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Original Research Article

Validation of Lung Ultrasound for Early Diagnosis of Ventilator Associated Pneumonia in ICU

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Abstract

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in critically ill patients which are often reported to be associated with morbidity, mortality, long duration of ICU stay, and mechanical ventilation (MV). Due to the lack of validated gold standard diagnostic test for VAP detection, delay in patient treatment results in increased patient mortality. A total of 40 patients were included in the study. Of the 40 patients, 28 patients had mini-BAL culture-confirmed VAP that was considered the gold standard for VAP diagnosis while 12 patients did not have mini-BAL culture confirmed VAP. The CXR, microbiological culture, CPIS and LUS score were recorded and compared from the Day 1 to Day 7 till the discharge of the patients. The mean lymphocyte and platelet count among the patients with mini-BAL culture-proven VAP was found to be higher in comparison to those without mini-BAL culture-proven VAP. The mean SOFA and APACHE score was also found to be significantly higher among the patients with mini-BAL culture-proven VAP. There was a significant decrease in the mean LUS score and CPIS score for the patients from Day 1 till the day of the discharge of the patients. The study concludes that the LUS score and the CPIS score are good diagnostic marker for the detection of VAP which can be utilized for clinical decision making of patients admitted in hospital with suspected VAP.

Keywords: VAP, LUS, CPIS, BAL

Introduction

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in critically ill patients which are often reported to be associated with morbidity, mortality, long duration of ICU stay, and mechanical ventilation (MV), which clearly affects patient care and management [1,2,3]. The lack of any available validated gold standard diagnostic procedures for the detection of VAP still remains a challenge in intensive care units [4].

Treatment includes identification of the causative organism and therapy with active antibiotics. Delayed initiation of antibiotics have been reported to be associated with increased severe sepsis resulting in mortality [5].

Therefore, there is an urgent need for a reliable diagnostic tool for early diagnosis of VAP so that treatment of the patients using antibiotics can be immediately started in order to avoid the two extreme approaches [6]. It has been observed that, waiting for positive broncho-alveolar lavage (BAL) results in treatment delays which lead to increased mortality. Meanwhile, antibiotics are administered to all patients with suspected VAP, and treatment is reduced or discontinued if the microbiome is negative [7] which results in inappropriate, massive use of antibiotics and fosters multi-resistant bacteria [8,9,10]. Therefore the present study has been aimed to study a score based diagnostic approach using LUS and CPIS for the early detection of VAP. The study would also look into the differences in the various clinical parameters among patients with and without mini-BAL proven VAP.

Materials and methods

The present research study was prospectively conducted among patients admitted in the intensive care unit of Indira Gandhi Institute Of Medical Sciences, Patna . The study was approved for research by the Institutional Ethics Committee of the IGIMS, Patna. The number of patients included in the study was 40 who were suspected to have clinical VAP. The following criteria was used for clinical suspicion of VAP: Patient admitted under minimum of 48 hrs of mechanical ventilation, Chest X-ray suggesting new or increased infiltrates, patients represented with at least 2 among 4 clinical criteria such as temperature more than 38.5ºC or less than 36ºC, total leucocyte count of more than 10,000μL^{-1} or less than 4000μL^{-1}, purulent tracheal secretions, PaO_2/FiO_2 ratio < 300. Those patients who did not met the following inclusion criteria were excluded from the study.

VAP diagnosis was confirmed by positive BAL (≥1 micro-organism with a concentration $\geq 10^4$ CFU/mL) or simultaneous presence of all clinical criteria with negative BAL if antibiotics had been modified/ introduced in the previous 48 hours. The Chest X-Ray (CXR), LUS score, clinical pulmonary infection score (CPIS) score, Microbiological culture, and BAL were performed on Day 1 to Day 7 of admission of the patient till the discharge of the patient.

Lung ultrasound

For each lung, comprehensive scans were performed in 6 regions (lower and upper regions, posterior and lateral regions using the posterior and anterior axillary lines as landmarks) and the following ultrasound findings were collected. (1) Minor subpleural enhancement: Echoes weak areas. >0.5cm diameter; (2) Lobe/ hemispheric coherence is determined by tissue-like models. (3) Dynamic linear/arboreal air-bronchography in lobar/hemilobar integration: inspired, synchronously moving hyperchoeic images. Simplified version of the clinical pulmonary infection score (CPIS) was used for the diagnosis of VAP [11].

Statistical analysis

For the research study the number of patients needed to do a power analysis could not be established. Consecutive patients were included as recommended. The 95% confidence intervals values were reported for indicating the statistical uncertainty.

Results are expressed as mean ± SD or median (inter-quartile range - IQR). Patients with and without VAP as well as patients from two groups were compared using the unpaired t-test for numerical data. The differences in the distribution of

frequency of patients from two groups were compared using Chi-square test. Sensitivity, specificity, positive/negative predictive values, and positive/negative likelihood were calculated for LUS signs (lobar/hemilobar consolidation, dynamic linear/arborescent air- bronchograms, subpleural consolidation) and for clinical (purulent secretions), and CPIS. All the statistical analysis were performed using SPSS version 24 software.

Results

A total of 40 patients got admitted during the study period. The patients were enrolled for the study after fulfilling the inclusion criteria. Of the 40 patients, 28 patients had mini-BAL culture-confirmed VAP that was considered the gold standard for VAP diagnosis while 12 patients did not have mini-BAL culture confirmed VAP.

Table 1: Table representing the demographic characteristics and outcome of included patients

Characteristics		All patients (n= 40)	Mini-BAL culture-proven VAP (n=28)	Without Mini-BAL culture-proven VAP (n=12)	P Value[a,b]
Age (mean±SD)		46.9±8.5	46.75±7.8	47.25±10.6	0.139[a]
Gender (n%)	Male	26 (65)	16 (57.1)	10 (83.3)	0.15[b]
	Female	14 (35)	12 (42.9)	2 (16.7)	
Height (mean±SD)		170.25±9.3	168.96±9.29	173.25±9.12	0.67[a]
Weight (mean±SD)		61.92±7.9	60.79±7.4	64.58±8.6	0.97[a]
Hb (%) (mean±SD)		11.26±1	11.24±0.9	11.3±1.2	0.75[a]
TLC (mean±SD)		8760±3751	9546±4160	6925±1471	0.09[a]
Platelet count ($x10^3$) (mean±SD)		327.35±213	367.36±228.3	234±140.4	0.04[a]*
Blood sugar (Random) (mean±SD)		161±20.9	159.21±22.2	165.33±17.9	0.24[a]
Serum Lactate (mean±SD)		7.95±3.2	8.19±2.8	7.4±4	0.11[a]
SOFA (mean±SD)		6.8±2.6	7.11±3	6.08±0.9	0.11[a]
APACHE (mean±SD)		16.07±5.7	16.64±6.6	14.75±2.3	0.19[a]
PaO2/FiO2 ratio (mm Hg) (mean±SD)		156±61.9	135.11±56.6	204.75±45.1	0.27[a]
Mean arterial pressure (mm Hg) (mean±SD)		108.16±13.2	107.7±13.9	109±11.9	0.5[a]

a- t test
b- Chi square test
* significant at $p<0.05$

Demographic characteristics of the patients revealed that there was no significant difference observed in the mean age, sex distribution, height, weight, Hb% and TLC among patients with mini-BAL culture-proven VAP and without mini-BAL culture-proven VAP. The mean lymphocyte count among the patients with mini-BAL culture-proven VAP was found to be higher in comparison to those without mini-BAL culture-proven VAP. The mean platelet count among the patients with mini-BAL culture-proven VAP was also higher in comparison to those without mini-BAL culture-proven VAP. The mean SOFA and APACHE

score was found to be higher among the patients with mini-BAL culture-proven VAP in comparison to those without mini-BAL culture-proven VAP; however, the result was not found to be statistically significant (Table 1).

Table 2: Table representing the Chest X-Ray detection outcome of patients with and without VAP from Day 1 of admission till discharge of the patients

Number of Days	Outcome	No VAP	With VAP
Day1	No	12 (100)	20 (71.4)
	Yes	0 (0)	8 (28.6)
Day2	No	12 (100)	24 (85.7)
	Yes	0 (0)	4 (14.3)
Day3	No	12 (100)	19 (67.9)
	Yes	0 (0)	9 (32.1)
Day4	No	12 (100)	26 (92.9)
	Yes	0 (0)	2 (7.1)
Day5	No	12 (100)	24 (85.7)
	Yes	0 (0)	4 (14.3)
Day6	No	12 (100)	28 (100)
	Yes	0 (0)	0 (0)
Day7	No	12 (100)	28 (100)
	Yes	0 (0)	0 (0)
Discharge	No	12 (100)	28 (100)
	Yes	0 (0)	0 (0)

Chest X-Ray detection outcome of patients with and without VAP from Day 1 of admission till discharge of the patients revealed that the number of patients with confirmed mini-BAL VAP detected with Chest X-ray was higher in the 3rd day of admission while no confirmed mini-BAL VAP was detected with Chest X-ray from the 6th day of admission till the discharge of the patients (Table 2).

Table 3: Table representing the mean LUS from Day 1 of admission till discharge of the patients

Number of Days	Mean	Standard Deviation	P value[a]
Day1	2.95	0.98	<0.01*
Day2	2.9	1.05	
Day3	2.37	1.05	
Day4	2.15	0.86	
Day5	1.82	0.71	
Day6	1.67	0.72	
Day7	1.4	0.49	
Discharge	1.2	0.40	

a- ANOVA

The mean LUS score from Day 1 of admission till discharge of the patients revealed that there was a significant decrease in the mean LUS score for the patients from Day1 till the day of the discharge of the patients (Table 3).

Table 4: Table representing the mean CPIS from Day 1 of admission till discharge of the patients

Number of Days	Mean	Standard Deviation	P value[a]
Day1	5	1.15	<0.01*
Day2	4.75	1.17	
Day3	4.22	1.02	
Day4	3.85	1.07	
Day5	3.47	1.17	
Day6	2.87	0.99	
Day7	2.47	1.06	
Discharge	1.9	0.87	

a- ANOVA

The mean CPIS score from Day 1 of admission till discharge of the patients revealed that there was a significant decrease in the mean CPIS score for the patients from Day1 till the day of the discharge of the patients (Table 4).

Table 5: Table representing the performance of CPIS for the diagnosis of VAP from Day1 of the admission until the discharge of the patients

Days	Criterion	AUC	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR-
Day 1	>4	0.832	85.71 (67.3-96)	66.67 (34.9-90.1)	2.53	99.78	2.57 (1.1-5.8)	0.21 (0.08-0.6)
Day 2	>4	0.845	75 (55.1-89.3)	83.33 (51.6-97.9)	3.49	99.75	4.5 (1.2-16.2)	0.3 (0.2-0.6)
Day 3	>3	0.807	85.71 (67.3-96)	66.67 (34.9-90.1)	2.03	99.82	2.57 (1.1-5.8)	0.21 (0.08-0.6)
Day 4	>3	0.903	82.14 (63.1-93.9)	83.33 (51.6-97.9)	3.81	99.82	4.93 (1.4-17.7)	0.21 (0.09-0.5)
Day 5	>3	0.801	64.29 (44.1-81.4)	83.33 (51.6-97.9)	3.01	99.65	3.86 (1.1-14.1)	0.43 (0.2-0.7)
Day 6	>2	0.885	82.14 (63.1-93.9)	83.33 (51.6-97.9)	3.82	99.82	4.93 (1.4-17.7)	0.21 (0.09-0.5)
Day 7	>2	0.841	60.71 (40.6-78.5)	91.67 (61.5-99.8)	5.55	99.65	7.29 (1.1-48.7)	0.43 (0.3-0.7)
Discharge	>1	0.799	75 (55.1-89.3)	75 (42.8-94.5)	2.36	99.73	3 (1.1-8.2)	0.33 (0.2-0.7)

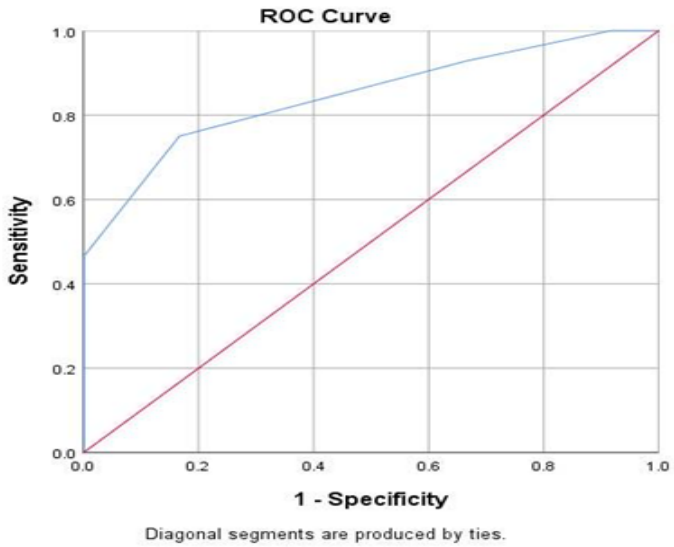

Figure 1: Receiver Operating Curve representing the Area under Curve of CPIS for the diagnosis of VAP for Day2

Table 6: Table representing the performance of LUS for the diagnosis of VAP for Day1 of the admission until the discharge of the patients

Days	Criterion	AUC	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR-
Day 1	>2	0.973	92.86 (76.5-99.1)	100 (73.5-100)	100	99.94	-	0.07 (0.02-0.3)
Day 2	**>2**	**0.979**	**92.86 (76.5-99.1)**	**100 (73.5-100)**	100	99.94	**-**	**0.07 (0.02-0.3)**
Day 3	>1	0.988	100 (87.7-100)	91.67 (61.5-99.8)	8.82	100	12 (1.8-78.4)	0
Day 4	>1	1	100 87.7-100)	100 (73.5-100)	100	100	-	-
Day 5	>1	0.964	92.86 (76.5-99.1)	100 (73.5-100)	100	99.94	-	0.07 (0.02-0.3)
Day 6	>1	0.875	75 (55.1-89.3)	100 (73.5-100)	100	99.79	-	0.25 (0.1-0.5)
Day 7	>1	0.786	57.14 (37.2-75.5)	100 (73.5-100)	100	99.65	-	0.43 (0.3-0.7)
Discharge	>1	0.643	28.57 (13.2-48.7)	100 (73.5-100)	100	99.42	-	0.71 (0.6-0.9)

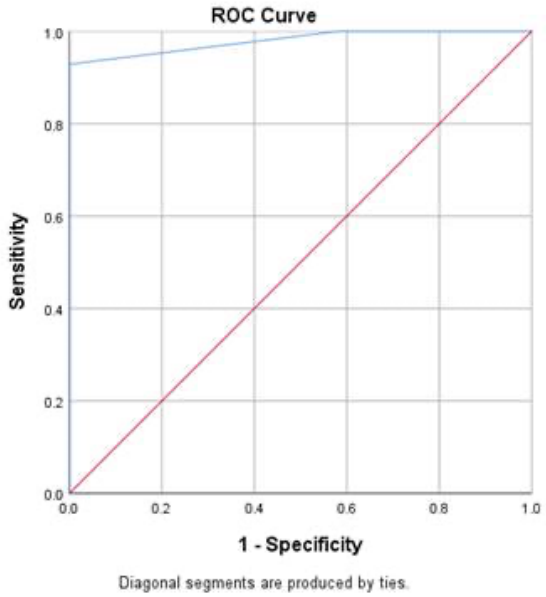

Figure 2: Receiver Operating Curve representing the Area under Curve of LUS for the diagnosis of VAP for Day2

Diagnostic accuracy of CPIS and LUS during different days of patient admission has been depicted in Table 5 and Table 6 respectively. The overall sensitivity and specificity of the LUS score among the patients for all days of admission has been found to be higher in comparison to that of the CPIS score. For the CPIS score, the best sensitivity and specificity for criterion with more than 4 was found to be for Day 2 of admission while the best sensitivity and specificity for criterion with more than 3 and 2 was found to be for Day 4 and Day 6 respectively. Similarly for the LUS score the best sensitivity and specificity for criterion with more than 2 was found to be for Day 2 of admission.

Discussion

Diagnosis and treatment of VAP remain problematic. VAP is suspected when new radiation infiltrates occur in patients with leukopenia, pyrexia/hypothermia, impaired oxygenation and purulent tracheal secretions. However, several non-infectious procedures can cause fever and lung infiltrates in ventilated patients, making the diagnosis of VAP difficult. Quantitative BAL culture positive ($\geq 10^4$ CFU/ml) is considered the gold standard for diagnosing VAP, but it takes 24-48 hours to obtain final results. This 'biological approach' aims to treat only microbiologically approved VAPs. This, of course, is very specific, but it can delay the introduction of antibiotics and increase mortality. Therefore, reliable diagnostic tools for early diagnosis of VAP are essential to initiate antibiotic therapy as soon as possible [12].

The mean lymphocyte and platelet count among the patients with mini-BAL culture-proven VAP was found to be higher in comparison to those without mini-BAL culture-proven VAP.

The mean LUS score and mean CPIS score from Day 1 of admission till discharge of the patients revealed that there was a significant decrease in the mean LUS score for the patients from Day1 till the day of the discharge of the patients. This may be attributed to the fact that upon treatment of the patient due to the suspected VAP, the LUS score and the CPIS score of the patients decreased with the increase in number of days of treatment. The LUS score and the CPIS score was observed to be minimum during the discharge of the patients.

Diagnostic ability of the LUS score and CPIS score using ROC analysis revealed that the overall sensitivity and specificity of the LUS score among the patients for all days of admission has been found to be higher in comparison to that of the CPIS score. For the CPIS score the best sensitivity and specificity for criterion with more than 4 was found to be for Day 2 of admission while the best sensitivity and specificity for criterion with more than 3 and 2 was found to be for Day 4 and Day 6 respectively. Pugin et al., first identified CPIS as a diagnostic parameter showing high sensitivity (93%) and specificity (100%) [13]. In another study by Croce et al., it was observed that CPIS score represented a sensitivity and specificity of 61% and 43% [14]. In another study by Schurink et al., it was observed that culture modified CPIS displayed an 83% sensitivity and 17% specificity [15]. In the present study we observed CPIS score with better sensitivity and specificity in comparison to that of the previous studies. In ICUs, LUS score is often used for the detection of lung consolidation, detection of effusion due to the very good sensitivity and specificity offered by the diagnostic test [16]. Previous study has supported the fact that LUS score can be a used as a very strong diagnostic parameter with high sensitivity and specificity [17]. LUS score along with the combination of other parameters can thus be used as a diagnostic parameter for accurate detection of VAP. [18]

There are various limitations to the study. Firstly, the study has been conducted in a small sample size as a result of which the diagnostic markers are needed to be tested in large population for validation of the markers. Secondly, the research study was a single-center observational study. Multi-center randomized trials should be performed in order to obtain more accurate findings.

Conclusion

The study concludes that the LUS score and the CPIS score are good diagnostic marker for the detection of VAP which can be utilized for clinical decision making of patients admitted in hospital with suspected VAP. Further study should be done in order to observe the relevance of multiple diagnostic markers for the early detection of VAP.

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