Late Admission to the ICU in Patients With Community-Acquired Pneumonia Is Associated With Higher Mortality

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Background: Limited data are available on the impact of time to ICU admission and outcomes for patients with severe community acquired pneumonia (CAP). Our objective was to examine the association of time to ICU admission and 30-day mortality in patients with severe CAP.

Methods: A retrospective cohort study of 161 ICU subjects with CAP (by *International Classification of Diseases, 9th edition*, codes) was conducted over a 3-year period at two tertiary teaching hospitals. Timing of the ICU admission was dichotomized into early ICU admission (EICUA, direct admission or within 24 h) and late ICU admission (LICUA, $\geq$ day 2). A multivariable analysis using Cox proportional hazard model was created with the primary outcome of 30-day mortality (dependent measure) and the American Thoracic Society (ATS) severity adjustment criteria and time to ICU admission as the independent measures.

Results: Eighty-eight percent ($n = 142$) were EICUA patients compared with 12% ($n = 19$) LICUA patients. Groups were similar with respect to age, gender, comorbidities, clinical parameters, CAP-related process of care measures, and need for mechanical ventilation. LICUA patients had lower rates of ATS severity criteria at presentation (26.3% vs 53.5%; $P = .03$). LICUA patients (47.4%) had a higher 30-day mortality compared with EICUA (23.2%) patients ($P = .02$), which remained after adjusting in the multivariable analysis (hazard ratio 2.6; 95% CI, 1.2-5.5; $P = .02$).

Conclusion: Patients with severe CAP with a late ICU admission have increased 30-day mortality after adjustment for illness severity. Further research should evaluate the risk factors associated and their impact on clinical outcomes in patients admitted late to the ICU.

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Abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; EICUA = early ICU admission; LICUA = late ICU admission

Community-acquired pneumonia (CAP) continues to be associated with significant morbidity and mortality, accounting for more than 1 million hospital admissions per year in the United States. Pneumonia and influenza together are ranked as the eighth leading cause of death in the United States,¹ and mortality rates in those admitted to the ICU have been reported higher than 35%. The most vulnerable patients include the elderly and those with comorbidities such as COPD and congestive heart failure.¹⁻⁷

Up to 36% of patients with CAP admitted to the hospital require ICU admission. These patients carry the highest morbidity, mortality, and cost of all patients with CAP.⁸ The mortality in these patients has been reported to be as high as 58%.⁹⁻¹¹ Direct admission to an ICU is usually required for patients who present in

septic shock requiring vasopressors, and/or acute respiratory failure requiring intubation and mechanical ventilation.^{3,7,9,12-16} However, limited data are available regarding the outcomes of patients with CAP who are not directly admitted to the ICU, such as those transferred from the general medicine ward.^{3,8,12,17} Delayed ICU transfers may represent rapidly progressive pneumonia that was not obvious on admission.³ Therefore, our aim was to determine the association of early vs late ICU admission with 30-day mortality after adjusting for other potential confounders.

METHODS

This is a retrospective cohort study of patients hospitalized with CAP at two academic tertiary care hospitals in San Antonio, Texas.

The Institutional Review Board of the University Health Science Center at San Antonio classified this project as an exempt study.

Inclusion and Exclusion Criteria

We identified all patients admitted to the study hospitals between January 1, 1999, and December 1, 2002, with a primary discharge diagnosis of pneumonia (*International Classification of Diseases, 9th edition*, codes 480.0-483.99 or 485-487.0) or secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (518.81) or sepsis (038.xx). Subjects were included if they were (1) older than 18 years of age, (2) had an admission diagnosis of CAP, and (3) had a radiographically confirmed infiltrate or other finding consistent with CAP on chest radiograph or CT scan of the chest obtained within 24 h of admission.

Exclusion criteria included discharged from an acute care facility within 14 days of admission, and "comfort measures" only on this admission. We excluded those patients admitted to the ICU after day 10 of initial presentation, as this transfer was likely to be due to reasons other than CAP. If a subject was admitted more than once during the study period, only the first hospitalization was abstracted.

Group Definitions

For these analyses, patients were dichotomized into two groups based on the time of ICU admission as early ICU admission (EICUA, direct admission or within 24 h) and late ICU admission (LICUA, day 2-10 of initial hospitalization). In addition, for the secondary analyses we separated patients into four groups: EICUA as a direct admission, EICUA within 24 h of presentation, LICUA between days 2 and 4, and LICUA between days 5 and 9.

Data Abstraction

Chart review data included demographics, comorbid conditions, physical examination findings, laboratory and microbiology data, and chest radiograph reports. Process measures previously reported associated with higher mortality were recorded, including

antibiotics within 4 h of admission, appropriate blood cultures collected before antibiotics and within 24 h of admission, and guideline concordant antibiotics.⁸ We assessed these measures either at the time of presentation to the emergency department, or, for those who were admitted directly from clinic, at time of admission to the hospital.

Diagnostic Criteria

Microbiologic data results were reviewed, and a microbiologic cause was assigned independently by two of the investigators (M. I. R. and E. M. M.). The cause of pneumonia was stratified as definitive or presumptive. The definitive diagnosis was considered if one of the following conditions were met: (1) positive blood cultures for bacterial pathogens (in the absence of extrapulmonary source of infection), (2) pleural fluid cultures yielding a bacterial pathogen, (3) endotracheal aspirates with moderate or heavy growth of bacterial pathogens, (4) significant quantitative culture growth from bronchoscopic respiratory samples (protected specimen brush cultures of at least 10^3 cfu/mL and in BAL of at least 10^4 cfu/mL), and (5) positive *Legionella* urinary antigen. A presumptive diagnosis was made if qualitative valid sputum sample yielded one or more predominant bacterial pathogens. Definitive and presumptive causes were combined for reporting purposes. When two or more microbiologic causes were present, the patient was considered to have a polymicrobial infection. A patient was considered to have CAP of unknown cause if microbiologic studies were not performed or were inconclusive.

Clinical Outcomes

The primary outcome was mortality within 30 days as this has previously been demonstrated to be primarily due to pneumonia.¹⁸ Secondary outcomes were length of hospital stay, need for mechanical ventilation, and use of vasopressors. Length of hospital stay was calculated as the date of discharge minus the date of admission.

Statistical Analyses

Bivariate statistics were used to test the association of demographic and clinical characteristics with all-cause 30-day mortality. Categorical variables were analyzed using the χ^2 test and continuous variables were analyzed using Student *t* test. Statistical significance was defined as $P \leq .05$. The American Thoracic Society (ATS) severity criteria were used to adjust for severity of illness.¹⁹ A Cox proportional hazard model was created with mortality as the dependent measure, and the ATS severity criteria and time to ICU admission as the independent measures.²⁰ All analyses were performed using SPSS version 17.0 for Windows (SPSS Inc.; Chicago, IL).

RESULTS

We identified 161 patients who were admitted to the ICU with a diagnosis of severe CAP with confirmatory radiology that met our eligibility criteria. Out of these, 88% ($n = 142$) of patients had direct ICU admission or admission within 24 h of presentation (EICUA) and 19 patients had late ICU admission (LICUA).

Patient Characteristics

Table 1 shows patient characteristics by study group: EICUA or LICUA. These patients had similar

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Table 1—Comparison of Demographic and Clinical Characteristics Among Patients With Community-Acquired Pneumonia Admitted to the ICU

Variable	EICUA (n = 142), N (%)	LICUA (n = 19), N (%)	P Value
Age, y (SD)	61 (16)	59 (11)	.5
Men	126 (88.7)	14 (73.7)	.8
Preexisting comorbid conditions			
Congestive heart failure	33 (23.2)	3 (15.8)	.6
History of stroke	20 (14.1)	2 (10.5)	1
Chronic liver disease	17 (12.0)	4 (21.1)	.3
History of malignancy	15 (10.6)	0 (0)	.2
Renal insufficiency	18 (12.7)	1 (5.3)	.7
Diabetes mellitus	45 (31.7)	6 (31.6)	1
Chronic obstructive lung disease	49 (34.5)	3 (15.8)	.1
Alcoholism	20 (14.1)	5 (26.3)	.2
History, physical, laboratory, and radiographic data			
Altered mental status	35 (24.6)	6 (31.6)	.6
Respiratory rate > 30 per min	28 (19.7)	2 (10.5)	.5
Systolic BP < 90 mm Hg	7 (4.9)	1 (5.3)	1
Heart rate > 125 per min	35 (24.6)	3 (15.8)	.6
Temperature < 95°F or > 104°F	5 (3.5)	0 (0)	1
Arterial pH < 7.35	33 (23.2)	3 (15.8)	.6
Arterial oxygenation saturation < 90%	62 (43.7)	6 (31.6)	.5
Hematocrit < 30%	19 (13.4)	2 (10.5)	1
Serum blood urea nitrogen > 30 mg/dL	48 (33.8)	9 (47.4)	.3
Serum glucose > 250 mg/dL	20 (14.1)	1 (5.3)	.5
Serum sodium < 130 mEq/L	29 (20.4)	6 (31.6)	.4
Pleural effusion	49 (34.5)	7 (36.8)	.8
Multilobar infiltrates	85 (60.3)	9 (47.4)	.3
Severe CAP by 2001 ATS criteria	76 (53.4)	5 (26.3)	.03

N = 161. ATS = American Thoracic Society; CAP = community-acquired pneumonia; EICUA = early ICU admission; LICUA = late ICU admission.

demographic, comorbidity, physiologic, laboratory, and radiologic characteristics at the time of admission despite the different time to ICU admission. LICUA patients had a similar percentage of outpatient use of corticosteroids compared with EICUA patients (11 [7.7%] vs 2 [10.5%]; $P = .7$). In addition, a similar proportion of EICUA vs LICUA patients received the pneumonia processes of care measures as recommended by the guidelines: early antibiotic administration within 4 h of admission (57 [40.1%] vs 7 [36.8%]; $P = .2$), appropriate blood culture collection (116 [81.7%] vs 13 [68.4%]; $P = .2$), and guideline-concordant antibiotic selection (96 [67.6%] vs 16 [84.2%]; $P = .2$). A higher proportion of EICUA patients presented with severe CAP on admission by ATS criteria when compared with LICUA patients (76 [53.5%] vs 5 [26.3%], $P = .03$) (Table 1). No specific risk factors were associated with early admission by the univariate analysis, except for those presenting with severe CAP according to the ATS criteria (odds ratio [OR] = 3.2; 95% CI, 1.10-9.43, $P = .03$).

Pneumonia Etiology

An etiologic diagnosis was found in 65 (40%) patients and was similar in both groups, LICUA patients (8/19 [42%]) vs EICUA patients (57/142 [40%]) (Table 2). Pathogens were more frequently isolated from EICUA

patients, except for *Staphylococcus aureus*. Half of the patients with LICUA had *S aureus* as the identifiable pathogen compared with 22% for the EICUA patients. In the univariable analysis, the risk of finding *S aureus* in LICUA patients was higher compared with EICUA (OR = 3.75; 95% CI, 0.82-17.23; $P = .09$), but different than acquiring *Streptococcus pneumoniae* (OR = 0.57; 95% CI, 0.11-3.09; $P = .5$).

Clinical Outcomes

Overall 30-day mortality was lower for EICUA patients compared LICUA patients: 23% vs 47% ($P = .02$). In addition, the mean (SD) length of hospital stay was longer by 5 days for the LICUA patients (17 days [SD 13]) compared with EICUA patients (12 days [SD 10]) ($P = .1$). A lower proportion of patients required mechanical ventilation in the LICUA group compared with the EICUA group (3 patients [16%] vs 71 patients [50%], $P = .006$). Vasopressor use was only measured in the first 24 h; therefore only 31 (22%) EICUA patients required vasopressor support ($P = .02$).

In the Cox proportional hazard model after adjusting for potential confounders, including severity of illness, LICUA patients had an increased risk of dying within 30 days of admission (hazards ratio 2.6; 95% CI, 1.2-5.5) (Table 3 and Fig 1). The survival curves

Table 2—Etiologic Diagnosis With an Identifiable Pathogen Causing Disease in CAP of Patients With EICUA vs LICUA

Microorganisms	EICUA (n = 57)	LICUA (n = 8)
<i>Streptococcus pneumoniae</i>	21 (36.8)	2 (25.0)
<i>Staphylococcus aureus</i>	12 (21.1)	4 (50.0)
Methicillin-resistant <i>S aureus</i>	2 (5.8)	0
<i>Pseudomonas aeruginosa</i>	8 (14.0)	0
<i>Haemophilus influenzae</i>	3 (5.3)	0
<i>Escherichia coli</i>	1 (1.8)	0
<i>Klebsiella pneumoniae</i>	2 (3.5)	1 (12.5)
<i>Proteus mirabilis</i>	1 (1.8)	1 (12.5)
Other ^a	3 (5.3)	0
Polymicrobial	6 (10.5)	0

Values are given as N (%). No comparisons showed statistical significant differences among the groups. Percentages have been rounded and may not sum 100.

^aOther consists of *Aspergillus* spp, *Haemophilus parainfluenzae*, and *Enterococcus* spp.

were similar among EICUA patients directly admitted to the ICU and those admitted within 24 h of presentation (Fig 2). In addition, LICUA had a similar survival curve whether admitted between days 2 and 4 or between days 5 and 9; however, both LICUA subgroups had lower survival rate compared with both EICUA subgroups (Fig 2 and Table 3).

DISCUSSION

The main finding of our study was that patients with severe CAP admitted to the ICU after 24 h of hospital admission have a much higher mortality compared with those with direct admission within 24 h of presentation. In addition, the survival curves suggest that those patients with late admission to the ICU, whether in days 2 to 4 or 5 to 9 had similar rates of higher mortality when compared with patients

Table 3—Cox Survival Analysis Results

Groups	HR	95% CI	P Value
Early vs late ICU admission			
EICUA (reference value)	...	...	...
LICUA	2.6	1.2-5.5	.02
ATS severe criteria	1.8	0.9-3.3	.08
Subgroup analysis			
EICUA (direct admission) (reference value)	...	...	...
EICUA (within 24 h)	0.9	0.4-1.9	.8
LICUA (2-4 d)	2.5	1.0-5.9	.04
LICUA (5-9 d)	2.5	0.6-10.9	.2
ATS severe criteria	1.8	0.9-3.3	.08

Patients with CAP admitted early vs those admitted late to the ICU and the subgroup analysis with those patients with direct admission to the ICU (as the reference value), within 24 h, 2-4 d after admission, or 5-9 d after presentation to the ICU, adjusted for severity of illness (ATS severe CAP criteria). HR = hazard ratio. See Table 1 for expansion of other abbreviations.

FIGURE 1. Cox survival curves of patients with community-acquired pneumonia admitted early vs those admitted late to the ICU. EICUA = early ICU admission; LICUA = late ICU admission.

admitted directly to the ICU or within 24 h, respectively. Despite the numerical longer length of hospital stay, there were no statistically significant differences among groups.

Several epidemiologic studies have focused on patients with severe CAP directly admitted to the ICU, but limited data are available regarding the time of ICU admission and its impact on clinical outcomes.^{3,4,9,15,17,21-24} Our data are provocative in showing that despite the broad use of severity illness scores directed to assist clinicians on which patients require ICU admission, there are a number of patients

FIGURE 2. Cox survival curves of patients with community-acquired pneumonia admitted directly, within 24 h, 2 to 4 days after admission, or 5 to 9 days after presentation to the ICU. See Figure 1 legend for expansion of abbreviations.

admitted after 24 h of presentation. The scores do not consider CAP as a continuum, and they usually assess variables only at the time of admission.^{8,11,13-15,17,23,25-27} However, clinical deterioration could happen at any time after the initial presentation and evaluation occurs. The concerning issue related to late admission to the ICU is that these patients have higher 30-day mortality.

Validation of clinical predictors has enhanced our ability to risk-stratify patients into those that can be treated as outpatients compared with those that require hospitalization.²⁵⁻²⁷ However, the decision to admit patients to the ICU vs the ward service has had much less attention.^{7,8} It has been suggested that it is clear that the decision to admit a patient to the ICU currently rests on the need for mechanical ventilation or vasopressor support, because there is no other place in the hospital that can provide this type of care.^{8,11,13-17} However, none of the current prediction tools consider events that develop after the time of admission in their evaluation to assess the need for ICU care. The fact that patients with severe CAP with late ICU admission have higher mortality and longer hospital stay should be addressed more carefully in future studies of hospitalized CAP patients. Perhaps other objective measures, such as the determination of the bacterial load, may identify the patients with CAP who will require eventual ICU admission. A recent article by Rello et al²⁸ examining pneumococcal bacterial load in patients with pneumonia showed that bacterial load counts were associated with higher in-hospital mortality and other clinical outcomes load.

In addition, it is interesting that a higher proportion of LICUA patients had more *S aureus* and a higher risk to present with this pathogen compared with EICUA. This could suggest that a contributing factor of LICUA is the presence of difficult-to-treat and unexpected pathogens. In addition, our data suggested that this difference was not related to a higher proportion of patients with methicillin-resistant *S aureus*, which may be due to health care-associated pneumonia. However, because of our study's small sample size we are unable to draw firm conclusions.

Our study has limitations that are important to acknowledge. First, this study was a retrospective cohort study, and there are inherent problems related to this design, including selection bias. However, we do not feel that this study has significant problems with bias because of our methods using admission and discharge diagnosis International Classification of Diseases, 9th revision codes to identify patients with CAP and the fact that we encountered only a small amount of missing data. Moreover, we were able to verify that all the patients had a radiologic diagnosis of CAP. Second, our sample was predomi-

nantly men since one of our sites was a veterans' hospital and we are unable to exclude the hypothesis that female patients with CAP admitted early or late to the ICU may have a different clinical course, or outcomes, as compared with male patients. Third, we are unable to review the LICUA patients to confirm that the admission to the ICU was directly related to clinical deterioration of CAP or not. Fourth, the small number of LICUA patients limits our ability to do additional statistical analysis between the groups and the conclusions should be interpreted with caution. However, it is unlikely that many of the late-admitted patients were incorrectly placed on the medical wards. The cutoff discrimination of 10 days was a conservative estimate out of the literature regarding the length of stay in the ICU for patients with severe CAP. In order to clarify this, we used the severity score for the ICU using the ATS severe CAP recommendation from 2001; we were not able to determine the 2007 Infectious Diseases Society of America/ATS severe CAP criteria as we did not collect the variables needed to construct the score. Fifth, no data were available regarding alternative nonantibiotic therapies in patients with CAP, such as systemic corticosteroids, early goal-directed therapy, and human activated protein C. However, the proportion of patients with outpatient use of corticosteroids was similar in both groups. It is possible that bed availability may play a role in the LICUA group and might have affected the results. However, in both hospitals the time to ICU admission is usually less than 24 h and if there is a need for an ICU bed that is not available, those patients are transferred to another facility or stay in the emergency department rather than being admitted to a ward bed.

In conclusion, we suggest that patients admitted late to the ICU (≥ 2 days) with CAP have a significant increase in mortality compared with those admitted directly or within the first 24 h of presentation. The initial clinical evaluation may be insufficient for patients who do not require mechanical ventilation or vasopressors, and they should be monitored within the first 24 h of admission. Current severity of illness tools only evaluate the patient at presentation, and do not consider the continuum of disease progression as a possibility. Further studies should examine variables that may allow clinicians to determine patients who will have a late clinical failure, and processes of care that may reduce the need for these late transfers. An effective tool for evaluation of disease progression will identify patients who are at risk for clinical deterioration.

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