

Prevalence and Significance of Coagulation Abnormalities in Community-Acquired Pneumonia

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Coagulation abnormalities are common in severe pneumonia and sepsis, yet little is known about the presence of coagulopathy or its significance in patients with lesser illness severity. We examined coagulation abnormalities in 939 subjects hospitalized with community-acquired pneumonia (CAP) in 28 US hospitals, hypothesizing that abnormalities would increase with illness severity and poor outcomes. We measured plasma coagulation markers (D-dimer, plasminogen activator inhibitor (PAI), antithrombin, factor IX, and thrombin-antithrombin complex (TAT)) at the time of patient presentation to the emergency department and daily during the first wk of hospitalization. Day-1 clinical laboratory test results for international normalized ratio, activated partial thromboplastin time, and platelet count were recorded from the medical record. In our cohort, 32.5% of patients developed severe sepsis and 11.1% died by d 90. Day-1 coagulation abnormalities were common, especially for D-dimer (80.6%) and TAT (36.0%), and increased with illness severity and poor outcomes. However, abnormalities also occurred in those patients who never developed organ dysfunction and differences between groups were modest. The proportion of patients with abnormalities changed over time, yet the magnitude of change was small and not always in the direction of normality. Many patients remaining in the hospital continued to manifest coagulation abnormalities on d 7, especially for D-dimer (86.5%) and TAT (36.9%). In conclusion, coagulation abnormalities were common and persistent in CAP patients, even among the least ill. These findings underscore the complexity of the coagulation response to infection and may offer insights into coagulation-based therapeutics in clinical sepsis trials.

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INTRODUCTION

For decades systemic inflammation has been considered a hallmark of severe sepsis (1). Community-acquired pneumonia (CAP) is the most common cause of severe sepsis (2), but therapies targeting systemic inflammation in severe sepsis have not improved outcomes (3,4). One explanation is that systemic inflammation is only a part of the host response to infection and that other pathology rivals the deleterious inflammatory response.

Subsequent work confirms this explanation, demonstrating that systemic inflammation occurred frequently even in individuals in whom organ dysfunction did not occur (5).

In recent years, attention has turned to other events in the host response to bacterial challenge, notably coagulation activation. Systemic overflow and disarray of the coagulation response to infection are more likely culprits in the pathogenesis of organ dysfunction. Early epidemio-

logic studies confirmed that such disorders were common in severe sepsis (1), but failed to measure the extent of coagulation abnormalities early during illness and in those at risk of severe sepsis whose infection resolved without progressing to acute organ dysfunction. These limitations notwithstanding, a number of therapies aimed at modulating the coagulation response have been tested, including antithrombin (6), tissue factor pathway inhibitor (7), platelet-activating factor acetylhydrolase (8), and activated protein C. Although initial results with activated protein C were promising (9), later results have been less positive (10,11), and positive results from animal studies with antithrombin, tissue factor pathway inhibitor, and platelet-activating factor acetylhydrolase have not been confirmed in large human studies (6–8,12).

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Given the complexity of the host response to infection and the pleiotropic effects of key components, it seems likely that the interplay between inflammatory molecules, the endothelium, and agents traditionally associated with coagulation will remain an important area of investigation, even if the conceptual model for the exact interplay of these agents is more sophisticated than first anticipated. The purpose of this study was, therefore, to step back and investigate more carefully just how much coagulation disorder is demonstrable in pneumonia patients with severe sepsis and in those with infection who never go on to develop organ dysfunction. Accordingly, we examined the incidence and time course of coagulation abnormalities across the spectrum of illness severity in a large, multicenter inception cohort study of subjects presenting to the emergency department with CAP. We hypothesized that coagulation abnormalities would increase with illness severity and be greater in those with poor outcomes.

MATERIALS AND METHODS

Sites and Subjects

The Genetic and Inflammatory Markers of Sepsis (GenIMS) study enrolled subjects at 28 academic and community hospitals in southwestern Pennsylvania, Connecticut, southern Michigan, and western Tennessee from December 2001 and November 2003. GenIMS included patients ≥ 18 years old with a clinical and radiologic diagnosis of pneumonia as per the criteria of Fine *et al.* (13). We excluded patients who were transferred from another hospital, had been discharged from a hospital within the prior 10 d, had suffered an episode of pneumonia within the prior 30 d, had undergone chronic mechanical ventilation, had cystic fibrosis or active pulmonary tuberculosis, had been admitted for palliative care, had been previously enrolled in the study, were incarcerated, or who were pregnant. Participants or their proxies provided

written consent. We obtained approval from the institutional review boards of the University of Pittsburgh and all participating sites. Other results of this study, not including the coagulation data we report here, have been published elsewhere (5,14). Some of the results of this study have been published in the form of an abstract (15).

Clinical Definitions and Outcome Variables

We prospectively collected detailed baseline and sequential clinical information using structured subject or proxy interviews, bedside assessments, and medical record abstraction. We ascertained comorbid conditions using the Charlson comorbidity index (16) and severity of illness using the Acute Physiology and Chronic Health Evaluation III (APACHE III) (17) and the Pneumonia Severity Index (13). We defined severe sepsis as pneumonia plus acute organ dysfunction, in accordance with the 2001 International Consensus Criteria (18). We defined acute organ dysfunction as a new Sequential Organ Failure Assessment (19) score of ≥ 3 in any of six organ systems, based on the recent international Sepsis Occurrence in the Acutely Ill Patient study (20). The initial empirical antibiotics received during the first 24 h of hospitalization were considered adequate if compliant with the 2001 American Thoracic Society (ATS) Guidelines for the Management of Adults with Community-acquired Pneumonia (21), which were in place at the time of the study. We performed telephone follow-up and National Death Index searches to monitor patient survival after discharge from the hospital. We used 90-d mortality as our primary measure of survival, based on recently formulated endpoint recommendations for sepsis trials from two recent international expert panels (22,23). We tracked clinical data and blood samples by using unique anonymized identification numbers, merging data only after assays had been completed. We observed strict data confidentiality and audited clinical data and assays for accuracy, including random

chart audits, repeat blood assays, and computer flags for inconsistencies.

Laboratory Procedures

Results of relevant blood investigations performed for clinical purposes [international normalized ratio (INR), activated partial thromboplastin time (PTT), and platelet count] were recorded from the medical records of study patients. We used INR rather than prothrombin time to minimize differences due to assay variations across clinical sites. In the first 939 (49.6%) of study participants enrolled, we obtained blood for measurement of plasma coagulation markers (D-dimer, PAI, antithrombin, factor IX, and TAT) at emergency department presentation and daily during the first week of hospitalization. Generally, day-1 blood samples were drawn at the time of enrollment, and subsequent samples were drawn at 8 AM. For logistic reasons, we did not obtain day-1 samples from subjects presenting after 11 PM or on weekends and holidays.

We analyzed coagulation markers by using a commercial laboratory (Essoterix, Agoura Hills, CA, USA). Specific methods and kits used were: D-dimer, latex immunoassay (Diagnostica Stago, Parsippany, NJ, USA); PAI, bioimmunoassay (Biopool Chromolize; Biopool International, Ventura, CA, USA); antithrombin, chromogenic (BioMerieux, Rhône-Alpes, France); Factor IX, clot (BioMerieux); and TAT, enzyme-linked immunosorbent assay (Behring, King of Prussia, PA, USA). We defined abnormal values according to the guideline of the clinical laboratory or manufacturer's assay. These abnormalities included: INR ≥ 1.3 , PTT >38 s, platelets $<150,000$ or $>400,000$ cells/mL, D-dimer >256 ng/mL, PAI activity >31 IU/mL, antithrombin activity $<70\%$, factor IX activity $<60\%$, and TAT >5.0 ng/mL.

Statistical Analysis

We analyzed data using SAS software, version 9.1 (SAS Institute, Cary, NC, USA), with α set at $P < 0.05$. We compared differences for single points in time

using a chi-square test or Fisher exact test for dichotomous data and Student *t* test or Mann–Whitney *U* test for continuous data. For day-1 comparisons of proportions with coagulation abnormalities by APACHE III quartiles, we used the Cochran–Armitage test for trend. For sequential comparisons of coagulation marker data, we transformed values into natural logarithm scale and conducted regression analysis with mixed models that accounted for correlation of repeated measures over time (24), incorporating Tobit models as necessary (for D-dimer, TAT, and PAI) to account for data that were truncated because they fell below detection thresholds (25). We compared differences in the proportion of subjects with abnormal concentrations over time by using logistic regression based on generalized estimating equations (26). Models included linear and quadratic terms to allow evaluation of trends. We determined differences across outcome groups by testing the significance of the regression coefficient in the models.

RESULTS

Study Population and Outcomes

We enrolled 2320 subjects, excluding 288 (12%) of patients because they were discharged from the emergency department and 137 (6%) because their treating physicians subsequently excluded pneumonia as the cause of their illness. Of the remaining 1895 subjects, in the first 939 subjects enrolled (49.6%) we obtained blood for measurement of plasma coagulation markers (D-dimer, PAI, antithrombin, factor IX, and TAT) (Figure 1 and Table 1). Day-1 platelet, INR, and PTT values were obtained by the clinical team for 889 (95%), 354 (38%), and 315 (34%) of study participants, respectively. Of the 939 patients in the analysis cohort, 60 (6.4%) had positive sputum cultures, 70 (7.5%) were bacteremic, 305 (32.5%) developed severe sepsis, 63 (6.7%) died within 30 d of enrollment, and 104 (11.1%) died within 90 d of enrollment. When present, severe sepsis first became clinically evident, as measured by signs of acute

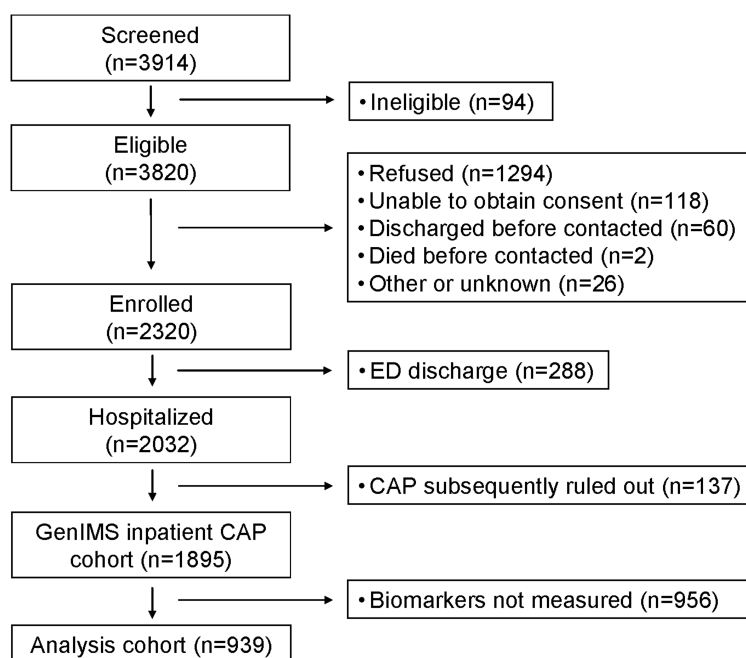


Figure 1. Flow diagram for the entire GenIMS cohort.

organ dysfunction, on d 1 in 157 (51.5%) of patients, d 2 in 56 (18.4%), d 3 in 32 (10.5%), and d 4 or later in 60 (19.7%).

Coagulation Markers at Presentation

We show day-1 coagulation abnormalities stratified by initial severity of illness (APACHE III score quartile), development of severe sepsis at any time during the hospitalization, and 90-d mortality in Figure 2. The proportion of subjects with coagulation abnormalities increased with initial illness severity, with the exception of PTT. Only platelet, PAI, and TAT abnormalities were greater in patients who developed severe sepsis compared with those without severe sepsis. Compared with patients alive at d 90, day-1 PTT, D-dimer, PAI, and TAT abnormalities were more common in patients who died by d 90, with INR, platelet, and antithrombin approaching significance ($P = 0.056$, $P = 0.074$, and $P = 0.063$, respectively). As evidenced by Figure 2, overall differences between groups, though significant, were modest. Coagulation abnormalities, especially D-dimer, were common even among the least ill and in those with good outcomes.

Because day-1–D-dimer was abnormal according to the manufacturer’s assay parameters far more commonly than the other markers, we explored the relationship between quintiles of D-dimer levels and 90-d mortality (Figure 3). There was a strong linear relationship between increasing D-dimer levels and 90-d mortality ($P < 0.001$). Compared with CAP patients with normal day-1–D-dimer levels (≤ 256 ng/mL), patients with levels from 256 to 1000 ng/mL had two- to three-fold higher mortality, whereas patients with levels greater than 1000 ng/mL had more than five-fold higher mortality.

Of those patients with all five nonclinical coagulation biomarkers measured on d 1, only 11.1% (81 of 729) had no abnormalities for any marker. Severe sepsis and 90-d mortality were less common in patients with no day-1 abnormalities compared with patients with at least one abnormality (23.5% versus 33.3%, $P = 0.08$; 2.5% versus 12.7%, $P = 0.005$), although only the latter difference was significant. Of the patients who eventually developed severe sepsis but had no clinical evidence of acute organ dysfunction on d 1, 86.9% had at least one coagulation abnormality

Table 1. Clinical characteristics at baseline and during the study.

Characteristics	All	APACHE III quartile				Severe sepsis		90-d Mortality	
		I	II	III	IV	Yes	No	Dead	Alive
n (%)	939 (100)	239 (25.5)	233 (24.8)	239 (25.5)	228 (24.3)	305 (32.5)	634 (67.5)	104 (11.1)	835 (88.9)
Age, years, mean (SD)	69.2 (15.8)	56.4 (15.6)	69.3 (14.2)	75.2 (11.8)	76.2 (12.8)	71.8 (14.5)	68.0 (16.2)	77.7 (11.9)	68.1 (15.9)
Male sex, n (%)	483 (51.4)	105 (43.9)	109 (46.8)	130 (54.4)	139 (61.0)	183 (60.0)	300 (47.3)	63 (60.6)	41 (50.3)
White, mean (SD)	818 (87.1)	195 (81.6)	198 (85.0)	220 (92.1)	205 (89.9)	272 (89.2)	546 (86.1)	98 (94.2)	720 (86.2)
Chronic conditions									
Charlson score, mean (SD) ^a	1.8 (2.2)	0.8 (1.0)	1.5 (1.8)	2.1 (2.3)	2.9 (2.8)	2.0 (2.3)	1.7 (2.2)	3.0 (2.8)	1.7 (2.1)
Any comorbidity, n (%)	651 (69.3)	133 (55.6)	148 (63.5)	187 (78.2)	183 (80.3)	224 (73.4)	427 (67.4)	87 (83.7)	564 (67.5)
Respiratory, n (%)	343 (36.5)	87 (36.4)	80 (34.3)	87 (36.4)	89 (39.0)	105 (34.4)	238 (37.5)	35 (33.7)	308 (36.9)
Cardiovascular, n (%)	212 (22.6)	29 (12.1)	52 (22.3)	74 (30.9)	57 (25.0)	76 (24.9)	136 (21.5)	28 (26.9)	184 (22.0)
Cirrhosis, n (%)	1 (0.001)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.004)	0 (0.0)	1 (0.002)	1 (0.001)	0 (0.0)
From nursing home, n (%)	49 (5.2)	3 (1.3)	4 (1.7)	18 (7.5)	24 (10.5)	31 (10.2)	18 (2.8)	18 (17.3)	31 (3.7)
Pneumonia Severity (SD)	98.2 (35.9)	65.2 (22.5)	88.1 (22.1)	107.1 (24.0)	133.6 (33.1)	117.0 (38.1)	89.1 (30.9)	135.8 (40.2)	93.5 (32.4)
Index, mean									
APACHE III, mean (SD)	57.0 (17.1)	36.8 (7.5)	51.0 (2.6)	61.3 (3.4)	79.8 (11.2)	65.5 (18.8)	52.9 (14.6)	73.3 (19.1)	55.0 (15.7)
Symptom duration prior to ED presentation, d, mean (SD)	4.7 (6.9)	5.2 (7.1)	4.9 (7.3)	4.6 (6.3)	4.2 (6.7)	4.3 (6.7)	4.9 (7.0)	4.8 (9.0)	4.7 (6.6)
Received antibiotics prior to presentation, n (%)	184 (19.6)	57 (23.8)	47 (20.2)	40 (16.7)	40 (17.5)	51 (16.7)	133 (21.0)	12 (11.5)	172 (20.6)
ATS-compliant initial antibiotics, n (%) ^b	739 (78.7)	194 (81.2)	188 (80.7)	186 (77.8)	171 (75.5)	238 (78.0)	501 (79.0)	79 (76.0)	660 (79.0)
Hospital length of stay, d, mean (SD)	7.3 (4.8)	6.0 (3.3)	6.7 (4.6)	7.5 (4.6)	8.9 (6.0)	9.9 (6.6)	6.0 (2.9)	9.4 (6.1)	7.0 (4.6)
Intensive care unit admission, n (%)	151 (16.1)	20 (8.3)	22 (9.4)	38 (15.9)	71 (31.1)	111 (36.3)	40 (6.3)	40 (38.5)	111 (13.3)
Mechanical ventilation, n (%)	60 (6.4)	11 (4.6)	6 (2.6)	12 (5.0)	31 (13.6)	60 (19.7)	0 (0.0)	25 (24.0)	35 (4.2)

^aAccording to the method of Charlson *et al.* (16).

^bThe reception of antibiotics during the first 24 h of hospitalization is consistent with the 2001 ATS Guidelines for the Management of Adults with Community-acquired Pneumonia (21).

at presentation. In this group, D-dimer was most commonly abnormal (76.6%), followed by TAT (41.1%), antithrombin (13.1%), factor IX (12.1%), and PAI (7.5%).

Coagulation Markers over Time

The proportion of hospitalized subjects with abnormal coagulation markers during hospital d 1 through 7 is shown in Figure 4. Although the proportion with abnormalities did change over time, the magnitude of the change was small and was not always in the direction of fewer abnormalities. We did not observe an obvious postpresentation spike in the proportion with abnormalities, with the possible exception of antithrombin. A large proportion of subjects remaining in the hospital continued to manifest coagulation abnormalities on d 7, especially for D-dimer and TAT. Abnormalities on d 1

through 7 did not differ when stratified by inpatient use of heparin products or warfarin (data not shown) apart from factor IX, which was more often abnormal in warfarin-treated patients, as would be expected pharmacologically.

Coagulation Markers over Time by Strata

Figure 5 demonstrates mean coagulation factor levels over hospital d 1 through 7 stratified by initial illness severity (APACHE III quartiles), development of severe sepsis, and 90-d mortality. Almost universally, those with greater illness severity, severe sepsis, or subsequent death had greater abnormalities over time compared with those with lesser illness severity, no severe sepsis, or survival (all $P < 0.05$). The only exceptions were PAI by APACHE III quartiles

and factor IX by severe sepsis and mortality. Differences between groups, although statistically significant, were clinically modest. Similar results were obtained when groups were compared for the proportion with abnormal values over time (data not shown).

DISCUSSION

We confirmed that there are substantial coagulation abnormalities in pneumonia with severe sepsis, consistent with prevailing hypotheses. We were surprised to find, however, that there are considerable abnormalities in CAP patients who do not develop organ dysfunction. Although coagulation abnormalities were more common in those patients who developed severe sepsis or died, the differences were modest, and there was no obvious temporal pattern to support the

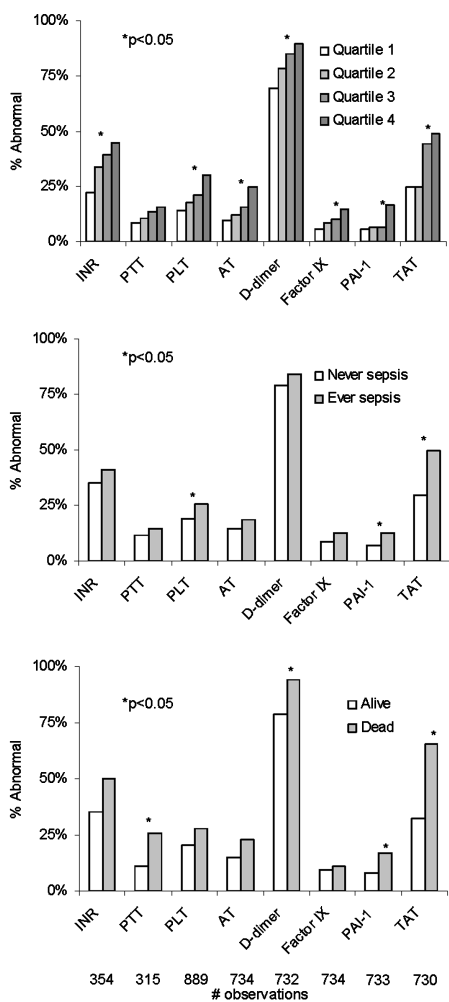


Figure 2. Day-1 coagulation abnormalities by initial APACHE III score quartile (top), development of severe sepsis (middle), and 90-d mortality (bottom). The total number of subjects providing at least one day-1 observation was 923 (98.3%), including 734 (78.2%) who had at least one non-clinical marker measured. Number of observations for each marker are listed below the figure. INR, international normalized ratio; PTT, activated partial thromboplastin time; PLT, platelets; AT, antithrombin; PAI, plasminogen activator inhibitor; TAT, thrombin-antithrombin complex. Ever sepsis indicates development of severe sepsis during the hospitalization. See Materials and Methods for cutoffs for abnormality.

notion that coagulation disorders were “causing” organ dysfunction.

Most of what is known of coagulation abnormalities in CAP comes from animal

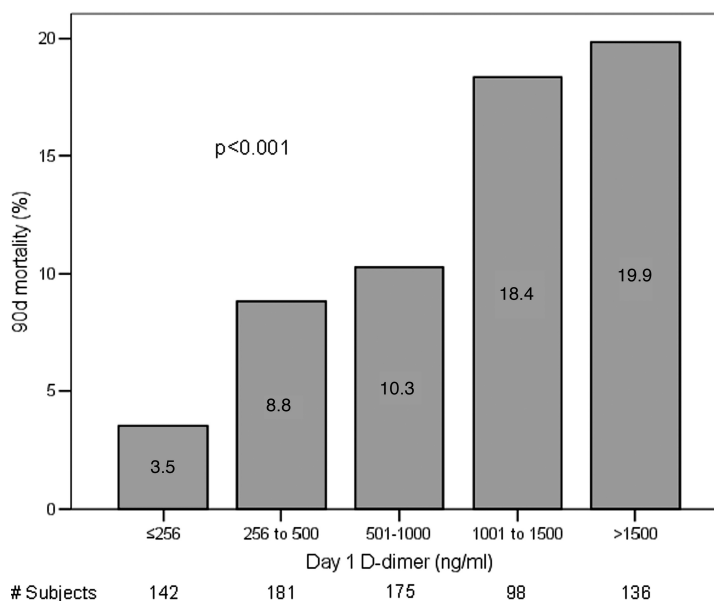


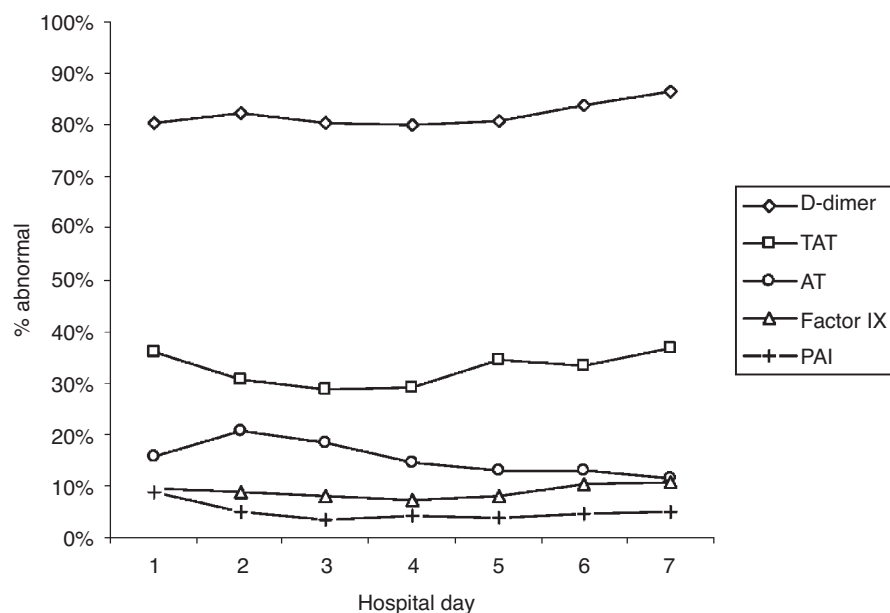
Figure 3. Mortality at 90 d by day-1-D-dimer quintiles. Mortality increased progressively with increasing D-dimer levels.

models and studies of patients with severe pneumonia and/or severe sepsis. Of the patients in our cohort who developed severe sepsis, nearly half had no clinical evidence of organ dysfunction on day 1. Thus, we were able to capture coagulation abnormalities early during illness, prior to the onset of organ dysfunction, something that studies enrolling patients at the onset of severe sepsis are unable to do. The abnormalities we found in those patients with severe sepsis were in agreement with those reported in existing literature (27,28), but the demonstration of significant systemic coagulation activation in subjects with CAP who neither developed severe sepsis nor died is relatively novel. Two small, single-center studies examined D-dimer in patients with CAP without severe sepsis. Similar to our study, in these studies the authors found that circulating D-dimer levels were frequently abnormal and associated with outcome (29,30). Other systemic components of the coagulation system, however, were not assessed. In our cohort, only 11% of subjects had no systemic coagulation abnormalities at all on presentation, suggesting that coagulation system activation is part of the normal

response to infection and not inherently harmful. Even so, death was uncommon in those with no day-1 abnormalities.

Why would pneumonia, which is originally a localized infection, lead to systemic coagulation activation? Local activation of the coagulation system is known to occur in pneumonia, with fibrin deposition in the alveolar compartment helping to contain infection but also enhancing vascular permeability, stimulating proinflammatory cytokines, and promoting neutrophil accumulation (31). This local coagulation activation appears to be driven primarily by tissue factor (32). Normally, very little tissue factor is exposed to circulating blood. Yet alveolar macrophages, neutrophils, and endothelial cells can express tissue factor on their surfaces, which may create a blood-borne pool of highly thrombogenic tissue factor to drive the development of systemic coagulopathy during lung infection (33).

Our observations offer potential insight into why some coagulation-based therapies for sepsis that appeared promising in animal models were unsuccessful in clinical trials (6-8). First, treatments designed to manipulate early coagulation system changes may be im-



# D-dimer	732	833	852	717	540	405	328
# TAT	730	831	850	717	537	403	328
# AT	734	832	850	717	538	404	328
# Factor IX	734	833	850	719	539	404	328
# PAI	733	833	851	714	539	405	327
# in hospital	939	936	916	826	669	512	392

Figure 4. Proportion of hospitalized subjects with abnormal coagulation markers over time. The total number of subjects providing at least one observation was 939. Number of observations for each marker and the number remaining hospitalized each day are listed below the figure. See Materials and Methods for cutoffs for abnormality.

practical because, as we have previously shown for systemic cytokines (5), many of these changes have already occurred prior to presentation. Second, a one-size-fits-all approach to coagulation-based therapeutics is likely to be ineffective because not all patients manifest coagulation abnormalities and many patients fare well even when these abnormalities exist. Future trials in this area might benefit from targeting therapy based on specific biomarkers of the coagulation factor of interest. Finally, the 96-hour dosing of coagulation-based strategies in prior trials (6,7,9–11) may be too short, given that in a large proportion of subjects coagulation abnormalities may continue to manifest as late as day 7 of their hospital stay, in contrast to systemic cytokines (5), which tend to decrease after day 1.

Our study was limited to patients with CAP, the most common cause of

severe sepsis. Focusing on CAP reduced unwanted heterogeneity, although our findings may not be generalizable to other types of infection. INR, PTT, and platelet counts were available only if drawn for clinical purposes, which after day 1 was uncommon and typically was done for a specific reason. This indication bias in testing precludes meaningful description of trends in these markers over time. We had insufficient data to score or diagnose disseminated intravascular coagulation, although one would expect disseminated intravascular coagulation to increase with illness severity and be more common in patients with poor outcomes. It was impractical to draw blood samples after hospital discharge; therefore our results describe only coagulation system changes during the hospital stay. Whether coagulation system abnormalities persist after hospital discharge remains to be seen. If

so, the postdischarge period might present a unique time to intervene if persistent abnormalities were also associated with adverse outcomes (34).

Very few subjects had positive blood or sputum cultures and cultures were not universally drawn, a situation that is typical for observational studies of CAP (35,36). Consequently, we could not reliably determine whether coagulation abnormalities varied by presence of bacteremia or by type of infecting organism. We measured circulating levels of a select group of coagulation markers thought to be important in the coagulation response to infection (28,37–39). In addition to the changes we observed, changes may well occur at the local level (31,40) or within other coagulation system components or factors that are not reflected in our selection of biomarkers.

In conclusion, we have shown that coagulation abnormalities are common in CAP, increasing with illness severity and poor outcome. Abnormalities existed across all levels of illness, and differences between groups, though significant, were not large. These data offer insight into the challenge of coagulation-based therapeutics in infection and severe sepsis.

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DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

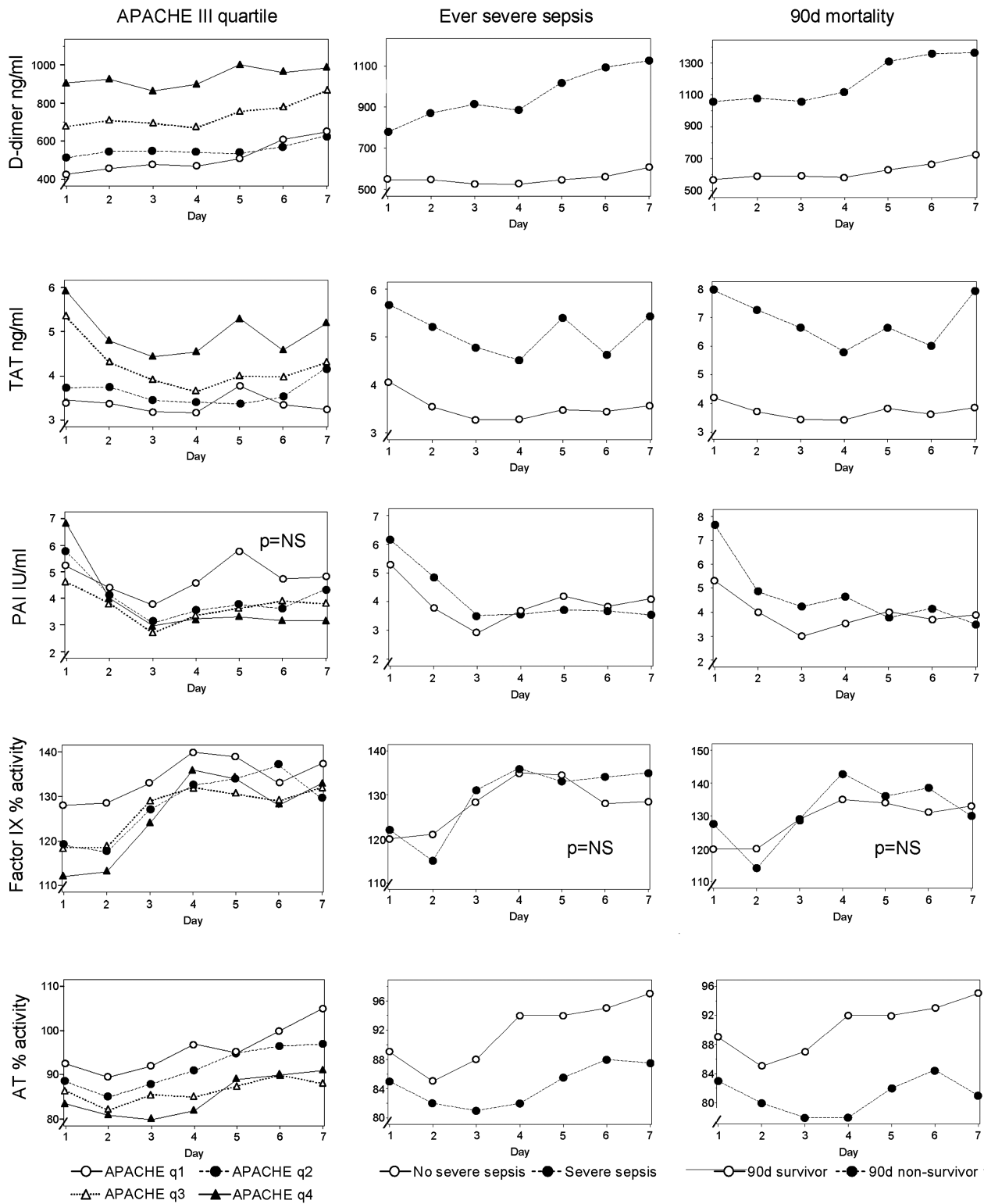


Figure 5. Mean coagulation factor levels over hospital d 1 through 7 in subjects hospitalized with CAP, stratified by initial illness severity (APACHE III quartiles (q)), development of severe sepsis, and 90-d mortality. To accentuate differences between groups, y-axes do not cross zero. Means are geometric means estimated from Tobit models when appropriate. Geometric means roughly approximate medians. Normal values are: D-dimer ≤ 256 ng/mL, TAT ≤ 5.0 ng/mL, PAI activity ≤ 31 IU/mL, factor IX activity $\geq 60\%$, and antithrombin activity $\geq 70\%$.

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