Running Title

Can soluble urokinase plasminogen receptor predict outcomes after cardiac surgery?

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Visual Abstract

Key Question: Does the biomarker suPAR have value in predicting postop complications in patients following cardiac surgery?

Key Findings: suPAR was predictive for prolonged hospital and ICU stay at all timepoints, including preop, and compared favourably to other scoring tools.

Take Home Message: In cardiac surgery patients, suPAR is a predictor of postop complications that can help perioperative clinical decision making.

Abstract

Objectives: Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker that has been implicated in several cardiac pathologies and has been shown to be elevated in critically-ill populations. We measured plasma suPAR in a cohort of cardiac surgical patients to evaluate its ability to predict prolonged intensive care unit (ICU) and hospital length of stay and development of complications following surgery. We compared suPAR against Euroscore II and CRP.

Methods: Ninety patients undergoing cardiac surgery were recruited with samples taken preoperatively and on postoperative days 1, 2 and 3. suPAR was measured using enzyme-linked immunosorbent assay. Area under the receiver operating characteristic curve (AUROC) was used to test predictive capability of suPAR. Comparison was made with Euroscore II and C-reactive protein (CRP).

Results: suPAR increased over time (p<0.001) with higher levels in patients requiring prolonged ICU and hospital stay, and prolonged ventilation (p<0.05). suPAR was predictive for prolonged ICU and hospital stay, and prolonged ventilation at all time-points (AUROC 0.66-0.74). Interestingly this association was also observed preoperatively, with preoperative suPAR predicting prolonged ICU (AUROC 0.66), and hospital stay (AUROC 0.67) and prolonged ventilation (AUROC 0.74). The predictive value of preoperative suPAR compared favourably to EuroSCORE II and CRP.

Conclusions: suPAR increases following cardiac surgery and levels are higher in those who require prolonged ICU stay, prolonged hospital stay and prolonged ventilation. Preoperative suPAR compares favourably to EuroSCORE II and CRP

in prediction of these outcomes. suPAR could be a useful biomarker in predicting outcome following cardiac surgery, helping inform clinical decision making.

Keywords

Biomarkers; Cardiac Surgical Procedures; Postoperative Complications; Receptors, Urokinase Plasminogen Activator; Thoracic surgery

Abbreviations

- ICU – Intensive Care Unit
- suPAR – Soluble Urokinase Plasminogen Receptor
- CRP – C Reactive Protein
- AUROC – Area Under the Receiver Operator Curve

Introduction

Patient's undergoing cardiac surgery are at risk of multisystem postoperative complications[1] resulting in prolongation of intensive care unit (ICU) admission[2] and hospital stay.[3] The ability to predict either preoperatively, or early postoperatively, those patients at increased risk of complications would aid clinical decision-making. A reliable prognostic biomarker[4] would enable identification of patients at increased risk, allowing them to receive additional monitoring and earlier intervention. Conversely, identification of patients unlikely to require extra support would allow these patients to be triaged to a fast-track recovery.

Soluble urokinase plasminogen activator receptor (suPAR) is the soluble form of the leukocyte membrane-bound urokinase plasminogen activator receptor (uPAR)[5] and has been linked to plasminogen activation, pericellular proteolysis, and chemotaxis.[5,6] suPAR is a novel biomarker that has been shown to have diagnostic and predictive value in cardiovascular disease,[7, 8] the critically ill,[9, 10] and patient's with sepsis.[11,12]

We hypothesised suPAR would increase following cardiac surgery and would be useful to identify patients requiring a prolonged stay in hospital and/or ICU. Furthermore, we compared the discriminative capability of suPAR against C-Reactive protein (CRP) and Euroscore II, both of which are measured and

calculated perioperatively, to assess suPAR's potential clinical applicability against established methods.

EuroSCORE II is a scoring system used prior to cardiac surgery to provide an estimate of predicted mortality.[13] It considers various patient-dependent factors, such as cardiac and renal function, as well as surgical factors, and quantifies the overall risk of death. It is intuitive that patients at higher risk of death have higher risk of increased intensive care requirement and EuroSCORE II has been demonstrated to predict prolonged ICU stay.[14] CRP is widely measured in this patient population and is used to identify patients mounting an inflammatory response and determine those at risk of complications such as infection. For these reasons, EuroSCORE II and CRP were compared to suPAR.

Finally, we wanted to assess whether a combined model integrating commonly used clinical information with inflammatory biomarkers would have a greater value in identifying those patients requiring prolonged stays.

Methods

Trial Enrolment and Ethics Approval

This study is a *post-hoc* analysis of a previous study examining acute kidney injury in patients undergoing cardiac surgery. The trial was registered in April 2012 at ClinicalTrials.Gov (Trial number NCT01573104). Ethical approval for this study (Ethic committee number: 12/WS/0179) was provided by the West of Scotland Research Ethics Service on the 21st of August 2012. A substantial amendment to allow the additional analyses was submitted on the 26th of September 2014 and approved by the same ethics committee on the 27th of April 2016. With informed consent, blood samples were collected from patients undergoing cardiopulmonary bypass cardiac surgery at the Golden Jubilee National Hospital between November 2011 and January 2014.

Data Collection

Exclusion criteria for the primary study were; patient/surgical refusal, preoperative renal replacement, emergency procedures, age <18 or >90 years, pregnancy, the use of ventricular-assist devices, severe chronic renal failure (defined as eGFR <30mL/min/1.73m^2) and impaired patient capacity to consent.

Baseline information was collected on admission about co-morbidity status, from which EuroSCORE II[13] was calculated. Intraoperative data were collected from the recall AIMS electronic anaesthetic charting system (Informatics Clinical Information Systems Limited, Glasgow) and postoperative data from the hospitals ICU clinical information system (Centricity CIS; GE Healthcare©, Buckinghamshire, UK).

In accordance with previous studies, prolonged ICU stay was defined as over 48 hours[14] and prolonged hospital stay was defined as 12 days or greater.[15] Often patients are discharged from intensive care or hospital for logistical rather than clinical reasons, at 'set times', such as following the morning ward round, which can confound the use of length of stay data as a continuous variable. To counter this, these variables were dichotomized to highlight patients that had deviated from normal recovery and required prolonged stays.

A composite endpoint of complications was used; surgical re-operation, stroke, deep sternal wound infection, postoperative renal failure, prolonged ventilation[16] and atrial fibrillation. Surgical re-operation, stroke and deep sternal wound infection were included if documented in the hospital's cardiac surgery database (Cardiac, Cardiology, and Thoracic Health Information System; CaTHi, Amor Group, Renfrew, Scotland). In line with previous studies, renal failure was defined as acute kidney injury network[17] stage 1 or greater[18] and prolonged ventilation was defined as over 24 hours.[19,20]

Blood samples were collected before induction of anaesthesia and were also collected on the morning of postoperative days 1, 2 and 3. Samples were centrifuged, frozen and stored at -80°C until analysis. suPAR was measured in duplicate using a commercially available solid phase enzyme linked immunosorbent assay (suPARnostic®, Virogates, Denmark) according to the manufacturer's instructions. The within-batch coefficient of variation (CV) was 6.2%, whilst the between-batch CV was 11.8%.

CRP was determined as a routine clinical sample by an enhanced immunoturbidimetric assay run on a Roche Cobas 6000 analyser. The reference range is <10mg/L, with a lower limit of detection of 1.0 mg/L and a CV of 1.7%.

Statistical Analysis

Analysis was undertaken using SPSS® (version 22, IBM, Armonk, NY). Variables were visually inspected and tested for normality using the Shapiro-Wilk test. Categorical data are presented as frequency(%) and continuous data are presented as mean(SD) or median(IQR) as appropriate.

Multiple comparisons across time-points were performed using repeated measures ANOVA or Friedman's test. Pairwise comparisons were performed using Wilcoxon signed rank test or a paired T-test with appropriate Bonferroni-adjusted *p*-values to avoid type 1 errors. Comparisons between independent groups were performed using Student's T-test or Mann-Whitney U-test; adjustment for multiple testing was not applied. Statistical significance was determined as $p<0.05$.

The area under the receiver operator curve (AUROC) was calculated to evaluate the discriminative capability of variables for predicting patients who would require prolonged ICU or hospital stay or who would develop complications. Sensitivity, specificity and positive and negative predictive values were calculated according to optimum cut off points defined as the point at which the sum of sensitivity and specificity were maximal (Youden's Index[21]). Multivariable logistic regression was used to develop a model incorporating preoperative suPAR and EuroSCORE II, with AUROC used to evaluate its discriminative capability.

This manuscript adheres to the STARD guidelines where appropriate.

Results

Ninety patients were recruited. Of the original cohort, two patients had their operations cancelled after recruitment for clinical reasons, and no blood samples were obtained in a further five patients; these patients were excluded from analysis. The median age was 66 years. The median for EuroSCORE II was 1.2%, ventilation time was 7 hours, ICU length of stay was 23 hours and hospital length of stay was 7 days (Table 1).

Seventeen patients (19.3%) had a prolonged ICU stay and 23 (26.1%) had a prolonged hospital stay. Those with a prolonged hospital stay were older (p<0.001), had a longer cardiopulmonary bypass time (p=0.004), had a longer aortic cross clamp time (p=0.027), and had a longer ICU stay (p=0.002) than those who did not. There was no difference in demographics between those having a longer ICU stay and those who did not (Table 2).

suPAR was higher at all postoperative time-points compared with baseline (Figure 1a). There were differences in suPAR levels both preoperatively and postoperative days 1 and 2 between those patients requiring a longer stay in the ICU and those who did not (Figure 2a). There were also significant differences in suPAR levels at all time-points between those patients who stayed longer in hospital and those who did not (Figure 2b).

CRP levels were higher at all postoperative time-points compared with baseline (Figure 1b). There was no difference in CRP levels at any timepoint between those patients who required prolonged ICU and those who did not (Figure 2d). There were differences in CRP levels on postoperative day 2 between those

patients requiring prolonged hospital and those that that did not, but not at other timepoints (Figure 2e).

Plasma suPAR levels preoperatively and postoperative day 2 were significant predictors of increased length of ICU and hospital stay, respectively. The predictive value of preoperative suPAR compared favourably to EuroSCORE II and CRP (Table 3, Figure 3a and 3b).

For predicting increased time in ICU, the optimum cut off point was for preoperative suPAR as identified by ROC curve analysis with a concentration of 1.96ng/mL, giving a sensitivity of 52.9% and a specificity of 79.7%. This corresponded to a positive predictive value of 30.8% and a negative predictive value of 90.7%. For predicting a prolonged hospital stay, the optimum cut off point was for postoperative day two suPAR with a concentration of 2.37ng/mL, sensitivity 63.2%, specificity 81.5%, positive predictive value (PPV) 54.5%, negative predictive value (NPV) 86.3%.

Complications

At least one of the composite complications developed in 40(45.5%) of the 88 patients: 31(35.2%) developed new onset atrial fibrillation, 16(18.2%) developed postoperative renal failure with 5(5.6%) patients requiring renal replacement therapy, eight(9.1%) required prolonged ventilation, six(6.8%) required re-operation, three(3.4%) had a deep sternal wound infection and one patient had prolonged neurological dysfunction. One patient died, equating to a mortality of 1.1% - for the purposes of analysis this patient was treated as having a prolonged ICU and hospital stay. There was no difference in EuroSCORE II or suPAR levels at any time-point between those patients who developed a composite

278 complication and those who did not. Median CRP levels were higher in patients
279 who went onto develop complications on postoperative days 1 and 2 (Figure 2f).

280 In post-hoc analyses, association between individual complications and suPAR
281 and CRP levels were analysed. Patients requiring prolonged ventilation had
282 higher levels of suPAR preoperatively and at all postoperative time-points (Figure
283 2c). Preoperative suPAR was predictive of prolonged ventilation with an AUROC
284 of 0.74 (Table 3). The optimum cut off point for preoperative suPAR as identified
285 by AUROC analysis was a concentration of 1.40ng/mL, sensitivity 100%,
286 specificity 46.6%, PPV 17.1% and NPV 100%. There was no difference in suPAR
287 levels between patients developing any of the other individual complications
288 compared with those who did not.

289 When CRP was analysed, levels were higher preoperatively in patients who
290 developed AF (3mg/L compared with 1mg/L; p=0.002). This difference was
291 present on postoperative day 1 (69mg/L compared with 47mg/L; p=0.001) and
292 postoperative day 2 (179mg/L compared with 145mg/L; p=0.021). There was no
293 difference in CRP levels between those patients developing any of the other
294 individual complications compared with those who did not.

295 **Surgical Procedure**

296 suPAR levels were compared between the 56 patients who had coronary artery
297 bypass grafting (CABG) and the 32 patients who had more complex cardiac
298 surgeries (Table 1). Those patients who had more complex procedures had
299 higher levels of suPAR on postoperative day 1 (2.37ng/mL compared with
300 1.57ng/mL; p=0.002), postoperative day 2 (2.42ng/mL compared with 1.86ng/mL;
301 p=0.004) and on postoperative day 3 (2.77ng/mL compared with 1.85ng/mL;

p=0.009), but not at baseline (1.81ng/mL compared with 1.44ng/mL; *p*=0.18). There was no difference in CRP levels at any timepoint.

Combined Model

A combined model of EuroSCORE II and preoperative suPAR levels produced similar AUROC to preoperative suPAR levels alone (Table 3).

Discussion

suPAR increases following cardiac surgery and is higher in patients requiring longer stays in the ICU and hospital and in those ventilated for more than 24 hours. This difference in suPAR concentrations was present preoperatively and compared favourably to EuroSCORE II and CRP.

We found suPAR was elevated from baseline at all postoperative timepoints. A study by Gozdzik and colleagues,[22] did not find elevated suPAR levels following cardiac surgery. This discrepancy in results could be explained by the difference in time frames over which suPAR was investigated, and the patient populations. Gozdzik and colleagues studied 60 patients undergoing isolated CABG surgery, whilst we included patients undergoing a variety of cardiac surgery procedures. We found those patients having CABG surgery only had lower suPAR postoperatively compared with those undergoing more complex procedures. Our study demonstrated a sustained rise in suPAR that was apparent on postoperative day 1, and beyond. This may not have been seen in Gozdzik and colleague's study[22] which looked at levels up to 24 hours only.

suPAR was higher in patients requiring prolonged ICU and hospital stay and prolonged ventilation compared with those that did not; unexpectedly this difference was demonstrated preoperatively. Increases in suPAR are associated with immune system activation[6] suggesting these patients had higher levels of inflammation at baseline. Some patients may have underlying co-morbidities which contribute to higher suPAR levels preoperatively and predispose to a more complicated postoperative course. For example, suPAR has been shown to be higher in those with coronary artery disease with levels increasing in parallel with

355 severity of disease;[25] it is plausible that those patients requiring prolonged stay
356 and ventilation could have more severe disease at baseline, explaining the higher
357 suPAR and poorer outcome.

358 A recent study by Hodges and colleagues[26] demonstrated that preoperative
359 suPAR levels predicted complications and mortality following aortic valve
360 replacement. Our study provides further evidence of the value of preoperative
361 suPAR levels in predicting outcomes following cardiac surgery.

362 Interestingly, CRP levels were not elevated in those who went on to require
363 prolonged stays preoperatively or on postoperative days 1 and 3. CRP can take
364 2-3 days for levels to peak after a surgical insult[27] and this delay can make it
365 difficult to differentiate between patients developing complications and those
366 demonstrating a 'normal' response. It is possible that suPAR is a faster-reacting
367 inflammatory biomarker, and therefore a better early discriminator, compared to
368 CRP with values closer to peak on postoperative day 1.

369 In the current study, EuroSCORE II was higher in patients who had prolonged
370 hospital stay but performed poorly in predicting prolonged ICU stay (AUROC
371 0.55)(Table3, Figure 3). A combined model, using preoperative suPAR and
372 EuroSCORE II was better at predicting these outcomes than EuroSCORE alone.
373 However, the predictive capability of the combined model was driven by suPAR
374 (See Supplementary Table 1).

375 The composite of complications used in our study was based upon a list of serious
376 complications following cardiac surgery as defined by the Society of Thoracic
377 Surgeons,[16] with the addition of atrial fibrillation which has been shown to
378 significantly affect mortality and morbidity.[28] To further explore the apparent

paradox that suPAR is predictive of prolonged intensive care and hospital stay, but not associated with postoperative complications, whilst CRP is not predictive of prolonged stay but is associated with complications, we conducted a post-hoc analysis of suPAR and CRP against individual complications.

Elevated suPAR was predictive only for prolonged ventilation. Geboers and colleagues examined the ability of suPAR to predict outcomes of patients admitted to ICU with acute respiratory distress syndrome, observing higher levels in those with more severe disease.[29] It is plausible, therefore, that the association between suPAR and prolonged ventilation reflects the development of lung injury. As this relationship between suPAR and duration of mechanical ventilation was also apparent preoperatively, we suggest suPAR may also serve as a predictor of *susceptibility* to lung injury rather than simply a measure of disease severity. Although the positive predictive value of suPAR in identifying patients who go on to require prolonged mechanical ventilation was poor (17.1%), the high negative predictive value (100%) was such that preoperative measurement of suPAR could help identify those patients *unlikely* to require prolonged ventilation. These patients could therefore be suitable for triage to fast-track recovery programs; an area of growing interest and study in the elective cardiac surgery population.[30]

When assessing CRP, we found higher levels postoperatively were associated with the development of atrial fibrillation. Although a common complication (35% of patients in this study), atrial fibrillation following cardiac surgery often responds promptly to medical management and therefore the presence of this complications would not necessarily prolong intensive care or hospital stay, explaining the lack of association observed.

To our knowledge, this is one of the largest studies examining suPAR in patients undergoing various types of cardiac surgeries and to describe the use of suPAR to predict outcomes. Given its retrospective nature, and the number of comparisons made the results of this study must be considered 'hypothesis generating' to support planning of subsequent, prospective studies. Further, the relatively small sample size of 90 patients and moderate predictive capability of suPAR make it difficult to come to concrete conclusions on the ability of this biomarker to predict prolonged stay and complications. It would be therefore informative to examine any additional predictive value of plasma suPAR in combination with other potential clinical predictors enabling robust multivariable analysis and greater predictive capability.

Conclusion

We found that suPAR levels increased after cardiac surgery and that high suPAR levels, both pre and postoperatively, were associated with prolonged ICU stay, prolonged hospital stay and prolonged duration of ventilation. In addition, suPAR compared favourably to EuroSCORE II and CRP in predicting these outcomes. The next step is to explore the applicability and effectiveness of suPAR as a predictive biomarker in conjunction with other currently utilised clinical prediction scores in patients undergoing cardiac surgery in a larger study. The aim of this would be to assess whether suPAR could improve prediction of outcomes in combination with other biomarkers and clinical predictors.

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Conflicts of Interest

None declared.

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Figure Legends

Figure 1 – Perioperative levels of **(A)** Soluble Urokinase Plasminogen Activator Receptor (suPAR) and **(B)** C-Reactive Protein (CRP). Preoperative baseline (PreOp), Postoperative Day 1 (POD1), Day 2 (POD2), and Day 3 (POD3). Bars demonstrate differences between two time points (Wilcoxon Signed-Rank test with applied Bonferroni adjustment) (*p<0.05; **p<0.01)

Figure 2 – Different levels of biomarkers and outcomes: Soluble Urokinase Plasminogen Activator (suPAR) levels between **(A)** Patients that required a Prolonged Intensive Care Unit Length of Stay (PICULOS) and those that did not (Non-PICULOS) **(B)** Patients that required a Prolonged Hospital Length of Stay (PHLOS) and those that did not (Non-PHLOS) and **(C)** Patients that required a Prolonged Ventilation and those that did not; C-reactive Protein (CRP) levels between **(D)** Patients that required a Prolonged Intensive Care Unit Length of Stay (PICULOS) and those that did not (Non-PICULOS) © Patients that required a Prolonged Hospital Length of Stay (PHLOS) and those that did not (Non-PHLOS) and **(F)** Patients that developed complications and those that did not (No-Complications) over time-points: Preoperative (PreOp), Postoperative Day 1 (POD1), Day 2 (POD2) and Day 3 (POD3). Bars demonstrate differences between groups (Mann-Whitney U Test) (*p<0.05;**p<0.01)

Figure 3 – Receiver Operator Characteristic Curves demonstrating the ability of Preoperative suPAR, labelled “PreOp suPAR”, and EuroSCORE II to predict patients that will require **(A)** Prolonged Intensive Care Unit Length of Stay (PICULOS) (**B)** Prolonged Hospital Length of Stay (PHLOS) and **(C)** Prolonged Ventilation. Area Under the Receiver Operator Curve (AUROC) is shown with a corresponding *p*-value in parentheses.

598 **Table 1** – Baseline patient characteristics

Characteristics	**All Patients** (n=88)
Age (Years)	66 (59,72)
Female Gender n (%)	19 (21.6)
Weight (Kg)	81 (SD:15.8)
EuroSCORE II	1.2 (0.71,1.57)
Actual Mortality (%)	1 (1.1)
Cardiovascular Co-Morbidities	
n (%)	68 (77.3)
Any[a]	28 (31.8)
Previous MI	59 (67.0)
Arterial Hypertension	50/82 (61.0)
Left Main Stenosis	42/82 (51.2)
Triple Vessel Disease	
Intervention type n (%)	
CABG	56 (63.6)
AVR	15 (17.0)
MVR	8 (9.1)
CABG + AVR	4 (4.5)
Other	5 (5.7)
CPB Time (Min)	84 (66,112.5)
Aorta Clamp Time (Min)	58 (40.5,74.5)
Surgical time (Min)	202.5 (180,255)
Ventilation Duration (Hr)	7 (4.1,12.4)
Intensive Care Unit Stay (Hr)	23 (21.5,46)
Hospital stay (Days)	7 (6,12)

Data presented as Median (IQR), mean (SD:) or frequency (%)

MI= Myocardial Infarction, CPB= Cardiopulmonary Bypass CABG= Coronary Artery Bypass Graft, AVR= Aortic Valve Repair, MVR= Mitral Valve Repair, Other= Unspecified, MVR + CABG, MVR + Foramen Ovale Closure, AVR + Ascending Aortic Aneurysm Repair

[a]Cardiovascular comorbidities refers to previous MI, Hypertension, Left Main Stenosis or Triple Vessel Disease

Table 2 – Key Group Characteristics and Variations

Characteristics	Prolonged ICU Stay (n=17)	Non-Prolonged ICU Stay (n=71)	Prolonged Hospital Stay (n=23)	Non-Prolonged Hospital Stay (n=65)	Prolonged Ventilation (n=8)	Non-Prolonged Ventilation (n=80)
Age (Years)	69(51,78)	66(59,72)	71(68,77)††	63(57,70)††	68(51,71)	66(59,73)
EuroSCORE II (%)	1.2(0.82,1.62)	1.1(0.71,1.59)	1.3(0.97,2.09)†	0.99(0.68,1.47)†	1.36(0.81,4.55)	1.14(0.71,1.49)
CPB Time (Min)	93(69.5,128.5)	80.5(63.8,108.8)	104(81,143)††	78(60.3,102.8)††	143(92.3,233.8)‡	81(64.5,108.5)‡
Aorta Clamp Time (Min)	70(39,75)	56(41,74)	70(56,81)†	51.5 (37,72)†	74.5(73,122.3)‡	56(39.5,72)‡
Surgical time (Min)	200(185,265)	205(180,251.3)	215(185,270)	200(177.5,247.5)	280(192.5,376.3)‡	200(180,243.8)‡
Ventilation Duration (Hr)	14.5(7,45.8)**	6.5(4,9)**	11.5(7,32)††	5.5(4,8.8)††	45.8(32.3,59)‡‡	6.5(4,9.8)‡‡
Intensive Care Unit Stay (Hr)	71(68.8,107.3)**	22.5(20,40.5)**	46(22,70.5)††	22.5(20.5,41.5)††	107.3(69.4,568.5)‡‡	23(21.5,44)‡‡
Hospital Stay (Days)	13(8.5,15)**	6 (6,9)**	14(13,16)††	6 (6,7)††	14(11.5,26.5)‡‡	7(6,10)‡‡

Data presented as Median (IQR)

Symbols denote a difference between Prolonged ICU Stay vs Non-Prolonged ICU Stay (Mann-Whitney U Test) *p<0.05,**p<0.01

Symbols denote a difference between Prolonged Hospital Stay vs Non-Prolonged Hospital Stay (Mann-Whitney U Test) †p<0.05,††p<0.01

Symbols denote a difference between Prolonged Ventilation vs Non-Prolonged Ventilation (Mann-Whitney U Test) ‡p<0.05,‡‡p<0.01

CPB, Cardiopulmonary Bypass

Table 3 – Area Under the Receiver Operator Curve of suPAR and Logistic EuroScore II for each outcome

	Prolonged ICU Stay	**Prolonged Hospital Stay**	**Prolonged Ventilation**
suPAR Levels[a]			
PreOp	**0.66**(0.52,0.81)	**0.67**(0.54,0.80)	**0.75**(0.61,0.88)
POD1	**0.68**(0.53,0.82)	**0.66**(0.52,0.79)	**0.74**(0.53,0.95)
POD2	-	**0.71**(0.57,0.86)	-
POD3	-	**0.68**(0.52,0.84)	-
EuroSCORE II			
PreOp	0.55(0.41,0.69)	**0.64**(0.51,0.77)	0.61 (0.39,0.84)
suPAR and EuroSCORE II			
PreOp	**0.67** (0.53,0.81)	**0.68** (0.55,0.81)	**0.74** (0.58,0.90)
CRP Levels[a]			
PreOp	0.43 (0.27,0.59)	0.59 (0.44,0.73)	0.56 (0.32,0.79)
POD1	0.62 (0.48,0.76)	0.59 (0.45,0.73)	0.59 (0.42,0.76)
POD2	-	**0.70** (0.57,0.82)	-
POD3	-	0.62 (0.42,0.82)	-

Values presented are Area Under the Receiver Operator Curve with (95% Confidence Intervals)

Values highlighted in bold are statistically significant $p<0.05$

[a]suPAR and CRP beyond POD1 was not used to predict Prolonged ICU stay or prolonged ventilation as those patients still in ICU or still ventilated on POD2 automatically qualified in those categories

PreOp = Preoperative; POD1, 2 or 3 = Postoperative days 1, 2 or 3

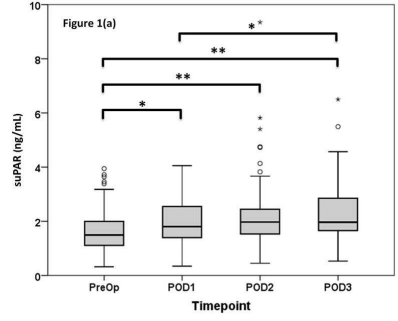


Figure 1(a)
suPAR (ng/mL)
10
8
6
4
2
0
*
**
**
**
*
PreOp
POD1
POD2
POD3
Timepoint

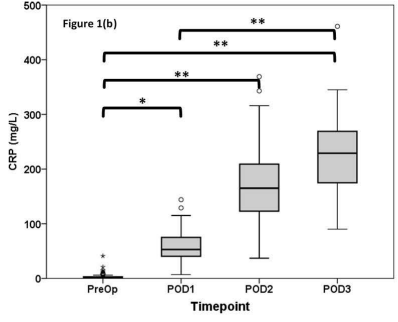


Figure 1(b)
CRP (mg/L)
500
400
300
200
100
0
*
**
**
**
**
PreOp
POD1
POD2
POD3
Timepoint

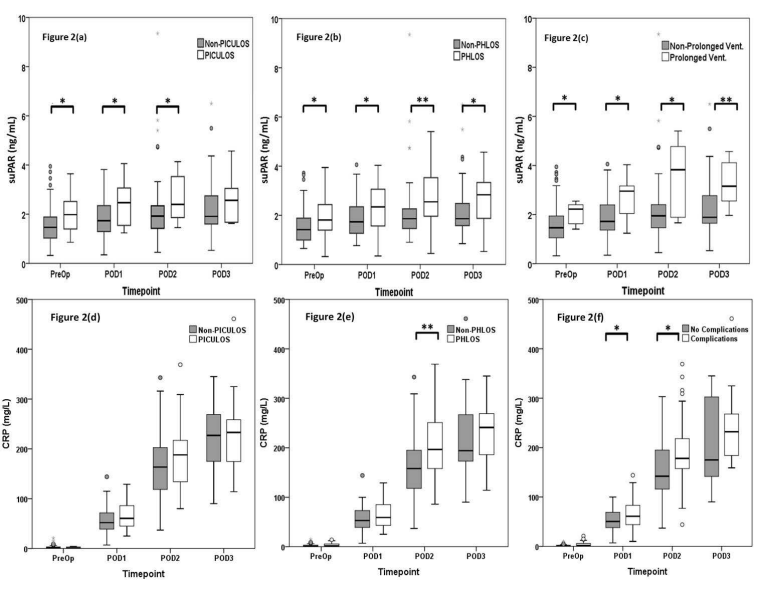


Figure 2(a)
Non-PICULOS
PICULOS
suPAR (ng/mL)
PreOp
POD1
POD2
POD3
Timepoint
Figure 2(b)
Non-PHLOS
PHLOS
suPAR (ng/mL)
PreOp
POD1
POD2
POD3
Timepoint
Figure 2(c)
Non-Prolonged Vent.
Prolonged Vent.
suPAR (ng/mL)
PreOp
POD1
POD2
POD3
Timepoint
Figure 2(d)
Non-PICULOS
PICULOS
CRP (mg/L)
PreOp
POD1
POD2
POD3
Timepoint
Figure 2(e)
Non-PHLOS
PHLOS
CRP (mg/L)
PreOp
POD1
POD2
POD3
Timepoint
Figure 2(f)
No Complications
Complications
CRP (mg/L)
PreOp
POD1
POD2
POD3
Timepoint

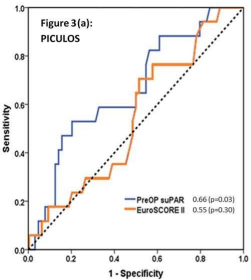


Figure 3(a):
PICULOS
Sensitivity
1 - Specificity
PreOP suPAR 0.66 (p=0.03)
EuroSCORE II 0.55 (p=0.30)

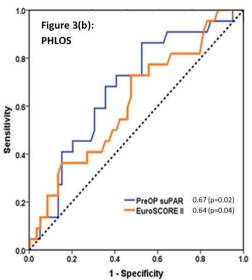


Figure 3(b):
PHLOS
Sensitivity
1 - Specificity
PreOP suPAR 0.67 (p=0.02)
EuroSCORE II 0.64 (p=0.04)

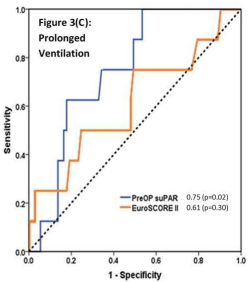
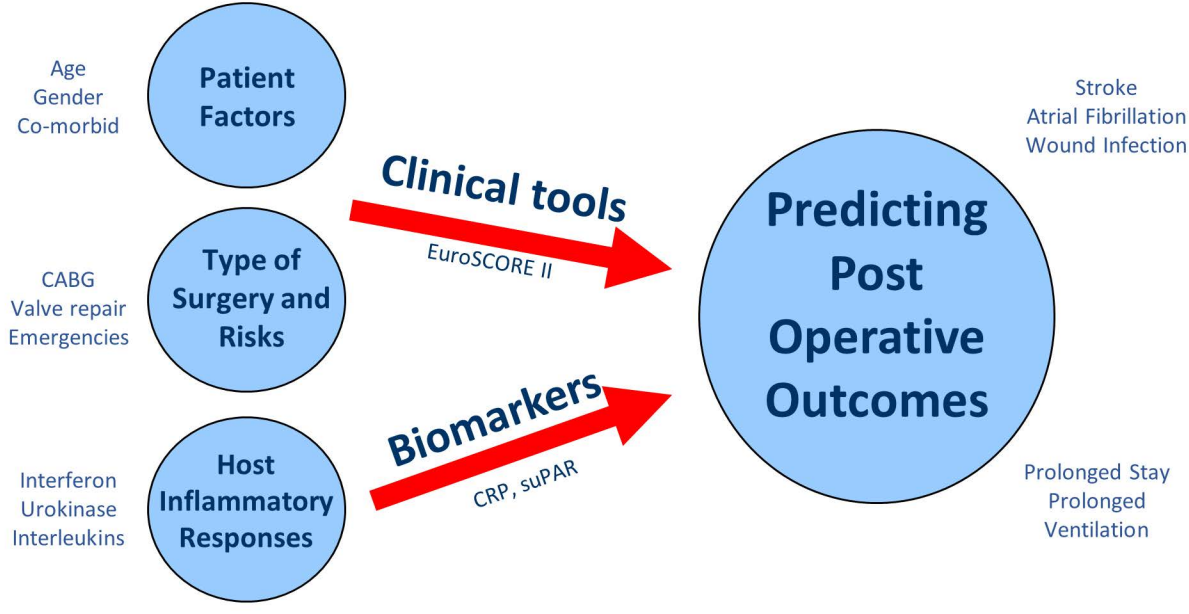


Figure 3(C):
Prolonged
Ventilation
Sensitivity
1 - Specificity
PreOP suPAR 0.75 (p=0.02)
EuroSCORE II 0.61 (p=0.30)


Age
Gender
Co-morbid
Patient Factors
CABG
Valve repair
Emergencies
Type of Surgery and Risks
Interferon
Urokinase
Interleukins
Host Inflammatory Responses
Clinical tools
EuroSCORE II
Biomarkers
CRP, suPAR
Predicting Post Operative Outcomes
Stroke
Atrial Fibrillation
Wound Infection
Prolonged Stay
Prolonged Ventilation