Inflammatory Markers at Hospital Discharge Predict Subsequent Mortality after Pneumonia and Sepsis

Sachin Yende[1,2], Gina D'Angelo[3], John A. Kellum[1,2], Lisa Weissfeld[2,3], Jonathan Fine[4], Robert D. Welch[5], Lan Kong[3], Melinda Carter[1,2], and Derek C. Angus[1,2], for the GenIMS Investigators*

[1]The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Laboratory, [2]Department of Critical Care Medicine, and [3]Department of Biostatistics, Graduate School of Pubic Health, University of Pittsburgh, Pittsburgh, Pennsylvania; [4]Beulah Hinds Center for Lung Studies, Section of Pulmonary and Critical Care Medicine, Norwalk Hospital, Norwalk, Connecticut; and [5]Department of Emergency Medicine, Detroit Receiving Hospital, Wayne State University School of Medicine, Detroit, Michigan

Rationale: **Survivors of hospitalization for community-acquired pneumonia (CAP) are at increased risk of cardiovascular events, repeat infections, and death in the following months but the cause is unknown.**

Objectives: **To investigate whether persistent inflammation, defined as elevating circulating inflammatory markers at hospital discharge, is associated with subsequent outcomes.**

Methods: **Prospective cohort study at 28 sites.**

Measurements and Main Results: **We used standard criteria to define CAP and the National Death Index to determine all-cause and cause-specific 1-year mortality. At hospital discharge, 1,799 subjects (77.5%) were alive and vital signs had returned to normal in 1,512 (87%) subjects. The geometric means (±SD) for circulating IL-6 and IL-10 concentrations were 6.9 (±1) pg/ml and 1.2 (±1.1) pg/ml. At 1 year, 307 (17.1%) subjects had died. Higher IL-6 and IL-10 concentrations at hospital discharge were associated with an increased risk of death, which gradually fell over time. Using Gray's survival model, the associations were independent of demographics, comorbidities, and severity of illness (for each log-unit increase, the range of adjusted hazard ratios [HRs] for IL-6 were 1.02–1.46, $P < 0.0001$, and for IL-10 were 1.17–1.44, $P = 0.01$). The ranges of HRs for each log-unit increase in IL-6 and IL-10 concentrations among subjects who did and did not develop severe sepsis were 0.95–1.27 and 1.07–1.55, respectively. High IL-6 concentrations were associated with death due to cardiovascular disease, cancer, infections, and renal failure ($P = 0.008$).**

Conclusions: **Despite clinical recovery, many patients with CAP leave hospital with ongoing subclinical inflammation, which is associated with an increased risk of death.**

Keywords: cytokines; mortality; pneumonia; IL-6; IL-10

Older individuals who survive community-acquired pneumonia (CAP) hospitalization are at increased risk of death in the subsequent months (1–7). This increased risk is not obviously explained by sociodemographic and health behavioral characteristics (1–7), preexisting chronic health and function (1–6), or nutritional status (6, 7). If CAP is playing a causal role in post-discharge mortality, the mechanism is unknown. Understanding mechanisms and predictors of increased long-term mortality would help design and target future interventions.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Reasons for increased long-term mortality among hospital survivors of pneumonia are not known.

What This Study Adds to the Field

Persistent inflammation, defined as elevated circulating levels of IL-6 and IL-10 at hospital discharge after community-acquired pneumonia, is associated with all-cause and cause-specific mortality over one year, despite resolution of clinical signs of an acute infection.

In apparently healthy older individuals, low-grade inflammation is associated with increased risk of CAP (6). Once pneumonia occurs, inflammatory marker concentrations are several times higher (8). The highest concentrations occur in individuals with severe sepsis and are associated with increased risk of short-term death. Whether the inflammatory response resolves at hospital discharge when patients appear to have recovered from the acute infection is not known. Persistent inflammation may precipitate deterioration in other diseases, such as cardiovascular disease, and increase long-term mortality. This theory is supported by a recent epidemiologic study linking lower respiratory tract infections to subsequent acute cardiovascular events (9). We therefore sought to understand whether serum markers of inflammation were elevated before discharge in subjects who appeared to have recovered from CAP and to determine whether serum concentrations were associated with all-cause and cause-specific mortality in the subsequent year. Some of the results of this study have been previously reported in the form of an abstract (10).

METHODS

Subjects and Design

The design is a 1-year follow-up study of all hospital survivors of the Genetic and Inflammatory Markers of Sepsis (GenIMS) study (8). GenIMS is a large, multicenter, observational cohort study of subjects with CAP presenting to the emergency departments of 28 teaching and nonteaching hospitals in four regions (western Pennsylvania, Connecticut, Michigan, and Tennessee) in the United States. We diagnosed CAP based on clinical and radiologic criteria (11). Details of the eligibility criteria are provided in the online supplement. The institutional review boards at the University of Pittsburgh and all participating sites approved the study, and written, informed consent was obtained from all participants or their proxies.

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*A complete list of GenIMS investigators is available at www.ccm.upmc.edu/genims_investigators.

Correspondence and requests for reprints should be addressed to Derek C. Angus, M.D., M.P.H., Department of Critical Care Medicine, University of Pittsburgh, 604 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 15261. E-mail: angusdc@upmc.edu

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Of the 2,320 subjects enrolled, 291 patients were excluded because they were discharged from the emergency department and another 134 were excluded because the clinical team ruled out CAP during the first 3 days of hospitalization (Figure 1). Of the remaining 1,895 subjects, 87 (4.6%) died in hospital and 9 subjects were excluded because blood samples were not obtained. We conducted our analyses on the remaining 1,799 subjects discharged alive.

Clinical and Outcome Variables

We ascertained comorbid conditions using the Charlson comorbidity index (12) and severity of illness using the Acute Physiology and Chronic Health Evaluation (APACHE) III and the Pneumonia Severity Index (PSI) (11, 13). We defined severe sepsis as pneumonia with acute organ dysfunction following the 2001 international consensus criteria (14). We defined acute organ dysfunction as a new Sequential Organ Failure Assessment (SOFA) score of 3 or greater in any of six organ systems (15). We assessed vital signs at hospital discharge to assess whether subjects met criteria for clinical stability at hospital discharge, as described by Halm and Teirstein (16). The primary outcome variable was all-cause mortality up to 1 year after hospital discharge. We ascertained all-cause and cause-specific mortality using National Death Index (NDI) search and NDI-coded causes of death (17). The reliability of NDI for epidemiologic studies has been previously validated (18).

Laboratory Procedures

We obtained blood for cytokine assays daily for the first week and once weekly thereafter while subjects remained in hospital (8). For this study, we analyzed only the last cytokine measurement. We measured IL-6 and IL-10 concentrations using an Immulite assay (Diagnostic Products, Los Angeles, CA). The minimum detectable limits for IL-6 and IL-10 were 2 and 5 pg/ml. We used the following upper limits of normal: IL-6, 5.9 pg/ml, and IL-10, 9.1 pg/ml, per the manufacturer's specifications. Intraassay coefficients of variation for IL-6 and IL-10 were 4.2 and 3.2%. Interassay coefficients of variation for IL-6 and IL-10 were 5.8 and 5.6%. We also monitored controls between different kit lots and no major variation was observed for control values. All outlier values were rechecked and laboratory personnel were blinded to clinical data.

Statistical Analyses

We first conducted univariate comparisons for those who survived or died at 1 year to ascertain predictors of mortality. We constructed Tobit models to compare cytokine concentrations to account for data that were truncated because they were below detection thresholds (38 and 81% of subjects for IL-6 and IL-10, respectively) (19). The Tobit model is used to model censored dependent variables. The likelihood specified for the Tobit model consists of two parts: the first part is the density of the observed (noncensored) data and the second part is the distribution of the censored data. Maximum likelihood estimation is used to obtain estimates of the regression coefficients. We used a Gray's survival model to estimate hazard ratios (HRs) for circulating cytokine concentrations and death over 1 year because the hazards failed Cox's proportionality assumption (20). The Gray's model estimates HRs over 10 intervals (with 11 time nodes) and thus provides a detailed description of the change in HRs over 1 year. For cause-specific mortality, we used Putter's competing risk model (21) to assess associations between cytokines and cause-specific mortality, because the associations between cytokines and different causes of death are dependent and these risks compete with one another until a subject dies due to a specific cause of death. Details of statistical analyses and sensitivity analyses are provided in the online supplement.

RESULTS

Baseline Characteristics and Clinical Course

Of the 1,799 subjects discharged alive after hospitalization for CAP, 136 (7.6%), 206 (11.5%), and 307 (17.1%) died by 90 days, 6 months, and 1 year, respectively. Table 1 compares baseline characteristics, severity of illness, and hospital course of all subjects, stratified by survival at 1 year. The mean age of all subjects was 67 years, approximately half were females, and three-fourths had at least one comorbid condition based on the Charlson score. Race was based on self-report and most subjects were non-Hispanic whites (n = 1,443, 80.2%), an additional 292 (16.2%) subjects were blacks, and the remaining 64 subjects represented other races. Severe sepsis occurred in a fourth of the participants and more than half had severe CAP, as indicated by a PSI class of IV or V. Mean hospital stay was 7 days.

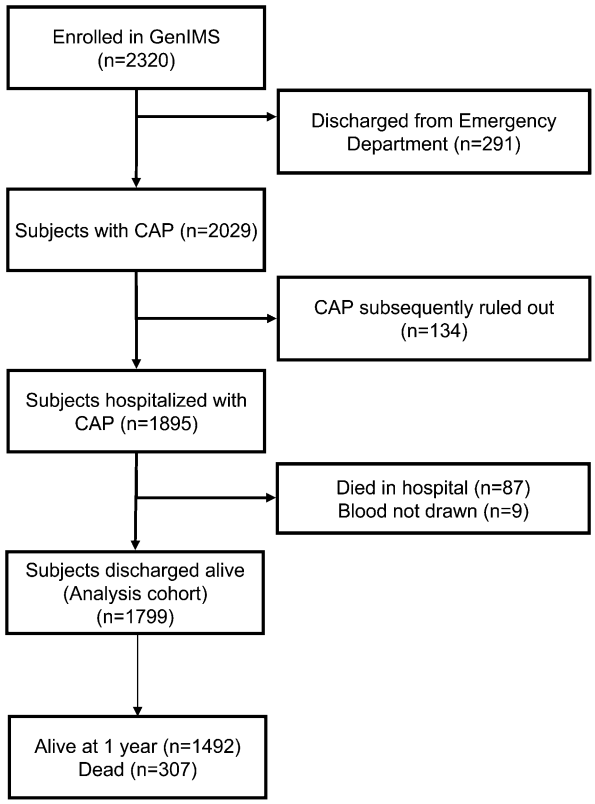

Figure 1. Subject disposition for the entire Genetic and Inflammatory Markers of Sepsis (GenIMS) cohort. CAP = community-acquired pneumonia.

Most subjects met the Halm criteria for clinical stability on the day of discharge. Only 48 (2.7%), 156 (8.7%), 41 (2.3%), and 33 (1.8%) subjects had a temperature higher than 37.8°C, heart rate higher than 100 beats/minute, respiratory rate higher than 24 breaths/minute, or systolic blood pressure of less than 90 mm of Hg, respectively. All four vital signs were normal in 1,512 (87%) subjects, one vital sign was abnormal in 191 (11%) subjects, and only 34 (2%) subjects had abnormalities in two or more vital signs.

Compared with survivors at 1 year, nonsurvivors were older, they had more comorbid conditions (as evidenced by higher Charlson scores), and they had more severe CAP on presentation (as evidenced by higher PSI and APACHE III scores) (Table 1). They were also more likely to develop severe sepsis and they incurred a longer duration of hospital stay. Whites had lower survival at 1 year compared with blacks, but these differences were no longer significant after controlling for age and higher baseline severity of illness seen in whites compared with blacks (data not shown).

Cytokine Concentrations and All-Cause Mortality

Cytokines were measured on the day of discharge in 967 (53%) subjects and within 48 hours before discharge in an additional 475 (27%) subjects. For a minority of subjects (n = 129, 9%), the last available cytokine concentration measurement was more than

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SURVIVORS AND NONSURVIVORS AT 1 YEAR

Variable	All Subjects (*n = 1,799*)	Nonsurvivors at 1 Year (*n = 307*)	Survivors at 1 Year (*n = 1,492*)	*P* Value
Demographics				
Age, mean (SD, median)	67 (17, 71)	76 (12, 78)	65 (17, 68)	<0.0001
Sex, female, n (%)	867 (48.2)	125 (40.7)	742 (49.7)	0.004
White race, n (%)	1,443 (80.2)	259 (84.4)	1,184 (79.4)	0.04
Severity of illness				
Charlson comorbidity score > 0, n (%)	1,297 (72.1)	263 (85.7)	1,034 (69.3)	<0.0001
Day 1 PSI*, mean (SD, median)	97 (36, 95)	122 (35, 118)	92 (34, 90)	<0.0001
PSI class I and II, n (%)	424 (23.6)	14 (4.6)	410 (27.5)	<0.0001
PSI class III, n (%)	389 (21.6)	40 (13.0)	349 (23.4)	
PSI class IV, n (%)	663 (36.9)	139 (45.3)	524 (35.1)	
PSI class V, n (%)	323 (18.0)	114 (37.1)	209 (14.0)	
Day 1 APACHE III score, mean (SD, median)	55 (17, 54)	65 (17, 64)	53 (16, 52)	<0.0001
Severe sepsis, n (%)	498 (27.7)	136 (44.3)	362 (24.3)	<0.0001
Hospital course				
Need for mechanical ventilation, n (%)	90 (5.0)	20 (6.5)	70 (4.7)	0.18
Required ICU stay, n (%)	250 (13.9)	53 (17.3)	197 (13.2)	0.06
Length of hospital stay, mean (SD, median)	7 (5,6)	9 (6, 7)	7 (5, 6)	<0.0001
Location after hospital discharge				
Home, n (%)	1,374 (77.5)	163 (54.7)	1,211 (82.1)	<0.0001
Acute or subacute care facility, n (%)	159 (9.0)	45 (15.1)	114 (7.7)	
Skilled nursing facility, n (%)	190 (10.7)	77 (25.8)	113 (7.7)	
Residential care facilities, n (%)	43 (2.4)	11 (3.7)	32 (2.2)	
Other, n (%)	6 (0.4)	2 (0.7)	4 (0.3)	

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; PSI = Pneumonia Severity Index.
* Based on PSI by Fine and colleagues (11).

96 hours before discharge. Based on the Tobit model, the geometric means of IL-6 and IL-10 concentrations at discharge for all subjects were 6.9 ± 1.0 and 1.2 ± 1.1 pg/ml, respectively. The median, range, and interquartile range for circulating IL-6 concentrations at hospital discharge were 7.4 pg/ml, 2–14,536 pg/ml, and 6.9–17.8 pg/ml, respectively. Similarly, the median, range, and interquartile range for circulating IL-10 concentrations at hospital discharge were 4.6 pg/ml, 1.2–416 pg/ml, and 1.2–1.2 pg/ml, respectively.

Higher IL-6 concentration at hospital discharge was associated with lower 1-year survival (Table 2). Figure 2 shows failure plots for 10th and 90th percentiles of circulating IL-6 concentrations and unadjusted HRs for survival over 1 year. The HRs remained unchanged after adjusting for demographics, comorbid conditions, and severity of illness. The adjusted HRs for each log-unit increase varied over time from 1.02 to 1.46. Figure 3 shows the varying HRs and 95% confidence intervals for IL-6 and IL-10 over 1 year. The HRs for IL-6 were highest at hospital discharge and decreased over the initial 100 days, and the association with mortality was no longer statistically significant after 100 days. The time-dependent effect of IL-6 on survival was also observed when IL-6 concentration (geometric means) at hospital discharge was compared among survivors and nonsurvivors at different time points. The IL-6 concentrations at hospital discharge were higher among subjects who did not survive at 100 days compared with those who survived at 100 days (12.9 vs. 6.6 pg/ml, $P < 0.001$). However, IL-6 concentrations at hospital discharge were similar among those who did and did not survive between 101 days and 1 year (7.7 vs. 6.5 pg/ml, $P = 0.16$).

TABLE 2. HAZARD RATIOS* FOR ASSOCIATION BETWEEN CIRCULATING IL-6 AND IL-10 CONCENTRATIONS AT DISCHARGE AND MORTALITY OVER 1 YEAR

Cytokines	Unadjusted Hazard Ratios	*P* Value	Adjusted Hazard Ratios†	*P* Value
All subjects (n = 1,796)				
IL-6‡	1.07–1.52	<0.0001	1.02–1.46	<0.0001
IL-10‡	1.17–1.55	0.002	1.17–1.44	0.01
IL-6§	1.05–1.46	<0.0001	1.00–1.42	<0.0001
IL-10§	1.11–1.30	0.12	1.14–1.30	0.08
With severe sepsis (n = 497)				
IL-6‡	0.97–1.27	0.13	0.95–1.27	0.17
IL-10‡	1.11–1.41	0.31	1.15–1.45	0.13
IL-6§	0.95–1.23	0.22	0.93–1.23	0.25
IL-10§	1.05–1.29	0.53	1.11–1.42	0.21
Without severe sepsis (n = 1,299)				
IL-6‡	1.15–1.65	<0.0001	1.07–1.55	0.0001
IL-10‡	1.21–1.65	0.005	0.97–1.41	0.07
IL-6§	1.14–1.57	<0.0001	1.07–1.52	0.0005
IL-10§	0.94–1.39	0.16	0.93–1.30	0.28

* Ranges of hazards ratios are reported for 10 time points over 1 year using the Gray's model (20).
† Adjusted for age, race, sex, Charlson comorbidity, and APACHE III.
‡ IL-6 and IL-10 were entered in the model independently.
§ IL-6 and IL-10 were entered in the model concurrently.

The unadjusted and adjusted HRs for mortality for increased circulating IL-10 concentrations were also similar and varied from 1.17 to 1.44 per log-unit increase (Table 2; Figure 2). The HRs were highest at hospital discharge and the association was statistically significant over the initial 6 months, but no longer significant between 6 months and 1 year (Figure 3). Again, the time-dependent effect of IL-10 on survival was observed when IL-10 concentrations at hospital discharge were compared among nonsurvivors and survivors at different time points. The IL-10 concentrations at hospital discharge were higher among subjects who did not survive at 6 months compared with survivors at the same time point (2 vs. 1.1 pg/ml, $P < 0.001$). However, concentrations were the same among nonsurvivors and survivors between 6 months and 1 year (1.1 vs. 1.1, $P = 0.95$). When both IL-6 and IL-10 were entered in the model concurrently, the association between increased IL-6 concentrations and survival remained statistically significant ($P < 0.0001$), but the significance for the association between IL-10 concentration and survival was lost ($P = 0.08$).

Compared with subjects with normal vital signs at hospital discharge, the 225 (13%) subjects with abnormal vital signs had higher IL-6 concentrations (10.5 vs. 6.5 pg/ml, $P < 0.001$), but no differences in IL-10 concentrations were seen between the

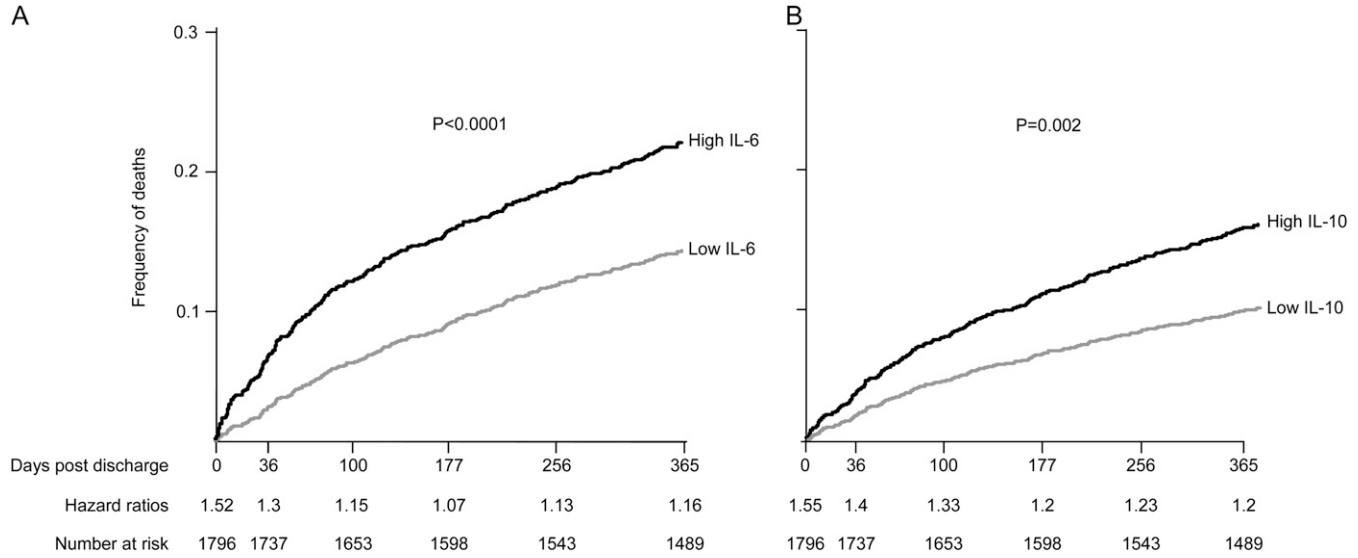

Figure 2. Failure plots for circulating IL-6 (*A*) and IL-10 (*B*) concentrations and mortality over 1 year. High and low concentrations are the 10th and 90th percentiles of cytokine concentrations. Using the Gray's model, the hazard ratios are estimated over 10 intervals (with 11 time nodes) over 1 year and hazard ratios over five representative periods are shown. *P* values are obtained from the Gray's survival model.

two groups (1.49 vs. 1.15, $P = 0.09$). No association was seen between abnormal vital signs at hospital discharge and 1-year mortality (20.6 vs. 16.5% for subjects with at least one abnormal vital sign and those without abnormal vital signs, $P = 0.12$).

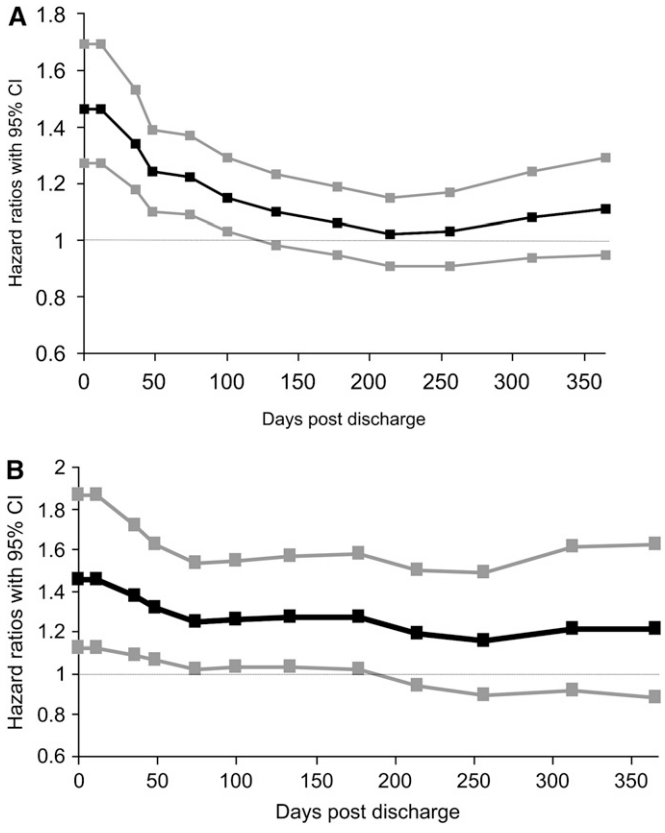

Figure 3. Varying hazard ratios with 95% confidence intervals (CI) for IL-6 (*A*) and IL-10 (*B*) and risk of death over 1 year. The hazard ratios are shown over 10 intervals (with 11 time nodes), based on the Gray's model. For IL-6, the 95% CI is above 1 for 100 days, whereas for IL-10 the 95% CI is above 1 for 177 days or approximately 6 months.

Furthermore, of the 307 deaths at 1 year, only 49 (16%) were associated with abnormal vital signs at hospital discharge.

The presence of severe sepsis during hospitalization did not influence the associations between IL-6 and IL-10 with survival (interaction $P = 0.07$ and 0.45 for IL-6 and IL-10, respectively). The HRs for subjects with and without severe sepsis were similar to that in the full analysis (Table 2), although the small sample precluded statistical significance for the severe sepsis subgroup. We also performed sensitivity analyses by restricting the analyses to subjects with a cytokine measurement within 48 hours (n = 1,440), subjects who did not develop organ dysfunction during the hospital course (n = 904), and those discharged home (n = 1,371). In these analyses, the HRs remained unchanged for the associations between both cytokines and 1-year survival (Table 3).

Cytokines and Cause-specific Mortality

Of the 307 deaths, a cause of death was obtained for 300 (98%) subjects. Cardiovascular disease and cancer were the most common causes of death and accounted for a third and a fourth of deaths (Table 4). Infections, renal failure, and chronic respiratory disease accounted for 11, 6, and 16% of deaths, respectively. Table 4 presents the estimated geometric means (obtained from a Tobit model) for IL-6 and IL-10 for each cause of death. We used a competing risk analysis to estimate the association between the individual cytokines and cause-specific mortality. The association between circulating IL-6 and cause-specific mortality was statistically significant ($P = 0.008$), whereas the association between IL-10 and cause-specific mortality was not significant ($P = 0.54$). Circulating IL-6 concentrations at hospital discharge were higher among subjects who subsequently died of cardiovascular diseases, renal failure, infections, and cancer compared with other causes of death.

Subjects with chronic health conditions have higher circulating inflammatory marker concentrations and they are more likely to die of the same cause. This relationship may confound the association between increased IL-6 concentrations and cause-specific mortality. Therefore, we analyzed causes of death stratified by presence or absence of the chronic health condition (Table E1 in the online supplement). More than a third of subjects who died of cardiovascular causes did not have cardiovascular disease. Deaths due to cancer and renal failure were more

TABLE 3. SENSITIVITY ANALYSES FOR ASSOCIATION BETWEEN CIRCULATING IL-6 AND IL-10 CONCENTRATIONS AT DISCHARGE AND MORTALITY OVER 1 YEAR

Cytokines	Adjusted Hazard Ratios*	*P* Value
Subjects in whom cytokines were drawn within 48 hours (n = 1,440)		
IL-6†	1.10–1.52	<0.0001
IL-10†	1.03–1.38	0.23
Subjects who did not experience organ dysfunction‡ (n = 904)		
IL-6†	0.90–1.29	0.1100
IL-10†	0.98–1.52	0.06
Subjects discharged home (n = 1,371)		
IL-6†	0.97–1.31	0.05
IL-10†	0.92–1.40	0.48

* Adjusted for age, race, sex, Charlson comorbidity, and APACHE III. Ranges of hazards ratios are reported for 10 time points over 1 year using the Gray's model (10).

† IL-6 and IL-10 were entered in the model independently.

‡ SOFA (Sequential Organ Failure Assessment) score did not increase by greater than 1 point during hospital stay.

common among subjects without these chronic health conditions before the occurrence of CAP. Therefore, the association between IL-6 and cause-specific mortality was not confounded by comorbid conditions.

DISCUSSION

Our study has shown that, after CAP hospitalization, circulating IL-6 concentrations are elevated at hospital discharge and associated with higher mortality over the subsequent 3 months. At discharge, circulating IL-6 concentrations were 10- to 15-fold lower than concentrations seen during severe sepsis (8, 22), but threefold higher than concentrations in older adults at risk for CAP (23). Only 13% of subjects had abnormal vital signs at hospital discharge, but more than half of the cohort had elevated IL-6 concentrations. These findings suggest that the inflammatory response to infection persists at hospital discharge, even though clinical signs have resolved and subjects appeared to be stable for discharge (16). The average IL-10 concentrations at discharge were similar to concentrations reported in healthy individuals, but subjects with above average concentrations also had an increased risk of death over the subsequent 6 months.

TABLE 4. ASSOCIATION BETWEEN IL-6 AND IL-10 AT HOSPITAL DISCHARGE AND CAUSE-SPECIFIC MORTALITY OVER 1 YEAR*

Causes of Death over 1 Year	No. (%)	Geometric Means of Inflammatory Markers in pg/ml (SD) at Hospital Discharge	
		IL-6	IL-10
Cardiovascular†	92 (31)	9.6 (1.2)	1.5 (1.3)
Infection‡	32 (11)	14.0 (1.3)	2.5 (1.4)
Cancer	73 (25)	11.9 (1.2)	1.5 (1.3)
Chronic lower respiratory disease	47 (16)	5.5 (1.3)	1.4 (1.4)
Renal failure	19 (6)	20.3 (1.4)	2.6 (1.6)
Others	33 (11)	5.9 (1.3)	1.9 (1.4)

* $P = 0.008$ for IL-6 and $P = 0.54$ for IL-10. Causes of death were missing in 11 subjects.

† Cardiovascular causes of death include atherosclerotic cardiovascular disease, acute myocardial infarction, chronic ischemic heart disease, congestive heart failure, and cerebrovascular accident.

‡ Infectious causes of death include pneumonia, influenza, and sepsis.

The associations between cytokines and mortality in our study were unlikely to be confounded by the severity of illness because associations were independent of APACHE III scores and were even seen in subjects without severe sepsis. Furthermore, sensitivity analyses showed that the HRs were similar when the analysis was restricted to subjects who did not experience new organ dysfunction during hospital stay. Our sensitivity analyses also showed that the association persists when the analyses were restricted to subjects discharged home, those presumably most likely to have adequately recovered from the acute illness as judged by their physicians. These findings suggest that cytokine concentrations are unlikely to be only surrogate markers for subjects with complicated hospital course.

The higher IL-6 concentrations observed at hospital discharge could be elevated before the occurrence of CAP due to chronic health conditions, secondary to slower resolution of inflammation in comparison to clinical recovery, or due to an interaction between poor chronic health and acute illness. We speculate that the latter is likely, because circulating IL-6 concentrations are lower in prior population-based studies (24), even in individuals at risk for CAP (23). Whatever the cause, our findings have important implications in understanding mechanisms of long-term sequelae of infection and to design risk stratification strategies at hospital discharge when patients appear to have recovered from the acute illness.

We examined IL-6 and IL-10, key markers of pro- and antiinflammatory responses because both persistent low-grade inflammation and immune suppression may play important roles in complications after CAP, including coronary (25) and cerebrovascular events (26) and repeat bouts of CAP (23, 27). Our findings are similar to cytokine signatures that predict survival after diagnosis of Hodgkin's lymphoma (28). Our findings of cytokine patterns associated with cause-specific mortality suggest that different mechanisms may influence different causes of death. For instance, a persistent, up-regulated proinflammatory response was associated with deaths due to cardiovascular disease, renal failure, infections, and cancer. This association is consistent with prior studies showing increased risk of these conditions in patients with higher proinflammatory cytokines (25, 26, 29). We also observed a higher risk of death among subjects with higher antiinflammatory cytokines. We speculate that this association could be due to alterations in immune status (30, 31), such as immune suppression observed with higher IL-10 concentrations. However, IL-10 concentrations were low and were detectable only in 19% of subjects in our study. Other assays, such as tumor necrosis factor (TNF) production after *ex vivo* stimulation of immune cells, should be evaluated in future studies to assess immune suppression (30, 31).

The causes of death in our study are similar to those seen in prior studies that examined causes of rehospitalization and death after CAP (6, 27). The high incidence of deaths due to cardiovascular disease, cancer, and renal failure in subjects without prior history of these health conditions suggests that mechanisms leading to death were perhaps accelerated during the CAP hospitalization. Improved surveillance and preventive strategies targeted to high-risk individuals for common causes of death, such as coronary artery disease, may improve long-term survival.

Our study has limitations. First, cytokine measurements were not collected on the day of discharge in all subjects. Our study protocol required blood collection for cytokine concentrations daily during the first week and weekly thereafter. Patients with longer duration of stay were more likely to have had circulating cytokine concentrations measured on days before discharge. However, more than 80% of subjects had cytokine measurements

taken within 48 hours of discharge, and sensitivity analyses excluding subjects with a cytokine measurement more than 48 hours before discharge did not change our results. Second, we only obtained cytokine measurements before, rather than after, hospital discharge. Future studies should explore the relationship of postdischarge cytokine trajectories on subsequent health-related outcomes. Finally, we examined the role of only two cytokines as markers of immune status. Nevertheless, these cytokines are widely used as markers of the pro- and antiinflammatory responses. The results of our study underscore the need to examine the cellular response and other cytokines to understand the recovery of the immune system after infection.

Conflict of Interest Statement: S.Y. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.A.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.D.W. has received $1,500 from Wyeth Research, $5,235 from Scios, Inc., $9,978 from the Blue Cross Blue Shield of MI Foundation, and $7,980 from Welch-Allen for clinical studies. R.D.W. is ready to start a study sponsored by RIB-X Pharmaceuticals and is currently working on a study with 3M to test a rapid detection of MRSA system. L.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.C.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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