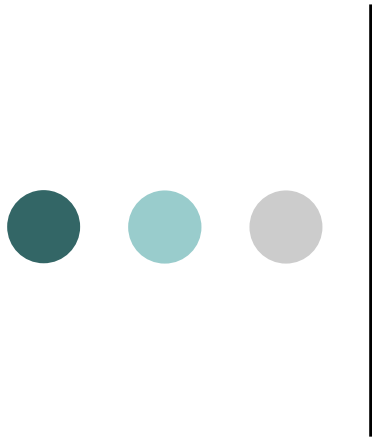




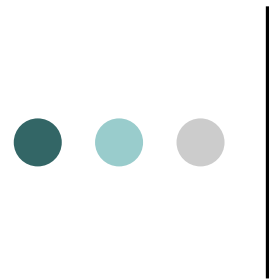
Clinical Pulmonary Infection Score Reflects Oxidative Stress in Patients with Pneumonia

WC Sin, JC Ho , C Pang , G Tang , WM Chan



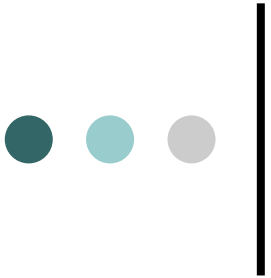
Background (1)

- Severe CAP and nosocomial pneumonia are common ICU problem with high mortality and morbidity
- Oxidant-antioxidant imbalance plays an important role in the pathogenesis
- Trials of supplementing critically ill patients with antioxidants, trace elements and vitamins yield conflicting results
 - May be due to differences in patient selection, baseline severity, timing, choice, route and dose of antioxidant administration.



Background (2)

- Key for antioxidant supplement: hit fast and hard
 - Therapeutic window
 - N-acetylcystine in ARDS failed to show benefit in terms of mortality. The initiation of antioxidant in these studies was ***after the development of organ failure***
 - Avery et al supplemented surgical trauma patients ***prophylactically*** with α -tocopherol and ascorbic acid. Organ failure was reduced but this cannot be transformed into mortality benefit.



Background (3)

- Severity dependent
 - Selenium in Intensive Care (SIC) study
 - 249 patients with septic shock
 - high dose selenium bolus followed by continuous infusion
 - Predefine –subgroup analysis: mortality was reduced in septic shock patient with disseminated intravascular coagulopathy , in patients with APACHE III score ≥ 102 and in patients with more than three organ dysfunctions



Background (4)

- Antioxidant measurement is not available as routine in most of the laboratory
- Need ***clinical surrogate marker*** to identify patient ***early*** who may benefit from antioxidant supplementation



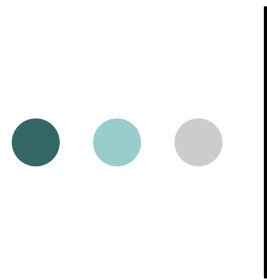
Study question

- To study the role of clinical pulmonary infection score in identifying antioxidant deficient patients with pneumonia in ICU



Method (1)

- Prospective observational study
- 9 months period
- Combined medical and surgical ICU
- ICU patients with pneumonia
 - severe CAP
 - nosocomial pneumonia
 - preexisting ICU patient with newly diagnosed nosocomial pneumonia
 - ventilator associated pneumonia (VAP)
- CPIS was evaluated on day 0 and day 3
- Antioxidant activity in erythrocytes activity were measured on day 0 and day 3
 - superoxide dismutase (SOD)
 - catalase
 - Glutathione (GSH)



Antioxidant

- Antioxidant

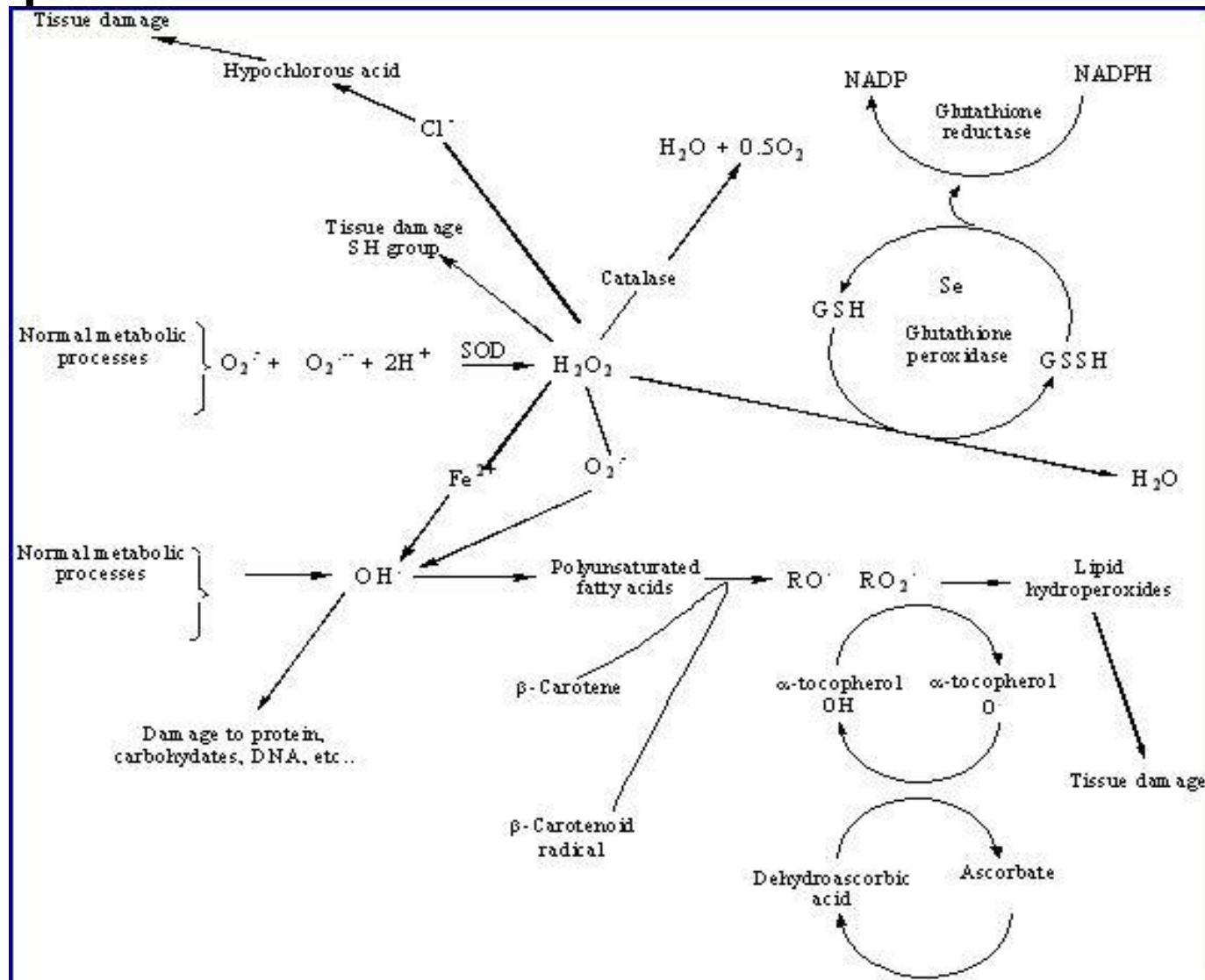
- enzymatic

- ***superoxide dismutase, catalase*** and glutathione peroxidase
 - trace elements copper (Cu), selenium (Se), manganese (Mn), and zinc (Zn) as part of the structure of the antioxidant enzymes

- non-enzymatic

- vitamins (e.g. vitamin E, C and β -carotene) [5], uric acid, bilirubin, thiols protein such as cysteine or ***glutathione (GSH)***, albumin

Inter-relationship between ROS and Antioxidant





Method (2)-CPIS calculation

CPIS points	0	1	2
1. Tracheal secretions	Rare	Abundant	Abundant + Purulent
2. Chest X-ray infiltrates	No infiltrate	Diffused	Localized
3. Temperature, °C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
4. Leukocytes count, per mm ³	$\geq 4,000$ and $\leq 11,000$	$< 4,000$ or $> 11,000$	$< 4,000$ or $> 11,000$ + band forms ≥ 500
5. PaO ₂ /FiO ₂ , mmHg	> 240 or ARDS		≤ 240 and no evidence of ARDS
6. Microbiology	Negative		Positive



Method (3)

- Exclusion criteria
 - CPIS calculation was inaccurate or baseline serum antioxidant being affected by means of medication or treatment
 - Known ***chronic diffuse pulmonary diseases***
 - Patient with positive sputum smear for acid fast bacilli or radiological feature suggestive of ***tuberculosis***
 - Patient with ***surgical operation*** within 7 days of onset of symptoms.
 - ***Immunocompromised patient***. Defined as white blood cell count < 1000/mm³, recent use of corticosteroid > 10 mg / day for 2 weeks, underlying malignancy, receiving cytotoxic drug or radiation therapy.
 - Patient taking ***drugs*** with antioxidant effect e.g. vitamin A, C, E , statin and N- acetylcystine.
 - Imminent death or patient with do not resuscitate (DNR) order.



Method (4)

- Statistic

- **Kolmogorov-Smirnov test** to verify the normality of distribution of continuous variables
- Correlations :**Pearson's or Spearman-rho** tests
- Comparisons between the two groups :**Student's T test or Mann-Whitney U exact** test according to their normality of distribution
- The predictive value of antioxidant concentration on ICU outcome :receiver operator characteristic (**ROC**) and the area under the curve (AUC)
- Association between antioxidant level and clinical scoring was adjusted for covariates: **Multiple linear regressions**
- **$P < 0.05$** was considered significant.

Result (1) : Basic Demographic data

Table 1. Demographic, diagnosis and ICU characteristic of the patients

Age, year		63±15 (median 64)
Gender (M/F), %		25/6, 80/20%
Admission APACHE II		24±7.6, (median 23)
Admission CPIS/ Day 3 CPIS		6.7±1.9 (median 7)/ 4.6±2.4(median 4)
Admission SOFA/Day 3 SOFA		8.7±5.0 (median 8)/ 6.3±5.1(median 5)
Duration of MV, days		6±6 (median 4)
Length of ICU stay, day		7±5 (median 4)
Mortality Day		
	3	3/31 (9.7%)
	14	6/31 (19.4%)
	28	8/31 (25.8%)
Pneumonia		
	CAP	23/31(74.2%)
	NP	8/31 (25.8%)
	VAP	0/31 (0%)
Culture		
	Gram +ve	6/31(19.4%)
	Gram -ve	8/31(25.8%)
	Mixed growth	3/31(9.7)
	No growth	13/31(41.9%)
	Virus	1/31(3.2%)

MV=Mechanical ventilation

CAP = Community acquired pneumonia

NP = nosocomial pneumonia

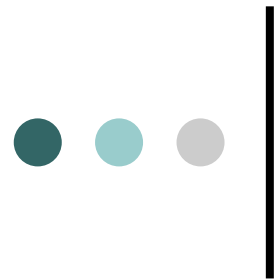
VAP = Ventilator associated pneumonia



Result (2): Antioxidant level

	Day 0	Day 3
Catalase* (U/g Hb),	0.47 (0.22) Mean (SD)	0.46 (0.23)
SOD # (U/g Hb)	23.17 (32.26)	26.52 (37.33)
GSH * (umol/g Hb)	11.16 (2.79)	10.60 (3.08)

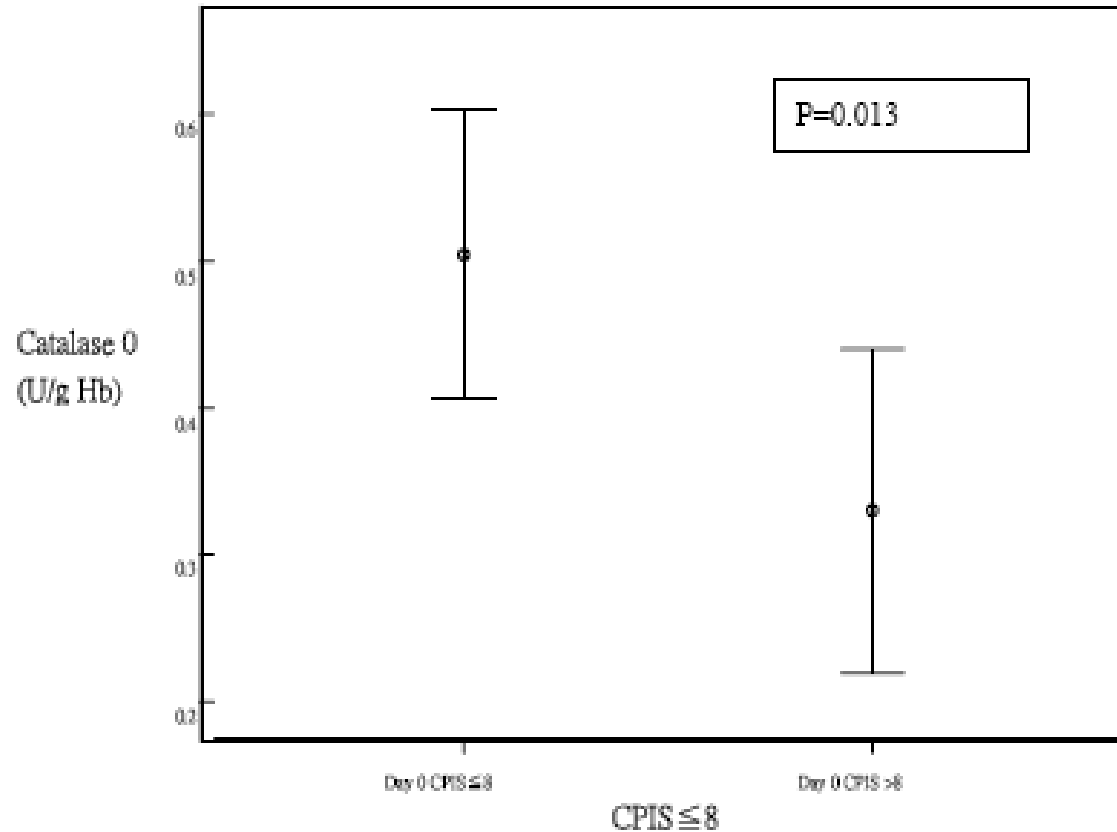
* In normal distribution # in normal distribution after log transformation



Result (3)

- There is no linear relationship between antioxidants and CPIS

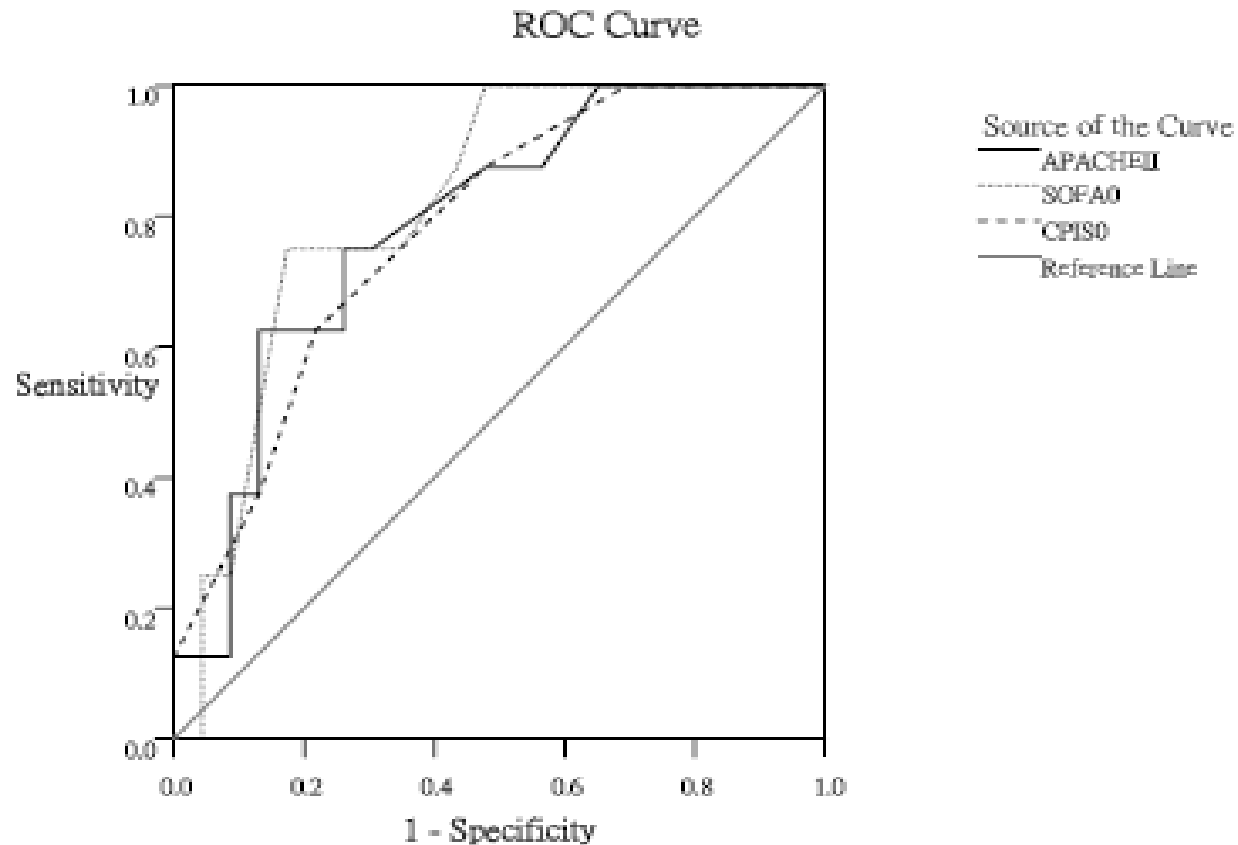
Result (4): CPIS(8) in discriminating patients with significantly lower catalase level



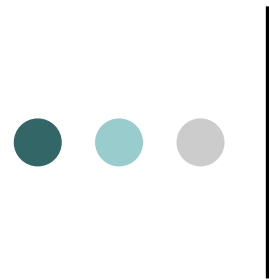
CPIS <8 (0.50 ± 0.24 U/gHb vs. 0.33 ± 0.11 U/gHb, 95%CI 0.04-0.31)

Result was adjusted for age , sex and co-morbidities

Result (5): ROC curve – clinical score



Cutoff of CPIS 8 point was found to have the best sensitivities / specificities values for D28 mortality (62.5% / 78.3%). AUC 0.78



Limitations

- Post hoc analysis
- CPIS is validated in VAP
 - Valid in severe CAP ?
 - Need further validation study
 - Pneumonia severity index does not include CXR and culture criteria



Limitations

- Small sample size (N=31)
 - explain no differences in SOD and GSH when a dichotomous cutoff (8) for CPIS was applied
 - study population is small to overcome the bias caused by a heterogeneous group of patients for whom many confounders (appropriate antibiotic treatment, co-medication which could influence redox status, co-morbidities, causative pathogens and transfusion)



Conclusion and Discussion

- CPIS 8 is an important cut-off point to identify patients who are at risk of antioxidant deficit and death
- Implication : ***EARLY*** selection of patient with pneumonia to receive antioxidant treatment



Thank you

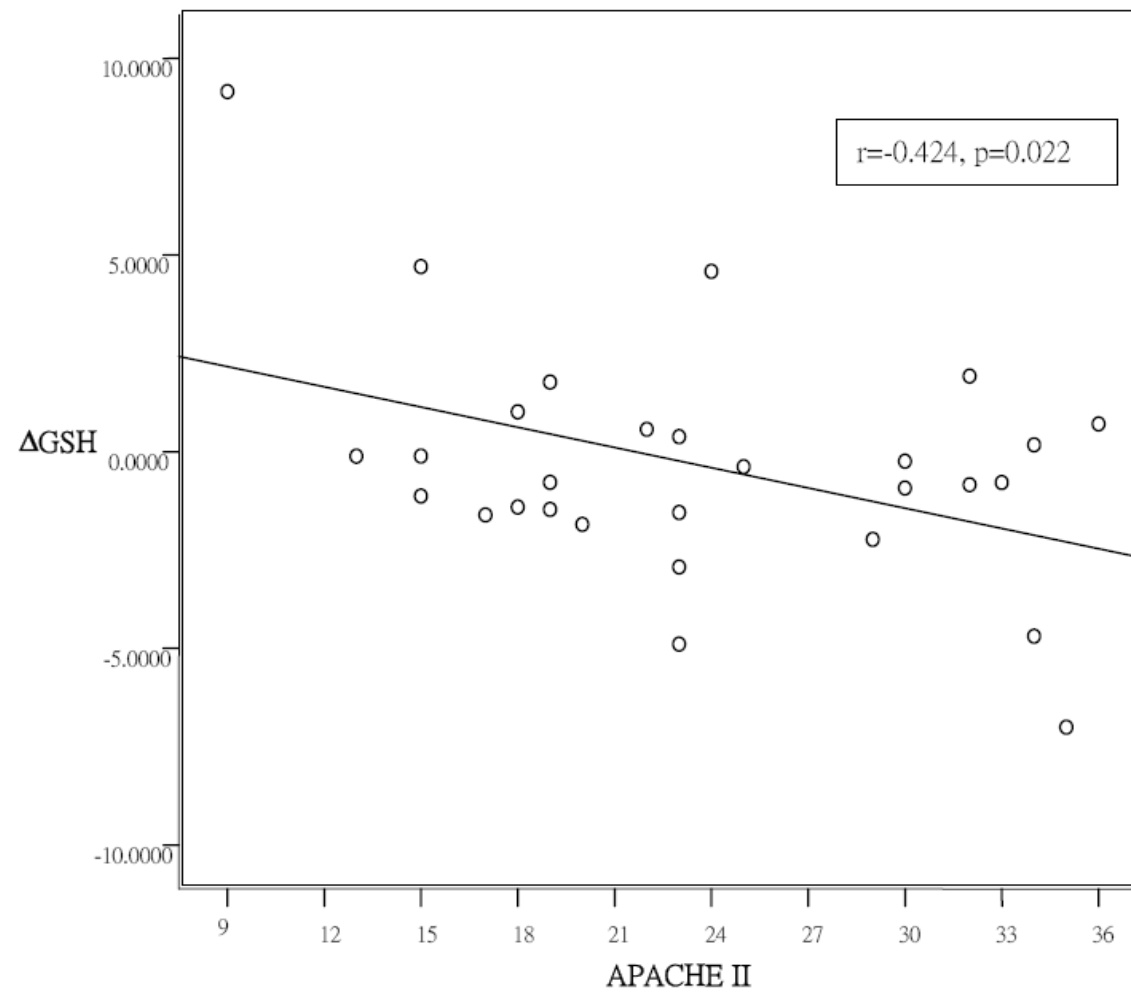
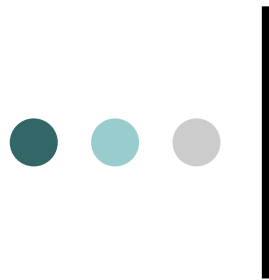


Figure 4. Correlation between change in erythrocyte GSH level with APACHE II score. GSH, glutathione. APACHE, Acute physiology and chronic health evaluation.



Calculation of sample size

- Published data on correlation of oxidative stress and clinical score - the r ranges from 0.28-0.426.
- Assuming $r = 0.43$ with $\alpha = 0.05$ (two-tailed) and power of 0.8 , 36 patients will be recruited