CHEST 2014; 146(6): 1578 - 1585

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文献精读

Diagnosis of Ventilator-Associated Pneumonia:

A Pilot, Exploratory Analysis of a New Score Based on Procalcitonin and Chest Echography

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Abstract

BACKGROUND: To facilitate the clinical diagnosis of ventilator-associated pneumonia (VAP) in the ICU, the Clinical Pulmonary Infection Score (CPIS) has been proposed but has shown a low diagnostic performance in subsequent studies. We propose a new score based on procalcitonin level and chest echography with the aim of improving VAP diagnosis: the Chest Echography and Procalcitonin Pulmonary Infection Score (CEPPIS).

- **METHODS:** Th is retrospective pilot study recruited patients admitted to the Intensive Care Unit of the Emergency Department, Careggi University Hospital (Florence, Italy), from January 2009 to December 2011. Patients were retrospectively divided into a microbiologically confirmed VAP group or a control group based on diagnosis of VAP and positive tracheal aspirate culture.

RESULTS:

A total of 221 patients were included, with 113 in the microbiologically confirmed VAP group and 108 in the control group. A CEPPIS>5 retrospectively fixed was significantly better in predicting VAP (OR, 23.78; sensitivity, 80.5%; specificity, 85.2%) than a CPIS . 6 (OR, 3.309; sensitivity, 39.8%; specificity, 83.3%). Th e receiver operating characteristic area under the curve analysis also showed a significantly higher diagnostic value for CEPPIS . 5 than CPIS . 6 (0.829 vs 0.616, respectively; *P , .0001).*

CONCLUSIONS: In this pilot, exploratory analysis, CEPPIS is eff ective in predicting VAP . Prospective validation is needed to confirm the potential value of this score to facilitate VAP diagnosis.

前言部分

- **Ventilator-associated pneumonia (VAP) is a nosocomial complication affecting up to 27% of patients in the ICU receiving mechanical ventilation.**
- **VAP is associated with a longer duration of mechanical ventilation; an increase in total hospital length of stay (LOS) and, consequently, health-care costs; and a high mortality rate (up to 70%).**

CPIS认识的变迁

1. Th e clinical diagnosis of VAP was traditionally made based on the criteria proposed in 1972 by Johanson and colleagues associating a new or progressive consolidation on chest radiograph with at least two of the following variables: fever, leukocytosis or leukopenia, and purulent tracheal secretions. To facilitate the clinical diagnosis of VAP,
2. Pugin and colleagues proposed the Clinical Pulmonary Infection Score (CPIS) based on six variables: fever, leukocytosis, tracheal aspirates,oxygenation, radiographic infi ltrates, and semiquantitative cultures of tracheal aspirates.

CPIS认识的变迁

- Despite its wide use, the CPIS has shown relatively low accuracy in various studies.
- A multicenter randomized trial testing the discriminative eff ectiveness of CPIS to detect VAP in 739 patients did not fi nd a signifi cant score threshold to predict VAP, indicating the limited clinical utility of this score.
- Th e aim of the present study was to test the diagnostic utility of a new clinical score, including clinical infection signs, chest echography information, and procalcitonin levels, in the diagnosis of VAP in critically ill patients.

Materials and Methods

Study Design

- Th is retrospective, controlled study considered for enrollment all consecutive patients admitted from First Aid to the Intensive Care Unit of the Emergency Department, Careggi University Hospital (Florence, Italy), from January 2009 to December 2011.
- The ethical committee of Careggi University Hospital approved the study. Informed consent for anonymous data publication was obtained from all patients or their relatives.

Patient Selection

- 纳入标准:

Patients were considered for the study if the duration of mechanical ventilation was . 48 h. Only patients with chest echography performed within 12 h before chest radiography at the time of VAP suspicion were Considered.

Patient Selection

- 排除标准:
- **Patients admitted for pulmonary infection, COPD exacerbation ,or other potential sources of sepsis at the time of VAP suspicion were excluded, as were all patients receiving antibiotics at the time of VAP suspicion.**
- 设立对照组:
- **Patients with clinical signs, new infiltrates on chest radiograph, and positive tracheal aspirate cultures were retrospectively included in the infected group (henceforth called the microbiologically confirmed VAP group),;**
- **whereas patients with the absence of clinical signs, no infiltrates on chest radiograph, and negative tracheal aspirate cultures were assigned to the control group.**

CEPPIS and CPIS

TABLE 1] The Proposed CEPPIS Compared With the Original CPIS

Parameter	Points 0	1	2
CEPPIS			
Tracheal secretion	Nonpurulent	...	Purulent
Procalcitonin, ng/mL	< 0.5	≥ 0.5 and < 1	≥ 1
Culture of tracheal aspirate	Negative	...	Positive
Temperature, °C	≥ 36 and < 38.4	≥ 38.5 and < 38.9	< 36 or ≥ 39
Infiltrates on chest echograph	Negative	...	Positive
Oxygenation: Pao_2/Fio_2	> 240 or ARDS	...	≤ 240 and no evidence of ARDS
CPIS			
Temperature, °C	≥ 36 and < 38.4	≥ 38.5 and < 38.9	< 36 or ≥ 39
Blood leukocytes, WBC/mm³	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	< 4,000 or > 11,000 and band forms ≥ 500
Oxygenation: Pao_2/Fio_2	> 240 or ARDS	...	≤ 240 and no evidence of ARDS
Tracheal secretions	Absent	Nonpurulent	Purulent
Pulmonary radiography	No infiltrate	Diffuse (or patchy) infiltrate	Localized infiltrate
Culture of tracheal aspirate	Pathogenic bacteria cultured in rare or light quantity or no growth	Pathogenic bacteria cultured in moderate or heavy quantity	Same pathogenic bacteria seen on Gram stain

ARDS is defined as a $Pao_2/Fio_2 \leq 200$, pulmonary artery wedge pressure < 18 mm Hg, and acute bilateral infiltrates. CEPPIS = Chest Echography and Procalcitonin Pulmonary Infection Score; CPIS = Clinical Pulmonary Infection Score.

- Tracheal cultures were obtained with a sterile catheter connected to a sterile microbiologic container. According to internal monitoring protocol,tracheal cultures were obtained at ICU admission and every 5 days in the absence of pulmonary infection suspicion. An oral cleaning withchlorhexidine 2% mouthwash was performed bid.
- All patients underwent chest echographic examination between the third and fi ft h day of their ICU stay (more frequently if clinically necessary)following internal surveillance protocol. 9 Procalcitonin dosing was performed daily in all patients. VAP diagnosis was made in the case of new infi ltrates on chest radiograph, leukocytosis, purulent secretions,or fever. Th e microbiologically confi rmed VAP group comprised patients in whom the tracheal aspirate culture results were positive (count . 10^4 colony-forming units/mL).

Data Management

- For each patient, the following data were collected: age, sex, BMI, medical history, Injury Severity Score in trauma patients, Simplifi ed AcutePhysiology Score II in all patients, duration of mechanical ventilation,laboratory and microbiologic data, LOS, and mortality. Admission diagnoses were divided into major trauma, medical (intracranial hemorrhages,intoxication,postanoxic coma, cardiac failure), and postsurgical(abdominal surgery, neurosurgery, vascular surgery). Chest echography was performed as previously described using a multifrequency (3.5-5 MHz) convex probe (Mylab 30CV; Esaote SpA).Patients were examined in the supine position with the convex probeapplied perpendicularly to the chest wall to ensure that all the intercostal spaces bilaterally from the base of the lung to the apex of the chest cavity were screened. Pneumonia was diagnosed as a subpleural echo-poorregion or one with tissue-like echo texture according to international evidence-based recommendations.

Score Definition

- Th e proposed new score, the Chest Echography and Procalcitonin Pulmonary Infection Score (CEPPIS) (Table 1), included the following
- changes:
- • Chest radiograph was replaced by chest echography.
- • Leukocyte count was replaced by plasma procalcitonin concentration

(ng/mL) based on Use of Procalcitonin to Reduce Patients'Exposure to Antibiotics in Intensive Care Units (PRORATA) trial indications.

- • Culture of tracheal aspirate signifi cance was considered positive if the count was . 10^4 colony-forming units/mL.
- • Tracheal secretion signifi cance was considered positive only if purulent,

independently from the number of aspirations performed by nurses. Definition of tracheal purulence was made by visual assessment performed by nurses and physicians

Statistical Analysis

- **SPSS, version 18, soft ware (IBM Corporation) was used for statistical analyses. Continuous variables were analyzed with two-tail Student *t test* or Mann-Whitney test (D'Agostino-Pearson normality test) as appropriate. Categorical variables were examined using Fisher exact test.*P < 0.05 was considered significant. Univariate comparison is reported* as OR with 95% CI.**
- **A logistic regression model was used to investigate the predictors of VAP. Each predictor likely to be related to the outcome was evaluated according to statistical and clinical bases. Covariates associated with the response variables (*P , .1) in univariate analysis were retained in the* final model; therefore, multivariable logistic regression comprised age, sex, BMI, duration of mechanical ventilation, and ICU LOS**

Data Management

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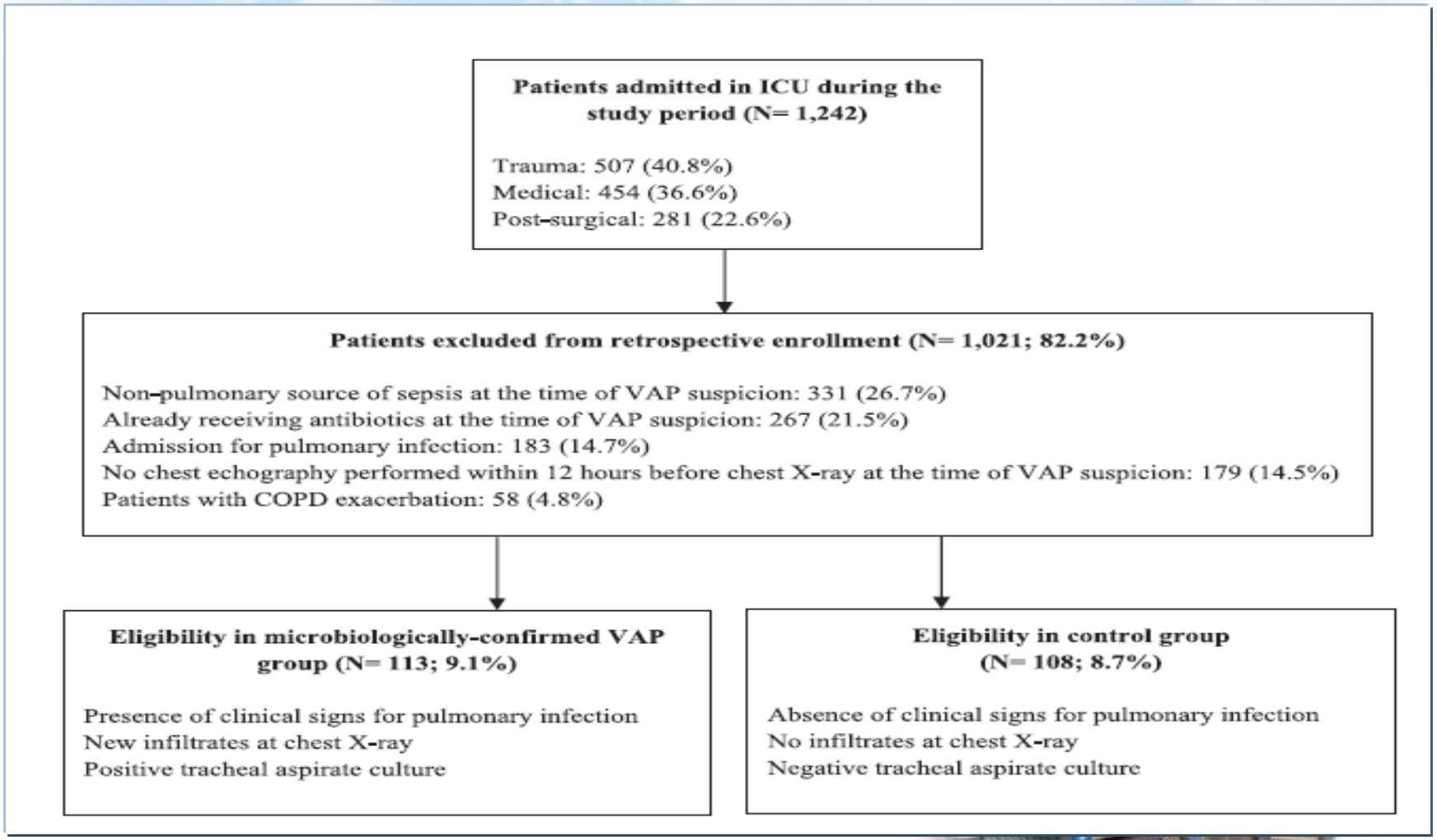
RESULTS

Reach flows


Patients admitted in ICU during the study period (N= 1,242)
Trauma: 507 (40.8%)
Medical: 454 (36.6%)
Post-surgical: 281 (22.6%)
Patients excluded from retrospective enrollment (N= 1,021; 82.2%)
Non-pulmonary source of sepsis at the time of VAP suspicion: 331 (26.7%)
Already receiving antibiotics at the time of VAP suspicion: 267 (21.5%)
Admission for pulmonary infection: 183 (14.7%)
No chest echography performed within 12 hours before chest X-ray at the time of VAP suspicion: 179 (14.5%)
Patients with COPD exacerbation: 58 (4.8%)
Eligibility in microbiologically-confirmed VAP group (N= 113; 9.1%)
Presence of clinical signs for pulmonary infection
New infiltrates at chest X-ray
Positive tracheal aspirate culture
Eligibility in control group (N= 108; 8.7%)
Absence of clinical signs for pulmonary infection
No infiltrates at chest X-ray
Negative tracheal aspirate culture

Clinical Characteristics of the Microbiologically Confi rmed VAP and Control Groups

TABLE 2] Clinical Characteristics of the Microbiologically Confirmed VAP and Control Groups

Characteristic	Overall	Microbiologically Confirmed VAP	Control Subjects
No. patients	221	113	108
Age, y	56.0 ± 20.9	55.2 ± 19.1	56.8 ± 22.6
Male sex	68.8 (152)	72.6 (82)	64.8 (70)
BMI, kg/m²	20.4 ± 5.6	26.1 ± 4.4	26.9 ± 6.7
Admission diagnosis			
Trauma	53.4 (118)	67 (76)	38.9 (42)
Medical	33.9 (75)	20 (22)	49.1 (53)
Postsurgical	12.7 (28)	13 (15)	12.0 (13)
SAPS II	46.6 ± 15.5	46.5 ± 14.0	46.8 ± 17.0
ISS	32.7 ± 12.9	33.4 ± 13.1	31.2 ± 12.4
Mechanical ventilation, d	9.2 ± 8.4	14.6 ± 11.2	8.2 ± 7.3
Intra-ICU mortality	17.2 (38)	15.0 (17)	19.4 (21)
ICU LOS, d	13.3 ± 9.8	19.3 ± 13.9	11.8 ± 7.8

Data are presented as mean ± SD or % (No.) unless otherwise indicated. Percentages refer to the total population of each group. For definition, ISS was calculated only in trauma patients. Statistical analysis included two-tailed Mann-Whitney test and two-tail Fisher exact test. $P < .05$ (infection vs control) was considered significant. ISS = Injury Severity Score; LOS = length of stay; SAPS = Simplified Acute Physiology Score; VAP = ventilator-associated pneumonia.

Results

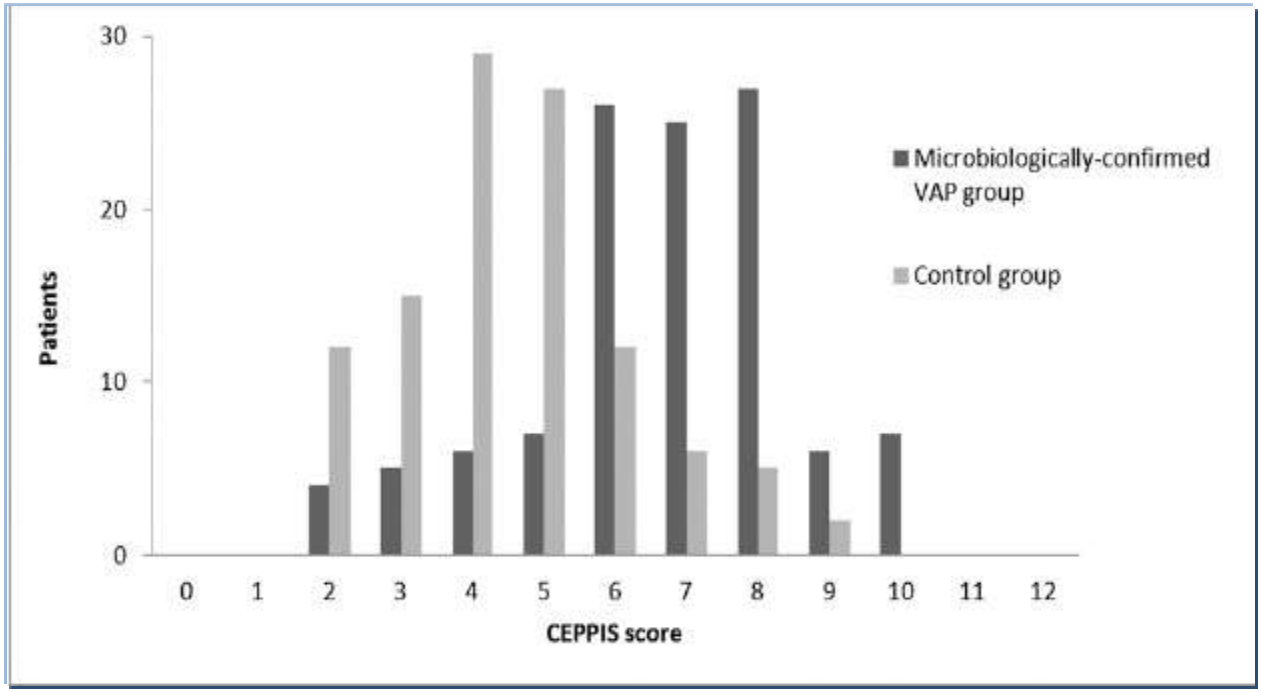


Figure 2 – *Distribution of CEPPIS values in microbiologically confirmed VAP and control groups. CEPPIS = Chest Echography and Procalcitonin Pulmonary Infection Score. See Figure 1 legend for expansion of other abbreviation.*

Results

TABLE 3] Microbiology Results in Microbiologically Confirmed VAP Group

Microorganism	No. Patients
Methicillin-sensitive *Staphylococcus aureus*	28
Pseudomonas aeruginosa	25
Klebsiella pneumoniae	24
Enterobacter	14
Candida albicans	7
Streptococcus pneumoniae	5
Haemophilus influenzae	2

See Table 2 legend for expansion of abbreviation.

Results

TABLE 4] Univariate and Multivariate (in $P<.10$, out $P<.05$) Analysis for VAP Risk in Overall Population

	Univariate			Multivariate		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age	0.9965	0.9839-1.0092	.5833	...	...	...
BMI	0.9753	0.9272-1.0260	.3335	...	...	...
Trauma	3.2278	1.8597-5.6025	<.0001	3.5938	1.6861-7.6602	.0009
Medical	0.2509	0.1378-0.4568	<.0001	0.2684	0.1258-0.5725	.0007
Postsurgical	1.1185	0.5054-2.4757	.7823	...	...	...
Duration of mechanical ventilation	1.1053	1.0535-1.1596	<.0001	...	...	...
ICU LOS	1.0912	1.0473-1.1369	<.0001	...	...	...

See Table 2 legend for expansion of abbreviations.

Discussion

- **Th is study demonstrates that the CEPPIS is a valuable new tool for predicting VAP development.**
- **Th e use of procalcitonin levels instead of leukocyte levels follows the current literature for antimicrobial therapy**
- **In the CEPPIS calculation, we chose to simplify this parameter by deleting the subjectivity of nurses in the scoring, simplifying the subscore into purulent and nonpurulent**
- **The value of the combination of variables included in CEPPIS was signifi cantly more reliable in VAP diagnosis**

Table 5

TABLE 5 Comparison of CEPPIS, CPIS, Chest Echography, Procalcitonin Level, and Chest Echography + Procalcitonin Level as Predictors of VAP Diagnosis

Predictor	OR (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	*P* Value
CEPPIS > 5	23.78 (11.74-48.20)	80.5 (72-87.4)	85.2 (77.1-91)	85.1 (76.7-91)	80.7 (72.3-87.5)	< .0001
CPIS > 6	3.309 (1.761-6.219)	39.8 (30.1-49.5)	83.3 (74.9-89.8)	71.4 (58.7-82.1)	57 (48.9-64.8)	.0002
Presence of infiltrates on chest echograph	8.011 (3.452-18.59)	59.3 (49.7-68.4)	84.6 (71.9-93.1)	89.3 (80.1-95.3)	48.9 (38.2-59.7)	< .0001
Procalcitonin > 1 ng/mL	0.8571 (0.4436-1.656)	44.3 (34.9-53.9)	51.9 (37.6-66)	66.7 (54.8-77.1)	.6)	.7369
Presence of infiltrates on chest echograph + procalcitonin > 1 ng/mL	6.738 (1.960-23.16)	29.2 (21-38.5)	94.2 (84.1-98.8)	91.7 (77.5-98.2)	7)	.0005

NPV = negative predictive value; PPV = positive predictive value. See Table 1 and 2 legends for expansion of other abbreviations.

Table 6

TABLE 6] Receiver Operating Characteristic AUCs of CEPPIS, CPIS, Chest Echography, Procalcitonin Level, and Chest Echography + Procalcitonin Level

Predictor	AUC	SE	95% CI	Significance Level *P* Value (Area = 0.5)
CEPPIS > 5	0.829	0.0254	0.772-0.876	<.0001
CPIS > 6	0.616	0.0293	0.548-0.680	<.0001
Presence of infiltrates on chest echograph	0.691	0.0320	0.615-0.761	<.0001
Procalcitonin > 1 ng/mL	0.517	0.0366	0.438-0.595	.6490
Presence of infiltrates on chest echograph + procalcitonin > 1 ng/mL	0.619	0.0351	0.541-0.694	.0007

AUC = area under the curve. See Table 1 legend for expansion of other abbreviations.

RESULTS

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NPV = negative predictive value; PPV = positive predictive value. See Table 1 and 2 legends for expansion of other abbreviations.

Limitations

- **The present study should be considered a pilot, exploratory analysis of a new type of score.**
- **Th e main limitation is that CEPPIS was constructed without a derivation cohort, having only been tested in a retrospective cohort.**

Conclusions

- **We propose that CEPPIS, a score principally based on chest echography and procalcitonin levels, might be better associated with the diagnosis of VAP. Despite its limitations, we are optimistic about the validity of CEPPIS. Prospective studies of unselected patients evaluating CEPPIS are needed before we can state solid conclusions regarding the potential value of this score to facilitate VAP diagnosis**

It can suggest us from the trial as follows:

- **1.It is very improtant for us to design a prospective clinical trial for the progressively increasing sensitivity and specificity of the diagnostic ventilation associated pneumonia.**
- **2.In the new clinical trial for the future ,we can select some more instructive infectious biomarkers such as CRP, IL-6,G trial or GM trial e.t.c. and other clinical monitoring data such as PVPI,EVLWI,and CVP, for re-evaluating the diagnositc VAP.**
- **The diagnosis of disease should be following by the acute and advanced medical technology ,in the critic care medicine,**

while these so –called- 'new technologies' have bursted out their magnificent forces.Why do we facilitate them?