater than or equal to 40 mg of prednisone (or prednisone equivalents) daily.

Boldface values indicate meaningful difference.

IL-6 appeared to perform comparably in patients with sepsis or ARDS in the absence of malignancy, in agreement with previous reports (12). However, the algorithms appeared to inconsistently predict mortality and discordantly assign subphenotype, specifically in patients with hematologic malignancy, the majority of whom had leukemia. These results persisted in a sensitivity analysis excluding the small number of patients who may have had sepsis-mimicking conditions, such as HLH or cytokine release syndrome. Our results demonstrate differential prognostic utility of the IL-6/sTNFR1/bicarbonate model in this specific population and raise questions about whether these particular comorbidities should influence subphenotyping strategy.

The larger proportion of patients with hematologic malignancy categorized as hyperinflammatory by the IL-8 algorithm (58%) over the IL-6 algorithm (32%) warrants attention. In prior publications, only a third of patients were identified as hyperinflammatory when either parsimonious or more complex LCA phenotyping algorithms were applied to ARDS trial cohorts (1, 2, 12). It is not possible to say if the IL-8 algorithm "over-assigns" the hyperinflammatory phenotype, the IL-6 algorithm "under-assigns" it, or if these inflammatory subphenotype labels cannot be directly applied to this population. Examination of the discordantly subphenotyped hematologic malignancy population reveals general similarity with those assigned a hyperinflammatory subphenotype by either algorithm. They are more likely to have leukemia as opposed to lymphoma or a plasma cell dyscrasia, are more likely to have severe neutropenia, and have comparably poor outcomes. Leukemia specifically may perturb endogenous IL-8 production in several ways. Leukemic blasts have been shown to stimulate IL-8 secretion from mesenchymal marrow stem cells (39). IL-8 also primarily functions as a neutrophil chemotactic and may be especially elevated in patients who are unable to mount a satisfactory granulopoietic response to a site of infection, as is more likely to be the case in patients with myeloid malignancy (40). The administration of exogenous granulocyte colony stimulating factor (G-CSF) may also increase baseline levels of IL-8, although a previous analysis of a subset of these patients suggests less than 10% of our leukemic cohort receive it (25, 41). These factors may in part explain why the IL-8 algorithm classifies more patients with hematologic malignancy as hyperinflammatory, and specifically why a large proportion of those assigned to the "IL-8 discordant" group had leukemia. In contrast, patients assigned a concordant hypoinflammatory subphenotype appeared more likely to have lymphoma and were less likely to be neutropenic. Infectious source may also exert an effect on subphenotype assignment, as we note that abdominal and bloodstream primary sources were less common in the concordantly hypoinflammatory patients though this may simply reflect infectious susceptibility patterns in patients with different hematologic malignancies.

To our knowledge, this is the first attempt to deploy subphenotyping algorithms in an adult oncologic population. The studied cohort is sizeable and contains detailed clinical and biomarker data that were prospectively collected. However, there are significant limitations. We did not derive de novo subphenotypes using LCA as a gold-standard comparator to our parsimonious subphenotype assignments. This was a single-center study at a quaternary referral center and as such our patient population and practice patterns, particularly as they pertain to the treatment of patients with hematologic malignancy, may not broadly generalize. We lacked granular data regarding timing and type of anticancer therapies given, including supportive measures such as G-CSF administration. As no cause-of-death adjudication was performed, it was not possible to determine what proportion of mortality in the malignant cohort was attributable to critical illness vs. complications of, or decision-making influenced by, the participant's malignancy. Given median survival times in our hematologic malignancy cohort ranging from 14 to 24 days depending on subphenotype assignment, we suspect that critical illness was more often the proximal cause of death. Finally, our analysis may overgeneralize "hematologic malignancy" as a single disease entity. Significant heterogeneity in treatment, prognosis, and immune perturbation exists between broad classifications such as "leukemia" and "lymphoma," and within these classifications, for example, acute myeloid leukemia with specific recurrent cytogenetic abnormalities or different types of non-Hodgkin lymphoma.

Patients with malignancy have long been excluded from randomized trials of critical care interventions despite their growing presence in modern ICUs. This exclusion is founded on reasonable concerns

regarding the clinical and immunologic heterogeneity expressed by this patient population, as well as concerns that cancer-related death may function as a competing risk that complicates interpretation of intervention-attributable mortality differences. As ICU survival, post-ICU survival, post-ICU disease control, and quality of life have greatly improved in cancer patients over the past several decades, their systematic exclusion from major randomized trials may no longer be justifiable (42). As clinical trials begin to introduce biologic stratification tools in the search for precision sepsis and ARDS treatments, we recommend independent derivation and validation in cohorts exclusively consisting of such patients (28, 29).

CONCLUSIONS

Two parsimonious phenotyping algorithms derived in ARDS patients were applied to a general cohort with sepsis and a high frequency of malignancy. The algorithm utilizing IL-6 as a discriminatory biomarker exhibited a heterogeneous effect on survival in the presence of hematologic malignancy, whereas an IL-8-utilizing model retained its association with mortality while classifying a high proportion of this subpopulation as hyperinflammatory. The differential behavior of these two algorithms in this specific population points to the need for validation or de novo derivation of subphenotyping algorithms in patients with hematologic malignancy.

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1 *Division of Hematology and Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA.*

2 *Division of Pulmonary and Critical Care Medicine and Center for Translational Lung Biology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

3 *Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

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Dr. Ronner was involved in conceptualization, formal analysis, methodology, visualization, writing the original draft, and reviewing and editing the writing. Dr. Giannini was involved in conceptualization and reviewing and editing the writing. Dr. Miano was involved in methodology, and reviewing and editing the writing. Dr. Ittner was involved in data curation, project administration, and reviewing and editing the writing. Ms. Turner was involved in project administration and reviewing and editing the writing. Mr. Dunn was involved in investigation, and reviewing and editing the writing. Ms. Agyekum was involved in investigation and reviewing and editing the writing. Ms. Dasgupta was involved in investigation and reviewing and editing the writing. Ms. West was involved in investigation and reviewing and editing the writing. Dr. Jones was involved in methodology and reviewing and editing the writing. Dr. Shashaty was involved in methodology, and reviewing and editing the writing. Dr. Reilly was involved in conceptualization, methodology, visualization, funding acquisition, and reviewing and editing the writing. Dr. Meyer was involved in conceptualization, methodology, visualization, project administration, funding acquisition, supervision, and reviewing and editing the writing.

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For information regarding this article, E-mail: lukas.ronner@pennmedicine.upenn.edu

This study was approved by the University of Pennsylvania Institutional Review Board (protocol number 808542), in accordance with the Declaration of Helsinki.

Informed consent was obtained from all participants (or a qualified consenting proxy when a subject was unable to consent for themselves).

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