

Allergic Immune Diseases and the Risk of Mortality Among Patients Hospitalized for Acute Infection

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Objectives: The immune response during sepsis remains poorly understood and is likely influenced by the host's preexisting immunologic comorbidities. Although more than 20% of the U.S. population has an allergic-atopic disease, the type 2 immune response that is overactive in these diseases can also mediate beneficial pro-resolving, tissue-repair functions. Thus, the presence of allergic immunologic comorbidities may be advantageous for patients suffering from sepsis. The objective of this study was to test the hypothesis that comorbid type 2 immune diseases confer protection against morbidity and mortality due to acute infection.

Design: Retrospective cohort study of patients hospitalized with an acute infection between November 2008 and January 2016 using electronic health record data.

Setting: Single tertiary-care academic medical center.

Patients: Admissions to the hospital through the emergency department with likely infection at the time of admission who may or may not have had a type 2 immune-mediated disease, defined as asthma, allergic rhinitis, atopic dermatitis, or food allergy, as determined by *International Classification of Diseases*, 9th Revision, Clinical Modification codes.

Interventions: None.

Measurements and Main Results: Of 10,789 admissions for infection, 2,578 (24%) had a type 2 disease; these patients were more likely to be female, black, and younger than patients without type 2 diseases. In unadjusted analyses, type 2 patients had decreased odds of dying during the hospitalization (0.47; 95% CI, 0.38–0.59, $p < 0.001$), while having more than one type 2 disease conferred a dose-dependent reduction in the risk of mortality ($p < 0.001$). When adjusting for demographics, medications, types of infection, and illness severity, the presence of a type 2 disease remained protective (odds ratio, 0.55; 95% CI, 0.43–0.70; $p < 0.001$). Similar results were found using a propensity score analysis (odds ratio, 0.57; 95% CI, 0.45–0.71; $p < 0.001$).

Conclusions: Patients with type 2 diseases admitted with acute infections have reduced mortality, implying that the type 2 immune response is protective in sepsis. (*Crit Care Med* 2019; XX:00–00)

Key Words: allergy; asthma; immunophenotype; sepsis

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Sepsis has been recently redefined as “life-threatening organ dysfunction caused by a dysregulated host response to infection.” (1) An appropriate host response should result in clearance of the infecting pathogen and an uneventful restoration of homeostasis. However, for many patients, the host response may be too strong, inadequate, or incorrectly targeted, resulting in the development of sepsis with significant morbidity and mortality (2). Understanding this variability in the host immune response is necessary for accurate immunologic phenotyping and development of a personalized therapeutic approach to treating the dysfunctional septic inflammatory response (3).

Many factors determine the nature of the host response, including age, genetics, exposures, use of immune-modulating medications, and presence of diseases such as HIV and malignancy (4). We recently discovered that several additional immunologic diseases such as lupus, ulcerative colitis, and multiple sclerosis are overrepresented among septic patients, suggesting that a dysregulated immune response associated with these diseases or their therapies may drive the risk of developing sepsis (5). In contrast, however, we and others have found that diseases associated with the type 2 (T2) inflammatory response, such as asthma and allergy, are underrepresented among septic patients (5, 6). Although these observations suggest that patients with T2 diseases are less likely to be hospitalized for sepsis, it remained unclear if such T2 patients had different outcomes compared with non-T2 patients when they were admitted to the hospital with acute infections.

In the current study, we conducted a single-center retrospective cohort analysis using electronic health record (EHR) data to compare hospitalizations of infected patients with or without T2 diseases, accounting for potential confounders and covariates. We hypothesized that the presence of T2 diseases among infected patients would reflect a novel phenotype associated with improved outcomes, independent of confounding factors such as demographics, other comorbidities, and processes of care.

MATERIALS AND METHODS

Data Collection

All adult patients admitted to the University of Chicago Medicine, a 500 bed urban academic tertiary medical center, from November 2008 to January 2016 were eligible for study inclusion. All EHR (Epic, Verona, WI) data, including demographics, *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes, clinician orders, laboratory values, and vital signs were collected by the University of Chicago's Clinical Research Data Warehouse. These data were subsequently de-identified and date-shifted at the patient level for up to a year (to further de-identify the data) and made available on a secure Microsoft SQL server (Microsoft, Redmond, WA) for analysis. Waivers of consent were granted by the University of Chicago Institutional Review Board (number 150195), based on minimal harm and general impracticality.

Patient Population and Study Setting

Patients with suspicion for infection were identified using criteria established by Rhee et al (7). Briefly, these criteria indicate that patients must have had a blood culture order and administration of parenteral antibiotics within 48 hours before or after the blood culture order, with at least 4 consecutive days of antibiotics (or antibiotics continued until 1 d prior to death or discharge). Our cohort of patients was further narrowed to include only those patients whose first order for a blood culture or antibiotics occurred in the emergency department, rather than the hospital ward, ICU, or outpatient setting. We also limited our cohort to patients who received appropriate empiric

antibiotics as defined in the Severe Sepsis and Septic Shock: Management Bundle (SEP-1) performance measures and consistent with recommendations by Septimus et al (8) within 24 hours of presentation, with presentation defined as time of first measured vital sign.

To identify patients with a T2 allergic immune disease, we determined if the patients in our cohort had ever had an ICD-9-CM code in either inpatient or outpatient encounters for a T2 comorbid disease, at any time point prior to, including, or after the index encounter for infection. T2 comorbid disease ICD-9-CM codes were as follows: asthma = 493.x, atopic dermatitis = 691.x, food allergy = 558.3 or 995.3, and allergic rhinitis = 477.x. In addition, we also analyzed only those patients who had received medical care within our hospital system prior to the index encounter for infection, as indicated by the presence of any ICD-9-CM codes in the EHR prior to admission.

Statistical Analysis

Demographics, comorbidities, physiologic characteristics (i.e., vital signs, laboratory results), and processes of care (e.g., time to antibiotics) were compared between patients with and without T2 comorbid diseases. For physiologic characteristics, both median values as well as the percentages of patients with abnormal values as established by either systemic inflammatory response syndrome criteria or quick Sequential Organ Failure Assessment (qSOFA) criteria, were compared between groups (9). To objectively measure severity of illness, SOFA scores were calculated as defined in the Sepsis-3 guidelines. In addition, to objectively estimate risk of deterioration, the electronic Cardiac Arrest Risk Triage (eCART) score, which is a statistically-derived early warning score that has been validated in patients with infections, was calculated (1, 10, 11). For these scores, the highest values noted in the first 24 hours of admission were used for analysis.

To analyze corticosteroid therapy, corticosteroid dosing for the various preparations (prednisone, prednisolone, methylprednisolone, hydrocortisone) was converted to prednisone equivalents to facilitate appropriate comparisons. Antibiotic therapies were divided into antipseudomonal (piperacillin-tazobactam, imipenem, meropenem, ceftazidime, ceftazidime, aztreonam, levofloxacin, and aminoglycosides), anti-methicillin-resistant *Staphylococcus aureus* (MRSA) (daptomycin, vancomycin, linezolid, and ceftaroline), and anti-atypical pathogen (azithromycin, moxifloxacin, doxycycline, and levofloxacin). Determination of the type of infection was done by evaluating ICD-9-CM codes for the index hospitalization, as described by others (12, 13).

Univariate and multivariate logistic regression analyses were used to develop our final adjusted model for risk of death among patients with T2 immune comorbid diseases. A sensitivity analysis was performed by only including patient admissions that had a preceding encounter in an inpatient or outpatient setting at the University. In addition, confounder adjustment was performed using propensity score matching (PSM) weights. This method uses weighting to ensure balance of confounding

variables between the two groups of interest. By using this approach, all study patients are retained in the analysis (albeit with some patients having low weights), as opposed to traditional 1:1 matching which will exclude individuals who have no match. This method improves covariate balance, provides a more accurate estimation of variance, is more efficient than 1:1 pair matching, and has been shown to provide the lowest bias when studying rare binary outcomes (e.g., in-hospital mortality in this study) (14, 15). Eighteen variables were used for both the adjusted logistic regression model and PSM: age, infection type (ear-nose-throat, pulmonary, gastrointestinal [GI], genitourinary, CNS, skin, and other), highest SOFA score in the first 24 hours, highest eCART in the first 24 hours, admission year (to account for variations over time in practice patterns or infectious disease epidemiology), antimicrobial spectrum (antipseudomonal, anti-MRSA, anti-atypical), highest corticosteroid dose in the first 24 hours (none, low-dose, medium-dose, or high-dose), sex, race (black vs non-black), and ethnicity (Hispanic vs non-Hispanic).

Continuous and categorical variables were tested for statistical significance using *t* tests, Wilcoxon rank-sum, or chi-square tests, as appropriate. Survival analysis for 28-day survival was conducted using Mantel-Cox log-rank testing, assuming that patients who had been discharged remained alive at 28 days after admission and only evaluating patients noted to die in-hospital. Two-tailed *p* values of less than 0.05 were considered statistically significant for all comparisons, and analyses were performed using Stata Version 14.1 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

Of 149,458 unique patient admissions during the study period, 13,084 admissions met criteria for infection in the emergency department (**Fig. 1S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). Of these, 10,789 received SEP-1-recommended empiric antibiotics within 24 hours of presenting to the hospital and were therefore included in the analysis. A total of 2,578 (24%) admissions were classified as having a T2 immune comorbidity. T2 patients were younger (median age 56 vs 60; $p < 0.001$), and more likely to be female (63% vs 50%; $p < 0.001$) and African-American (81% vs 68%; $p < 0.001$) (**Table 1**). The most prevalent T2 disease was asthma (81% of T2 patients and 19% of the total cohort), followed by allergic rhinitis (21% of T2 patients and 5.1% of the total cohort), while 93% of patients had either asthma or allergic rhinitis; these data are consistent with national epidemiologic data (16).

T2 patients were more likely to be admitted with pneumonia (32% vs 23%; $p < 0.001$), but less likely to be admitted with genitourinary (21% vs 24%; $p = 0.003$) and gastrointestinal infections (10% vs 12%; $p = 0.005$) (**Table 1**). There were no differences between the groups for other sites of infection.

Physiologic Characteristics in the First 24 Hours

The median first recorded vital sign values were compared between both groups to determine if there were significant

differences that might reflect a distinct host response to infection or portend a different outcome (**Table 2**). T2 patients had a median presenting temperature slightly higher than those without T2 diseases (36.9°C vs 36.7°C; $p < 0.001$). T2 patients were less likely to be hypothermic with a temperature less than or equal to 36°C (18% vs 22%; $p < 0.002$). Although T2 patients also had significantly higher median respiratory rates, heart rates, and systolic blood pressures, the percentages of patients with abnormal values were not statistically different between groups, nor were the percentage of patients with abnormal Glasgow Coma Scales (GCSs), defined as any GCS less than 15.

To compare laboratory values between the groups, the highest values within the first 24 hours were used. Median WBC counts and neutrophil counts were similar, although T2 patients were less likely to be leukopenic (5.7% vs 8.0%; $p < 0.001$) (**Table 2**). Further, T2 patients had higher median eosinophil counts. The median lactate level and percentage of patients with an elevated lactate level greater than 2 mmol/L were both lower among T2 patients (1.6 vs 1.7; $p < 0.001$ and 47% vs 57%; $p < 0.03$). The maximum SOFA score in the first 24 hours was similar between both groups, while the highest eCART score was slightly but significantly lower among T2 patients (26 vs 31; $p < 0.001$). Overall, T2 patients present with similar vital sign and laboratory derangements compared with non-T2 patients, albeit with slightly lower lactate and blood urea nitrogen levels and a decreased tendency to leukopenia.

Selected Medication Use During the First 24 Hours

Significantly more T2 patients received corticosteroids in the first 24 hours, compared with non-T2 patients (31% vs 18%; $p = 0.001$) (**Table 1S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). The specific corticosteroid dose administered was subdivided into low-dose (≤ 10 mg prednisone equivalent), medium/stress-dose (> 10 to ≤ 75 mg prednisone equivalent), or high/anti-inflammatory dose (> 75 mg prednisone equivalent); T2 patients were more likely to receive higher doses of corticosteroids than non-T2 patients.

Time from first recorded vital signs to antibiotic administration was slightly but significantly higher among T2 patients (5.3 vs 5.1 hr; $p = 0.03$). T2 patients were less likely to be treated with anti-pseudomonals (79% vs 83%; $p < 0.001$) and anti-MRSA antibiotics (69% vs 72%; $p = 0.005$), and more likely to be treated with anti-atypical pathogen therapies (43% vs 33%; $p < 0.001$) (**Table 1S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). In addition, T2 patients were more likely to receive empiric antimicrobial coverage that included a combination of anti-pseudomonals, anti-MRSA, and anti-atypical pathogen treatment (27% vs 22%; $p < 0.001$).

Interventions and Outcomes During the Index Hospitalization

T2 patients were more than twice as likely (6.8% vs 3.0%; $p < 0.001$) to require either bi-level noninvasive positive pressure or high-flow nasal cannula, although they were no more likely to require intubation (**Table 2S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). However, they

TABLE 1. Characteristics of Patients With and Without Type 2 Immune Comorbidities

Variables	No Type 2 Disease (n = 8,211)	With Type 2 Disease (n = 2,578)	p
Age, yr, median (interquartile range)	60 (48–73)	56 (43–68)	< 0.001
Female sex (%)	49.5	62.7	< 0.001
Race ^a , %			< 0.001
White	25.7	15.9	
Black	67.7	80.8	
Asian/Pacific Islander	2.1	0.89	
Unknown/declined	2.3	0.97	
Ethnicity, %			< 0.001
Hispanic/Latinx	5.7	3.1	
Not Hispanic/Latinx	91.0	95.5	
Unknown/declined	3.3	1.4	
Specific type 2 immune comorbidity, %			
Asthma	NA	80.6	
Atopic dermatitis	NA	4.2	
Food allergy	NA	8.7	
Allergic rhinitis	NA	21.4	
Type of infection ^b , %			
Pulmonary	22.7	31.5	< 0.001
Ears/nose/throat	1.0	1.2	0.24
Genitourinary	24.0	21.2	0.003
Gastrointestinal	12.1	10.1	0.005
Skin/soft tissue	18.1	18.6	0.56
CNS	1.1	0.8	0.17
Other (including bacteremia)	26.4	26.0	0.71

NA = not applicable.

^aPatients identifying as “more than one race” or “American Indian or Native Alaskan” constituted < 1% of patients and were not included in this table for simplification purposes (but were included in all analyses).

^bPercentages for infection type sum to greater than 100% because some patients had multiple documented sites of infection.

International Classification of Diseases, 9th Revision, Clinical Modification codes for type 2 comorbidities as follows: asthma = 493.x, atopic dermatitis = 691.x, food allergy = 558.3 or 995.3, and allergic rhinitis = 477.x.

were less likely to require vasopressors (8.2% vs 11.5%; $p < 0.001$), and there was no difference in requirement for ICU-level care or hospital length of stay. As shown in **Figure 1**, T2 patients had a markedly lower 28-day mortality ($p < 0.0001$) and only 3.7% of T2 patients died during their hospitalization, compared with 7.6% of non-T2 patients ($p < 0.001$) (Table 2S, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>).

Association Between T2 Diseases and In-Hospital Mortality

Unadjusted logistic regression revealed an odds ratio (OR) for dying among T2 patients of 0.47 (CI, 0.38–0.59; $p < 0.001$), while multivariable logistic regression adjusting for the indicated

covariates (demographics, illness severity, type of infection, class of antibiotics, and maximal corticosteroid dose in the first 24 hr) shown in **Table 3** resulted in an OR of 0.55 (0.44–0.70; $p < 0.001$). Given that patients with chronic diseases such as asthma and allergy may interface more frequently with the healthcare system (and interaction with the healthcare system could confound our findings), we conducted a sensitivity analysis that only included patient admissions with prior encounters within the health system and found similar results (OR, 0.51; 95% CI, 0.39–0.67). PSM weights analysis revealed an OR for death among T2 patients of 0.57 (CI, 0.45–0.71; $p < 0.001$), with standardized mean differences (SMDs) less than 0.1 for all covariates with the exception of age (SMD = 0.19) (**Table 3S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). Nonparametric test-for-trend

TABLE 2. Comparison of First Recorded Vital Signs and First Measured Laboratory Values

Variables	No Type 2 Disease (n = 8,211)	With Type 2 Disease (n = 2,578)	p
Temperature, °C, median (IQR)	36.7 (36.0–37.8)	36.9 (36.2–37.9)	< 0.001
Temperature ≤ 36, %	21.6	17.7	0.002
Temperature ≥ 38, %	18.2	19.3	0.93
Respiratory rate, breaths/min, median (IQR)	18 (18–20)	18 (18–22)	< 0.001
Respiratory rate ≥ 22, %	20.0	23.8	0.28
Heart rate, beats/min, median (IQR)	103 (88–119)	104 (90–120)	0.05
Heart rate > 90, %	64.6	66.8	0.17
SBP, median (IQR)	123 (107–141)	125 (109–144)	< 0.001
SBP < 100 mm Hg, %	15.3	12.4	0.62
GCS ^a , median (IQR)	15 (15–15)	15 (15–15)	0.006
GCS < 15, %	1.9	0.9	> 0.99
WBC/μL, median (IQR)	11.7 (7.8–17.1)	11.6 (7.8–16.8)	0.64
WBC/μL > 12,000, %	48.1	47.0	0.17
WBC/μL < 4,000, %	8.0	5.7	0.001
Band forms > 10%, %	18.6	16.3	0.15
Eosinophils ^b (×10 ³ /μL), median (IQR)	0 (0–0.03)	0 (0–0.05)	< 0.001
Neutrophils ^c (×10 ³ /μL), median (IQR)	8.7 (4.8–13.4)	8.6 (5.0–12.8)	0.76
Lactate ^d mmol/L, median (IQR)	1.7 (1.2–2.8)	1.6 (1.1–2.6)	< 0.001
Lactate > 2, %	56.8	46.9	0.03
BUN, mg/dL, median (IQR)	21 (13–36)	18 (12–30)	< 0.001
BUN > 20, %	51.1	41.4	0.03
Highest Sequential Organ Failure Assessment in first 24 hr	3 (1–5)	3 (1–5)	0.38
Highest electronic Cardiac Arrest Risk Triage in first 24 hr	31 (12–102)	26 (10–84)	< 0.001

BUN = blood urea nitrogen, GCS = Glasgow Coma Scale, IQR = interquartile range, SBP = systolic blood pressure.

^aGCS: number tested was 1,154 (14.1%) for non-type 2 patients; 311 (12.1%) for type 2 patients.

^bEosinophils: number tested was 5,427 (66.1%) for non-type 2 patients; 1,647 (63.9%) for type 2 patients.

^cNeutrophils: number tested was 5,549 (67.6%) for non-type 2 patients; 1,662 (64.5%) for type 2 patients.

^dLactate: number tested was 5,282 (64.3%) for non-type 2 patients; 1,544 (59.9%) for type 2 patients.

analysis revealed that each additional T2 disease comorbidity decreases the mortality risk; only one of 49 of patients (2.1%) with three T2 diseases died, compared with a 2.9% mortality rate for patients with two T2 diseases, and a 4.0% mortality rate for patients with only one T2 disease (**Fig. 2S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). By analyzing the odds of death as a function of the type of T2 disease in our fully adjusted logistic regression model, we found that the point estimates for the individual T2 diseases ranged from an OR of 0.31 to 0.56, suggesting that all types of T2 diseases are associated with a protective effect (**Fig. 3S**, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>).

Given that the types of infections between T2 and non-T2 patients were not balanced, the OR for death among T2 patients as a function of the type of infection was evaluated in the fully adjusted model. Although T2 patients were much

more likely to be admitted with pneumonia (Table 1), they were much less likely to die of their pneumonia compared with non-T2 patients (4.5% vs 10.4%; OR, 0.53; CI, 0.36–0.78; $p = 0.002$); indeed, although the sample sizes are small, the ORs suggest a protective effect of T2 diseases on all infection subtypes except for GI infection (**Fig. 2**). Although T2 patients were more likely to be treated for infections with the combination of anti-pseudomonals, anti-atypical pathogens, and anti-MRSA antibiotics, including this variable in the fully adjusted logistic regression model did not alter the OR for death among T2 patients (OR, 0.55; CI, 0.43–0.70; $p < 0.001$).

Although T2 patients were more likely than non-T2 patients to receive corticosteroids, only 30% of T2 patients did receive corticosteroids (Table 1S, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>). Further, the effect of corticosteroid administration in asthma and allergy is to suppress

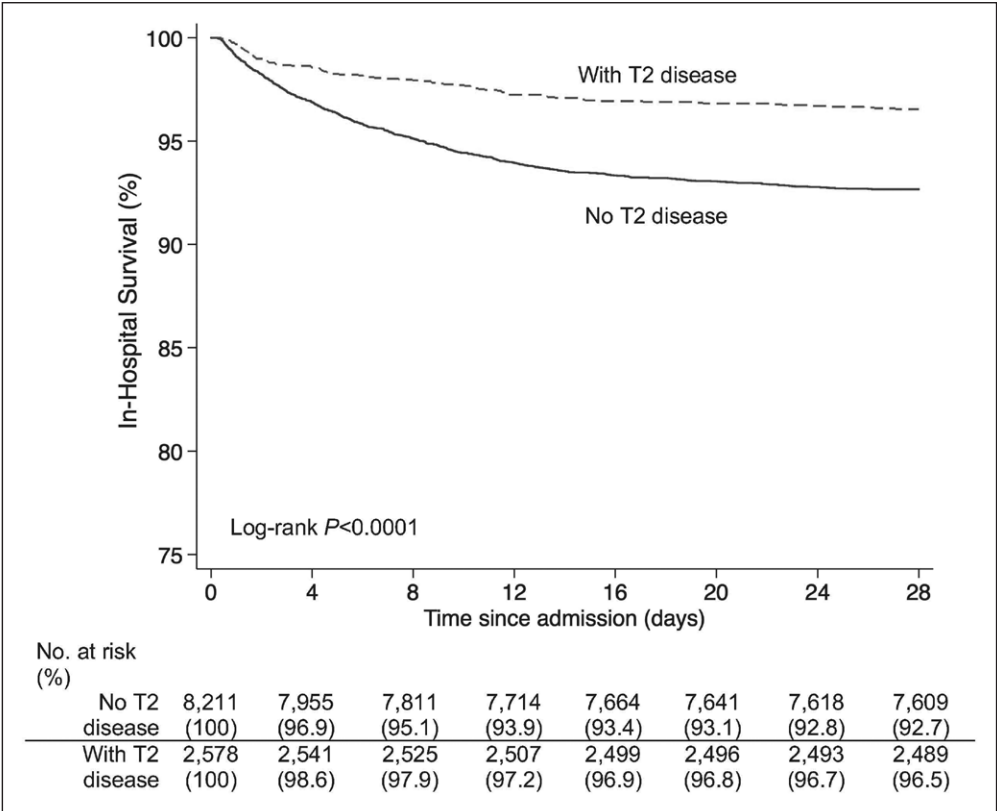


Figure 1. Kaplan-Meier survival curve for patients admitted to the hospital with infection, with and without T2 diseases. Discharged patients were assumed to be alive at 28 d; only patients who died in-hospital were considered to have suffered the event for this analysis.

the T2 immune response, and we hypothesized that this might impact survival among T2 patients. However, when we performed a sensitivity analysis assessing mortality among only T2 patients as a function of whether or not they received corticosteroids in an otherwise fully adjusted model, no significant difference was observed (Table 4S, Supplemental Digital Content 1, <http://links.lww.com/CCM/E957>).

DISCUSSION

In this retrospective cohort study of hospitalized patients admitted with infection, we found that those patients with allergic, T2 diseases were much less likely to die in the hospital, even when controlling for demographics, severity of illness,

prior to lethal *S. aureus* bacteremia or pneumonia also confers protection (unpublished results) (5, 19). Many of the cell types associated with the T2 immune response play important roles in promoting and regulating repair of damaged tissue; indeed, the T2 immune response may have evolved to perform these roles, which would be beneficial during acute infection (20–26). Within our data, asthma and allergic rhinitis (both diseases dependent on the respiratory mucosal barrier) accounted for nearly 93% of patients with a T2 disease, and the presence of T2 disease was most beneficial in patients with pulmonary infections; this implies there may be a site-specific protection by which the T2 response can limit damage specifically at mucosal sites, perhaps through goblet cell hyperplasia and mucus secretion, or enhanced mucosal tissue repair.

corticosteroid use, antibiotic use, and infection source. This analysis supports the hypothesis that it is the host’s specific immune bias favoring T2 immune responses that protect them from development and death from sepsis.

These results are important for several reasons: first, they imply a protective mechanism for T2 immunity during acute infection that has not been fully appreciated, although a growing body of literature supports this observation. For instance, Hübner et al (17) have suggested that the activation of T2 immunity by helminth infection may suppress the initial pro-inflammatory cytokine storm of sepsis. Linch et al (18) found that the T2 cytokine interleukin (IL)–5 may play a protective role in sepsis, using both patient samples and mouse models. We have noted that stimulation of the T2 immune response in mice

TABLE 3. Logistic Regression for Odds of Dying Among Patients With Type 2 Diseases

Logistic Model	OR (95% CI)	p
Unadjusted	0.47 (0.38–0.59)	< 0.001
Adjusting for demographics (race, sex, age, admit year, ethnicity)	0.50 (0.40–0.63)	< 0.001
Adjusting for demographics + illness severity (highest electronic Cardiac Arrest Risk Triage and Sequential Organ Failure Assessment in first 24 hr)	0.56 (0.44–0.72)	< 0.001
Adjusting for demographics + illness severity + type of infection	0.54 (0.42–0.69)	< 0.001
Adjusting for demographics + illness severity + type of infection + interventions (highest steroid dose, antibiotic classes) delivered in first 24 hr	0.55 (0.43–0.70)	< 0.001

OR = odds ratio.

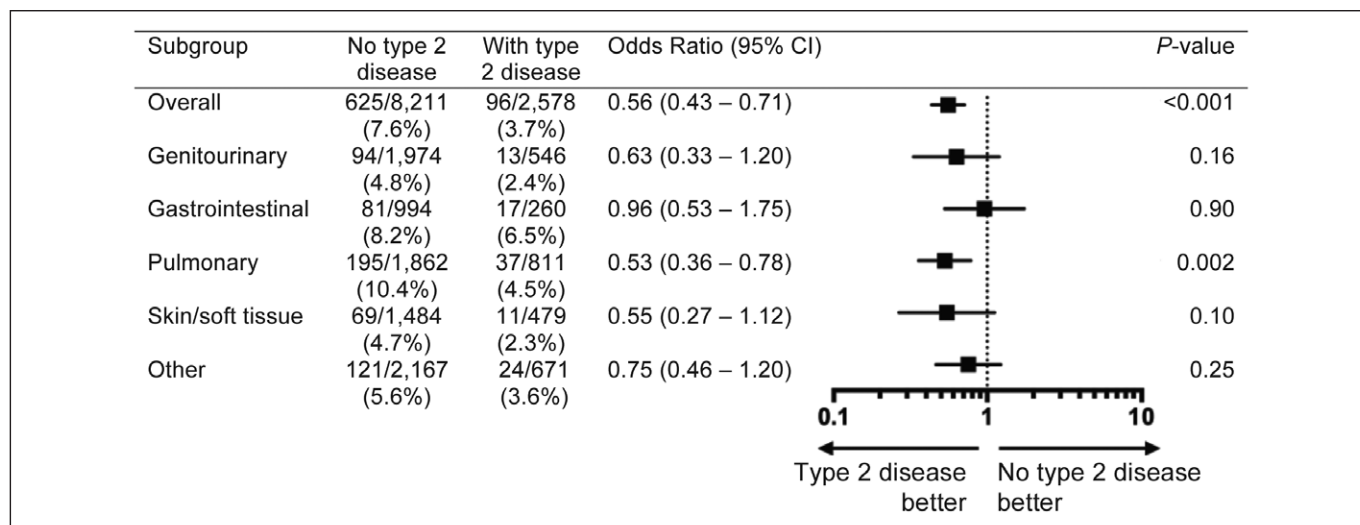


Figure 2. Odds of death as a function of infection type in an otherwise fully adjusted model. The fully adjusted model shown in Table 3 (but without adjustment for infection type) was used to determine the odds of death for specific infection types.

Given that patients who die of infections often do so because of inflammation-induced tissue injury, modulation of this arm of the immune response may have great therapeutic potential in sepsis.

By extension, these results raise the possibility that modulating T2 immunity to treat allergic diseases may not be without risks, as has been observed for other immunomodulators (27). Several biologic therapies have been recently approved to treat refractory asthma and allergy, including omalizumab (targeting immunoglobulin E), dupilumab (blocking the IL-4 receptor), mepolizumab and reslizumab (blocking IL-5), and benralizumab (blocking the IL-5 receptor). Unfortunately, no patients in this dataset were on any of these medications, and therefore we cannot determine their impact on the risk of sepsis. If the T2 immune response is beneficial in the setting of acute infection, as our data suggest, disrupting T2 immunity with these targeted biologic agents might result in an untoward increase in sepsis morbidity and mortality. This hypothesis can be easily tested in the near future, as these therapies are rapidly becoming part of the standard of care for treatment of refractory asthma and allergies.

These data also suggest that there are several features of T2 patients with infection that indicate a unique phenotype which determines their hospital course and outcomes. T2 patients presented with distinct types of infections, received a different set of therapies, and were more likely to have measurable eosinophil counts at admission; while none of these factors confounded our finding of improved mortality among these patients, they indicate a distinct propensity that might have ramifications for the development of personalized therapies. There may be a genetic basis underpinning this proposed phenotype, given that a single nucleotide polymorphism in the gene for myosin light chain kinase has been identified that is negatively associated with development of asthma but conferred risk for severe sepsis (28). A growing body of epidemiologic evidence indicates that the presence of T2 diseases may be positively or negatively associated with the development

of seemingly unrelated diseases, independent of medication use or disease severity, further supporting the notion of this unique phenotype (29–33). Its mechanistic nature merits further biologic exploration to determine if it represents a novel endotype that can inform sepsis therapy.

Our analysis also reveals the utility of using granular EHR data to identify novel features that may reflect or undergird the immune dysfunction of sepsis. Several tools (PheNorm, PheProb) currently exist which use EHR data to improve identification of patients with a specific diagnosis; however, our work indicates that EHR data may also be used to identify immunologic sepsis endotypes that reflect the mechanism of protection, namely T2 immune activation (34, 35). Further, incorporation of T2 immune comorbidities into risk-prediction models and scoring systems such as SOFA may improve the prognostic value of such models. By extension, machine-learning approaches designed to improve phenotyping of septic patients, such as those proposed by Vranas et al (36), should consider specific immune comorbidities rather than simply using scoring systems that presume a direct relationship between comorbidities and a poor outcome.

Although we performed several statistical analyses to minimize type 1 error in this study, several important limitations remain. We depended on ICD-9-based coding to identify patients with T2 diseases, rather than confirmatory testing (such as pulmonary function testing or allergen testing). In addition, given that patients may receive outpatient care at institutions/health systems other than our hospital, we may be over- or under-estimating the number of patients with T2 diseases; limiting our analysis to patients previously seen at our institution did not change our results, but a multicenter study could overcome this caveat. Further, the diagnosis of “asthma” may represent several distinct subtypes of disease; indeed, a significant minority of asthma patients do not have eosinophilic, corticosteroid-responsive, T2-mediated asthma (37). Thus, our grouping of patients with asthma as specifically T2 likely includes a significant number of non-T2-biased

patients, and incorporating biomarkers or outpatient medication use may allow improved classification of patients. We excluded children under age 18 for this analysis, but many T2 diseases develop in childhood (and often resolve by adulthood). Finally, these data were limited to analysis at a single-center and should be validated in other granular EHR datasets.

In summary, we have demonstrated that patients with allergic, T2-mediated immune diseases have decreased mortality when challenged with an acute infection, potentially reflecting a more appropriately regulated immune response rather than the dysregulated response of sepsis. This work provides important insight into a protective immunologic phenotype which may improve risk prediction, lead to targeted therapeutic strategies, and enhance understanding of the dysregulated host response in sepsis.

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