SRYAHWA PUBLICATIONS

Archives of Emergency Medicine and Intensive Care
ISSN: 2638-5007 | Volume 5, Issue 1, 2024
https://doi.org/10.22259/2638-5007.0501001

RESEARCH ARTICLE

Positive Fluid Balance Worsens Clinical Outcomes in Hospitalized Pneumonia Patients

ChingFang Tiffany Tzeng[1], Sen-Kuang Hou[2,3], Chuan-Chin Huang[4,8], Gyorgy Frendl[5,6,8], Peter C Hou[7,8]

[1]Department of Emergency Medicine, Baylor Scott & White All Saints Medical Center, Fort Worth, TX, USA.

[2]Department of Emergency Medicine, Taipei Medical University Hospital, Taipei, Taiwan.

[3]Department of Emergency Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

[4]Department of Medicine, Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA.

[5]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA, USA.
[6]Surgical Intensive Care Unit Translational Research (STAR) Center, Brigham and Women's Hospital, Boston, MA, USA.

[7]Division of Emergency Critical Care Medicine, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA.

[8]Harvard Medical School,Boston, MA, USA.

Received: 30 January 2024 Accepted: 14 February 2024 Published: 23 February 2024
Corresponding Author: Peter C Hou, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, Massachusetts75 Francis St, Boston, MA 02115, USA.

Abstract

Objective: To evaluate the impact of fluid balance on the outcomes of patients admitted for pneumonia and to describe the clinical risk factors associated with these outcomes in hospitalized pneumonia patients.

Methods: This is a subgroup analysis using data from a multicenter, observational cohort (LIPS1 study). Adult ED patients presenting with pneumonia were enrolled from March through August in 2009. Fluid balance was categorized as ≤1, 1-2, 2-3, and >3 liters within the first 6 hours of care. Outcomes were defined as a composite of acute respiratory failure (ARF) requiring invasive or non-invasive mechanical ventilation (MV) or in-hospital mortality. Multivariate logistic regression analysis incorporating covariates with biological effect and significant differences in univariate analysis was performed to determine the adjusted odds ratios for the fluid balance categories and composite outcome.

Results: Univariate analysis of 896 ED patients showed an increasing rate of combined ARF requiring MV and hospital mortality with incremental positive fluid balance ($p < 0.001$). The covariates of shock index, admission source, and aspiration had a significant effect in univariate analysis. Multivariate regression modeling continued to show a statistically significant difference between categories of fluid balance ≤1 liter vs. >3 liters with respect to our composite outcome (odds ratio 2.14; 95% confidence interval, 1.12 to 4.08).

Conclusion: For pneumonia patients, we found a significant association between positive fluid balance within the first six hours and the composite outcomes of ARF requiring MV and hospital mortality. This finding is consistent with similar observations for other critically ill patients.

Keywords: Pneumonia, Fluid Balance, Respiratory Failure.

Citation: ChingFang Tiffany Tzeng, Sen-Kuang Hou, Chuan-Chin Huang, *et al*. Positive Fluid Balance Worsens Clinical Outcomes in Hospitalized Pneumonia Patients. Archives of Emergency Medicine and Intensive Care. 2024;5(1):1-7

1. Introduction

Pneumonia is the most common cause of sepsis and is also the leading etiology of infection-related mortality in Unites States, resulting in about 4.2 million hospitalizations[1]. Despite advances in antimicrobial therapies and critical care, approximately 10 - 26% of adult hospitalized pneumonia patients required admission to intensive care unit (ICU) with septic shock or acute respiratory failure with or without ARDS[2]. Predictive rules[3], such as Pneumonia Severity Index (PSI) and CURB-65, were developed to predict the severity and outcomes in community-acquired pneumonia patients. However, little is known in hospitalized pneumonia patient regarding the relationship between fluid administration and outcomes.

There has been consensus that aggressive fluid resuscitation in critically ill septic patients should be initiated early and targeted to physiologic endpoints to improve intravascular volume deficits and maintain adequate organ perfusion. Although fluid therapy has been shown to be important, recent studies have demonstrated that positive fluid balance may contribute to worse clinical outcomes, such as acute kidney injury, severe sepsis, and septic shock[4]. Furthermore, conservative fluid strategy after shock resolution was suggested in patients with ARDS to improve outcomes including lung function, duration of ventilator dependence, and ICU length of stay[5].

The Surviving Sepsis Campaign 2016[6] provided goals of fluid resuscitation in patients with severe sepsis and septic shock and a conservative fluid strategy for patients with establish ARDS and after shock resolution. However, the association between fluid administration strategies in patients with pneumonia and acute respiratory failure (ARF) requiring mechanical ventilation (MV) has not been elucidated. The goal of this study was to evaluate the impact of fluid balance on the outcomes of patients admitted for pneumonia and to describe the clinical risk factors associated with these outcomes in hospitalized pneumonia patients.

2. Materials and Methods

2.1 Study Design and Setting

This is a subgroup analysis using a database from a multicenter, observational cohort study, the United States Critical Injury and Illness trial Group – Lung Injury Prevention Study 1 (USCIITG-LIPS 1, NCT00889772)[7]. A total of 22 hospitals participated in this study, and the institutional review board of each hospital approved the study. Patients admitted from the ED presenting with at least one of ARDS predisposing conditions were enrolled from March through August in 2009. This study followed STROBE guidelines.

2.2 Selection of Participants

Adult patients (aged 18 years and older) admitted to acute care hospitals with the presentation of pneumonia were enrolled in this study. The definition of pneumonia was defined according to the 2005 International Sepsis Forum Consensus on definitions of infection in the intensive care unit[8]. Pneumonia patients with less than two systemic inflammatory response syndrome (SIRS) criteria or already in shock status were excluded. We also excluded patients for whom complete fluid data information was not available, were admitted for elective surgery, or who already had ARDS diagnosed during their initial ED assessment, were currently on comfort or hospice care, were not committed for full support, or who were re-admitted during the study period.

2.3 Data Collection

Baseline characteristics including demographic characteristics, physiologic data, admission sources, and comorbidities were obtained from the medical chart and/or electronic records by trained investigators. Cumulative fluid balance was defined as the sum of crystalloids (saline, ringer's lactate), colloid (albumin), blood products (pack red blood cells, fresh frozen plasma platelets), and other inputs minus urine and other outputs recorded. These continuous fluid data during the first 6 hours of care were then categorized as: $\leq$ 1 liter, 1-2 liters, 2-3 liters, and $\geq$ 3 liters. Fluid balance was calculated to evaluate the impact of initial fluid management on the outcomes of hospitalized pneumonia patients. Because urine and other output data were sometimes not available in emergency department (ED) clinically, we also used cumulative crystalloid infusion as a surrogate for cumulative fluid balance and for ease of clinical use.

The method for de-identification, data collection, secure storage, and data validation has been already described in a prior study[7]. Although APACHE II score was significantly different during the initial univariate analysis, we did not include it in further analysis because it is not routinely available during the initial ED assessment; hence as a surrogate, shock index was used to adjust for severity of illness.

2.4 Outcome Measures

The primary composite outcome was defined as the development of acute respiratory failure requiring invasive or non-invasive mechanical ventilation or in-hospital mortality.

2.5 Data Analysis

The baseline characteristics of our study cohort were presented as percentages for categorical variables and mean (± standard deviation [SD]) for continuous variables. The difference of cumulative fluid balance or crystalloid infusion between hospitalized pneumonia patients with or without the composite outcome was compared using Mann-Whitney rank sum test. Univariate analysis was applied to evaluate the baseline characteristics and other covariates of interest. Variables with biological risk of mortality in pneumonia patients and significant impact in the initial univariate analysis were tested and then retained into the further multivariate logistic regression models to examine the independent effects of predictors on composite outcomes and minimize potential bias. Odds ratio and its 95% confidence intervals were reported. A two-sided p value of 0.05 or less was considered significant. All statistical analyses were performed using SAS (version 9.3; SAS Institute, Inc., Cary, NC).

3. Results

3.1 Characteristics of Study Subjects

From March to August in 2009, 22 academic and community acute care hospitals screened 5,992 patients who were at risk for ARDS in the original LIPS 1 cohort, and among them, 4,361 were admitted from the ED. Of the 1227 patients that met the criteria of pneumonia, the following patients were excluded: 222 patients did not have any date regarding fluid administration in the first 6 hours, 60 patients presented with shock, and 49 patients with less than 2 SIRS criteria. A total of 896 patients were included into this subgroup analysis.

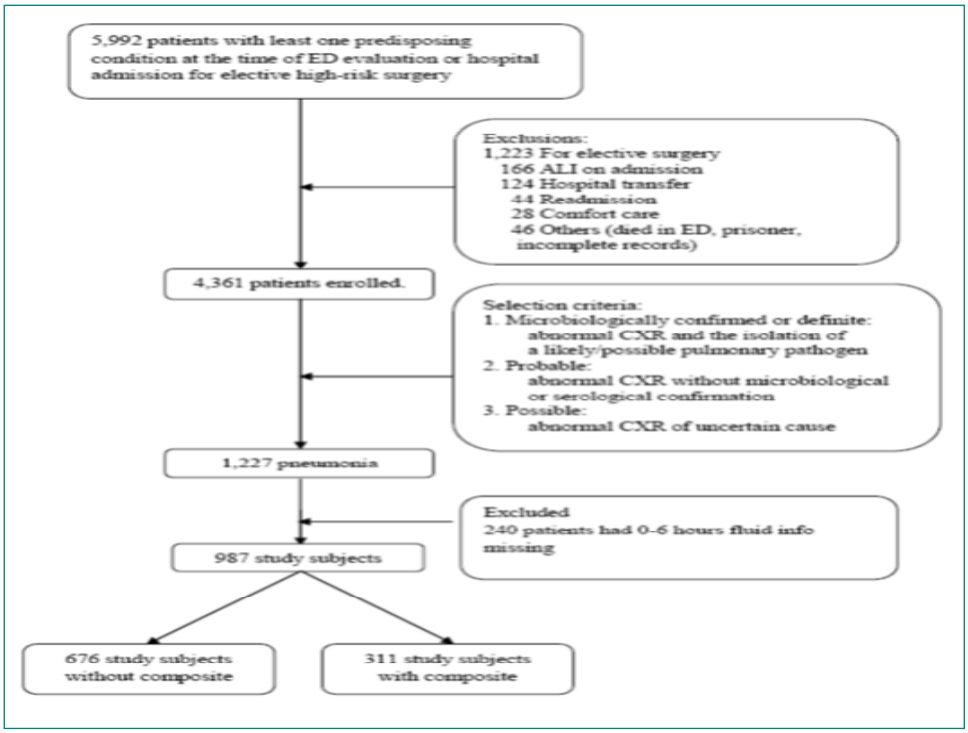

Figure 1. *Summary and outcome of the study protocol*

3.2 Main Results

A total of 267 of 896 patients (29.8%) developed the composite outcome of acute respiratory failure (ARF) or hospital mortality in our cohort. In-hospital mortality was 5.2%, and the rates of noninvasive and invasive mechanical ventilation were 19.1% and 13.3%, respectively. Baseline characteristics and clinical risk conditions were compared between pneumonia patients who did and those who did not develop the composite outcome (Table 1). Hospitalized patients with pneumonia who developed acute respiratory failure or died in the hospital were significantly older ($p = 0.011$), had higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ($p < 0.001$), shock index (defined by the ratio of heart rate to systolic blood pressure) ($p = 0.004$), more frequent aspiration events (40 [15%] vs. 20 [3%], $p < 0.001$), and were more likely to present by transfer from another ED or nursing homes ($p < 0.001$).

Table 1. *Baseline characteristics and clinical conditions*

Variables	Composite outcome *		*p* value
	No (*N=676*)	Yes (*N=311*)	
Demographics			
Age, year	61.1 ± 18.4	64.1 ± 17.9	0.02
Gender (male), no. (%)	349 (51.6%)	155 (49.8%)	0.6
Admission sources, no. (%)			<0.001
Home	539 (79.7%)	212 (68.2%)	
Nursing facilities	70 (10.4%)	53 (17.0%)	
Outside ED	28 (4.1%)	28 (9.0%)	
Other	33 (4.9%)	12 (3.9%)	
Missing	6 (0.9%)	6 (1.9%)	
BMI	26.9 ± 12.2	27.6 ± 8.8	0.4
ED vital signs			
Heart rate	102 ± 21.2	106 ± 24.2	0.007
Systolic blood pressure	124 ± 28.3	120 ± 34.5	0.1
Shock index	0.88 ± 0.32	0.96 ± 0.41	0.001
Risk modifiers			
Fluid balance 0-6 hours (ml)	918 ± 1114	1421 ± 2416	<0.001
Crystalloid infusion 0-6 hours (ml)	926 ± 1104	1609 ± 2346	<0.001
Blood product 0-6 hours (ml)	3.4 ± 50	14.3 ± 111	0.1
Urine output 0-6 hours (ml)	166 ± 346	311 ± 467	<0.001
Aspiration, no. (%)	22 (3%)	45 (14%)	<0.001
CHF (NYHA IV), no. (%)	35 (5%)	16 (5%)	0.999
Creatinine	1.7 ± 2.2	1.5 ± 2.0	0.3
Asthma, no. (%)	95 (14.1%)	34 (10.9%)	0.19
APACHE II score	10.6 ± 5.1	15.6 ± 6.8	<0.001

**Composite outcome: acute respiratory failure requiring invasive or non-invasive mechanical ventilation or in-hospital mortality*

Categorical data presented as no. (%).

Continuous data presented as mean ± SD

Definition of abbreviations: ARDS = Acute respiratory distress syndrome; ED = Emergency department; BMI = Body mass index; CHF NYHA = Congestive heart failure, New York Heart Association Classification; APACHE = Acute physiology and chronic heart evaluation.

In this study, there was no significant difference of serum creatinine level and congestive heart failure (NYHA class IV) between patients who developed or did not develop the composite outcome. Although chronic respiratory conditions may affect the incidence of acute respiratory failure in pneumonia patients, the frequency of chronic lung disease, like asthma, was not significantly different between these two groups.

The average fluid balance in the first 6 hours was significantly higher in hospitalized pneumonia patients who developed the composite outcome than those who did not (1.18 ± 1.58L vs. 0.87 ± 1.06L, $p < 0.001$). Further analysis of cumulative fluid balance data found that the average volume of cumulative intravenous crystalloids was 1.34 ± 1.51L vs. 0.88 ± 1.03L ($p < 0.001$) whereas urine output averaged 0.30 ± 0.47L vs. 0.17 ± 0.35L ($p < 0.001$) between pneumonia patients with and without the composite outcome.

In the first 6 hours of care, we found that majority of pneumonia patients (N = 616, 68.8%) received more restrictive fluid resuscitation (≤ 1L of fluid balance), and the incidence of composite outcome increased significantly ($p < 0.001$) with increasing fluid balance. In the model using crystalloid infusion only as a surrogate for total fluid balance, 622 patients (69.4%) received less than 1 liter of crystalloid infusion in first 6 hours, and with increasing crystalloid infusion, more patients succumbed to mechanical ventilation and death in the hospital ($p < 0.001$).

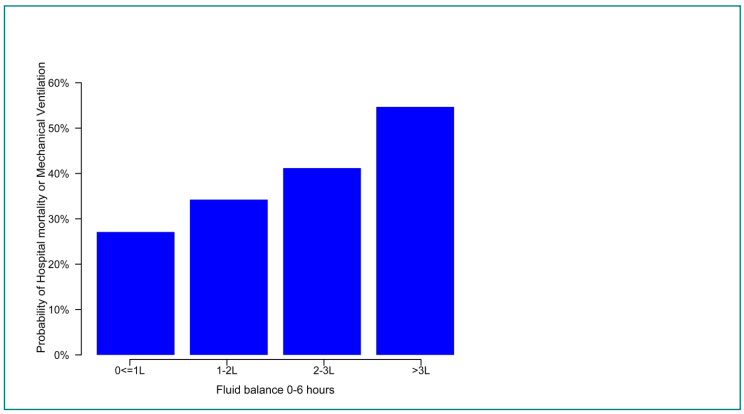

Figure 2. *Fluid balance 0-6 hours*

Composite Outcome n (%)	Fluid balance 0-6 hours				
	≤1 L (N=657)	1-2L (N=187)	2-3L (N=68)	>3L (N=75)	***P* Value**
					<0.001
No	479 (73%)	123 (66%)	40 (59%)	34 (45%)	
Yes	178 (27%)	64 (34%)	28 (41%)	41 (55%)	

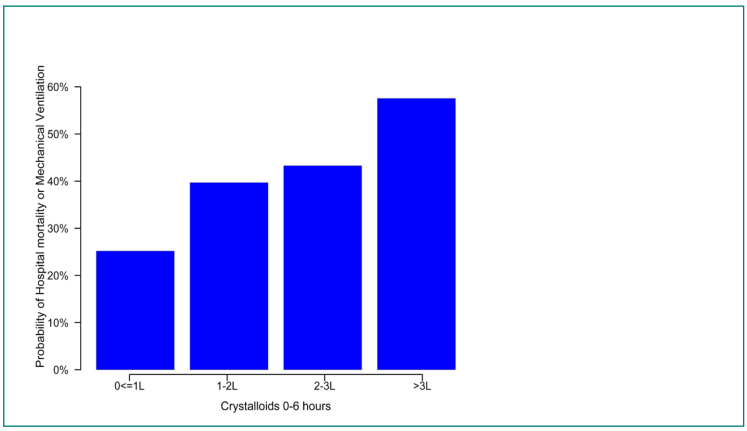

Figure 3. *Crystalloids 0-6 hours*

Composite Outcome n (%)	Crystalloids 0-6 hours				
	≤1 L (N=663)	1-2L (N=184)	2-3L (N=67)	>3L (N=73)	***P* Value**
					<0.001
No	496 (75%)	111 (60%)	38 (57%)	31(42%)	
Yes	167 (25%)	73 (40%)	29 (43%)	42 (58%)	

In the multivariate logistic regression analysis, admission source (p = 0.001), aspiration (p < 0.001) and categorized fluid balance (p = 0.032) were independently associated with acute respiratory failure or hospital mortality in hospitalized pneumonia patients (Table 2). More importantly, there was a statistically significant difference between categories of fluid balance ≤ 1 liter vs. > 3 liters with respect to the composite outcome (odds ratio (OR) 2.14; 95% Confidence Interval (CI) 1.12 to 4.08). Another model using crystalloid infusion also showed significant difference between categories of crystalloid infusion ≤ 1 liter vs. > 3 liters with respect to our composite outcome (OR 2.57; 95% CI 1.30 to 5.08) (Table 3).

Table 2. *Univariate analysis of the association between the composite outcome of ARF or in-hospital mortality and potential predictors.*

Predictors	OR	95% CI	P-value
Fluid balance 0-6 hours			Test for trend: p<0.001
1-2L vs. <1L	1.4	0.99-1.98	0.058
2-3L vs. <1L	1.88	1.13-3.15	0.015

>3L vs. <1L	3.25	2-5.28	<0.001
Crystalloid infusion 0-6 hours			Test for trend p<0.001
1-2L vs. <1L	1.95	1.39-2.75	<0.001
2-3L vs. <1L	2.27	1.36-3.79	0.002
>3L vs. <1L	4.02	2.45-6.61	<0.001
Aspiration	5.03	2.96-8.54	<0.001
Shock index	1.98	1.36-2.88	<0.001
Admission sources			
Nursing facilities vs. Home	1.92	1.30-2.85	0.001
Eds vs. Home	2.54	1.47-4.4	0.001
Others vs. Home	0.92	0.47-1.82	0.821

Table 3. *Multivariate analyses of the association between ARF or in-hospital mortality (Study Composite Outcome) and total fluid balance or categorized crystalloid infusion (0-6 hours) as one of the predictors.*

Predictors	OR	95% CI	P-value	OR	95% CI	P-value
Fluid balance						
1-2L vs. <1L	1.39	0.96-1.99	0.077	-	-	-
2-3L vs. <1L	1.69	0.98-2.93	0.061	-	-	-
>3L vs. <1L	2.57	1.48-4.44	0.001	-	-	-
Crystalloid infusion						
1-2L vs. <1L	-	-	-	1.98	1.34-2.78	<0.001
2-3L vs. <1L	-	-	-	2.15	1.25-3.70	0.006
>3L vs. <1L	-	-	-	3.25	1.86-5.8	<0.001
Aspiration	4.19	2.42-7.25	<0.001	4.14	2.38-7.18	<0.001
Shock index	1.46	0.95-2.22	0.082	1.25	0.81-1.94	0.305
Admission sources						
Nursing facilities vs. Home	1.95	1.3-2.92	0.001	1.93	1.28-2.91	0.002
Eds vs. Home	2.4	1.35-4.26	0.003	2.34	1.31-4.18	0.004
Others vs. Home	1.01	0.47-1.93	0.077	0.92	0.45-1.85	0.805

4. Discussion

In recent years, some authors contend that fluid therapy should be regarded as a specific medication, and potentially, a valuable biomarker of critical illness[2,8]. While fluid resuscitation may improve markers of systemic illness, overly aggressive fluid administration may adversely impact patient outcome. Further, it is possible that aggressive fluid administration may adversely impact patients with specific disease processes, such as pneumonia, that may be predisposed to negative impact by this intervention. To our knowledge, this is the first study to evaluate the effect of the cumulative fluid balance on hospitalized pneumonia patients' outcomes.

In our study, hospitalized pneumonia patients received an average of 1.01±1.21 liters of crystalloid infusion during the first 6 hours of care, and the average of cumulative fluid balance was 0.96±1.25 liters. Because this was an observational study, fluid administration for pneumonia patients was not standardized and the dose of fluid balance during the initial management was based on the clinical team's evaluation of the patients' physiologic condition and co-morbidities.

We found that fluid management with higher positive fluid balance and crystalloid infusion in the first 6 hours of care were both significantly associated with the composite outcome among hospitalized pneumonia patients. Further analysis showed that patients who received a more restrictive fluid balance (< 1L in first 6 hours) have significantly lower incidence of ARF or mortality compared to those who received a higher positive fluid balance (> 3L). This finding remained significant in the surrogate model using cumulative crystalloid infusion and is supported by several recent studies focused on patients with critically

ill conditions, such as acute respiratory distress syndrome[4]. The adverse effect of more positive fluid balance/crystalloids infusion may result in pulmonary edema.

Because increased illness severity and worsened physiological condition could account for increased fluid administration and APACHE II scores are not unavailable for patients during their Emergency Department care, we used shock index to adjust for severity of hypovolemia in this study. Sankaran and colleagues reported that shock index (> 1.0) predicts mortality within 6 weeks from admission in community-acquired pneumonia[10]. In contrast, there was no significant association between shock index and composite outcomes in our study, whether in either the cumulative fluid balance or crystalloid infusion models.

Admission source also showed a significant difference in our study, and most of the hospitalized pneumonia patients presented from home (76.5%) compared to nursing facilities (12.5%) and other EDs (5.4%). In multivariate analysis, pneumonia patients admitted from nursing facilities and other EDs were most likely to develop the composite outcome of acute respiratory failure or in-hospital death compared to patients from home.

There are limitations in this study including the retrospective design that used data from a multicenter observation cohort where the nature of the pneumonia (community-acquired or hospital-acquired) as well as initial antibiotic and other non-fluid treatments were not standardized. Patients who were diagnosed with pneumonia and had missing fluid data in the first 6 hours were excluded.

5. Conclusion

In this study of the impact of fluid balance on hospitalized pneumonia patients without shock, we found a significant association between positive fluid balance within the first six hours and the composite outcomes of ARF requiring MV or in-hospital death. This finding is consistent with similar observations for ARDS patients, and further studies are needed to confirm and better understand the impact of this finding.

Grant/Financial Support or Conflicts of Interest to Disclose.

PCH reports grant/contract payments made to his institution from National Institute of Health, US Department of Defense, US Center for Disease Control, Good Ventures, Rapid Pathogen Screening, Day Zero Diagnostics, iDoc Telehealth Solutions, Novartis, Kinevant Sciences GmbH, Mesoblast, Ophirex, Faron Pharmaceuticals, and CalciMedica.

6. References

1. File TM, Jr., Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med. 2010;122(2):130-141.
2. Ito A, Ishida T, Tokumasu H, et al. Prognostic factors in hospitalized community-acquired pneumonia: a retrospective study of a prospective observational cohort. BMC Pulm Med. 2017;17(1):78.
3. Kolditz M, Ewig S. Community-Acquired Pneumonia in Adults. Dtsch Arztebl Int. 2017;114(49):838-848.
4. van Mourik N, Geerts BF, Binnekade JM, et al. A Higher Fluid Balance in the Days After Septic Shock Reversal Is Associated With Increased Mortality: An Observational Cohort Study. Crit Care Explor. 2020;2(10):e0219.
5. Ma K, Patel K, Naddour M, et al. Acute Respiratory Distress Syndrome Novel Therapies. Crit Care Nurs Q. 2019;42(4):411-416.
6. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-377.
7. Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med. 2011;183(4):462-470.
8. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005;33(7):1538-1548.
9. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol. 2018;14(9):541-557.
10. Tekten BO, Temrel TA, Sahin S. Confusion, respiratory rate, shock index (CRSI-65) score in the emergency department triage may be a new severity scoring method for community-acquired pneumonia. Saudi Med J. 2020;41(5):473-478.