Accuracy of C-reactive protein, procalcitonin and mid-regional pro-atrial natriuretic peptide to guide site of care of community-acquired pneumonia

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Presenter; PGY 高碧珍
Supervisor; VS吳柏衝
20100622

Background & Objective

- Aim ; to test whether blood concentration of CRP, PCT and ANP at initial ED visit could help physicians to accurately identify those who should be treated as inpatients among low-risk CAP patients (not hemodynamic or respiratory failure, unstable comorbidities, and pleural effusion)
- primary objective : assess the overall effectiveness of CRP, PCT, and ANP levels to discriminate between gold-standard inpatients and outpatients.
- secondary objective: identify useful cutoffs for any of those biomarkers to guide gold-standard hospitalization decision

Methods

- **Design**: Multicenter, prospective, observational study with blind evaluation
- **Setting**: Emergency departments of 12 French hospitals. (November 2004 to November 2007)
- **Patients:** 549 consecutive, immunocompetent adult patients with mild CAP.
- Microbiological findings were positive in 74 (15%) ; 32 Strep pneumoniae, 6 Strept species, 17 E. coli, 9 Staph aureus, 5 Legionella pneumophila, 5 Haemophilus influenzae, 6 miscellaneous
- **Measurements:** Centralized and blind measure of baseline CRP, PCT, and ANP; sensitivity, specificity, and positive and negative likelihood ratios (LR+, LR-) for determining hospital admission.

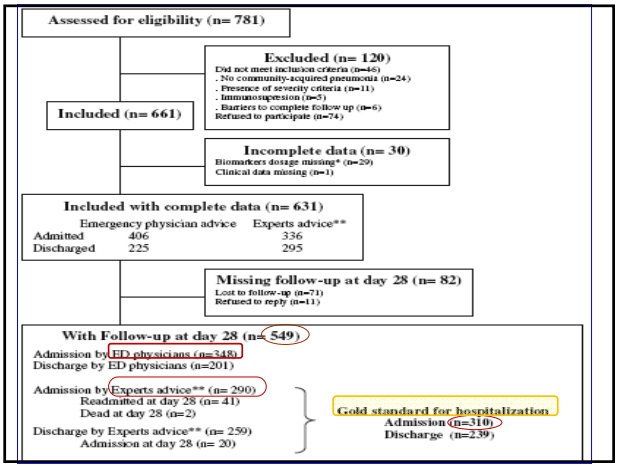


Table 1 Baseline characteristics of the study population and comparison of study groups according to gold-standard hospital admission decision

	Total (n = 549)	Gold-standard hospital admission decision[a]		p Value[b]
		Discharge (n = 239)	Admission (n = 310)	
Demographic factor				
Male sex, n (%)	297 (54.1)	124 (51.9)	173 (55.8)	0.39
Age (years), mean (SD)	54.7 (20.2)	42.3 (14.3)	64.3 (18.8)	<0.01
Nursing home resident, n (%)	10 (1.8)	2 (0.8)	8 (2.6)	0.10
Comorbid conditions:				
Diabetes mellitus, n (%)	59 (10.7)	5 (2.1)	54 (17.4)	<0.01
Liver disease, n (%)	7 (1.3)	0 (0.0)	7 (2.2)	0.02
Congestive heart disease, n (%)	103 (18.8)	6 (2.5)	97 (31.3)	<0.01
Cerebrovascular disease, n (%)	12 (2.2)	1 (0.4)	11 (3.5)	0.02
Chronic renal disease, n (%)	6 (1.1)	0 (0.0)	6 (1.9)	0.04
PSI risk class (no. of points)				<0.01
I–II (≤70), n (%)	362 (65.9)	235 (98.3)	127 (41.0)	
III (71–90), n (%)	90 (16.4)	4 (1.7)	86 (27.7)	
IV–V (>91), n (%)	97 (17.7)	0 (0.0)	97 (31.3)	
CURB-65 (no of points)				<0.01
0, n (%)	36 (6.6)	21 (8.8)	15 (4.9)	
1, n (%)	269 (49.2)	174 (72.8)	95 (30.8)	
2, n (%)	147 (26.9)	38 (15.9)	109 (35.4)	
3, n (%)	78 (14.3)	6 (2.5)	72 (23.4)	
4, n (%)	17 (3.1)	0 (0)	17 (5.5)	
Biomarker level				
CRP (mg/L), median [IQR]	126.6 [56.8; 234.6]	103.0 [45.8; 192.1]	150.2 [67.2; 256.7]	<0.01
PCT (ng/mL), median [IQR]	0.3 [0.1; 2.0]	0.2 [0.1; 0.8]	0.5 [0.1; 3.4]	<0.01
ANP (pmol/L), median [IQR]	82.1 [55.0; 129.4]	64.8 [45.5; 84.8]	110.1 [73.0; 179.4]	<0.01

Pneumonia severity index

Step 1: Stratify to Risk Class I vs. Risk Classes II-V	
Presence of:	
Over 50 years of age	Yes/No
Altered mental status	Yes/No
Pulse ≥125/minute	Yes/No
Respiratory rate >30/minute	Yes/No
Systolic blood pressure <90 mm Hg	Yes/No
Temperature <35°C or ≥40°C	Yes/No
History of:	
Neoplastic disease	Yes/No
Congestive heart failure	Yes/No
Cerebrovascular disease	Yes/No
Renal disease	Yes/No
Liver disease	Yes/No
If any "Yes", then proceed to Step 2	
If all "No" then assign to **Risk Class I**	

Demographics	Points Assigned
If Male	+Age (yr)
If Female	+Age (yr) - 10
Nursing home resident	+10
Comorbidity	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical Exam Findings	
Altered mental status	+20
Pulse ≥125/minute	+20
Respiratory rate >30/minute	+20
Systolic blood pressure <90 mm Hg	+15
Temperature <35°C or ≥40°C	+10

CURB-65

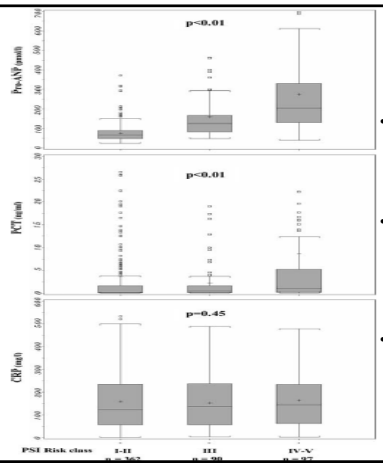
- **Each risk factor scores one point, for a maximum score of 6**:
- **C**onfusion of new onset
- **U**rea > 7 mmol/l (BUN > 19)
- **R**espiratory rate ≥ 30/min
- **B**lood pressure ; SBP < 90
  DBP < 60
- age **65** or older

- **The risk of death increases as the score increases**:
- 0—0.6%
- 1—3.2%
- 2—13.0%
- 3—17.0%
- 4—41.5%
- 5—57.0%

Accuracy of biomarkers to indicate admission requirement

Table 2 Distribution of baseline biomarkers levels and adverse medical outcome of patients according to gold standard and ED physicians' advice

ED physicians' advice	Gold-standard hospital admission decision[a]			
	Discharge (n = 239)		Admission (n = 310)	
	Discharge n (%) = 143 (60)	Admission n (%) = 96 (40)	Discharge n (%) = 58 (19)	Admission n (%) = 252 (81)
Characteristics and outcomes				
CRP (mg/L), median [IQR]	83 [31; 181]	145 [72; 226]	103 [52; 188]	162 [76; 264]
PCT (ng/mL), median [IQR]	0.1 [0.1; 0.4]	0.3 [0.1; 1.8]	0.2 [0.1; 0.9]	0.7 [0.2; 4.4]
ANP (pmol/L), median [IQR]	61 [43; 80]	72 [51; 94]	97 [58; 159]	113 [74; 187]
Subsequent admission[b], n (%)	0 (0)	0 (0)	14 (10)	47 (19)
ICU admission, n (%)	0 (0)	0 (0)	1 (2)	43 (17)
Death, n (%)	0 (0)	0 (0)	0 (0)	2 (1)



- ***CRP, PCT, and ANP across Pneumonia Severity Index (PSI) risk classes.***
- PCT and ANP levels consistently differed between PSI risk groups, whereas CRP levels did not.
- Comparisons between groups were performed using the **Kruskal–Wallis test**

Midregional pro-atrial natriuretic peptide (ANP)

- increased in patients > 55 years and with underlying congestive heart failure
- decreased in septic patients (neutral endopeptidases)
- 135 pmol/L was the best cutoff value to determine admission requirement according to gold standard
- 80%patients with ANP level <135 pmol/L were PSI I–II patients
- 46% with ANP level >135 pmol/L were PSI I–III, and 50% were qualified 0–2 according to CURB-65.

- gold-standard ; 37% inpatients→ ANP >135 pmol/L.
  92% outpatients→ ANP <135 pmol/L
- patients with ANP >135 pmol/L, admission was required in
  → 91% according to gold standard
  → 83% according to attending ED physicians.
- 93.7% of gold-standard outpatients treated as inpatients by attending physicians had ANP level>135 pmol/L.
- patients with ANP level >135 pmol/L initially discharged, (6.7%) required admission during 28-day follow-up.
- The combination of PSI and ANP threshold did not improve performance to predict appropriate admission (AUC 0.88 [0.85–0.91]).

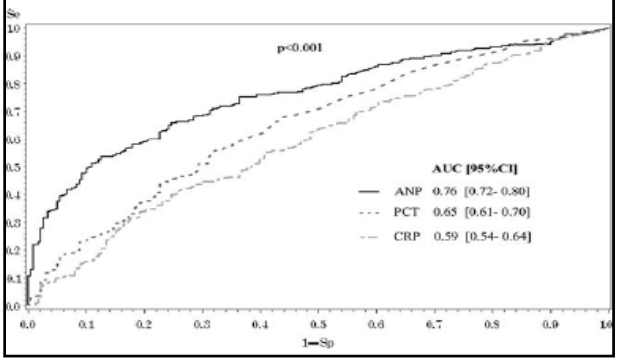
Ability of mid-regional atrial natriuretic peptide (ANP) to predict admission for medical purpose according to gold standard

Table 3 Ability of mid-regional atrial natriuretic peptide (ANP) to predict admission for medical purpose according to gold standard

ANP (pmol/L) cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
Maximum Youden index						
37	94.5 (92.0; 97.1)	10.0 (6.2; 13.9)	0.58 (0.53; 0.62)	0.59 (0.43; 0.74)	1.05 (1.00; 1.91)	0.55 (0.30; 0.99)
48	90.0 (86.7; 93.3)	28.9 (23.1; 34.6)	0.62 (0.58; 0.67)	0.69 (0.60; 0.78)	1.27 (1.16; 1.87)	0.35 (0.23; 0.51)
56	84.8 (80.8; 88.8)	41.4 (35.2; 47.7)	0.65 (0.61; 0.70)	0.68 (0.60; 0.75)	1.45 (1.29; 1.96)	0.37 (0.27; 0.50)
63	80.0 (75.5; 84.5)	46.4 (40.1; 52.8)	0.66 (0.61; 0.71)	0.64 (0.57; 0.71)	1.49 (1.31; 1.94)	0.43 (0.33; 0.56)
92	59.0 (53.6; 64.5)	79.9 (74.8; 85.0)	0.79 (0.74; 0.84)	0.60 (0.55; 0.65)	2.94 (2.25; 3.41)	0.51 (0.44; 0.59)
100	54.5 (49.0; 60.1)	84.9 (80.4; 89.5)	0.82 (0.77; 0.88)	0.59 (0.54; 0.64)	3.62 (2.63; 4.13)	0.54 (0.47; 0.61)
104	53.5 (48.0; 59.1)	87.4 (83.2; 91.6)	0.85 (0.80; 0.90)	0.59 (0.54; 0.64)	4.27 (3.01; 4.85)	0.53 (0.47; 0.60)
112	49.4 (43.8; 54.9)	90.0 (86.1; 93.8)	0.86 (0.81; 0.91)	0.58 (0.53; 0.63)	4.91 (3.31; 5.53)	0.56 (0.50; 0.63)
135	37.4 (32.0; 42.8)	95.0 (92.2; 97.7)	0.91 (0.86; 0.96)	0.54 (0.49; 0.59)	7.45 (4.22; 8.16)	0.66 (0.60; 0.72)
162	31.6 (26.4; 36.8)	97.1 (94.9; 99.2)	0.93 (0.89; 0.98)	0.52 (0.48; 0.57)	10.79 (5.11; 11.68)	0.70 (0.65; 0.76)

PPV positive predictive value, *NPV* negative predictive value, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio
Youden index = sensitivity + specificity − 1

3 Receiver operating characteristics (ROC) curves of biomarkers with respect to gold-standard hospital admission decision.



Discussion 1

Usefulness of CRP;

- CRP level was always above 10 mg/L in 96 inpatients .
- A cutoff at 110 mg/L was proposed to discriminate between 118 inpatients and 83 outpatients with CAP
- poor prognosis value .

Use of PCT

- improves identification of CAP in ED patients, severity assessment, site-of-care guidance and implemented to reduce use of antimicrobial agents .
- unable to predict adverse outcomes in PSI class I–II patients
- diagnosis tool rather than a prognosis marker

ANP

- ANP (AUC 0.76) more accurately predicted admission requirement than did PCT (AUC 0.65) or CRP (AUC 0.59) (both p values\0.01)
- ANP level 135 pmol/L was a threshold to discriminate admission requirement (positive likelihood ratio 7.45 [95% CI 4.22–8.16]).
- **PCT and ANP levels increased with PSI risk categories.**

Conclusions

- In a selected population of CAP with low risk of complication, *a single ANP measurement was more accurate* than CRP and PCT to predict appropriate admission