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Including Organ Dysfunctions in a Predictive Score for Nosocomial Pneumonia After Cardiothoracic Surgery

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BACKGROUND: Clinical diagnosis of ICU-acquired pneumonia after cardiothoracic surgery is challenging. Johanson criteria (chest radiograph infiltrate, purulent tracheal secretions, fever, and leukocytosis) fail in half the cases. A high Clinical Pulmonary Infection Score (CPIS) and ≥ 2-point increase in Sequential Organ Failure Assessment (SOFA) score (SOFA↑ ≥ 2) may improve diagnosis. The aim of the study was to evaluate whether CPIS or SOFA↑ ≥ 2 contributes to predict ICU-acquired pneumonia in subjects after cardiothoracic surgery. METHODS: We used a prospective observational design. Spiegelhalter-Knill-Jones scoring systems including CPIS or SOFA↑ ≥ 2, together with other clinical and laboratory variables, were developed in a derivation cohort. A positive quantitative pulmonary sample culture was required to confirm ICU-acquired pneumonia. Area under the receiver operating characteristic curve (AUROC) was computed for each of the 2 scoring systems. The best system was evaluated in a validation cohort. RESULTS: Derivation and validation cohorts included 172 and 108 subjects, with 410 and 216 suspected ICU-acquired pneumonia episodes, respectively. AUROC was 0.53 ± 0.03 for CPIS ($P = .29$) and 0.54 ± 0.03 for SOFA↑ ≥ 2 ($P = .29$). Adding purulent tracheal secretions and leukocytosis to SOFA↑ ≥ 2 (SOFA model) increased AUROC to 0.65 ± 0.03 ($P < .001$). Adding catecholamine use to CPIS (CPIS model) increased AUROC only slightly, to 0.57 ± 0.03. The probabilities predicted by the SOFA model were reliable, especially when high or low. CONCLUSIONS: A clinical scoring system including at least SOFA↑ ≥ 2 increase barely improved ICU-acquired pneumonia prediction in subjects after cardiothoracic surgery. *Key words: hospital-acquired pneumonia; nosocomial pneumonia; sepsis; SOFA score; CPIS; prediction model development.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Postoperative nosocomial pneumonia after cardiothoracic surgery is the most common infection in surgical ICU patients and contributes to increase mortality.[1,2] ICU-acquired pneumonia occurs in both ventilated (ventilator-associated pneumonia [VAP]) and nonventilated patients.[3,4] The diagnosis is challenging, as many patients with the typical picture combining a fever, leukocytosis, purulent respiratory secretions, and radiographic lung infiltrates will only have confirmed VAP in 50% of cases.[5,6] Clinical Pulmonary Infection Score (CPIS) has been proposed to improve management of VAP,[7] but for diagnosis purpose, results were disappointing.[8-11] Few studies have evaluated CPIS after cardiothoracic surgery.[4] We hypothesized that if performance of CPIS was not optimal in non-surgical patients it might be worse in surgical patients, especially after cardiothoracic surgery, and therefore, an alternative way is needed. Other clinical signs can also serve to assess likelihood of ICU-acquired pneumonia.[9,12,13]

Unrecognized infection can cause new onset organ dysfunction: Development of unexplained organ dysfunction should, therefore, prompt a search for an underlying infection.[14] An increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2 points (SOFA↑ ≥ 2) combined with evidence suggesting infection is now used to define sepsis.[14] Since ICU-acquired pneumonia is by far the most frequent postoperative infection, performance of SOFA↑ ≥ 2 in improving its diagnosis and management deserves to be evaluated.

International guidelines recommend antibiotic therapy initiation as soon as ICU-acquired pneumonia is suspected.[15-18] Both undertreatment and overtreatment of ICU-acquired pneumonia may increase patient mortality and microbial selection pressure.[19-21] The decision to start antibiotics is guided by

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illness severity and by the probability of ICU-acquired pneumonia suggested by physical findings and investigations.[22] When assessing performance of a physical finding, investigation result, or score, the pretest probability of disease is important to consider. Consequently, populations used for studies of diagnostic performance should be uniform regarding likelihood of condition to be diagnosed.

The objective of this study was to compare diagnostic performance of 2 prediction models, one including CPIS and the other including SOFA↑ ≥ 2, in ICU subjects with suspected ICU-acquired pneumonia after cardiothoracic surgery. We also evaluated 5 bedside physical and laboratory findings as aids to diagnosis of ICU-acquired pneumonia.

QUICK LOOK

Current knowledge

Clinical diagnosis of nosocomial pneumonia after cardiothoracic surgery is challenging. Johanson criteria and more recently Clinical Pulmonary Infection Score (CPIS) have been proposed to improve diagnosis of nosocomial pneumonia, but results were disappointing. Unrecognized infection can cause sepsis, which is defined by a 2-point increase in Sequential Organ Failure Assessment (SOFA) score.

What this paper contributes to our knowledge

A score based on a ≥ 2-point SOFA score increase, purulent tracheal secretions, and leukocytosis barely improved prediction of nosocomial pneumonia compared to CPIS in cardiothoracic surgery subjects.

Methods

The design was observational: No changes were made to patient care for the study. The study protocol for the derivation cohort was approved by our institutional review board (IRB 2016–22), which waived the requirement for informed patient consent in compliance with French law on studies of anonymized health care data. The protocol for study of the validation cohort was approved by the appropriate ethics committee (Comité de Protection des Personnes Sud-Méditerranée II [number 2018-A02806]). A statement of nonrefusal to participate was obtained for each subject or surrogate in the validation cohort, in compliance with French law. The study was registered on ClinicalTrials.gov (NCT02683122) and was conducted in compliance with the Declaration of Helsinki.

Study Design and Subjects

We conducted a prospective single-center observational study in 2 cohorts of consecutive patients admitted between January 1, 2016–April 31, 2017 (derivation cohort) then between May 1, 2018–April 31, 2019 (validation cohort). All subjects were admitted after cardiothoracic surgery then suspected to have ICU-acquired pneumonia.

Data Collection

We prospectively recorded age, sex, type of surgery, acute-illness severity evaluated using Simplified Acute Physiology Score II, whether invasive mechanical ventilation was used, time from ICU admission to first bacteriological sampling, number of bacteriological samples, ICU length of stay, and vital status at ICU discharge. For each of the following variables, we determined the change between day before and day of bacteriological sampling (D−1 and D0, respectively): highest or lowest body temperature (°C), P_{aO_2}/F_{IO_2}, peripheral blood leukocyte and platelet counts, C-reactive protein level, and radiologic score.[23] We recorded presence on D0 of Johanson criteria, that is, new or progressive chest radiograph infiltrate, purulent tracheal secretions, fever > 38.3°C, and leukocytosis >10.0 G/L.[24] Purulent tracheal secretions were reported by the nurse or physician as change in sputum color from transparent to yellow-green. We computed a modified CPIS taking into account the 5 criteria available before bacteriological sampling (Supplemental e-Table 1, see related supplementary materials at http://www.rcjournal.com) and considered that scores > 6 suggested ICU-acquired pneumonia.[8,18,25]

We also recorded 5 clinical variables that can help to assess likelihood of ICU-acquired pneumonia, namely a need for catecholamine dosage increase, need for fluid expansion, failure to achieve fluid depletion, confusion (according to Confusion Assessment Method for the ICU),[26] and abnormal liver tests (aspartate aminotransferase ≥ 74 IU/mL [≥ 2N] and/or alanine aminotransferase ≥ 126 IU/mL [≥ 2N] and/or gamma-glutamyl transferase

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The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://rcjournal.com.

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≥ 110 IU/mL [≥ 2N] and/or alkaline phosphatase ≥ 174 IU/mL [≥ 1.5N] and/or bilirubin > 25 μmol/L [≥ 1.5N]).

Definitions, Sampling Techniques, and Antimicrobial Treatments

Sepsis can be defined as acute SOFA↑ ≥ 2 points due to infection.[14] Baseline SOFA score is assumed to be zero in patients with no known preexisting organ dysfunction.[14]

We defined ICU-acquired pneumonia as suggestive clinical findings and positive bacteriological results. Clinical suspicion of ICU-acquired pneumonia was based mainly on Johanson criteria (fever, presence of new pulmonary infiltrate, purulent secretions, and leukocytosis) but also on warning signs of incipient sepsis (altered mental status, thrombocytopenia, liver test alterations). Microbiological samples were collected routinely on D0[4,19]: A spontaneous sputum sample was collected from spontaneously breathing subjects,[4] whereas in subjects who were unable to produce spontaneous sputum or were receiving mechanical ventilation a senior physician performed fiberoptic bronchoscopy if allowed by blood gas values, with bronchoalveolar lavage (BAL) whenever possible.[4,19] When BAL was deemed hazardous to the subject or technically challenging, an endotracheal aspirate specimen was collected through inner channel of bronchoscopy tube via a sputum suction trap. Culture cutoffs for confirming ICU-acquired pneumonia were ≥ 10^7 CFU/mL for spontaneous sputum and ≥ 10^5 CFU/mL for endotracheal aspirate. For BAL, cutoffs were intracellular bacteria by direct examination in > 4% of recovered cells and/or culture ≥ 10^4 CFU/mL. Cultures positive above these cutoffs were the diagnostic reference standard. Using > 10^4 bacteria/mL of BAL fluid as the discriminative value, BAL has sensitivity of 71.1% and specificity of 79.6% relative to histopathology in a meta-analysis.[27] The positive likelihood ratio of BAL is the highest among bronchoscopic or non-bronchoscopic sampling methods.[27]

Our antibiotic strategy has been published previously.[19] The narrowest-spectrum antibiotic possible was given for 7 d to subjects with confirmed ICU-acquired pneumonia. We recorded any antibiotics already given on D0, with the duration collected as < 72 h or ≥ 72 h.

Sample Size Estimate

To estimate diagnostic accuracy of CPIS with an estimated area under the receiver operating characteristic curve (AUROC) 0.60[8] and margin of error ≤ 0.07, 122 confirmed ICU-acquired pneumonia episodes were required. We assumed that 15% of episodes would have missing data and, therefore, decided to include 140 episodes of confirmed ICU-acquired pneumonia. Assuming a prevalence of ICU-acquired pneumonia 0.40, 183 episodes of unconfirmed suspected ICU-acquired pneumonia were required (number of controls = number of cases/[prevalence/1-prevalence]). If 15% of episodes had missing data, we needed 210 episodes of suspected ICU-acquired pneumonia. The total estimated sample size was thus 350.

Statistical Analysis

Study variables are described as mean ± SD or median [interquartile range] for normal and non-normal continuous variables, respectively, and *n* (%) for categorical variables. The unit of analysis was episode of suspected ICU-acquired pneumonia. Comparisons of groups of confirmed ICU-acquired pneumonia and unconfirmed ICU-acquired pneumonia relied on Student *t* test or Mann-Whitney U test for continuous variables and chi-square test or Fisher exact test for categorical variables. Two-sided *P* values < .05 were taken to indicate statistically significant differences.

For each study variable, standard formulas were applied to calculate sensitivity (Se), specificity (Sp), positive likelihood ratio (LR+, Se/[100-Sp]), negative likelihood ratio (LR−, [100-Se]/Sp), positive predictive value (PPV), and negative predictive value (NPV). We computed AUROC values to assess diagnostic accuracy of ICU-acquired pneumonia of modified CPIS and SOFA↑ ≥ 2 and changes from D−1 to D0 in body temperature, S_{pO_2}/F_{IO_2}, leukocyte count, platelet count, C-reactive protein level, and radiologic score. AUROC values were compared as described by Hanley et al.[28]

We developed 2 prediction models using the simple scoring system developed by Spiegelhalter and Knill-Jones. This system combines elements of Bayes theorem and logistic regression,[29,30] which adds precision to risk assessment in individual subjects. The result is a system that neatly sidesteps some of the main disadvantages of the 2 original techniques. For example, it does not assume that all risk factors are acting independently within each outcome class (the "independence Bayes" assumption) because an adjustment is made, whereas at the same time predictions are presented in a form that many clinicians make diagnoses (by weighing up points for and against) and is mathematically simple to use (Supplemental e-Appendix 1, see related supplementary materials at http://www.rcjournal.com). Variables whose logistic regression coefficients are not significantly different from zero and/or for which adjusted weight of evidence is below one are dropped from the system. Presentation of predictions is less mathematical and much more clinically relevant than that of conventional logistic regression. One of our models included CPIS (CPIS model) and the other SOFA↑ ≥ 2 (SOFA model). The CPIS model was based on CPIS > 6 and the 5 bedside clinical variables (increased catecholamine dosage, fluid expansion, failure to achieve fluid depletion, confusion, and liver test alterations). The SOFA model included SOFA↑ ≥ 2, Johanson criteria (which constitute 4 of the 6 CPIS items), and the same 5 bedside clinical variables. Current

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Table 1. Main Features of Subjects in Derivation and Validation Cohorts

	Derivation Cohort $n = 172$	Validation Cohort $n = 108$	P
Age, y	61 ± 13	61 ± 14	.70
Male	124 (72)	81 (75)	.59
Reasons for ICU admission			.48
Cardiac surgery	53 (31)	37 (34)	
Pulmonary resection	14 (8)	11 (10)	
Pulmonary endarterectomy	50 (29)	26 (24)	
Aortic surgery	12 (7)	6 (6)	
ECMO	16 (9)	5 (5)	
Venoarterial	14 (8)	5 (5)	
Venovenous	2 (1)	23 (21)	
Miscellaneous	27 (16)		
SAPS II score	37.8 ± 13.8	35.8 ± 13.3	.24
Time from ICU admission to D0[a], d	2.5 [2.0–4.0]	3.0 [2.0–5.0]	.44
Number of bacteriological samples	2.0 [1.0–3.0]	2.0 [1.0–3.0]	.83
Invasively ventilated subjects	136 (79)	82 (76)	.54
ICU length of stay, d	15.0 [7.0–27.0]	13.0 [7.0–22.5]	.45
Death in ICU	34 (19.8)	22 (20.4)	.54

Data are presented as mean ± SD, *n* (%), or median [interquartile range].
[a]D0 was the day nosocomial pneumonia was first suspected and day first bacteriological samples were collected.
ECMO = extracorporeal membrane oxygenation
SAPS II = Simplified Acute Physiology Score II.

antibiotic therapy alters diagnostic abilities and mechanical ventilation is a major risk factor for ICU-acquired pneumonia and were, therefore, included in both models. We applied Hosmer-Lemeshow test to assess goodness of fit of the models. We compared AUROC values of the 2 models then assessed predictive accuracy of the model with the best AUROC in validation cohort. We determined expected number of subjects with ICU-acquired pneumonia (E), assuming that prediction was fully reliable. According to null hypothesis of perfect reliability, observed number of subjects with ICU-acquired pneumonia (O) would be approximately distributed, with mean E and standard error (SE) equal to (E [1-E/n]).[1,2] Consequently, Z = (O-E)/sensitivity would be approximately a standard normal statistic. Values of $Z > 2$ would suggest excessively low probabilities attributed to ICU-acquired pneumonia and values of $Z < -2$ excessively high probabilities.[30]

We computed Net Reclassification Index (NRI) to assess improvements in model performance compared to CPIS.[31] NRI is an index that attempts to quantify how well a new model reclassifies subjects, either appropriately or inappropriately, as compared to an old model. This method was created as an alternative to comparing AUROC. A low probability of ICU-acquired pneumonia was defined as CPIS ≤ 6 [8,18,25] or probability ≤ 35%.[8]

Results

Table 1 reports main features of subjects in the 2 cohorts and Supplemental e-Table 2 (See related supplementary materials at http://www.rcjournal.com) the microorganisms identified.

The derivation cohort comprised 1,384 subjects, of whom 172 (12.4%) had 410 episodes of suspected ICU-acquired pneumonia. Among criteria of Johanson, abnormal temperature was present in 25.8%, abnormal leukocytosis in 81.9%, purulent tracheal secretions in 62.2%, and chest radiograph infiltrate in 84.1%, irrespective of whether diagnosis of pneumonia was definitively established or excluded. All Johanson criteria were present in only 10.2% of suspected episodes of ICU-acquired pneumonia. Respiratory samples were BAL fluid 364 (88.8%) episodes, endotracheal aspirate 22 (5.4%) episodes, and spontaneous sputum 24 (5.8%) episodes. Of the 172 subjects, 78 (45.3%) had 165 episodes of confirmed ICU-acquired pneumonia. Six extrapulmonary infections (3.6%) were diagnosed during 165 episodes of ICU-acquired pneumonia and 32 extrapulmonary infections (13.1%) during 245 episodes of unconfirmed ICU-acquired pneumonia ($P = .001$). Thirty-nine episodes (15.9%) of non-confirmed ICU-acquired pneumonia received empirical antibiotic therapy compared to 140 (84.8%) of confirmed ICU-acquired pneumonia ($P < .001$) (Supplemental e-Fig. 1, see related supplementary materials at http://www.rcjournal.com). Empirical antibiotic therapy was stopped in 31 subjects and pursued in 8 subjects because of another infection. In the 140 episodes of ICU-acquired pneumonia, antibiotic therapy was reduced 72 times, modified or expanded 20 times, and unchanged 48 times. Mortality in subjects who received or not received empirical antibiotic

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therapy was similar: 22.9% (47/231) versus 20.3% (41/179) ($P = .53$).

The validation cohort was composed of 108 (10.7%) of the 1,039 subjects admitted to our ICU during the relevant period. These 108 subjects had 216 episodes of suspected nosocomial pneumonia investigated by BAL (no. 184, 85.2%), endotracheal aspirate (no. = 25, 11.6%), or spontaneous sputum (no. = 7, 3.2%). Of the 108 subjects, 62 (57.4%) experienced 84 episodes of confirmed ICU-acquired pneumonia. Four extrapulmonary infections (4.8%) were diagnosed during 84 episodes of ICU-acquired pneumonia and 17 extrapulmonary infections during the 132 episodes of unconfirmed ICU-acquired pneumonia ($P = .049$).

Reliability of CPIS, SOFA↑ ≥ 2, Johanson Criteria, and the 5 Bedside Criteria

CPIS was available for 396 episodes of suspected ICU-acquired pneumonia. The AUROC was 0.53 ± 0.03 (95% CI 0.47–0.59, $P = .29$). CPIS was > 6 in 38/160 (24%) episodes of confirmed nosocomial pneumonia versus 33/236 (14%) episodes of unconfirmed ICU-acquired pneumonia ($P = .01$). SOFA score was available for 403 episodes of suspected ICU-acquired pneumonia. The AUROC for SOFA↑ ≥ 2 was 0.54 ± 0.03 (95% CI 0.48–0.60, $P = .29$). SOFA↑ ≥ 2 occurred in 52/164 (32%) episodes of confirmed ICU-acquired pneumonia versus 37/239 (15%) of unconfirmed suspected ICU-acquired pneumonia episodes ($P < .001$). The difference between AUROC values for CPIS and SOFA↑ ≥ 2 (0.01 ± 0.04) was not significant ($P = .81$).

Table 2 reports Se, Sp, PPV, NPV, LR+, and LR− values for CPIS > 6, SOFA↑ ≥ 2, Johanson criteria, and the 5 bedside criteria. Table 3 shows changes between D−1 and D0 in leukocyte and platelet counts, C-reactive protein level, radiologic score, and S_{pO_2}/F_{IO_2}. The only variable for which change differed significantly between the groups with confirmed and unconfirmed suspected ICU-acquired pneumonia was leukocyte count, which was higher when ICU-acquired pneumonia was not confirmed. The AUROC values for these changes were 0.42 ± 0.03 (95% CI 0.36–0.48, $P = .008$) leukocytes, 0.51 ± 0.03 (95% CI 0.45–0.57, $P = .61$) platelets, 0.54 ± 0.03 (95% CI 0.48–0.60, $P = .24$) C-reactive protein, 0.48 ± 0.03 (95% CI 0.48–0.60, $P = .47$) radiologic score, 0.55 ± 0.03 (95% CI 0.49–0.60, $P = .09$) S_{pO_2}/F_{IO_2}, and 0.51 ± 0.29 (95% CI 0.45–0.57, $P = .79$) body temperature.

Spiegelhalter-Knill-Jones Models and Application to Individual Subjects

CPIS Spiegelhalter-Knill-Jones model included CPIS > 6, ongoing antibiotic therapy, mechanical ventilation, and increased catecholamine dosage. The AUROC for CPIS model was 0.57 ± 0.03 (95% CI 0.51–0.63, $P = .29$). The Hosmer-Lemeshow test indicated good fit of the model (chi-square 3.51 for 5 degrees of freedom, $P = .62$). The SOFA Spiegelhalter-Knill-Jones model included SOFA↑ ≥ 2, ongoing antibiotic therapy, mechanical ventilation, purulent tracheal secretions, and leukocytosis. AUROC for the SOFA model was 0.65 ± 0.03 (95% CI 0.59–0.70, $P < .001$). Model fit was good according to Hosmer-Lemeshow test (chi-square 3.68 for 6 degrees of freedom, $P = .72$). The difference between AUROC values for CPIS and SOFA models was −0.08 ± 0.04 ($P = .050$).

Table 4 lists the starting score (prior probability) and adjusted weights of evidence needed to predict risk of nosocomial pneumonia in individual subjects using SOFA model. Starting score was added to appropriate adjusted weights of evidence for that subject. Total score thus obtained was converted to probability of ICU-acquired pneumonia as shown in Figure 1. An example is provided in Supplemental e-Appendix 2 (See related supplementary materials at http://www.rcjournal.com).

Predictive Accuracy of the SOFA Model

We tested SOFA Spiegelhalter-Knill-Jones model (available for 210 episodes of suspected ICU-acquired pneumonia) in a prospective validation cohort of subjects comparable to those in derivation cohort (Table 1). The AUROC was 0.67 ± 0.04. The difference between AUROC values in derivation and validation cohorts was not significant (−0.02 ± 0.04; $P = .61$).

Figure 2 gives reliability of adjusted predictions. Predicted probabilities were reliable, especially when probability was high. For instance, among subjects with predicted probability 60%, about 60% had confirmed ICU-acquired pneumonia.

Impact on Clinical Decision Making

CPIS was available in 213 episodes of suspected nosocomial pneumonia. Low probability of nosocomial pneumonia was defined as either CPIS ≤ 6 or probability ≤ 35% given by the model. Event NRI was 0.295, and non-event NRI was −0.146. Thus, compared to CPIS, the SOFA Spiegelhalter-Knill-Jones model correctly reclassified 29.5% of subjects with confirmed nosocomial pneumonia and incorrectly reclassified 14.6% of subjects without confirmed ICU-acquired pneumonia. (Supplemental e-Table 3, see related supplementary materials at http://www.rcjournal.com). Overall NRI was 0.148.

Discussion

Our study documents just how limited correlation is between core clinical criteria used to diagnose ICU-acquired pneumonia and actual presence or absence of ICU-acquired

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Table 2. Accuracy of Variables Used to Predict Hospital-Acquired Pneumonia

Variable	Se	Sp	PPV	NPV	LR+	LR−
CPIS > 6	0.24 (0.17–0.31)	0.86 (0.81–0.90)	0.53 (0.41–0.65)	0.62 (0.57–0.68)	1.70 (1.11–2.59)	0.89 (0.80–0.98)
SOFA↑ ≥ 2	0.32 (0.25–0.39)	0.84 (0.79–0.89)	0.58 (0.47–0.69)	0.64 (0.59–0.69)	2.05 (1.41–2.97)	0.81 (0.72–0.91)
Johanson criteria						
New or progressive chest radiograph infiltrate	0.84 (0.77–0.89)	0.15 (0.11–0.21)	0.40 (0.35–0.45)	0.58 (0.45–0.70)	0.99 (0.91–1.08)	1.06 (0.67–1.66)
Purulent tracheobronchial secretions	0.70 (0.62–0.76)	0.43 (0.37–0.49)	0.45 (0.39–0.51)	0.68 (0.60–0.75)	1.22 (1.05–1.41)	0.71 (0.54–0.93)
Fever > 38.3°C	0.24 (0.22–0.31)	0.72 (0.69–0.78)	0.36 (0.27–0.46)	0.58 (0.52–0.64)	0.84 (0.59–1.18)	1.06 (0.95–1.20)
Leukocytosis > 12×10^9/mL	0.78 (0.71–0.84)	0.15 (0.11–0.20)	0.38 (0.33–0.44)	0.51(0.39–0.62)	0.92 (0.84–1.01)	1.44 (0.95–2.18)
Probable pulmonary infection according to Johanson criteria[a]	0.18 (0.12–0.25)	0.81 (0.76–0.86)	0.39 (0.28–0.51)	0.60 (0.54–0.65)	0.96 (0.63–1.47)	1.01 (0.92–1.11)
Definite pulmonary infection according to Johanson criteria[b]	0.10 (0.06–0.16)	0.89 (0.84–0.93)	0.10 (0.06–0.16)	0.60 (0.54–0.65)	0.92 (0.51–1.66)	1.01 (0.94–1.08)
Increase in catecholamine dosage	0.24 (0.18–0.32)	0.72 (0.66–0.77)	0.36 (0.28–0.46)	0.58 (0.53–0.64)	0.86 (0.62–1.20)	1.05 (0.94–1.19)
Need for fluid expansion	0.25 (0.19–0.33)	0.75 (0.69–0.80)	0.41 (0.31–0.51)	0.60 (0.54–0.65)	1.02 (0.73–1.44)	0.99 (0.89–1.11)
Fluid depletion failure	0.33 (0.26–0.40)	0.66 (0.59–0.72)	0.39 (0.31–0.48)	0.59 (0.53–0.65)	0.95 (0.72–1.26)	1.02 (0.89–1.18)
Confusion	0.18 (0.12–0.24)	0.82 (0.76–0.86)	0.39 (0.28–0.51)	0.59 (0.54–0.65)	0.96 (0.63–1.46)	1.01 (0.92–1.11)
Abnormal blood liver tests	0.43 (0.35–0.51)	0.56 (0.49–0.62)	0.39 (0.32–0.47)	0.59 (0.53–0.66)	0.98 (0.78–1.22)	1.02 (0.86–1.21)

Data are presented as (95% CI).
[a]Probable infection was defined as fever, leukocytosis, and either of the other 2 criteria.
[b]Definite infection was defined as presence of all 4 criteria.
Se = sensitivity
Sp = specificity
PPV = positive predictive value
NPV = negative predictive value
LR+ = positive likelihood ratio
LR− = negative likelihood ratio
CPIS = Clinical Pulmonary Infection Score
SOFA = Sequential Organ Failure Assessment
SOFA↑ ≥ 2 = ≥ 2-point increase in SOFA score

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Table 3. Changes in White Blood Cell Count, Platelet Count, C-Reactive Protein, Radiologic Score, and S_{pO_2}/F_{IO_2} Between Day Before and Day When First Respiratory Bacteriological Sample Was Taken in Derivation Cohort

Variable	Nosocomial Pneumonia ($n = 165$)	No Nosocomial Pneumonia ($n = 245$)	*P*
White blood cells D−1, G/L	14.6 ± 7.0	14.9 ± 8.3	.75
White blood cells D0, G/L	15.2 ± 8.4	16.3 ± 8.6	.19
White blood cells D0–D−1, %	3.8 [−15.3 to 22.1]	8.1 [−6.6 to 31.0]	.008
Platelets D−1, G/L	205 ± 135	227 ± 134	.11
Platelets D0, G/L	209 ± 134	233 ± 141	.09
Platelets D0–D−1, %	3.0 [−7.0 to 15.0]	1.0 [−7.0 to 18.0]	.73
C-reactive protein D−1, mg/L	133 ± 91	129 ± 88	.64
C-reactive protein D0, mg/L	150 ± 90	144 ± 92	.53
C-reactive protein D0–D−1, %	8.8 [−14.7 to 53.1]	11.3 [−6.9 to 43.4]	.73
Radiologic score D−1	5.3 ± 2.4	5.4 ± 2.4	.81
Radiologic score D0	5.7 ± 2.3	6.0 ± 2.5	.20
Radiologic score D0–D−1	0 [0–1.0]	0 [0–1.0]	.43
S_{pO_2}/F_{IO_2} D−1, mm Hg	214 ± 84	223 ± 100	.35
S_{pO_2}/F_{IO_2} D0, mm Hg	190 ± 92	203 ± 96	.17
S_{pO_2}/F_{IO_2} D0–D−1, %	−9.9 [−30.4 to 9.1]	−6.6 [−28.6 to 16.4]	.15

Data are presented as mean ± SD or median [IQR].
D−1 = day before bacteriological sampling
D0 = day of bacteriological sampling

Table 4. Crude Weights of Criteria for Confirmed and Unconfirmed Episodes of Suspected Nosocomial Pneumonia and Effect of Adjustment by Logistic Regression. Goodness of Fit Assessed Using Chi-Square Test Was Not Significant ($P = .72$)

Criteria	Nosocomial Pneumonia ($n = 165$)	No Nosocomial Pneumonia ($n = 245$)	Crude Weights	Shrinkage Factors From Logistic Regression (SE)	Adjusted Weight (SE)	Range of Adjusted Weights
Prior probability	0.40	0.60	−41		−41	
SOFA↑ ≥ 2[a], yes/no	52/112	37/200	72/−21	1.00 (0.26)	72 (19)/−21 (−5)	93
Purulent tracheal secretions, yes/no	115/140	50/105	20/−34	0.54 (0.22)	11 (4)/−18 (−7)	29
Leukocytosis, yes/no	38/123	68/173	−8/36	0.50 (0.28)	−4 (2)/18 (10)	22
Mechanical ventilation, yes/no	146/19	204/41	6/−37	0.47 (0.32)	3 (2)/−17 (−12)	20
Ongoing antibiotic therapy, yes/no	30/135	59/186	−27/8	0.21 (0.27)	−6 (−7)/2 (2)	8

Data are presented as *n* unless other indicated.
[a]Data missing for 7 episodes of confirmed nosocomial pneumonia.
SE = standard error
SOFA = Sequential Organ Failure Assessment
SOFA↑ ≥ 2 = ≥ 2-point increase in SOFA score

pneumonia. A prediction model including SOFA↑ ≥ 2, ongoing antibiotic therapy, mechanical ventilation, purulent tracheal secretions, and leukocytosis barely improved diagnosis of ICU-acquired pneumonia in postoperative cardiothoracic-surgery subjects.

In keeping with scant earlier data on CPIS after cardiothoracic surgery, the contribution of this tool to diagnosis of ICU-acquired pneumonia was small.[4] In a large multicenter randomized trial[9] that included a third of postoperative subjects, the AUROC for modified CPIS was 0.47. Two smaller studies[10,11] obtained AUROC values 0.55 and 0.67. Even when CPIS > 6 was combined with other potentially relevant variables such as catecholamine dosage increase, AUROC values were < 0.60.

Many components of CPIS are derived from criteria described by Johanson et al[24] 4 decades ago. Most studies used these criteria, although the result was a mistaken diagnosis in 50% of subjects[5,6,8] Se and Sp values of Johanson criteria for diagnosing definite ICU-acquired pneumonia have ranged from 15.5–23.1% and from 91.0–92.0%,

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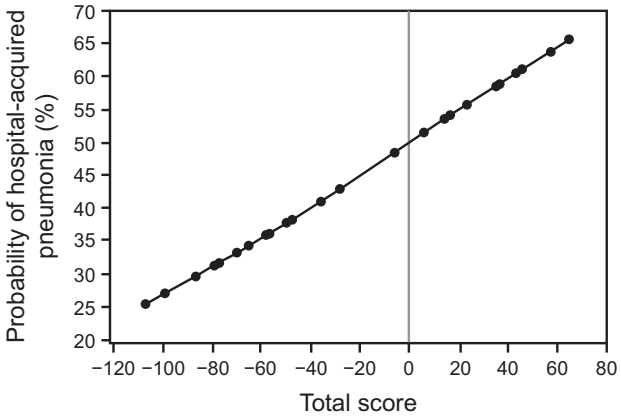
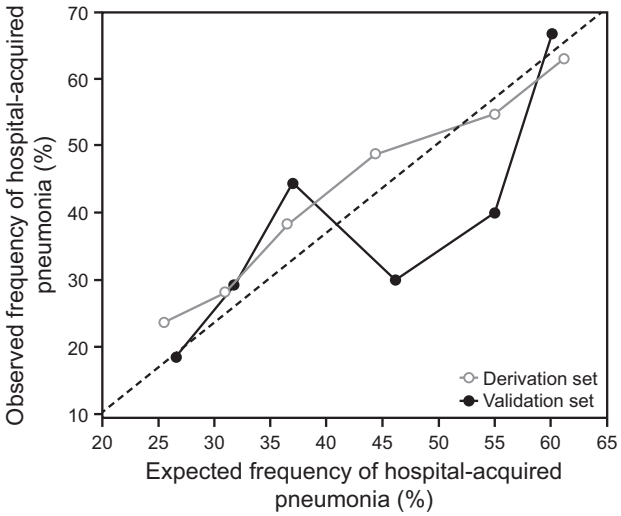


Fig. 1. Relationship between total score given by our scoring system and theoretical probability of ICU-acquired pneumonia. Probability = $1/(e^{-T/100+1})$; score = 100 Ln (probability/[1-probability]).



Subjects, *n*						
Derivation:	17	111	151	47	36	41
Validation:	38	62	45	19	27	27

Fig. 2. Observed and expected (predicted) frequencies of ICU-acquired pneumonia in validation cohort of 216 episodes of suspected ICU-acquired pneumonia. A perfect predictor would produce a line coinciding exactly with the diagonal line running from bottom left to top right (identity line). Z statistic values are within the −2 to +2 range, indicating good fit of the predictor to the identity line, that is, reliable predictions.

respectively,[27,32] in accordance with our results. In our population, purulent tracheal secretions and chest radiograph infiltrate had best sensitivity but worst specificity.[27,32] Chest radiography after surgery has been reported to be only 25% sensitive and 75% specific.[33] A normal chest radiograph does not exclude VAP, and neither does a focal infiltrate confirm diagnosis of VAP.[33] Purulent tracheal secretions, with LR+ 1.22 in our study, may be the most useful among Johanson criteria for diagnosing ICU-acquired pneumonia.[27,32] We also looked for links between ICU-acquired pneumonia and other clinical variables including unexplained hypotension,[12,13] increased catecholamine requirements,[9,13] need for fluid expansion, failure to achieve fluid depletion, confusion,[12] and abnormal blood liver tests.[12] Interestingly, some of these variables are used in SOFA score. None, whether used alone or in combination with other variables using the Spiegelhalter-Knill-Jones method, contributed substantially to diagnosis of ICU-acquired pneumonia. The only laboratory variable that changed significantly from D−1 to D0 was leukocyte count, which was higher when suspected ICU-acquired pneumonia was not confirmed, in keeping with a previous report.[32] Leukocyte count elevation after cardiothoracic surgery may be related to surgical trauma, blood loss, blood transfusion, and cardiopulmonary bypass.[34]

Sepsis is now defined as at least SOFA↑ ≥ 2 combined with suspected infection.[14] Pneumonia develops in patients with immune-defense dysregulation that can result in sepsis with organ dysfunction. Consequently, the onset of organ dysfunction may constitute an early sign of ICU-acquired pneumonia.[14] SOFA↑ ≥ 2 may serve as a warning sign in patients with or without[35] suspected infection. In a 2021 retrospective study,[36] SOFA↑ ≥ 2 was 40% sensitive and 91% specific for VAP, suggesting limited accuracy of this variable. However, SOFA↑ ≥ 2 is not intended for use as a standalone criterion for ICU-acquired pneumonia.[36]

In a study of heart surgery, 9.5% of subjects with suspected or proven infection met Sepsis-3 criteria.[37] The respiratory tract was most frequent site of proven infection (72.1%).[37] On the other hand, 5% of subjects had SOFA↑ ≥ 2 but no infection.[37] We built a Spiegelhalter-Knill-Jones clinical scoring system that combined SOFA↑ ≥ 2 with 2 Johanson criteria (purulent secretions and leukocytosis). This model is easy to use at bedside and has good predictive accuracy, notably in patients with low or high probability of ICU-acquired pneumonia. Although our SOFA model does not perform sufficiently well to be used alone, it may help to decide whether an invasive management strategy and/or antibiotics are in order.[19,21] Our clinical scoring system improved identification of subjects with ICU-acquired pneumonia by 30% compared to CPIS, which is meaningful given higher risk of death among patients with untreated ICU-acquired pneumonia.[18,22,32] ICU-acquired pneumonia was mistakenly predicted by the model in only 15% of subjects. Patients whose probability of ICU-acquired pneumonia is ≤ 35%[8] should not be started on antibiotics but should benefit from a diagnostic culture of lung secretions. In addition, an alternative diagnosis should be sought and include at least a more complete bacteriological workup and assessment of extracellular volumes. In these patients, there is sufficient time to gather additional data to determine whether the potential benefits of antibiotics outweigh their risks.[20,21] The proportion of

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subjects with extrapulmonary infections was higher in our group without versus with ICU-acquired pneumonia, consistent with earlier data.[19]

One limitation of our study is the single-center design with recruitment of derivation and validation cohort subjects at the same ICU. Validation in cohorts from other ICUs is needed. Importantly, suspected ICU-acquired pneumonia was an inclusion criterion, and suspicion of ICU-acquired pneumonia relied on several variables used in our prediction model. The reference standard for the diagnosis of ICU-acquired pneumonia was the result of microbiological tests on respiratory samples, but these consisted of endotracheal aspirate or spontaneous sputum, as opposed to BAL fluid, in some subjects, albeit a small minority. Our unit of evaluation was suspected ICU-acquired pneumonia episode and not subjects with suspected ICU-acquired pneumonia. However, ICU-acquired pneumonia recurrence or relapse is common after cardiothoracic surgery.[23]

Conclusions

CPIS and other widely used clinical and laboratory variables showed limited usefulness for diagnosing ICU-acquired pneumonia after cardiothoracic surgery. A clinical scoring system including a SOFA↑ $\geq$ 2, purulent tracheal secretions, and leukocytosis barely helped to predict ICU-acquired pneumonia. A randomized trial is warranted to determine whether this scoring system improves decisions about invasive investigations and antibiotics in patients with suspected ICU-acquired pneumonia after cardiothoracic surgery.

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REFERENCES

1. Ailawadi G, Chang HL, O'Gara PT, O'Sullivan K, Woo YJ, DeRose JJ, et al. Pneumonia after cardiac surgery: experience of the National Institutes of Health/Canadian Institutes of Health Research Cardiothoracic Surgical Trials Network. J Thorac Cardiovasc Surg 2017;153(6):1384-1391.
2. Vincent JL, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, et al; EPIC III Investigators. Prevalence and outcomes of infection among patients in intensive care units in 2017. JAMA 2020;323(15):1478-1487.
3. Esperatti M, Ferrer M, Theessen A, Liapikou A, Valencia M, Saucedo LM, et al. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus non-ventilated patients. Am J Respir Crit Care Med 2010;182(12):1533-1539.
4. Stéphan F, Zarrouki Y, Mougeot C, Imbert A, Kortchinsky T, Pilorge C, et al. Non-ventilator ICU-acquired pneumonia after cardiothoracic surgery: accuracy of diagnostic tools and outcomes. Respir Care 2016;61(3):324-332.
5. Fagon JY, Chastre J, Hance AJ, Domart Y, Trouillet JL, Gibert C. Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. Chest 1993;103(2):547-553.
6. Wunderink RG. Clinical criteria in the diagnosis of ventilator-associated pneumonia. Chest 2000;117(4 Suppl 2):191S-194S.
7. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991;143(5 Pt 1):1121-1129.
8. Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the Clinical Pulmonary Infection Score revisited. Am J Respir Crit Care Med 2003;168(2):173-179.
9. Lauzier F, Ruest A, Cook D, Dodek P, Albert M, Shorr AF, et al; Canadian Critical Care Trials Group. The value of pretest probability and modified clinical pulmonary infection score to diagnose ventilator-associated pneumonia. J Crit Care 2008;23(1):50-57.
10. Gaudet A, Martin-Loeches I, Povoa P, Rodriguez A, Salluh J, Duhamel A, et al; TAVeM study group. Accuracy of the Clinical Pulmonary Infection Score to differentiate ventilator-associated tracheobronchitis from ventilator-associated pneumonia. Ann Intensive Care 2020;10(1):101.
11. Schurink CAM, Nieuwenhoven CAV, Jacobs JA, Rozenberg-Arska M, Joore HCA, Buskens E, et al. Clinical Pulmonary Infection Score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med 2004;30(2):217-224.
12. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369(21):2063.
13. Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med 2020;46(5):888-906.
14. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801-810.
15. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63(5):e61-111-e111.
16. Masterton RG, Galloway A, French G, Street M, Armstrong J, Brown E, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2008;62(1):5-34.
17. Leone M, Bouadma L, Bouhemad B, Brissaud O, Dauger S, Gibot S, et al. Hospital-acquired pneumonia in ICU. Anaesth Crit Care Pain Med 2018;37(1):83-98.
18. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017;50(3):1700582.
19. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stéphan F, et al Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med 2000;132(8):621-630.
20. Kalil AC, Timsit JF. Less is more: critically ill status is not a carte blanche for unlimited antibiotic use. Intensive Care Med 2020;46(11):2075-2078.
21. Mi MY, Klompas M, Evans L. Early administration of antibiotics for suspected sepsis. N Engl J Med 2019;380(6):593-596.

RESPIRATORY CARE Paper in Press. Published on September 13, 2022 as DOI: 10.4187/respcare.09911

22. Brun-Buisson C. Guidelines for treatment of hospital-acquired pneumonia. Semin Respir Crit Care Med 2002;23(5):457-469.
23. Combes A, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Chastre J. Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. Crit Care Med 2007;35(1):146-154.
24. Johanson WG, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with Gram-negative bacilli. The significance of colonization of the respiratory tract. Ann Intern Med 1972;77 (5):701-706.
25. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 2000;162(2):505-511.
26. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286(21):2703-2710.
27. Fernando SM, Tran A, Cheng W, Klompas M, Kyeremanteng K, Mehta S, et al. Diagnosis of ventilator-associated pneumonia in critically ill adult patients–a systematic review and meta-analysis. Intensive Care Med 2020;46(6):1170-1179.
28. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143(1):29-36.
29. Spiegelhalter DJ, Knill-Jones RP. Statistical and knowledge-based approaches to clinical decision-support systems, with an application in gastroenterology. Journal of the Royal Statistical Society Series A (General) 1984;147(1):35-77.
30. Spiegelhalter DJ. Statistical methodology for evaluating gastrointestinal symptoms. Clin Gastroenterol 1985;14(3):489-515.
31. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27(2):157-172.discussion 207-212.
32. Klompas M. Does this patient have ventilator-associated pneumonia? JAMA 2007;297(14):1583-1593.
33. Butler KL, Sinclair KE, Henderson VJ, McKinney G, Mesidor DA, Katon-Benitez I. The chest radiograph in critically ill surgical patients is inaccurate in predicting ventilator-associated pneumonia. Am Surg 1999;65(9):805-809.discussion 809-810.
34. Laffey JG, Boylan JF, Cheng DCH. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 2002 Jul;97(1):215-252.
35. Seymour CW, Angus DC. Clinical criteria to identify patients with sepsis–reply. JAMA 2016;316(4):454.
36. Gaudet A, Devos M, Keignart S, Pouly O, Lecailtel S, Wallet F, et al. Usefulness of sepsis-3 in diagnosing and predicting mortality of ventilator-associated lower respiratory tract infections. PLoS One 2021;16 (1):e0245552.
37. Howitt SH, Herring M, Malagon I, McCollum CN, Grant SW. Incidence and outcomes of sepsis after cardiac surgery as defined by the sepsis-3 guidelines. Br J Anaesth 2018;120(3):509-516.