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THE ASSOCIATION BETWEEN COMMUNITY-ACQUIRED PNEUMONIA AND CARDIAC COMPLICATIONS

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ABSTRACT
The community-acquired pneumonia (CAP) is globally spread disease and affects more than 5 million adults each year in the United States. Although incident cardiac complications occur in patients with community-acquired pneumonia, their incidence, risk factors, timing and associations with short-term mortality are not well understood. This prospective cohort study was carried out in the general hospital of Falluja/Iraq on a total of 200 patients, 134 inpatients and 66 outpatients, with community-acquired pneumonia and followed up prospectively for 30 days after presentation. Incident cardiac complications (new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction) were diagnosed in 37 inpatients (28%) and 5 outpatients (8%). Although most events (89.2% in inpatients, 80% in outpatients) were diagnosed within the first week, more than half of them were recognized in the first 24 hours. Factors associated with their diagnosis included older age, pre-existing as DM, cerebrovascular disease, COPD, chronic renal disease, smoking, altered mental state, respiratory rate more than 30 per minute, pH less than 7.35, blood urea nitrogen ≥30 mg/dL, Glucose ≥250 mg/dL (14 mmol/L), Hematocrit <30%, Po2 <60 mm Hg or O2 sat <90 mm Hg, pleural effusion on chest x-ray, site of care and pneumonia severity index. Incident cardiac complications are common in patients with community-acquired pneumonia and are associated with increased short-term mortality. Older age, preexisting cardiovascular disease, and pneumonia severity are associated with their occurrence. Further studies are required to test risk stratification and prevention and treatment strategies for cardiac complications in this population.

KEYWORDS: Community acquired pneumonia (CAP), cardiac diseases, cardiac complications.

INTRODUCTION
Community-acquired pneumonia (CAP) affects more than 5 million adults, causes 1.1 million hospital admissions, and is responsible for more than 60 000 deaths each year in the United States.[1,2] Cardiac diseases affect more than 30 million adult Americans and are responsible for 5 million hospital admissions and more than 300 000 deaths each year in this country.[3,4] Both CAP and cardiac diseases occur more commonly in middle-aged and elderly individuals.[4,5] It is estimated that more than half of the elderly patients with CAP who present to the hospital with this infection have chronic cardiac conditions.[5]

Pneumonia contributes to the acute worsening of preexisting cardiac conditions and can trigger new cardiac events. Infection-induced changes in myocardial function, the conduction system of the heart, the stability of coronary plaques, vascular tone, and blood coagulability may all account for this effect.[6] Recent retrospective clinical observations suggest that incident (new or worsening) cardiac complications occur in a significant proportion of high-risk CAP patients (ie, elderly veterans and diabetics).[7] However, the frequency of these complications in unselected CAP patients, the contribution of specific cardiac events to this burden, the timing of these complications in the course of CAP, the factors associated with their development, and their association with the short-term mortality of this infection remain unclear.

This study aimed to determine: (1) the type, frequency, and timing of incident cardiac complications; (2) their risk factors; and (3) their associations with short-term mortality.

METHODS
This study was approved by the Fallujah General Hospital Research Ethics Board.

Inclusion criteria were age ≥18 years, the presence of ≥1 acute clinical symptoms suggestive of pneumonia, radiographic evidence of pneumonia within 24 hours of presentation, and appropriate informed consent for

participation. Chest radiographs used for the diagnosis of pneumonia were independently reviewed by a 3-member panel of staff radiologists at Falluja hospital who had no patient-specific clinical information. Patients were excluded if the radiographic findings were considered to represent a preexisting infiltrate or if they were consistent with an alternative diagnosis. Other exclusion criteria were discharge from an acute-care hospital within 10 days preceding presentation, presence of an alternative diagnosis that likely explained the pulmonary symptoms and x-ray infiltrate (e.g, lung carcinoma, pulmonary edema, or pulmonary embolus). Patients initially treated in an ambulatory setting were classified as outpatients, and patients admitted to a hospital on presentation were classified as inpatients.

Baseline sociodemographic characteristics and clinical data were obtained from all subjects by interviews and review of medical records. Clinical information included preexisting comorbidities, symptoms, and physical examination findings at presentation and pertinent laboratory findings within 48 hours of presentation. Severity of illness at presentation was quantified by means of the Pneumonia Severity Index (PSI), a validated prediction rule for 30-day mortality in patients with CAP.[8] This rule calculates a score based on 3 demographic characteristics, 5 comorbid conditions, 5 physical examination findings, and 7 laboratory and radiographic findings from the time of presentation. On the basis of this score, CAP patients are classified into 1 of 5 risk classes, each with an increasing risk of 30-day mortality ranging from 0.1% for class I (lowest risk) to 27.0% for class V (highest risk).[8]

Data regarding the incidence and timing of new or worsening morbid complications within 30 days of enrollment were prospectively ascertained for outpatients and inpatients. We focused on the development of 3 acute cardiac events: (1) new or worsening heart failure, ie, the simultaneous presence of clinical signs of new or worsening pulmonary edema or acute congestive heart failure (rales, increased jugular venous pressure, S3 gallop, peripheral edema) detected by the managing physician on physical examination and documented in the medical record, and a chest x-ray read by the local radiologist as showing pulmonary edema, cardiomegaly, vascular congestion, or congestive heart failure; (2) new or worsening arrhythmias, ie, documentation in the medical record, ECG, rhythm strips, ECG monitor, or Holter monitor of newly recognized or worsened atrial fibrillation, atrial flutter, supraventricular tachycardia, multifocal atrial tachycardia, ventricular tachycardia (≥3-beat run), or ventricular fibrillation; and (3) myocardial infarction (MI), ie, documentation in the medical record of myocardial ischemia or injury established by 2 of 3 criteria: chest pain, acute ECG changes (ST-segment and T-wave changes without the formation of Q waves, new Q waves, or a clear loss of R waves or sustained ventricular tachycardia or fibrillation), or elevated cardiac enzymes (creatine phosphokinase-MB) determined from criteria provided by participating laboratories. These cardiac events were ascertained by means of detailed medical review by trained research assistants. We recorded only the index occurrence of each type of event and its date. Overall, incident cardiac complications were defined by the occurrence of any of the cardiac events above.

To explore the temporal relationships among specific cardiac events, we also classified them by their sequential occurrence. When a cardiac event occurred in the absence of other cardiac events during the observation period, it was classified as the only cardiac event; a cardiac event that preceded the development of other events in the same patient by at least 1 day was described as the first cardiac event; a primary cardiac event was said to be present when either a first or an only cardiac event occurred. Finally, a secondary cardiac event was any event that followed other cardiac events by at least 1 day or for which its precedence over the others could not be established (ie, occurred on the same day).

Statistical analysis

All statistical analysis were performed using SPSS (version 19) program. For uninvariable analysis of baseline factors and incident cardiac complications, unpaired *t* tests or Wilcoxon rank-sum tests were used for continuous variables and χ^2 or Fisher exact tests for categorical variables as appropriate. We defined statistical significance as a 2-tailed value of $P<0.05$.

RESULTS

In the current study, 200 patients were enrolled. Characteristics of eligible individuals not enrolled in the study and the reasons for no enrollment are detailed elsewhere Of the enrolled patients, 134 (67.0%) were treated as inpatients and 66 (33.0%) as outpatients.

Overall, incident cardiac complications occurred in 37 inpatients (27.6%) and 5 outpatients (7.6%). New or worsening heart failure, new or worsening arrhythmias, and MI cases were the primary cardiac events in 25 (19.0%), 8 (6.0%) and 4 (3%) in the inpatients group; and 3 (5.0%), 2 (3.0%), and 0, 0 in the outpatients group, respectively as shown in figure (1).

The specific incidence of each type of cardiac event and the temporal relations among them are shown in figure (2). New or worsening heart failure was the single most common cardiac event, occurring in 25 inpatients (19.0%) and 3 outpatients (5.0%). New or worsening heart failure was the only, first, and secondary cardiac event in 17 (68.0%), 4 (16.0%), and 4 (16.0%) inpatients who had this event and 2 (66.7%), 1 (33.3%), and 0 of the corresponding outpatients, respectively. New or worsening arrhythmias occurred less frequently in 8 inpatients (6.0%) and 2 outpatients (3.0%), presenting as the only, first, and secondary cardiac event in 4 (50.0%), 1 (10.0%), and 3 (40.0%) patients of the former and 2

(100.0%), 0, and 0 of the latter, respectively. Finally, MI was documented in only 4 inpatients (3.0%) and 0 outpatients. In contrast to the other cardiac events above, MI presented as a secondary cardiac event in the majority of inpatients with this complication (3 of 4 cases, 75%) and none in outpatients, whereas it was the only and first cardiac event in just 0 and 1 (25.0%) of the inpatients who developed it, respectively. Overall, 6 inpatients (16.2%) and 1 outpatients (20%) with incident cardiac complications had ≥2 types of cardiac events during the observation period.

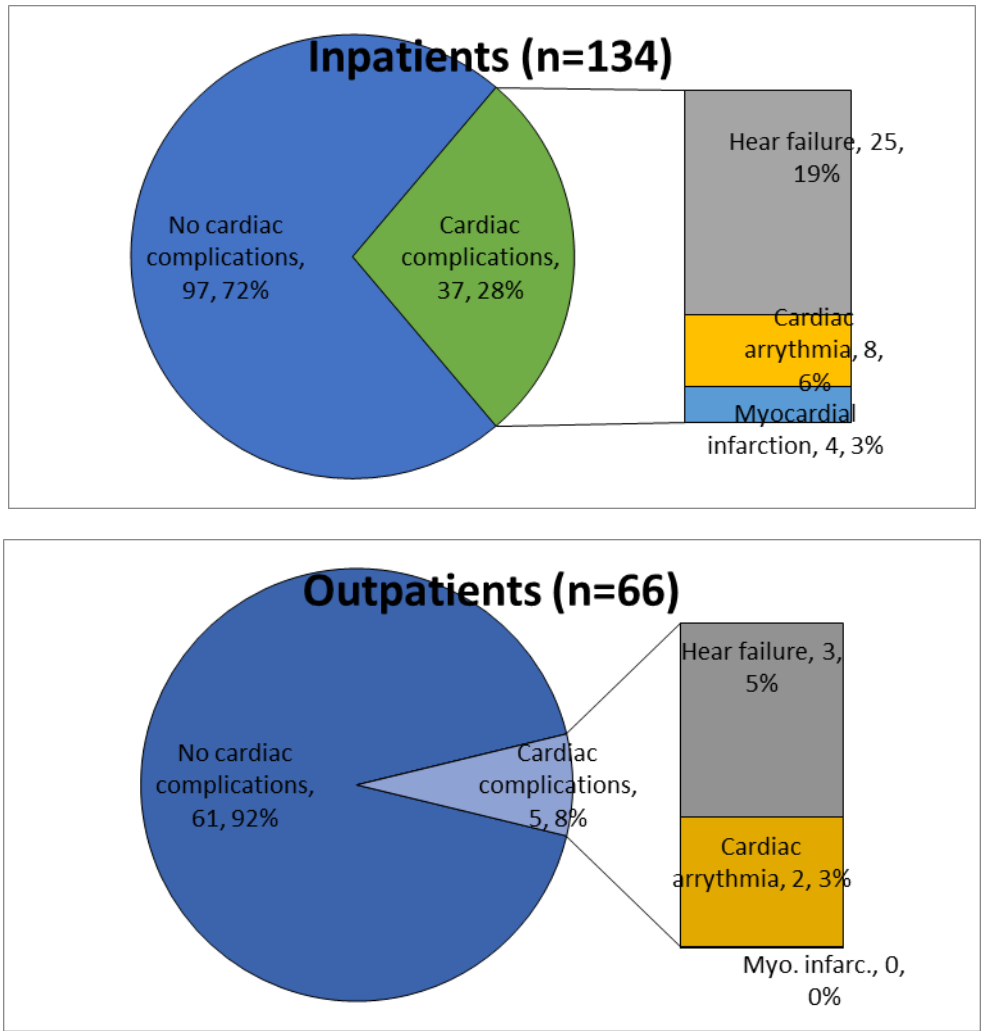
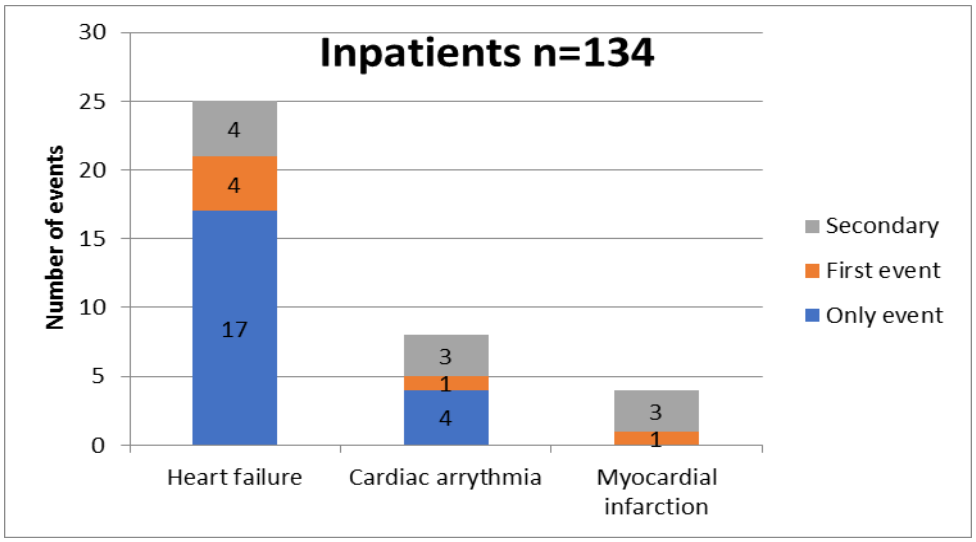


Figure 1: Incident cardiac complications in patients with community-acquired pneumonia.



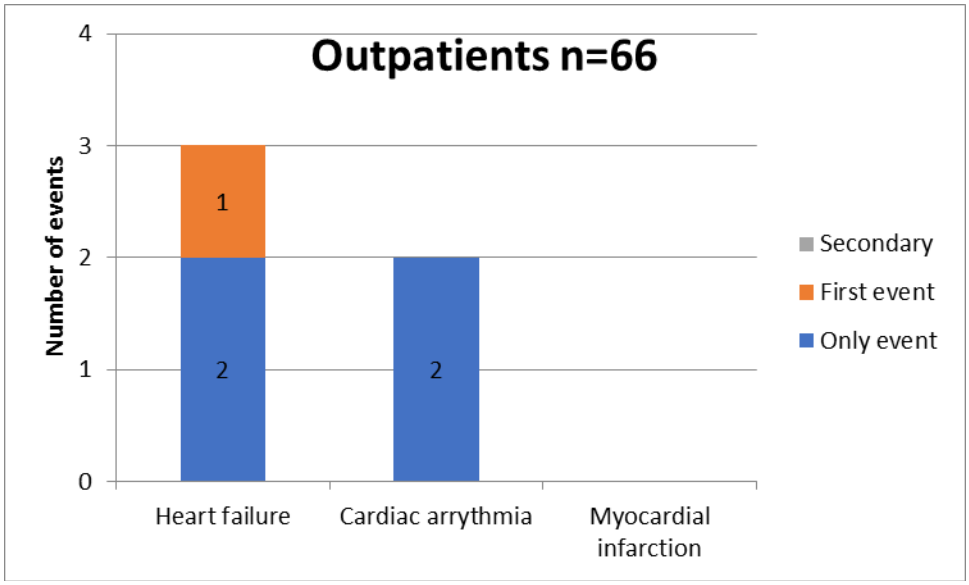


Figure 2: Incident cardiac events in patients with community-acquired pneumonia.

Among inpatients with incident cardiac complications, 19 (51.4%) had their primary cardiac event the same day of presentation, whereas 33 (89.2%) had this event within 1 week of enrollment. The corresponding numbers for outpatients with cardiac complications were 3 (60%) and 4 (80%) as illustrated in figure (3).

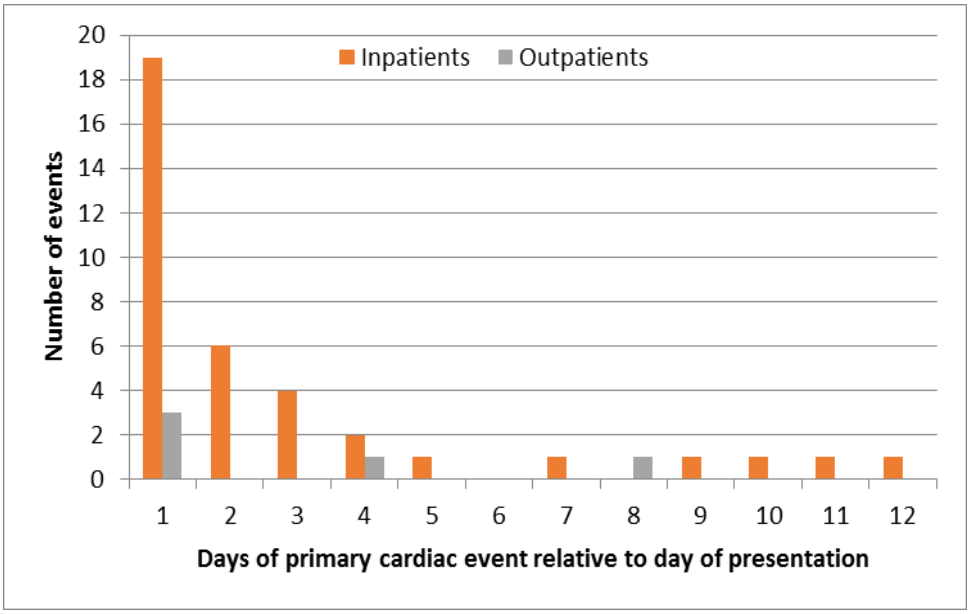


Figure 3: Timing of primary cardiac events in patients with community-acquired pneumonia who developed incident cardiac complications.

There were 13 patients (31.0%) in whom these cardiac complications were the first manifestation of clinical cardiac disease (ie, had no previous history of congestive heart failure, cardiac arrhythmias, coronary artery disease, or cardiac valvular disease).

Characteristics of patients who developed and did not develop incident cardiac complications are presented in Table 1. Sixteen of these factors had significant associations with incident cardiac complications. The baseline PSI score was significantly higher in patients who developed incident cardiac complications compared with those who did not (105±41 versus 51±36; $P<0.01$).

Table 1: Comparison of patients with community-acquired pneumonia with and without incident cardiac complications*.

Patient Characteristics	With Cardiac Complications n=42, (%)	Without Cardiac Complications n=158, (%)	*P*
Age, mean±SD	60±17	50±11	<0.01
male:female	1:1	1:1	0.52
Preexisting comorbid conditions			
Diabetes mellitus	8 (19.0)	10 (6.3)	<0.05
Cerebrovascular disease	9 (21.4)	12 (7.6)	<0.05
Chronic obstructive pulmonary disease	16 (38.1)	32 (20.3)	<0.05
Chronic renal insufficiency	7 (16.7)	9 (5.7)	<0.05
Smoking	8 (19.0)	60 (38.0)	<0.05
Physical examination findings			
Altered mental status	8 (19.0)	12 (7.6)	<0.05
Respiratory rate ≥30 breaths/min	15 (35.7)	16 (10.1)	<0.01
Pulse ≥125 bpm	6 (14.3)	14 (8.9)	0.46
Systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg	6 (14.3)	13 (8.2)	0.37
Temperature <35°C or ≥40°C	1 (2.4)	2 (1.3)	0.85
Laboratory and radiographic findings			
pH <7.35	5 (11.9)	4 (2.5)	<0.05
Blood urea nitrogen ≥30 mg/dL	15 (35.7)	15 (9.5)	<0.01
Sodium <130 mmol/L	3 (7.1)	5 (3.2)	0.48
Glucose ≥250 mg/dL (14 mmol/L)	8 (19.0)	5 (3.2)	<0.01
Hematocrit <30%	6 (14.3)	7 (4.4)	<0.05
Po_2 <60 mm Hg or O_2 sat <90 mm Hg	16 (38.1)	30 (19.0)	<0.01
Pleural effusion on chest x-ray	8 (19.0)	7 (4.4)	<0.01
Bacteremia	3 (7.1)	7 (4.4)	0.75
Site of care			
Inpatient Outpatient	37 (88.1) 5 (11.9)	97 (61.3) 61 (38.7)	<0.01
Pneumonia Severity Index score			
Total score, mean±SD	105±41	51±36	<0.01

Incident cardiac complications included any of the following cardiac events: new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction.

DISCUSSION

Using high-quality clinical outcomes data from the Pneumonia PORT cohort study, we demonstrate the following: (1) Incident cardiac complications occur in a substantial proportion of patients with CAP, affecting more than one quarter of those hospitalized for this infection; (2) the great majority of CAP patients who develop incident cardiac complications have their primary cardiac event within 7 days of presentation, with >50% occurring the same day of CAP diagnosis; (3) current tools for risk stratification of CAP patients underestimate the risk of incident cardiac complications in a large number of cases; and (4) the development of incident cardiac complications is independently associated with a 60% increase in the risk of short-term mortality in patients with CAP.

Given the burden of CAP in our population. Our findings have important implications. First, clinicians need to realize the importance of incident cardiac complications in patients with CAP and exercise appropriate clinical alertness for their timely recognition, mainly during the week after the diagnosis of CAP but especially in the first 24 hours of this period. Second, health officials need to increase efforts to optimize the rates of influenza and pneumococcal vaccination among the elderly and those with chronic cardiac conditions to reduce the incidence of pneumonia in these high-risk groups. Third, further research is required to test risk stratification, prevention, and treatment strategies for incident cardiac complications in patients with CAP. Finally, the prevention and optimal management of these events may significantly reduce the burden of death associated with this infection.

Several characteristics distinguish our analysis from previous studies dealing with cardiac complications in CAP.[9] As summarized in Table 2, these retrospective studies involved heterogeneous populations, used diverse methodologies for ascertaining the exposure (CAP) and outcomes (cardiac events) of interest, and defined different lengths for their observation periods. It is likely that most of the variability in their reported rates of cardiac events is explained by these factors. In contrast, our study represents the analysis of prospectively collected data on incident cardiac complications in

patients with CAP. It involved a large multicenter cohort of unselected individuals enrolled only after careful evaluation of clinical and radiological evidence of pneumonia. The ascertainment of incident cardiac complications was based on prespecified clinically relevant definitions and was systematically carried out for all patients; accordingly, the rate of missing data for these outcomes was extremely low (<2% for the entire cohort). Importantly, our study is also involving both inpatients and outpatients, capturing the burden of incident cardiac complications across the full spectrum of CAP severity, and the first in which a detailed account of the timing of these events is possible.

Several mechanisms, related largely to the systemic response to infection, can account for the development of incident cardiac complications in patients with CAP. Acute systemic inflammation can directly depress myocardial function and increase left ventricular afterload. Hypoxemia decreases myocardial oxygen delivery and raises pulmonary arterial pressure and right ventricular afterload.[10,11] Tachycardia increases myocardial oxygen needs and shortens diastole (when coronary perfusion occurs).[12,13] The net effect is a negative shift of the cardiac metabolic supply-to-demand ratio and further myocardial dysfunction. Myocardial inflammation (myocarditis) may also play a role.[14] Acute infections can promote inflammatory activity within coronary atherosclerotic plaques and induce prothrombotic changes in the blood and endothelium, resulting in plaque instability and facilitating coronary thrombosis.[6] Preexisting coronary artery disease that is insufficient to produce myocardial ischemia under baseline conditions can also result in significant ischemia in the face of increased myocardial oxygen demand. The ability of pneumonia to cause acute abnormalities in the cardiac conduction system has been recognized since the early 20th century and consistently confirmed thereafter.[15,16] In concordance with our findings, these effects would be more prominent when the influence of the pneumonia is stronger (ie, the first few days after CAP diagnosis).

Previous studies have treated the different types of cardiac events that occur in CAP largely as unrelated clinical outcomes.[9] However, given the likely mechanisms at play, it is expected that their development is interrelated. Our study identifies specific factors associated with the occurrence of incident cardiac complications in CAP patients. These factors are markers of higher baseline general risk like age, preexisting comorbid conditions, and more severe pneumonia at presentation (respiratory rate ≥30 breaths per minute, blood pH <7.35, blood urea nitrogen ≥30 mg/dL, sodium <130 mmol/L, hematocrit <30%, pleural effusion on chest x-ray, and need for inpatient care), which is concordant with previous reports. The PSI, the most widely validated tool for disease severity assessment in CAP patients[8], incorporates most of these factors.

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