Critical Care Medicine
December 2025 • Volume 53 • Number 12 • Pages e2429–e2439

FEATURE ARTICLE

Prognostic Relevance of Inflammatory Subphenotypes in Immunocompromised Patients With Sepsis

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OBJECTIVES: Hyperinflammatory and hypoinflammatory molecular subphenotypes in sepsis and acute respiratory distress syndrome have divergent mortality and treatment responses in secondary analyses of randomized controlled trials. However, the prevalence of immunocompromise is low in these populations, and how preexisting immunocompromise contributes to subphenotypes is unknown. We studied two observational sepsis cohorts to test associations between immunocompromise and the hyperinflammatory subphenotype and to assess whether the prognostic relevance of molecular subphenotypes is generalizable to immunocompromised populations.

DESIGN: Observational cohort study.

SETTING: Prospective data from two ICU cohorts in the United States.

PATIENTS: We included 1826 patients from two combined sepsis cohorts.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We defined immunocompromise as a history of solid organ transplant, AIDS, hematologic malignancy, solid malignancy on chemotherapy, or immunosuppressive medication use. Subphenotype was previously assigned using latent class analysis. We used logistic regression to investigate associations between type of immunocompromise and hyperinflammatory subphenotype. Models were repeated with individual covariates known or hypothesized to be associated with the hyperinflammatory subphenotype. Kaplan-Meier survival plots were used to assess mortality differences by subphenotype. Hematologic malignancy was strongly associated with the hyperinflammatory subphenotype (odds ratio [OR], 4.3; $p < 0.0001$), an association that persisted after adjustment for identified pathogen, presence of bacteremia, or illness severity. History of solid organ transplantation was also associated with the hyperinflammatory subphenotype (OR, 1.6; $p = 0.02$) but was no longer significant after accounting for bacteremia. Hyperinflammatory classification was associated with a decreased likelihood of survival in hematologic malignancy, but not in organ transplant or solid malignancy populations.

CONCLUSIONS: Preexisting immune status is associated with subphenotype assignment and may influence its prognostic utility.

KEYWORDS: hematologic malignancy; immunocompromise; molecular subphenotypes; organ transplant; sepsis

Sepsis, defined as a dysregulated host response to infection, is a common cause of death in critical illness (1, 2). Despite extensive preclinical research and clinical trials, morbidity and mortality attributed to sepsis worldwide remain high (3). Recent research efforts have focused on describing biologic and clinical subphenotypes within the broad syndrome of

This article has an accompanying editorial.

DOI: 10.1097/CCM.0000000000006920

KEY POINTS

Question: What are the associations between preexisting immunocompromising conditions and molecular subphenotypes of sepsis, and is the hyperinflammatory phenotype associated with worse outcomes across different subgroups of immunocompromise?

Findings: In a study combining two prospective critically ill sepsis cohorts in the United States, we report associations between both hematologic malignancy and solid organ transplantation and the hyperinflammatory subphenotype. Interestingly, the hyperinflammatory subphenotype was not consistently associated with worse outcomes in all subgroups.

Meaning: Hematologic malignancy is strongly associated with the hyperinflammatory subphenotype, an association that persisted after adjustment for severity of illness and bacteremia. Additional studies are needed to fully understand the role of phenotyping in immunocompromised patients with critical illness.

sepsis to identify patients most likely to benefit from therapies (4).

Using clinical parameters and plasma biomarkers, latent class analysis has identified two molecular subphenotypes, termed hyperinflammatory and hypoinflammatory, in randomized clinical trials and observational cohorts of patients with acute respiratory distress syndrome (ARDS) and sepsis (5, 6). The hyperinflammatory subphenotype is characterized by higher levels of plasma biomarkers, including interleukin (IL)-6, IL-8, tumor necrosis factor receptor 1, and plasminogen activator inhibitor-1, as well as more severe shock, higher rates of bacteremia, and nearly double the mortality compared with the hypoinflammatory subphenotype (6–9). RNA sequencing of peripheral blood has identified increased expression of innate immune cell pathways and decrease in adaptive immune signaling pathways in the hyperinflammatory phenotype compared with hypoinflammatory patients (10). These data suggest that a patient's individual immune response to a given insult may be a key factor associated with molecular subphenotypes. However, preexisting conditions that impact the host response to infection have been understudied in this context, largely because the initial studies describing these subphenotypes were nested within randomized controlled trials (RCTs) in which the prevalence of severe immunosuppression was low, and datasets lacked granular information regarding the type of immunosuppression of enrolled patients. Thus, the relationship between preadmission immunocompromise and molecular subphenotypes is not well understood.

To address this knowledge gap, we used clinical and biologic data from two prospective observational cohorts of patients admitted to the ICU with a diagnosis of sepsis. We hypothesized that preexisting immunocompromise would influence molecular subphenotype classification and that the strength of the association would vary by type of immunocompromising condition. We further hypothesized that the prognostic utility of subphenotype classification would be modified by preexisting immunocompromising conditions.

MATERIALS AND METHODS

Observational Patient Cohorts

Based on the estimated sample size needed from our a priori power calculations (see "Statistical Analyses" below), we included patients who met Sepsis-3 criteria from two prospective observational cohorts, the Early Assessment of Renal and Lung Injury (EARLI) and the Validating Acute Lung Injury biomarkers for Diagnosis (VALID) (**Supplemental Methods**, https://links.lww.com/CCM/H821). The EARLI and VALID studies recruit patients admitted to the ICU directly from the emergency department (EARLI) or from the emergency department, floor, or outside hospital (VALID) to identify novel risk factors and biomarkers of organ injury in sepsis and ARDS. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its amendments and was approved by the University of California, San Francisco Institutional Review Board (IRB No. 10-02852, August 17, 2010) and Vanderbilt University IRB (No. 051065, 2006) with a waiver of consent if the patient or surrogate were unable to provide consent. Plasma biomarkers were measured from peripheral blood samples collected within 24 hours of ICU admission in EARLI and 48 hours of ICU admission in VALID (Supplemental Methods, https://links.lww.com/CCM/H821). Patients were followed until

death, 60 days (EARLI), or hospital discharge. Details of the inclusion and exclusion criteria of both cohort study protocols have been previously published (9); in brief, exclusion criteria include declined consent, ICU admission for greater than 24 hours (EARLI) or 48 hours (VALID), uncomplicated overdose, or clinically significant gastrointestinal bleed. Molecular subphenotype was previously assigned using latent class analysis (6). Description of missing data is provided in **Table S10** (https://links.lww.com/CCM/H821).

Definition of Immunocompromise

Type of immunocompromise was defined according to Infectious Diseases Society of America (IDSA) guidelines as history of: 1) solid organ transplant, 2) HIV with a CD4+ T-cell count under 200/AIDS, 3) active hematologic malignancy, 4) solid malignancy on chemotherapy within 4 weeks, or 5) immunosuppressive medication use for reasons not listed above (11, 12). Tumor necrosis factor-alpha blockers, methotrexate, azathioprine, and mycophenolate mofetil and 20 mg of prednisone or equivalent dose for over 1 week were considered immunosuppressive, in line with Centers for Disease Control and Prevention and IDSA guidelines (11, 12). Patients with a history of bone marrow transplant greater than 2 years before enrollment were excluded from the active hematologic malignancy group. Definitions of immunocompromise in VALID differed somewhat due to data availability. Information regarding active chemotherapy treatment, corticosteroid dose, or duration and timing of bone marrow transplant was unavailable in VALID (Supplemental Methods, https://links.lww.com/CCM/H821).

Statistical Analyses

Assuming a 5% prevalence of the exposure (each type of immunocompromise) and 30% prevalence of the hyperinflammatory subphenotype in the unexposed group, a sample size of 1800 patients was needed to detect a 15% difference in our outcome measure at a two-tailed alpha of 0.05. To achieve this sample size, we combined data from EARLI (n = 690) and VALID (n = 1136). Descriptive data are presented as mean (SD) for continuous data, median (interquartile range) for skewed data, or count (%). Biomarker values were log transformed for ease of data visualization. Differences between groups were assessed using Student t test, Wilcoxon rank-sum test or chi-square test, respectively.

We used logistic regression to test associations between type of immunocompromise and the hyperinflammatory subphenotype, using immune competent as the comparison group. Enrollment cohort was included as a covariate to adjust for cohort level effects. Regression models were repeated with individual covariates known or hypothesized to be associated with the hyperinflammatory subphenotype to explore which clinical or biologic factors might contribute to the observed associations, including the presence of bacteremia, pathogen type, and severity of illness (**Fig. S1**, https://links.lww.com/CCM/H821) (6, 7, 13). Presence of leukopenia was also included given the high proportion of immunocompromised patients on bone marrow suppressing medications and an observed association between lower WBC count and the hyperinflammatory subphenotype (6). We examined the relationship between type of immune compromise and previously measured plasma biomarkers of sepsis using multivariate linear regression with adjustment for age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and presence of bacteremia.

To determine whether molecular subphenotypes were associated with mortality in immunocompromised populations, we plotted Kaplan-Meier curves for in-hospital mortality, censored at 30 days, stratified by molecular subphenotype, for each immunocompromise subgroup. Patients were censored at the time of discharge from the hospital. Statistical significance of survival distributions between groups was determined using log-rank test with Benjamini-Hochberg correction for multiple comparisons. A separate logistic regression analysis including an interaction term between type of immunosuppression and subphenotype was used to test whether associations between hyperinflammatory subphenotype and mortality at 30 days differed by subgroup. To determine whether subphenotype assignment adds independent prognostic information in hematologic malignancy patients, we used multivariable Cox proportional hazards regression including APACHE II, WBC count, bacteremia, and cohort with an interaction term as covariates.

All statistical analyses were performed using R software on RStudio (Version 4.3.1; Posit, Boston, MA).

RESULTS

There were 1826 patients in the combined cohort who met inclusion criteria. Of those, 596 (33%) were classified as immunocompromised. Baseline characteristics and prevalence of immunocompromising conditions are described in **Table 1** and **Table S1** (https://links.lww.com/CCM/H821). Immunocompromised patients were younger on average (mean, 57.9 [SD, 14.5] vs. 60.1 [SD, 17.1]; $p = 0.003$). Medical comorbidities were similar between the groups with exception of cirrhosis, which was more prevalent in immune competent patients ($p = 0.01$). Vasopressor use at enrollment and prevalence of bacteremia were similar between immune compromised and immunocompetent groups, while APACHE II score on enrollment (mean, 28.2 [SD, 8.7] vs. 27.1 [SD, 8.8]; $p = 0.02$) and in-hospital mortality were significantly higher in immunocompromised patients (41% vs. 28% mortality at 60 d; $p < 0.001$). These findings were similar when comparing hematologic malignancy patients or solid organ transplant patients to the immune competent group (**Tables S2** and **S3**, https://links.lww.com/CCM/H821). Bacterial pathogens were the most common identified pathogen in all groups, although prevalence of Gram-negative sepsis varied by immunocompromising condition (**Table S4**, https://links.lww.com/CCM/H821). Culture negative sepsis occurred in 25–61% of patients across all groups, with the exception of hematologic malignancy patients in EARLI where a pathogen was identified in all but 16% of cases (Table S4, https://links.lww.com/CCM/H821).

In unadjusted analyses, compared with immune competent patients with sepsis, immunocompromised patients were more likely to be classified in the hyperinflammatory subphenotype (odds ratio [OR], 1.8; 95% CI, 1.4–2.2; $p < 0.0001$). When further stratifying immunocompromised patients, hematologic malignancy (OR, 4.3; 95% CI, 3.1–6.0; $p < 0.0001$) and solid organ transplant (OR, 1.6; 95% CI, 1.1–2.4; $p = 0.02$) were both associated with the hyperinflammatory subphenotype of sepsis (**Fig. 1**). In contrast, there was no association between AIDS, solid malignancy, or immunosuppressive medication use and subphenotype. These results were consistent when assessed in the individual enrollment cohorts (**Fig. S2**, https://links.lww.com/CCM/H821). Unsurprisingly, hyperinflammatory patients with immunocompromising conditions had higher APACHE II scores, lower bicarbonate, and higher vasopressor use compared with hypoinflammatory patients. Hematologic malignancy patients classified as hyperinflammatory had significantly lower WBC and platelet counts compared with other subgroups (**Tables S5–S7**, https://links.lww.com/CCM/H821). Malignancy cell lineage (myeloid vs. lymphoid) was similar between patients across subphenotypes in EARLI (Table S5, https://links.lww.com/CCM/H821).

In multivariate analysis, hematologic malignancy remained a strong independent predictor of the hyperinflammatory subphenotype of sepsis after adjusting in individual models for bacteremia, APACHE II score, type of pathogen, and leukopenia (**Fig. 2*A***). In contrast, associations between history of solid organ transplant and the hyperinflammatory subphenotype were no longer significant after adjustment for presence of bacteremia or leukopenia (**Fig. 2*B***).

To investigate underlying biology, we compared plasma biomarkers between immunocompromised and immune competent patients. Patients with a history of hematologic malignancy had significantly higher levels of plasma IL-6, IL-8, soluble tumor necrosis factor receptor 1 (sTNFr1), and lower protein C compared with immune competent patients ($p = 0.028$; $p < 0.0001$; $p < 0.0001$; $p = 0.01$; and **Fig. S3*A***, https://links.lww.com/CCM/H821). In multivariate linear regression analysis adjusting for age, severity of illness, and presence of bacteremia, hematologic malignancy remained associated with elevated IL-8 and sTNFr1 ($R^2 = 0.21$; $p < 0.0001$ for IL-8 and $R^2 = 0.18$; $p < 0.001$ for sTNFr1; and **Table S8**, https://links.lww.com/CCM/H821). Patients with a history of solid organ transplant admitted with sepsis had significantly higher levels of plasma sTNFr1 compared with immune competent patients ($p < 0.0001$; **Fig. S3*B***, https://links.lww.com/CCM/H821), even after adjusting for age, severity of illness and bacteremia ($R^2 = 0.18$; $p < 0.0001$; and Table S8, https://links.lww.com/CCM/H821).

Hematologic malignancy patients classified as hyperinflammatory had worse survival in time-to-event analysis compared with both hematologic malignancy hypoinflammatory patients and immune competent patients of both subphenotypes ($p < 0.0001$; $p = 0.003$; $p < 0.0001$; and **Fig. 3**). To assess whether the hyperinflammatory subphenotype adds independent prognostic information in patients with hematologic malignancy, we used multivariable Cox proportional hazards regression adjusting for WBC count, severity

TABLE 1.
Baseline Characteristics for the Early Assessment of Renal and Lung Injury and Validating Acute Lung Injury Biomarkers for Diagnosis Cohorts

Characteristic	Immunocompromised (*n* = 596)	Immune Competent (*n* = 1230)	*p*
Age, yr, mean (SD)	57.9 (14.5)	60.1 (17.1)	0.0034
Gender, *n* (%)			0.11
Male	342 (57.4)	692 (56.3)	
Female	252 (42.3)	538 (43.7)	
Race, *n* (%)			0.005
White	452 (75.8)	818 (66.5)	
Black	70 (11.7)	164 (13.3)	
Asian	45 (7.6)	142 (11.5)	
Hispanic	24 (4.0)	69 (5.6)	
Native American	0 (0)	4 (0.3)	
Pacific Islander	1 (0.2)	6 (0.5)	
Other	4 (0.7)	20 (1.6)	
Type of immunocompromise, *n* (%)			
Solid organ transplant	116 (19.5)	NA	NA
AIDS	49 (8.2)		
Hematologic malignancy	175 (29.4)		
Solid malignancy	124 (20.8)		
Immunosuppressive medication	130 (21.8)		
Type II diabetes, *n* (%)	154 (25.8)	360 (29.3)	0.14
Cirrhosis, *n* (%)	34 (5.7)	113 (9.2)	0.013
End-stage kidney disease, *n* (%)	28 (4.7)	77 (6.3)	0.22
Maximum WBC count in the first 24 hr of ICU admission, median (IQR)	12.2 (5.6–19.3)	14.3 (9.8–20.4)	< 0.001
Platelets, median (IQR)	145.0 (61.0–239.5)	191.0 (124.0–270.0)	< 0.001
Minimum serum bicarbonate in the first 24 hr of ICU admission, median (IQR)	20.0 (17.0–23.0)	21.0 (17.0–24.0)	0.16
IL-6, ng/mL, median (IQR)	72.1 (20.6–356.7)	75.8 (20.3–369.8)	0.95
IL-8, ng/mL, median (IQR)	29.5 (11.8–162.6)	18.2 (8.1–59.3)	< 0.001
Soluble tumor necrosis factor receptor 1, ng/mL, median (IQR)	4709.8 (2552.7–9272.4)	3586.1 (1936.6–7311.2)	< 0.001
Protein C, % normal, median (IQR)	61.7 (37.8–91.2)	57.1 (38.3–90.2)	0.39
Hyperinflammatory, *n* (%)	242 (40.6)	362 (29.4)	< 0.001
Any vasopressor use in the first 24 hr of ICU admission, *n* (%)	298 (50.0)	660 (53.7)	0.13
Acute Physiology and Chronic Health Evaluation II score in first 24 hr of ICU admission, median (IQR)	27.0 (22.0–33.0)	27.0 (21.0–33.0)	0.05
Sequential Organ Failure Assessment, median (IQR)	9 (7–11.3)	9 (6–11)	0.61
Pulmonary etiology of sepsis, *n* (%)	242 (40.6)	493 (40.1)	0.88
Bacteremia, *n* (%)	162 (27.2)	331 (26.9)	0.67

(*Continued*)

TABLE 1. (*Continued*)

Baseline Characteristics for the Early Assessment of Renal and Lung Injury and Validating Acute Lung Injury Biomarkers for Diagnosis Cohorts

Characteristic	Immunocompromised (*n* = 596)	Immune Competent (*n* = 1230)	*p*
Mechanical ventilation, *n* (%)	318 (53.3)	798 (64.9)	< 0.001
Mechanical ventilation length, d, median (IQR)	2 (0–5)	3 (0–6)	< 0.001
Mortality, 30 d, *n* (%)	203 (34.1)	304 (24.7)	0.0068
Mortality, 60 d, *n* (%)	243 (40.8)	349 (28.4)	< 0.001

IL = interleukin, IQR = interquartile range, NA = not applicable.
Duration of mechanical ventilation includes survivors and nonsurvivors. Mortality at 30 and 60 d is in-hospital mortality.

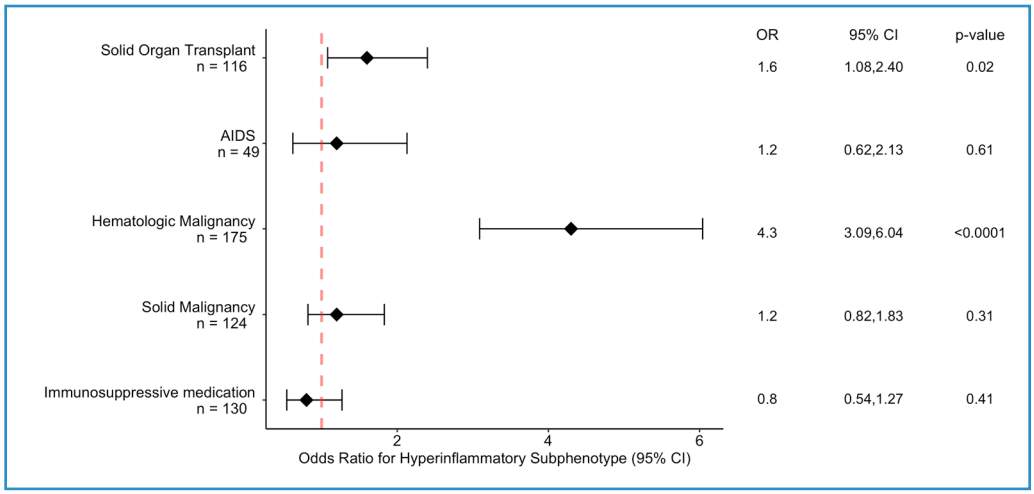

Figure 1. Adjusted odds ratios (ORs) for the association between type of immune compromise and hyperinflammatory subphenotype in the combined cohort, adjusted for cohort.

of illness as measured by APACHE, bacteremia, and enrollment cohort and found that hyperinflammatory classification remained strongly associated with mortality (hazard ratio, 3.88; 95% CI, 1.85–8.14; $p < 0.001$; and **Table S9**, https://links.lww.com/CCM/H821). In contrast, survival in patients with a history of solid organ transplant, solid malignancy, and AIDS was not statistically different between the hyperinflammatory and hypoinflammatory subphenotypes in time-to-event analysis ($p = 0.08$; $p = 0.87$; $p = 0.22$; **Fig. 4**; and **Figs. S4-S6**, https://links.lww.com/CCM/H821). In individual logistic regression models of 30-day mortality, adjusted for cohort and including an interaction term between type of immunosuppression and hyperinflammatory subphenotype, there was a significant interaction for history of solid organ transplant ($p = 0.045$), hematologic malignancy ($p = 0.044$), and solid malignancy ($p = 0.034$), indicating that associations between hyperinflammatory classification and mortality varied by immunocompromise subgroup.

DISCUSSION

Building on prior work in patients with comorbid malignancy, we report a comprehensive analysis on associations between comorbidities affecting the host immune system and molecular subphenotypes in critical illness (14). In a combined cohort of patients enrolled in EARLI and VALID, a history of hematologic malignancy was strongly associated with the hyperinflammatory subphenotype: a finding that persisted in each cohort separately. A history of solid organ transplant was also associated with the hyperinflammatory subphenotype in the combined cohort, while there was no association between subphenotype and a history of AIDS, solid malignancy on chemotherapy, or immunosuppressive medication use. Interestingly, we did not observe higher mortality in the hyperinflammatory subphenotype across all subgroups of immunocompromise. Our results suggest that immunocompromise before admission may be associated with inflammatory subphenotypes in sepsis and may influence their prognostic utility. These findings highlight the hematologic malignancy subgroup as an interesting population for future study

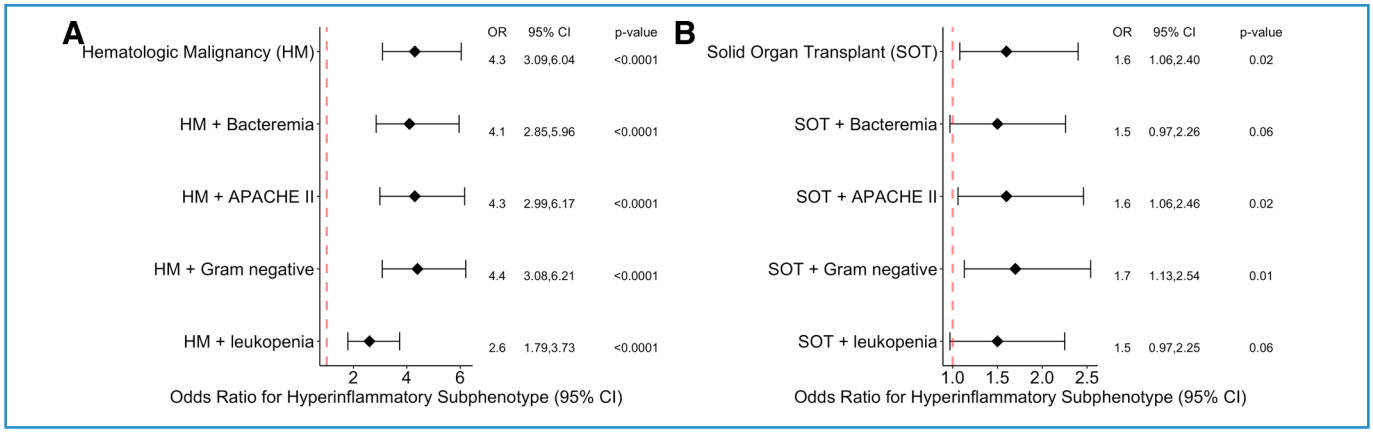

Figure 2. Adjusted odds ratio (OR) from individual regression models to explore contributing factors of the association between hyperinflammatory subphenotype and immunocompromised subgroup; hematologic malignancy (HM; **A**) and solid organ transplant (SOT; **B**) in the combined cohort. All models adjusted for cohort. APACHE II = Acute Physiology and Chronic Health Evaluation II.

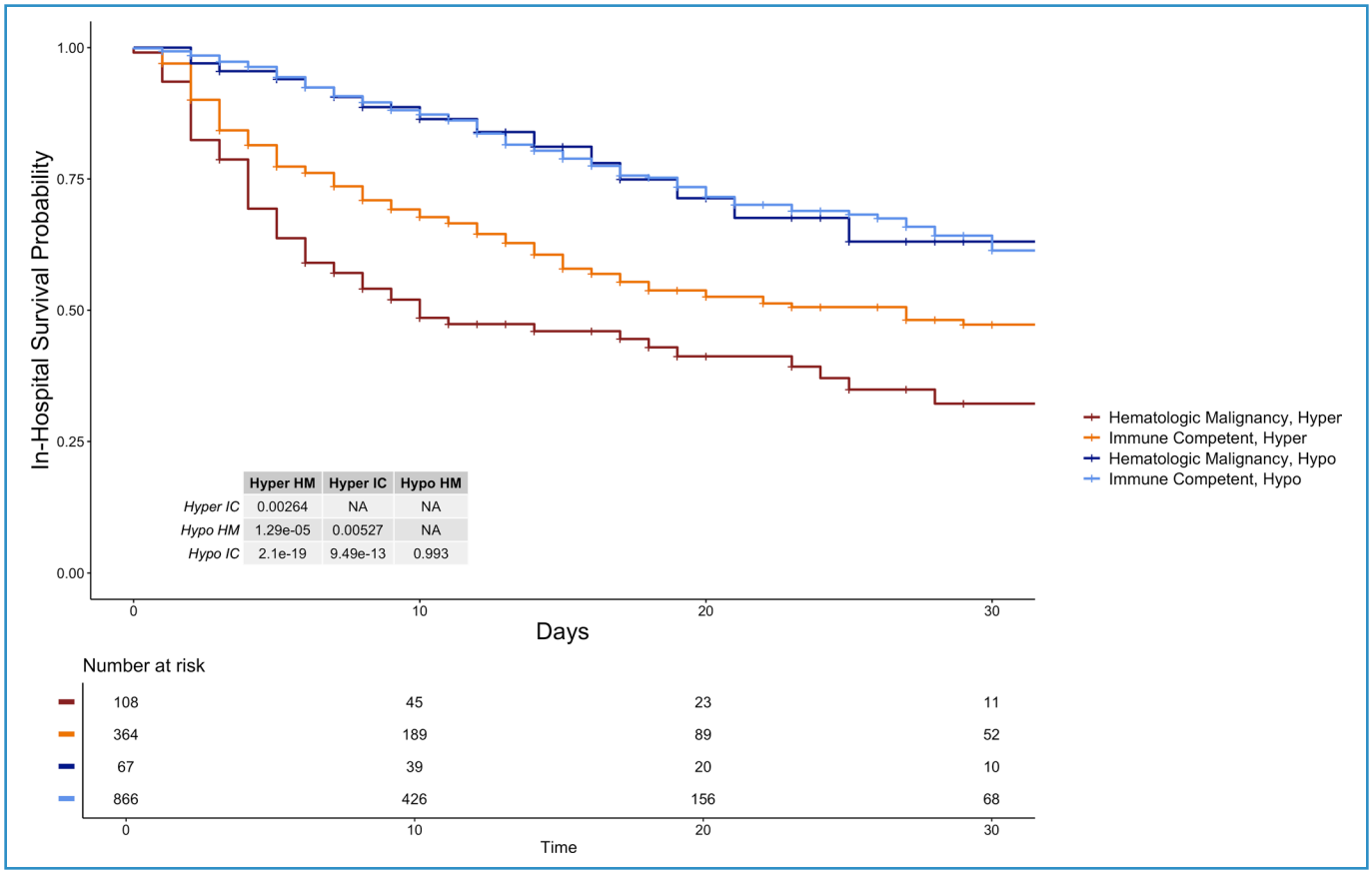

Figure 3. Kaplan-Meier survival plots displaying in-hospital mortality in hematologic malignancy (HM) and immune competent (IC) patients in the combined cohort, stratified by molecular subphenotype. Patients were censored at the time of discharge from the hospital. Significance was determined by pairwise log rank-sum test with Benjamini-Hochberg correction to adjust for multiple comparisons. NA = not applicable.

and suggest that tailored subphenotype derivation in immunocompromised subgroups may be warranted. Thoughtful consideration should be given toward inclusion of immunocompromised subgroups in phenotype-driven clinical trials.

Immunocompromised populations remain understudied in critical illness, despite increasing prevalence in the general population (15–17). The hyperinflammatory and hypoinflammatory molecular subphenotypes were originally described in secondary analyses

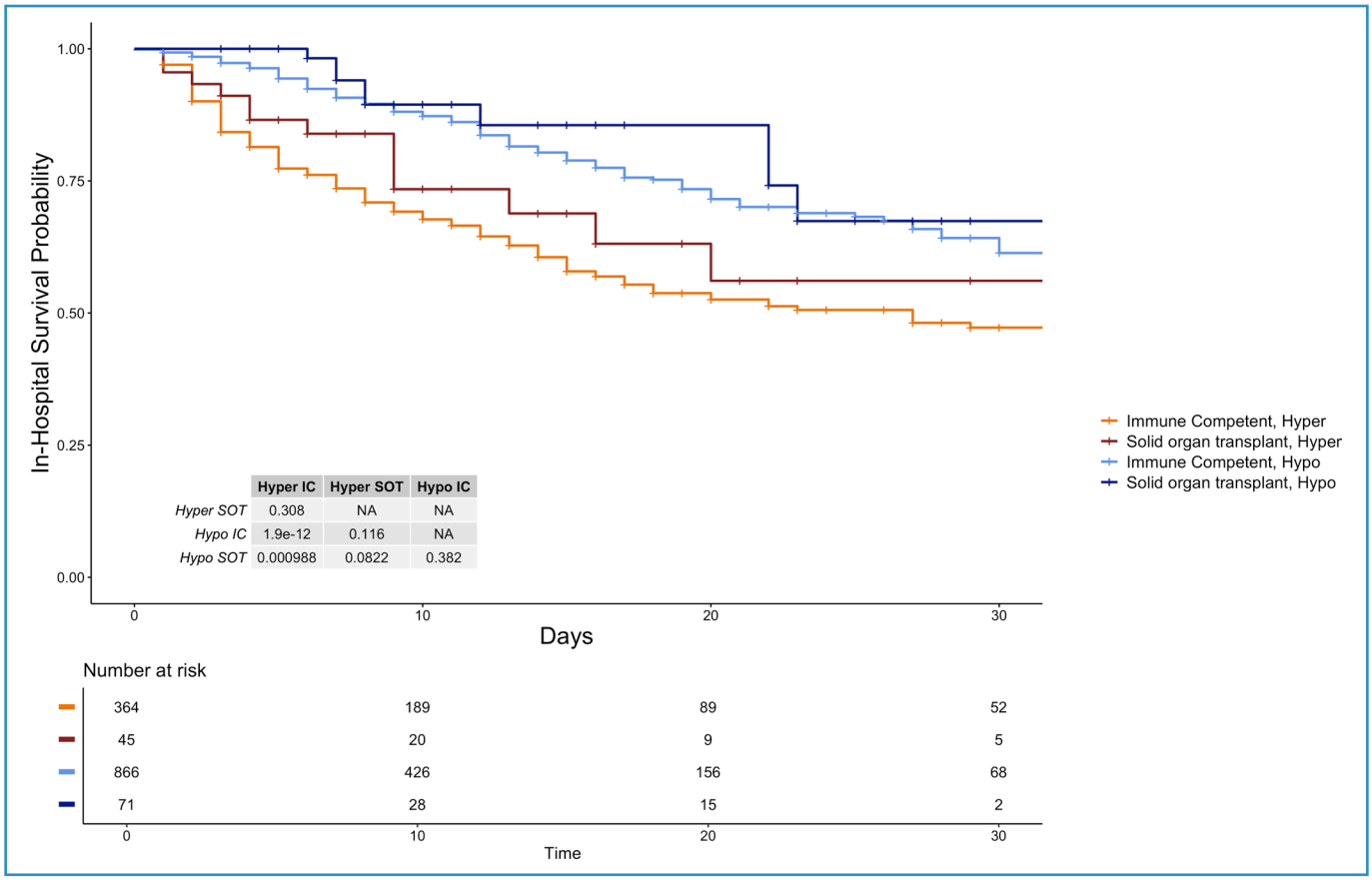

Figure 4. Kaplan-Meier survival plots displaying in-hospital mortality for solid organ transplant (SOT) and immune competent (IC) patients in the combined cohort, stratified by molecular subphenotype. Patients were censored at the time of discharge from the hospital. Significance was determined by pairwise log rank-sum test with Benjamini-Hochberg correction to adjust for multiple comparisons. NA = not applicable.

of RCTs, which largely exclude immunocompromised populations (7, 8, 18). Similarly, prior phenotyping studies in observational cohorts have lacked granularity regarding immunocompromising conditions (9, 19). Heijnen et al (20) reported a higher prevalence of broadly defined "immunodeficiency" in the hyperinflammatory subphenotype of septic patients with acute hypoxemic respiratory failure, and several transcriptomic analyses have demonstrated differential prevalence of immunocompromise in sepsis subgroups, but specific immunocompromising conditions that contribute to these findings are not clear, and sample sizes were small (21–23). Here, we present a novel finding using comprehensive clinical data in two prospective sepsis cohorts, identifying an association between specific preexisting immunocompromising conditions and inflammatory subphenotypes, strengthening the evidence for the importance of the host response in molecular subphenotypes of sepsis.

Patients with active hematologic malignancies or a history of solid organ transplant are commonly described as unable to mount an effective immune response (24, 25). Perhaps surprisingly, we found that both these populations are more likely to be classified as hyperinflammatory. Compared with other immunocompromised subgroups, patients with hematologic malignancies are more likely to experience profound bone marrow suppression due to both direct effects of the malignancy and the intensity of treatment regimens. Additionally, these patients often exhibit elevated inflammatory markers, reflecting both underlying disease activity and immune dysregulation (25–28). Hyperinflammatory patients in this subgroup of our cohort had more profound myelosuppression—evidenced by significantly lower WBC and platelet counts—and significantly higher IL-8 levels compared with individuals in other subgroups. Given IL-8's role in recruiting neutrophils, its elevation in the context

of marrow suppression or neutropenia may reflect a state of persistent proinflammatory signaling due to ineffective cell recruitment from the bone marrow or lack of a neutrophil-mediated feedback mechanisms, contributing to early organ injury and early death. This mechanism may contribute to the strong association in this subgroup and highlights hematologic malignancy patients as a compelling population for further study of the functional immunologic profile and underlying biologic mechanisms of molecular subphenotypes.

Patients with a history of solid organ transplantation are routinely on medications that suppress cellular immunity, and increased levels of exhausted T-cell populations have been described in these patients (26, 27). Recently published data indicates that a relative overexpression of the cellular immune response is characteristic of hypoinflammatory sepsis, possibly reflecting less T-cell exhaustion compared with hyperinflammatory patients (10). Our observation that solid organ transplant patients are more likely to be classified as hyperinflammatory points toward a potential role for exhausted T-cell populations in molecular subphenotypes and is in line with a recent study demonstrating paradoxical hyperinflammation in solid organ transplant recipients with COVID-19 (28).

The hyperinflammatory subphenotype has consistently been associated with higher mortality and differential response to treatments in secondary analyses of RCTs and observational ARDS and sepsis cohorts (5–7, 9). As such, there is an increased emphasis on clinical implementation of subphenotypes for prognostication and treatment enrichment in clinical trials (4). Whether the hyperinflammatory subphenotype is still associated with mortality in immunocompromised populations and whether they should be included in trials based on subphenotype is therefore increasingly relevant. In our study, the hyperinflammatory subphenotype was strongly associated with mortality in patients with hematologic malignancy but was not associated with mortality in those with a history of solid organ transplant or solid malignancy on chemotherapy, suggesting that prognostic value may be less robust in these specific populations. We hypothesize that underlying mechanisms of immune system dysregulation may differ by subgroup. Patients with solid malignancies may have inflammatory biomarkers influenced by tumor biology or treatment effects, whereas transplant recipients may experience a different balance between immune suppression and activation. These observations raise the possibility that distinct subphenotypes may exist within specific immunocompromised populations or that previously described subphenotypes derived from populations where immunocompromised patients were relatively underrepresented may not be as applicable to this subgroup of patients. Taken together, these findings suggest that tailored subphenotype derivation—particularly in groups such as patients with solid organ transplant and solid malignancies—may be warranted. Alternatively, although our a priori sample size calculation indicated that our analysis should have adequate power to detect sizable differences in outcomes, the relatively modest numbers of patients with solid organ transplant ($n = 116$), solid tumors ($n = 124$), and AIDS ($n = 49$) may have limited our power to identify smaller associations with mortality; thus, these findings will need to be validated in larger cohorts.

This study has several strengths. We leveraged two relatively large and well-characterized prospective sepsis cohorts with granular data regarding immunosuppression before admission. We used prior latent class analysis to classify subphenotypes, and we report plasma biomarker profiles of the largest cohort (to our knowledge) of critically ill immunocompromised patients with this type of data. This study also has some limitations. To meet our required sample size, we used a combined patient cohort of EARLI and VALID patients and, therefore, do not have a separate validation cohort. Even with a combined sample size of over 1800, the prevalence of some types of immunocompromise, such as AIDS and specific immunosuppressive medications, was relatively low; thus, conclusions in these groups should be interpreted cautiously. Timing of sample collection differed in the two cohorts (24 hr in EARLI vs. 48 hr in VALID), which may influence subphenotype classification particularly in a dynamic immunocompromised population. Larger, well characterized cohorts of immunocompromised patients will be needed for phenotyping in critical illness. Second, our definition of immunosuppression is conservative and intentionally did not include other chronic medical comorbidities, which may influence the immune response, including diabetes, cirrhosis, or congestive heart failure, due to a lack of granular data on severity and disease control. Immunocompromised populations and their treatments have evolved significantly

since 2007, raising issues around generalizability to a rapidly evolving immunocompromised population. More studies are needed to assess the influence of these conditions on molecular subphenotypes. Third, data availability was not uniform across the patient cohorts. Our definition of immunosuppressive medication use varied by cohort, as described in the methods, limiting our ability to draw meaningful conclusions around specific medications or mechanisms. We were unable to report granular clinical details such as date of solid organ transplantation, treatment regimens and duration, or timing of bone marrow transplant. Grouping such diverse immunosuppressive states together introduces clinical heterogeneity, which presents an opportunity for future research with refined definitions of immunosuppression. Finally, in depth immunophenotyping of specific immune cell populations and signaling pathways in sepsis will be needed to determine the functional implications of these findings.

CONCLUSIONS

Among patients admitted to the ICU with sepsis, a history of hematologic malignancy and solid organ transplantation were associated with the hyperinflammatory subphenotype. Hematologic malignancy patients are characterized by elevated levels of IL-8, more profound myelosuppression and are more likely to be classified as hyperinflammatory, suggesting this as a compelling subgroup for future studies on the immune biology of hyperinflammatory subphenotypes. These findings suggest that preexisting immune status is a key factor of sepsis subphenotypes and that tailored subphenotype derivation may be warranted in certain immunocompromised subtypes. As molecular subphenotypes are implemented clinically, more studies are needed to validate these findings.

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Dr. Weingart is the guarantor. Drs. Weingart, Calfee, Matthay, and Ware contributed to study design. Dr. Weingart, Mr. Magee, Ms. Chao, Ms. Chak, Ms. Bardillon, Ms. Leroux, Ms. Schmiege, Ms. Hariharan, Ms. Lin, Ms. Obeidalla, Dr. Kerchberger, Dr. Sullivan, Dr. Langelier, Dr. Sarma, Dr. Alipanah-Lechner, Dr. Langelier, Dr. Zhuo, Dr. Evrard, Dr. Kangelaris, Dr. Matthay, Dr. Calfee, and Dr. Ware contributed to data generation and/or collection. Dr. Weingart and Mr. Willmore contributed to data analysis. Drs. Weingart and Calfee contributed to drafting of the article. All authors contributed to editing and approval of the article.

Supported, in part, by grant from the R35HL140026 and R35HL177135 (to Dr. Calfee), H158906 and HL164937 (to Dr. Ware), La Société de Reanimation de Langue Française (to Dr. Evrard), Philippe Foundation (to Dr. Evrard), and L'Institut Servier (to Dr. Evrard).

Dr. Weingart received funding from the National Institutes of Health (NIH; 5T32HL007185-48). Dr. Weingart, Mr. Willmore, Dr. Zhuo, Mr. Magee, Ms. Chao, Ms. Lin, Ms. Schmiege, Ms. Hariharan, Ms. Chak, Ms. Bardillon, Dr. Kerchberger, Dr. Sullivan, Dr. Langelier, Dr. Hendrickson, Dr. Kangelaris, Dr. Sarma, Dr. Alipanah-Lechner, Dr. Sinha, Dr. Matthay, Dr. Ware, and Dr. Calfee received support for article research from the NIH. Drs. Zhuo's, Kerchberger's, Kangelaris', and Matthay's institutions received funding from the National Heart, Lung, and Blood Institute (NHLBI). Ms. Schmiege's, Drs. Langelier's, Matthay's, and Ware's institutions received funding from the NIH. Dr. Sullivan received funding from the NIH (T32HL007185). Dr. Sarma received funding from the NHLBI and InflaRx. Dr. Sinha's institution received funding from the National Institute of General Medical Sciences (R35 GM142992) and the NHLBI (R01 HL175531); he received funding from AstraZeneca and Prenosis. Dr. Matthay's institution received funding from Roche-Genentech, Quantum Health, California Institute for Regenerative Medicine, the National Institute of Allergy and Infectious Diseases, Merck, CSL Behring, and Healios. Dr. Ware received funding from Novartis, Akebia, and Arrowhead. Dr. Calfee's institution received funding from Genentech and Quantum Leap HealthCare Collaborative; she received funding from the NIH, Healios, Arrowhead, Vasomune, GEn1E Lifesciences, Cellenkos, CalciMedica, Enlitisa, Novartis, Aerogen, Boehringer, and Merck. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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The patient cohorts used in this analysis were approved by ethics committees at University of California, San Francisco (Early Assessment of Renal and Lung Injury [EARLI]) and Vanderbilt University (Validating Acute Lung Injury biomarkers for Diagnosis [VALID]) and have been performed in accordance with the ethical

standards laid down in the 1964 Declaration of Helsinki and its amendments.

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