

RCoA Research, Education & Travel Grants 2014

Award: The Ernest Leach Fund

Applicant: Dr Philip McCall

Project Title: The novel inflammatory biomarker 'soluble urokinase-type plasminogen activator receptor' (suPAR); does it have a prognostic role following cardiac surgery

Project Description:

In the UK in 2012 over 34,000 people underwent cardiac surgery, with a mortality of 2.98%. Even with increasing risk factors, (ageing population, multiple co-morbidities) mortality has fallen. Despite this, it is still associated with significant morbidity. Post-operative complications have significant patient and financial costs, are associated with prolonged cardiothoracic intensive care unit (CICU) stay and increase resource dependency.

There is increasing pressure to reduce resource consumption and make more efficient use of CICU. Minimising post-operative recovery time is key and fast-track programmes have been introduced with this aim. Early identification of patients requiring more critical care support would be valuable. Low-risk patients could continue on a fast-track programme, safely being discharged from CICU. Conversely, higher risk patients could be kept in CICU, minimising unexpected readmissions.

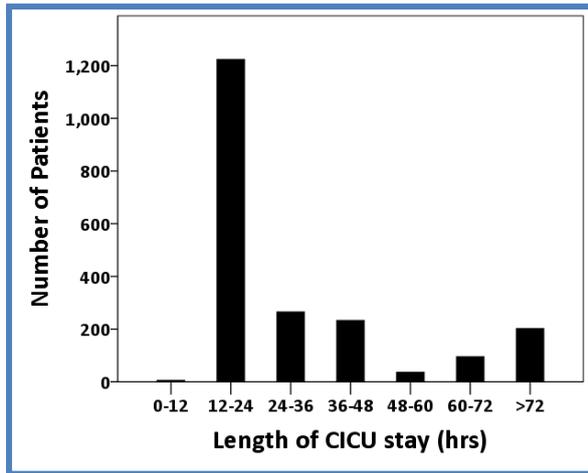
Predicting those needing more support is difficult; responses vary and are partially determined by individual susceptibility. Most have an uncomplicated course; in a cohort of 2059 patients undergoing surgery at our institution, 1361 (66.10%) had no complications. The majority required one night in CICU (Median stay 27h), however 566 patients (27.5%) required care for >36 hours (Table 1 and Figure 1).

	n = 2059
Age (years)	65 (35-88)
Post-operative atrial fibrillation	587 (28.51%)
Post-operative intra-aortic balloon pump	43 (2.09%)
Length of CICU stay (hours)	27 (0-1677)
Length of hospital stay (days)	6.9 (0-124.8)
Length of ventilation (hours)	9 (0-1169)
Mortality	27 (1.31%)

Table 1. Demographics and outcomes of patients undergoing coronary artery bypass grafting (CABG) with cardio pulmonary bypass (CPB).

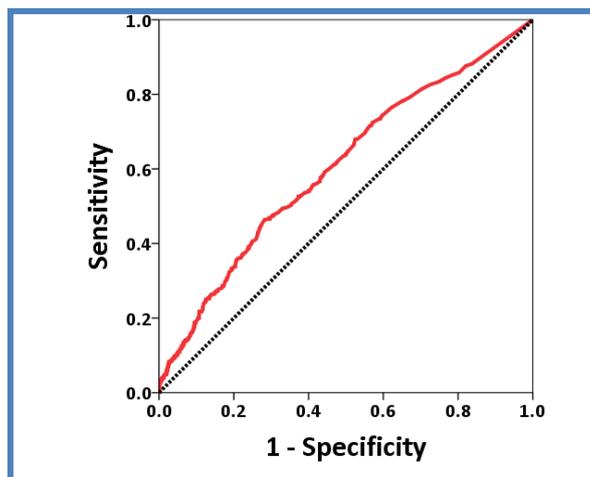
Data are presented as value (%) or median (range)

Vassalos et al. Unpublished.



**Figure 1. Length of CICU stay (n=2059).
Vassalos et al. Unpublished.**

EuroSCORE is a scoring system incorporating patient risk factors; although designed for prediction of mortality following cardiac surgery, it has been validated for prediction of prolonged CICU stay.(1) In our population logistic Euroscore did not perform well (Figure 2).



**Figure 2.
Logistic EuroSCORE for predicting ICU stay >36 hours. Area under the receiver operating characteristic (AUROC) curve = 0.61 (CI 0.58 -0.63, p<0.001, n=2059)
Vassalos et al. Unpublished.**

Risk stratification is multi-factorial; in other areas of critical care medicine, adding biomarkers has been shown to improve clinical prediction models.(2) Soluble urokinase-type plasminogen activator receptor (suPAR) is a novel inflammatory biomarker that has been described as a marker of “immunoactivation”, and has been shown to have prognostic value in the general intensive care (ICU) population. SuPAR levels relate to organ dysfunction, correlating with Sequential Organ Failure Assessment (SOFA) scores over time ($r=0.536$ $p<0.001$) and are superior to CRP as a predictor of ICU and 28d mortality.(3) In pilot work, our group has demonstrated elevated suPAR in patients with sepsis compared to a critically ill population without infection (Figure 3).

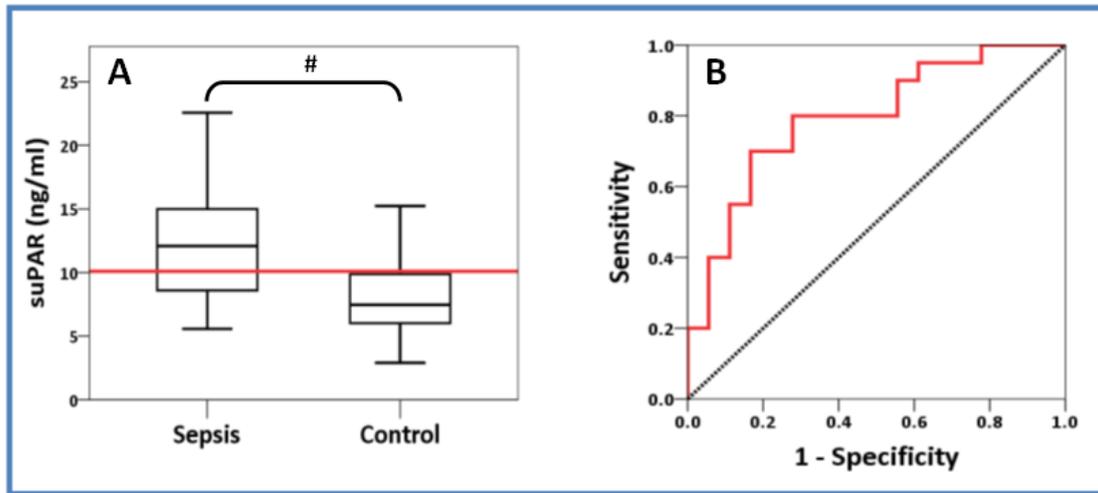


Figure 3.

A. Plasma suPAR in patients with sepsis compared to critically ill patients without infection (n=20). Median, IQR and full range

p = 0.001 (Mann-Whitney U test)

B. A suPAR level of 10.1 (horizontal line in fig. A) was 70% sensitive and 83% specific for the diagnosis of sepsis, signified by AUROC curve of 0.79 (CI 0.65 - 0.94, p = 0.002)

Galley et al. Unpublished.

With research ethics committee approval and informed patient consent we have collected plasma samples from 90 patients undergoing cardiac surgery at the Golden Jubilee National Hospital. Samples were collected at induction of anaesthesia and on post-operative day (POD) 1, 2 and 3.¹ We propose to undertake a retrospective observational cohort study (the first characterising changes in plasma suPAR following CPB) assessing the role of suPAR as a prognostic biomarker in the early period following cardiac surgery. We will plot the AUROC of suPAR on POD1 and compare with EuroSCORE. By choosing a cut off with high sensitivity for both suPAR and EuroSCORE; we will then combine the variables hypothesising an improved predictive effect with a higher AUROC. AUROC will be compared using the z-test.(4)

With an event rate of 27.5% (CICU stay >36 hours) and considering AUROC of 0.8 as clinically useful, we will be able to achieve 85% power (significance 5%) to detect a difference from the null hypothesis of AUROC 0.61.(5)

498 words

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2. Ware LB, Koyama T, Billheimer D, Wu W, Bernard GR, Thompson BT, et al. Prognostic and Pathogenetic Value of Combining Clinical and Biochemical Indices in Patients With Acute Lung Injury. *Chest*. 2010;137(2):288-96.

3. Donadello K, Scolletta S, Taccone FS, Covajes C, Santonocito C, Cortes DO, et al. Soluble urokinase-type plasminogen activator receptor as a prognostic biomarker in critically ill patients. *Journal of Critical Care*. 2014;29(1):144-9.

^{A11} "An evaluation of the use of novel urinary proteomics for the detection of acute kidney injury in the cardiac surgical setting" RECrefer: 12/WS/0179

4. Hanley JA, McNeil BJ. A method of comparing the areas under the receiver operating characteristic curves derived from the same cases. *Radiology*. 1983;148(3):839-43.
5. Johnson RG. The Ghost of Christmas Future: Predicting Pneumonia After Cardiac Operations. *Critical Care Medicine*. 2014;42(5):1302-3.