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ORIGINAL ARTICLE

Clinical characteristics and prognosis of pneumonia and sepsis: multicenter study

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ABSTRACT

Background. Pneumonia is the primary source of sepsis and is significantly associated with mortality. However, only a few studies focus on its clinical characteristics and outcomes.

Methods. We evaluated 500 intensive care unit patients who met severe sepsis or septic shock criteria, dividing them into two distinct groups (43%, sepsis with pneumonia; 41%, sepsis with an infection other than pneumonia).

Results. Moderate differences between the groups were observed. The group of sepsis with pneumonia had a higher 28-day in-hospital mortality (41% vs. 30%; P=0.02). Multivariate analysis revealed that the presence of pneumonia associated significantly with mortality (OR 1.76, 95% CI 1.11-2.78) along with cardiopulmonary resuscitation (OR 4.20, 95% CI 1.50-11.74), serum lactate ≥3.5 mmol/L (OR 1.92, 95% CI 1.20-3.08), and SOFA score ≥12 (OR 2.41, 95% CI 1.52-3.82). Survival analysis revealed for both groups that the patients with PaO_2/FiO_2 (PF) ratio <170 and lactate ≥3.5 mmol/L had a worse prognosis than the patients with PF ratio ≥170 and lactate ≥3.5 mmol/L or PF ratio <170 and lactate <3.5 mmol/L.

Conclusion. In patients admitted with sepsis, the pneumonia infection independently predicts 28-day in-hospital mortality. Combining the levels of serum lactate and PF ratio could be a useful approach in predicting mortality of these patients. . *(Minerva Anestesiol 2013;79:1356-65)*

Key words: Sepsis - Pneumonia - Mortality - Prognosis.

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Severe sepsis and septic shock are major healthcare problems that affect millions of patients globally each year.[1-4] In the United States, severe sepsis hospitalizations have doubled over the last decade and now affect at least 750,000 patients annually.[1]

The compliances of hospitals in the United States, Europe, and South America with Surviving Sepsis Campaign bundles between January 2005 and March 2008 were determined by analyzing 15,022 subjects at 165 sites.[5] About 44% of these patients had pneumonia as a primary sepsis source. Notably, a multivariate mortality prediction model revealed that the pneumonia was associated with higher mortality than the other infections.[5] Similarly, several clinical studies found that the pneumonia was a leading source of infection with high mortality,[6-8] but few detailed information exists on sepsis associated with pneumonia infection compared to non-pneumonia infection.

Recently, several studies suggested various sepsis biomarkers as means of aiding early diagnosis, initiating early antibiotics, and predicting mortality,[9-12] although none of them were definitely recommended due to lack of sensitivity and specificity and limited availability. Serum lactate, which is increased via the anaerobic pathway caused by tissue hypoxia, was shown recently to be a strong mortality predictor in patients with infection.[13] In addition, the PaO_2/FiO_2 (PF) ratio could be an important factor for explaining the mortality in sepsis when associated with acute respiratory failure such as acute lung injury or acute respiratory distress syndrome (ARDS). However, clinical studies evaluating the ability of the PF ratio to predict mortality in sepsis have not been performed.

We hypothesized that sepsis with pneumonia as a primary infection source would differ from one without. Accordingly, the aim of this study was to compare the baseline characteristics and clinical outcomes of patients presenting sepsis with pneumonia versus other infections. We also evaluated the mortality-related significance of serum lactate and PF ratio in the two groups.

Materials and methods

Study design

This was a retrospective analysis of a prospective multicenter cohort. According to the etiology of infection, patients who met criteria for severe sepsis or septic shock were divided into pneumonia (PN) and non-pneumonia (NPN) groups. The primary outcome was 28-day in-hospital mortality. The baseline characteristics, clinical outcomes, and prognostic factors related to mortality were assessed. This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review board (IRB) or independent ethics committee of each hospital approved the protocol (IRB of Asan Medical Center, Protocol No. 2012-0131). The written informed consent was waived due to the observational nature of the study.

Subjects

The subject of analysis was the Validation of SAPS 3 in Korean Intensive care unit (VSKI) cohort, which originally evaluated 5063 subjects who were admitted to one of the 22 tertiary or referral hospital's intensive care units (ICUs) (14 medical, 6 surgical, 2 multidisciplinary) in Korea between July 2010 and January 2011. Our exclusion criteria were patients under 17 years of age, incomplete data for analysis, and lack of clarity regarding the treatment outcome, which was ICU or in-hospital mortality. Patients who met criteria for severe sepsis or septic shock [14] were included in the final analysis. Patients with infection of unknown origin or mixed infection (infection with more than one known source) were excluded.

Data collection and definition

The demographic characteristics of each patient including comorbidities were reviewed thoroughly, and the initial vital signs at ICU admission were recorded by attending physicians or trained clinical research nurses. Performance status was evaluated according to the Eastern Cooperative Oncology Group

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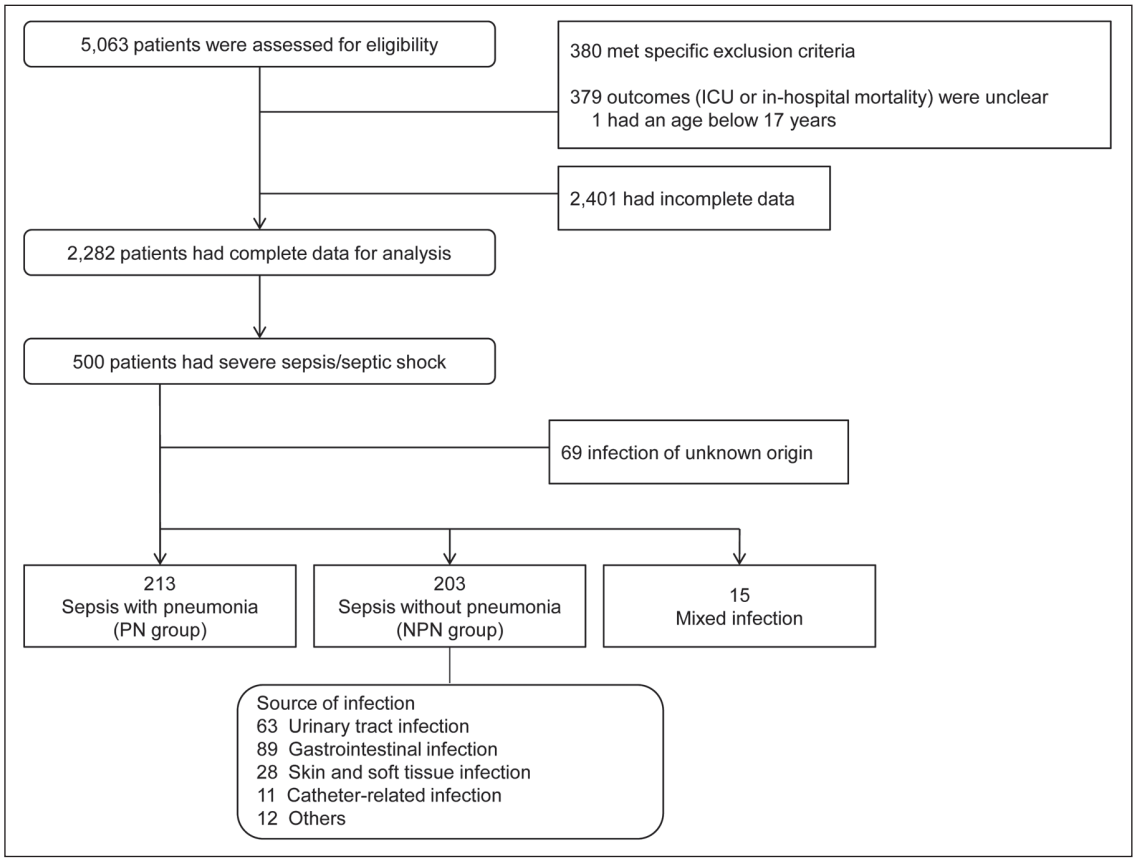

Figure 1.—Study flow diagram indicating patient enrollment. Mixed infection is defined as an infection with more than one source.

performance scale.[15] Patients' status within 24 hours of ICU admission (cardiopulmonary resuscitation, total volume administered, mechanical ventilation, renal replacement therapy, vasopressor use) were assessed. Laboratory data such as complete blood cell count, chemistry, and arterial blood gas analysis were also collected within 24 hours of ICU admission. Illness severity was assessed by using the Sequential Organ Failure Assessment (SOFA) score [16] and Simplified Acute Physiology Score (SAPS II).[17]

Statistical analysis

The Kruskall-Wallis test served to compare continuous data and the chi-square or Fisher's exact test served to compare categorical data. Multiple logistic regression was used to assess the factors associated with the 28-day in-hospital mortality. When necessary, the cutoff value of each variable was selected on the median value or using a receiver operating characteristics (ROC) analysis as appropriate. First, the univariate analyses were performed on all possible confounders and variables with P values of <0.20 were selected for further analysis. To prevent multicollinearity, variables with high correlation between each other were controlled. As a result, total of eight variables was selected for an adjusted model. Then, the multivariate regression analysis by using stepwise backward selection procedures was performed. The area under the ROC curve (AUC) was reported to assess overall model discrimination. Model calibration was assessed by using the Hosmer-Lemeshow test. Kaplan-Meier survival estimates were built stratified by initial serum lactate and PF ratio to analyze their discriminating power in terms of predicting mortality. All significance tests were two-tailed and

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TABLE I.—*Baseline characteristics and clinical outcomes of the sepsis with pneumonia (PN group) and the sepsis without pneumonia (NPN group).*

	All patients (N.=416)	PN group (N.=213)	NPN group (N.=203)	P
Age (years)	66 (57-73)	67 (58-74)	65 (54-73)	0.11
Gender (N., % male)	264 (64%)	143 (68%)	121 (60%)	0.10
Body mass index (kg/m^2)	22 (20-25)	22 (19-25)	23 (20-25)	0.02
Hospital stay before ICU admission (days)	0 (0-7)	0 (0-9)	0 (0-6)	0.25
Premorbid performance status (PS)				0.70
— PS 0	120 (29%)	54 (26%)	66 (33%)	
— PS 1	83 (20%)	43 (20%)	40 (20%)	
— PS 2	102 (25%)	60 (28%)	42 (21%)	
— PS 3	78 (19%)	39 (19%)	39 (19%)	
— PS 4	30 (7%)	15 (7%)	15 (7%)	
Comorbidities (N.)				
— Liver cirrhosis	36 (9%)	11 (5%)	25 (12%)	0.01
— Hypertension	153 (37%)	79 (37%)	74 (37%)	0.92
— Chronic heart failure	28 (7%)	12 (6%)	16 (8%)	0.44
— Stroke	34 (8%)	12 (6%)	22 (11%)	0.07
— Chronic pulmonary failure	10 (2%)	10 (5%)	0	0.002
— Diabetes	127 (31%)	61 (29%)	66 (33%)	0.40
— Chronic renal failure	42 (10%)	20 (9%)	22 (11%)	0.63
— Immunosuppression	167 (40%)	99 (47%)	68 (34%)	0.01
Within 24h of ICU admission (N.)				
— CPR	22 (5%)	12 (6%)	10 (5%)	0.83
— Mechanical ventilation	240 (58%)	167 (78%)	73 (36%)	<0.001
— Total volume administered (L)	4.0 (2.8-5.4)	4.0 (2.9-5.2)	4.1 (2.8-5.7)	0.95
— Vasopressor use	314 (76%)	161 (76%)	153 (75%)	>0.99
— Renal replacement therapy	93 (23%)	48 (23%)	45 (22%)	0.82
Vital signs and Laboratory data				
— Systolic blood pressure (mmHg)	85 (74-96)	85 (73-97)	83 (75-95)	0.56
— Glasgow Coma Scale (3-15)	11 (8-14)	10 (7-13)	14 (9-15)	<0.001
— Platelet count (1000 cells/mm^3)	93 (43-178)	114 (45-196)	77 (41-160)	0.02
— Total bilirubin (mg/dL)	1.3 (0.8-2.9)	1.1 (0.7-1.8)	1.8 (0.9-3.6)	<0.001
— Creatinine (mg/dL)	1.4 (0.9-2.2)	1.3 (0.8-2.1)	1.4 (1.0-2.4)	0.01
— PaO_2/FiO_2 ratio	169 (110-268)	129 (90-183)	240 (148-313)	<0.001
— Lactate (mmol/L)	3.1 (1.9-5.8)	2.7 (1.7-4.9)	3.6 (2.1-6.7)	0.003
SOFA score	11 (8-14)	11 (9-14)	11 (8-14)	0.24
SAPS II	52 (40-66)	57 (45-68)	46 (37-60)	<0.001
Length of stay (days)				
— ICU	4 (2-11)	7 (3-19)	3 (2-6)	<0.001
— Hospital	16 (8-34)	18 (8-42)	15 (8-28)	0.21
28-day in-hospital mortality (N.)	148 (36%)	87 (41%)	61 (30%)	0.02

The data are presented as medians (interquartile ranges) or (%) of patients unless indicated otherwise. ICU: intensive care unit; CPR: cardiopulmonary resuscitation; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score.

P value <0.05 were considered to be significant. All analyses were performed with SPSS version 18.0K for Windows (SPSS Inc, Chicago, IL, USA).

Results

Figure 1 is the study flow diagram. Of the 5,063 patients in the initial cohort, 2,282

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Table II.—*Univariate and multivariate analysis of 28-day in-hospital mortality.*

Variable	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Body mass index <22 kg/m^2	1.40 (0.93-2.10)	0.10		
Performance status ≥2	1.58 (1.05-2.38)	0.03	1.50 (0.95-2.35)	0.08
Immunosuppression	1.58 (1.05-2.38)	0.03		
CPR	5.29 (2.02-13.84)	0.001	4.20 (1.50-11.74)	0.01
Pneumonia as source of infection	1.61 (1.07-2.41)	0.02	1.76 (1.11-2.78)	0.02
Tachycardia (heart rate ≥125/min)	2.23 (1.45-3.41)	<0.001	1.50 (0.94-2.41)	0.09
Lactate ≥3.5 mmol/L	2.46 (1.63-3.70)	<0.001	1.92 (1.20-3.08)	0.01
SOFA score ≥12	3.10 (2.03-4.73)	<0.001	2.41 (1.52-3.82)	<0.001
Area under the ROC curve	0.75			
Hosmer and Lemeshow χ^2	5.90	(P=0.66)		

OR: odds ratio; ROC: receiver operating characteristics.

fulfilled the inclusion criteria and had complete data for analysis. Of these, 500 met the criteria for severe sepsis or septic shock. Excluding 69 patients with unknown origin of infection, there were 213 patients (43%) in the PN group and 203 (41%) in the NPN group. Fifteen patients had more than one infection source and were excluded from the final analysis.

Table I shows the baseline characteristics and clinical outcomes of the study groups. The PN group had a significantly lower body mass index. The groups did not differ in terms of age, gender, and premorbid performance status. Regarding comorbidities, patients in the NPN group were more likely to have liver cirrhosis, while patients in the PN group were more likely to have chronic pulmonary failure and immunosuppression. As expected, the PN group needed more mechanical ventilation within 24 hours of ICU admission and had significantly lower PF ratios (median, 129 *vs*. 240; P<0.001). However, the groups were similar in terms of the fluid therapy and the need for renal replacement therapy or vasopressors. The median (interquartile range) systolic blood pressure (SBP) was 85 (73-97) mmHg for the PN group and 83 (75-95) mmHg for the NPN group, and the difference was not statistically significant (P=0.56). Initial serum lactates were higher than normal (<2 mmol/L) in both groups, but the NPN group had a much higher median lactate level (2.7 mmol/L *vs*. 3.6 mmol/L; P=0.003). Among other vital signs and laboratory data, the PN group had lower Glasgow Coma Scale, serum creatinine, and total bilirubin, while the NPN group had lower platelet count. The groups did not differ with regard to SOFA score but the PN group had significantly higher SAPS II.

The primary outcome, 28-day in-hospital mortality, was observed in 87/213 (41%) of the patients in the PN group and 61/203 (30%) of the patients in the NPN group (P=0.02) (Table I). The PN group had a significantly longer ICU stay, but the groups did not differ in terms of total hospital stay.

Table II shows the univariate and multivariate analyses of 28-day in-hospital mortality. Multivariate analysis adjusted for variables associated with 28-day in-hospital mortality indicated that cardiopulmonary resuscitation, pneumonia infection, serum lactate ≥3.5 mmol/L, and SOFA score ≥12 associated significantly with mortality. Poor performance status and tachycardia were associated with mortality only in univariate analysis. This model had acceptable discrimination and calibration.

Figure 2 shows the Kaplan-Meier survival curves of patients that were stratified by serum lactate and PF ratio. In both groups, the curves diverged the most when the patients were stratified by using a lactate cutoff at 3.5 mmol/L or higher and a PF ratio cutoff lower than 170. When stratified only by PF ratio (cutoff at 170), the curves diverged significantly in the PN group but not in the NPN group (Figure 3).

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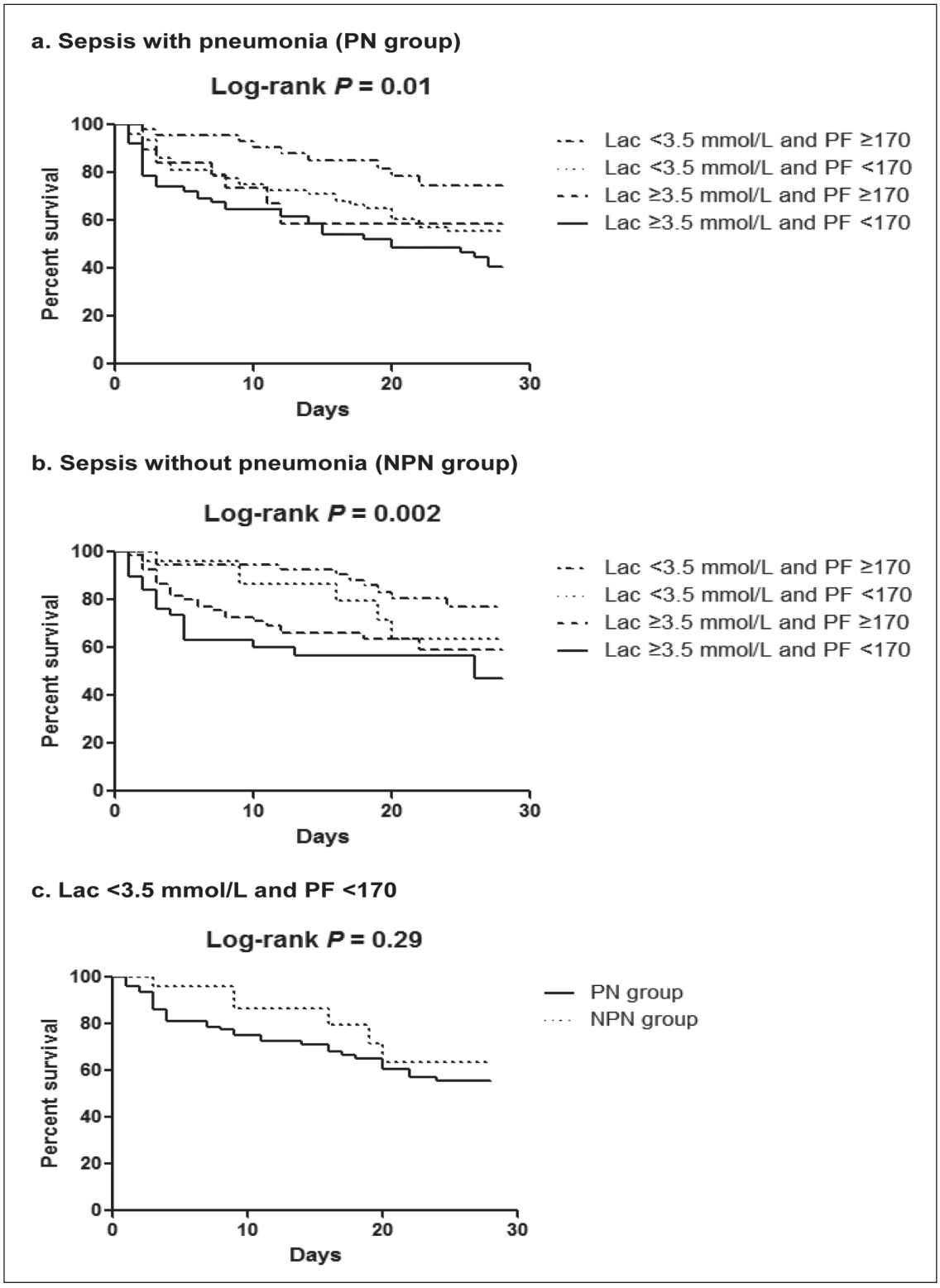

Figure 2.—Kaplan-Meier survival curves of patients stratified by serum lactate (Lac) and PaO_2/FiO_2 (PF) ratio.

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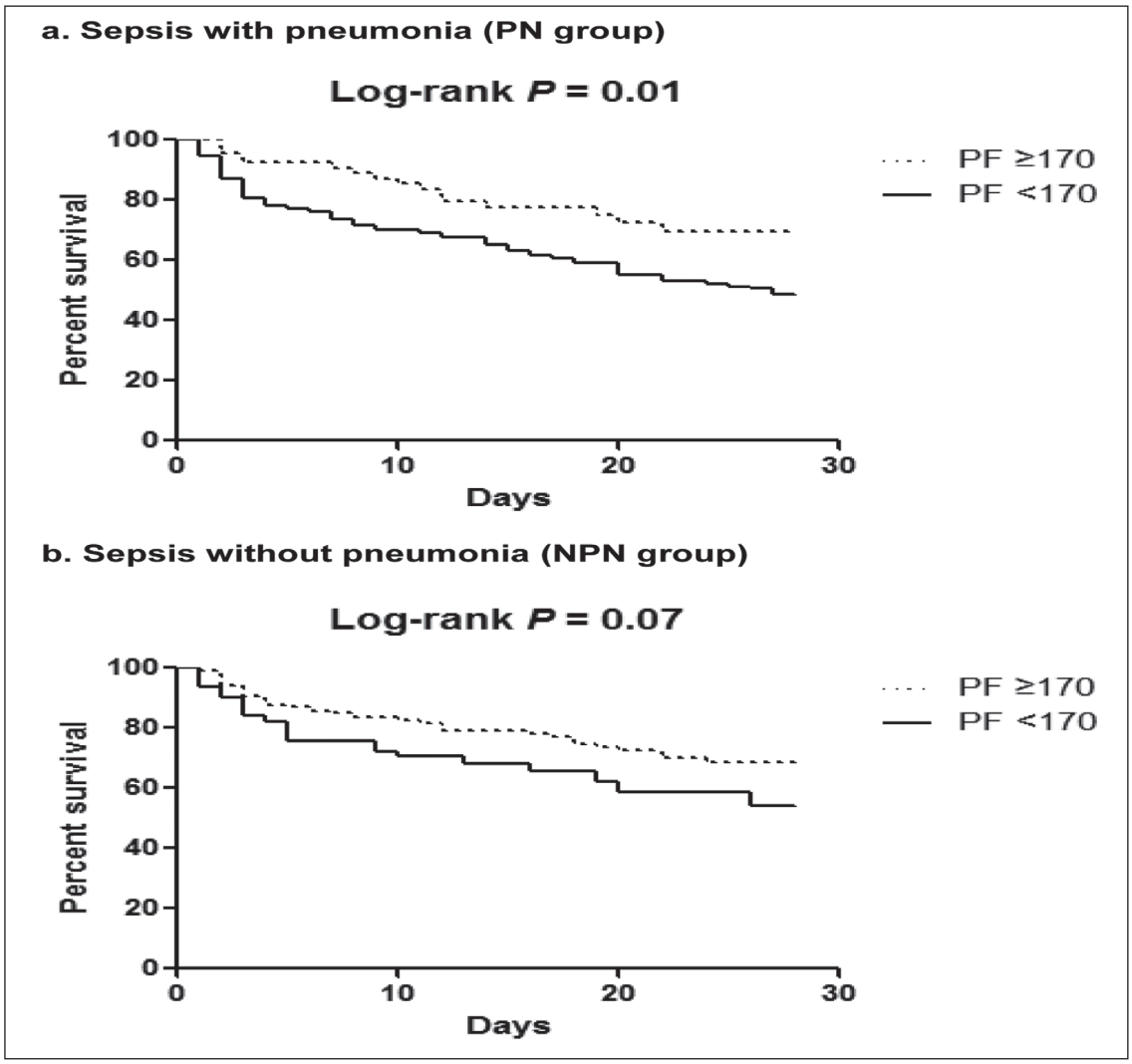

Figure 3.—Kaplan-Meier survival curves of patients stratified by PaO_2/FiO_2 (PF) ratio of 170.

Discussion

The present study indicates that the clinical characteristics and outcomes of sepsis with pneumonia differed moderately from those of sepsis with other infections. Pneumonia as etiology of sepsis had strong association with mortality. Combining the levels of serum lactate and PF ratio had a high discriminating power in predicting early mortality regardless of etiology of sepsis. To our knowledge, this is one of few studies that evaluated patients with pneumonia and sepsis as a specific subgroup.

Critical illness, such as severe sepsis or septic shock, is characterized by disruptions in homeostasis that result in multiple organ injury and irreversible organ dysfunction.[18] It is highly important that organ dysfunction in patients with sepsis is recognized as early as possible, so that early interventions could be applied to improve their outcomes.

Serum lactate is an accepted tool of assessing for tissue hypoxia and is of prognostic value in various critical care populations including sepsis.[13, 19] Two retrospective studies,[20, 21] a prospective study,[6] and *post-hoc* analysis of a randomized controlled trial [7] suggested that serum lactate elevation concomitant with normal blood pres-

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sure (so-called cryptic shock) carries a worse prognosis than when normal serum lactate is observed. Our study was comparable to the results of previous studies in that serum lactate was an independent prognostic factor of mortality. Serum lactate reflects the balance between the net production and net consumption or clearance of lactate. This may involve various organs such as skeletal muscle, liver, kidney, heart, and brain.[22] In critically ill patients, these usual lactate producers and metabolizers can be altered by hypoxia, infection, and organ failure.[23-25] Interestingly and also unexpectedly, the PN group was associated with relatively lower serum lactate than the NPN group in our study. In critical illness, there may be increased production of lactate by unusual lactate-producing organs such as the lungs. Supporting this is the study by Weil *et al*. that found that the serum lactate concentrations in venous blood samples from pulmonary artery catheters were equivalent to those in arterial blood from critically ill patients.[26] In our study, it is possible that respiratory dysfunction, which is likely to be more common in sepsis with pneumonia, may have impaired the lactate production by the lungs. However, about half of the patients in the initial cohort (2781/5063) were not included in this analysis, and the other organ dysfunctions were not considered. Therefore they may be biased data; however, the result is still interesting and should be confirmed in future studies.

The PF ratio is an important mortality factor in patients with ARDS together with severity of chest radiograph findings and ventilator settings.[27, 28] Since the relationship between the sepsis and the development of ARDS is well established,[29, 30] PF ratio may act as a supplementary factor to other biomarkers for explaining the prognosis in sepsis. In our study, survival analysis showed that combining the levels of serum lactate ≥3.5 mmol/L and PF ratio <170 had a high discriminating power in terms of predicting mortality in both groups. This finding suggests that acute respiratory failure associated with sepsis may be as important for patient survival as hypoperfusion itself. Another important finding was that the survival curve of PF ratio <170 in the PN group tended to diverge early during the course of sepsis, even when serum lactate level was not high (Figure 2C). Moreover, the survival difference was significant only in the PN group when stratified by PF ratio of 170 (Figure 3). The phenomenon may be explained due to the fact that the patients who had low baseline PF ratio or required mechanical ventilation were more prevalent in sepsis presented with pneumonia. Aggressive volume resuscitation in this group may result in devastating conditions such as pulmonary edema or subsequent lung injury, thereby hampering treatment. Therefore, together with vital signs and other biomarkers, PF ratio facilitates the selection of critically ill sepsis patients who would benefit from early resuscitation while minimizing exposure to isotonic fluids.

The present study has several limitations. First, a substantial proportion of patients were excluded because of lack of clarity about mortality or incomplete data. There is a possibility that inclusion of these patients might have influenced the study outcomes. Moderate differences were observed of the baseline characteristics between the study group and the excluded group. When we combined the two groups and divided them into pneumonia and non-pneumonia groups, the baseline characteristics were not so different compared to previous ones (see supplementary materials for details). Therefore, this limitation does not undermine the original conclusion. Second, there is a lack of data on some of the treatment modalities (resuscitation goals, timing and appropriateness of antibiotics, time to shock reversal, duration of mechanical ventilation or renal replacement therapy) because these data were not collected due to the purposes of the initial cohort study. It remains possible that the two exposure groups were not similarly treated, and this may have affected the treatment outcome. Third, the significance of serial lactate or PF ratio values could not be assessed in the present study. This analysis would be interesting because previous registry data and randomized controlled trials [31-33] have shown that early lactate clearance associates with decreased mortality. Thus, to further evaluate our observations in the study patients, it will be necessary to analyze lactate clearance measurements and changes in PF ratio.

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Conclusions

The present analysis showed that the clinical findings of sepsis with pneumonia differed from those of sepsis without pneumonia. The presence of pneumonia was an independent predictor of mortality. A combination of the levels of serum lactate and PF ratio was a reliable factor in terms of indicating mortality risk in sepsis regardless of etiology, especially in the early course of the disease.

Key messages

— Baseline characteristics of sepsis with pneumonia differed moderately from those of sepsis with other infections.

— A significant mortality difference was observed between the pneumonia and the non-pneumonia groups. Pneumonia infection was an independent predictor of mortality.

— Initial PaO_2/FiO_2 ratio, when combined with serum lactate, was useful in terms of predicting mortality in the patients with sepsis.

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ONLINE SUPPLEMENT

Supplementary Table I.—*Baseline characteristics of the patients that were excluded in the study, compared with the patients included in the study.*

	Excluded group (All patients) (N.=2781)	Excluded group (Sepsis patients)[a] (N.=169)	Study group (N.=416)
Age (years)	63 (49-73)**	69 (54-76)	66 (57-73)
Gender (N., % male)	1,684 (64%)	109 (57%)	264 (64%)
Body mass index (kg/m^2)	23 (20-25)*	22 (20-25)	22 (20-25)
Hospital stay before ICU admission (days)	1 (0-3)	0 (0-2)	0 (0-7)
Premorbid performance status (PS)			
— PS 0	1,069 (47%)**	30 (17%)*	120 (29%)
— PS 1	516 (23%)**	49 (28%)*	83 (20%)
— PS 2	422 (19%)**	57 (32%)*	102 (25%)
— PS 3	175 (8%)**	23 (13%)*	78 (19%)
— PS 4	98 (4%)**	17 (10%)*	30 (7%)
Comorbidities (N.)			
— Liver cirrhosis	166 (6%)*	10 (5%)	36 (9%)
— Hypertension	924 (33%)	75 (38%)	153 (37%)
— Chronic heart failure	90 (3%)**	2 (1%)*	28 (7%)
— Stroke	169 (6%)	20 (10%)	34 (8%)
— Chronic pulmonary failure	50 (2%)	5 (3%)	10 (2%)
— Diabetes	547 (20%)**	51 (26%)	127 (31%)
— Chronic renal failure	192 (7%)*	17 (9%)	42 (10%)
— Immunosuppression	203 (7%)**	30 (15%)**	167 (40%)
Within 24h of ICU admission (N.)			
— CPR	70 (3%)*	13 (7%)	22 (5%)
— Mechanical ventilation	789 (29%)**	101 (52%)	240 (58%)
— Total volume administered (L)	2.9 (2.1-3.9)**	4.0 (2.6-5.3)	4.0 (2.8-5.4)
— Vasopressor use	544 (20%)**	141 (72%)	314 (76%)
— Renal replacement therapy	102 (4%)**	23 (13%)*	93 (23%)
Vital signs and Laboratory data			
— Systolic blood pressure (mmHg)	100 (90-114)**	80 (70-93)	85 (74-96)
— Glasgow Coma Scale (3-15)	15 (11-15)**	11 (4-15)	11 (8-14)
— Platelet count (1000 cells/mm^3)	166 (108-223)**	115 (55-173)	93 (43-178)
— Total bilirubin (mg/dL)	0.9 (0.6-1.5)**	1.0 (0.6-1.8)**	1.3 (0.8-2.9)
— Creatinine (mg/dL)	0.9 (0.7-1.4)**	1.5 (1.0-2.2)	1.4 (0.9-2.2)
— PaO_2/FiO_2 ratio	309 (192-429)**	184 (100-312)	169 (110-268)
— Lactate (mmol/L)	2.2 (1.5-3.8)**	3.2 (1.6-5.6)	3.1 (1.9-5.8)
SOFA score	4 (2-8)**	10 (7-13)*	11 (8-14)
SAPS II	28 (18-43)**	51 (32-75)	52 (40-66)

The data are presented as medians (interquartile ranges) or (%) of patients unless indicated otherwise. ICU: intensive care unit; CPR: cardiopulmonary resuscitation; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score. [a] Patients who were excluded in the main analysis, but met severe sepsis or septic shock criteria and had neither unknown infection nor mixed infection. * P<0.05 (when compared with the study group); **P<0.001 (when compared with the study group).

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Supplementary Table II.—*Baseline characteristics of the sepsis with pneumonia (PN group) and the sepsis without pneumonia (NPN group).*[a]

	All patients (N.=612)	PN group (N.=313)	NPN group (N.=299)	p
Age (years)	67 (56-74)	68 (57-76)	66 (54-73)	0.07
Gender (N., % male)	373 (62%)	209 (67%)	164 (56%)	0.01
Body mass index (kg/m^2)	22 (20-25)	22 (19-24)	23 (20-25)	0.002
Hospital stay before ICU admission (days)	0 (0-5)	0 (0-6)	0 (0-4)	0.18
Premorbid performance status (PS)				0.14
— PS 0	150 (26%)	68 (23%)	82 (29%)	
— PS 1	132 (22%)	65 (22%)	67 (23%)	
— PS 2	159 (27%)	91 (30%)	68 (24%)	
— PS 3	101 (17%)	49 (16%)	52 (18%)	
— PS 4	47 (8%)	29 (10%)	18 (6%)	
Comorbidities (N.)				
— Liver cirrhosis	46 (8%)	15 (5%)	31 (10%)	0.01
— Hypertension	228 (37%)	114 (36%)	114 (38%)	0.66
— Chronic heart failure	30 (5%)	12 (4%)	18 (6%)	0.21
— Stroke	54 (9%)	25 (8%)	29 (10%)	0.46
— Chronic pulmonary failure	15 (3%)	15 (5%)	0	<0.001
— Diabetes	178 (29%)	85 (27%)	93 (31%)	0.28
— Chronic renal failure	59 (10%)	27 (9%)	32 (11%)	0.38
— Immunosuppression	197 (32%)	118 (38%)	79 (26%)	0.003
Within 24h of ICU admission (N.)				
— CPR	35 (6%)	22 (7%)	13 (5%)	0.17
— Mechanical ventilation	341 (56%)	241 (77%)	100 (33%)	<0.001
— Total volume administered (L)	4.0 (2.8-5.4)	4.0 (2.8-5.3)	4.1 (2.8-5.5)	0.99
— Vasopressor use	455 (75%)	238 (76%)	217 (73%)	0.29
— Renal replacement therapy	116 (20%)	60 (20%)	56 (19%)	0.87
Vital signs and Laboratory data				
— Systolic blood pressure (mmHg)	84 (72-95)	84 (71-94)	83 (74-97)	0.22
— Glasgow Coma Scale (3-15)	11 (7-14)	10 (4-13)	14 (10-15)	<0.001
— Platelet count (1000 cells/mm^3)	102 (45-176)	118 (48-189)	85 (42-164)	0.003
— Total bilirubin (mg/dL)	1.2 (0.7-2.5)	1.0 (0.7-1.7)	1.6 (0.8-3.4)	<0.001
— Creatinine (mg/dL)	1.4 (0.9-2.2)	1.3 (0.8-2.1)	1.5 (1.0-2.4)	0.002
— PaO_2/FiO_2 ratio	173 (108-282)	127 (87-188)	249 (152-334)	<0.001
— Lactate (mmol/L)	3.1 (1.9-5.7)	2.8 (1.7-4.9)	3.6 (2.1-6.8)	0.002
SOFA score	11 (8-14)	11 (9-14)	10 (7-13)	0.002
SAPS II	52 (39-67)	58 (45-72)	46 (34-58)	<0.001

The data are presented as medians (interquartile ranges) or (%) of patients unless indicated otherwise. ICU: intensive care unit; CPR: cardiopulmonary resuscitation; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score. [a] 196 previously excluded sepsis patients who had neither unknown infection nor mixed infection were included in the analysis.

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