A Comparative Study of the Diagnostic and Prognostic Utility of Soluble Urokinase-type Plasminogen Activator Receptor and Procalcitonin in Patients with Sepsis and Systemic Inflammation Response Syndrome

Ankita Sharma1, Sumit Ray2, Ramya Mamidipalli3, Atul Kakar4, Parul Chugh5, Ridhima Jain6, Manvender S Ghalaut7, Sangeeta Choudhury8

ABSTRACT

Introduction: Differentiation between sepsis and systemic inflammation response syndrome (SIRS) remains a diagnostic challenge for clinicians as both may have similar clinical presentation. A quick and accurate diagnostic tool that can discriminate between these two conditions would aid in appropriate therapeutic decision-making. This prospective study was conducted to evaluate the diagnostic and prognostic utility of soluble urokinase-type plasminogen activator receptor (suPAR) and procalcitonin (PCT) in sepsis and SIRS patients.

Materials and methods: Eighty-eight patients were enrolled, of which 29 were SIRS and 59 were sepsis patients. The levels of suPAR and PCT were measured on the day of admission (day 1), day 3, and day 7.

Results: The levels of suPAR and PCT were significantly higher (p = 0.05 and p < 0.001, respectively) in sepsis group as compared to the SIRS group. The soluble urokinase-type plasminogen activator receptor was a better diagnostic tool in predicting sepsis over PCT (area under curve (AUC) 0.89 vs 0.82) on day 1. The best cutoff for suPAR was 5.58 pg/mL (96% sensitivity and 90% negative predictive value (NPV)) and the best cut-off for PCT was 1.96 ng/mL (93.1% sensitivity and 80% NPV). However, PCT had better prognostic trends (p = 0.006) to identify nonsurvivors in sepsis group.

Conclusion: Our findings suggest that both suPAR and PCT can be used as potential test tools to differentiate between SIRS and sepsis. Procalcitonin showed significant prognostic trends to identify nonsurvivors. The soluble urokinase-type plasminogen activator receptor showed better diagnostic potential than PCT on day 1.

Clinical significance: Both suPAR and PCT can be used as surrogate biomarkers to distinguish sepsis from SIRS. Procalcitonin showing a significant prognostic trend to identify nonsurvivors can help the clinicians to take relevant clinical decisions. Also, the use of biomarkers like PCT and suPAR could reduce the inappropriate use of antibiotics in noninfective SIRS.

Keywords: Procalcitonin, Sepsis, Soluble urokinase-type plasminogen activator receptor, Systemic inflammation response syndrome.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23385

INTRODUCTION

During the last decade, there has been a worldwide increase in the incidence of sepsis.1,2 This has led to a twofold increase in hospitalization rate (11.6 to 24.0 per 10,000 population).3 Although in recent years management of sepsis has improved survival, the overall mortality is still rising as the number of sepsis cases has been increasing.4,5 According to the consensus definition of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM), sepsis is defined as a systemic inflammatory host response (SIRS) to infection and characterized by alterations in physiologic parameters such as temperature, heart rate, respiratory rate, mentation, etc.6 These changes in physiologic parameters are nonspecific in the clinical context and may manifest in many other non-infectious causes of SIRS such as trauma, burns, pancreatitis, etc. Recently, the Third International Consensus Definitions for Sepsis and Septic Shock (2017) has redefined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, as it has been now observed that the immune response in sepsis is more complex than just an inflammatory cytokine response.7 It has been observed that a subset of patients shows a predominant surge of anti-inflammatory cytokines but the initial clinical response is still guided by SIRS criteria.7

© The Author(s). 2020 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
a need to identify biomarkers that not only are more sensitive and specific but can also be performed quickly and cost-effectively. Review of published literature suggests procalcitonin (PCT) as a good biomarker which can differentiate patients with SIRS and sepsis and has been evaluated extensively. Procalcitonin is a precursor of the hormone calcitonin and is produced by parafollicular cells of thyroid and neuroendocrine cells of lungs and intestine. The levels of PCT rises in response to an inflammatory stimulus, especially of bacterial origin.

A new biomarker, soluble urokinase-type plasminogen activator receptor (suPAR), demonstrated to have the ability to predict disease severity in bacteremia, ventilator-associated pneumonia, SIRS, and sepsis. Immunologically, suPAR is a three-domain glycosylated protein (D1–D3) which binds to glycosylphosphatidylinositol (GPI) anchor on cell surface to release its soluble form, i.e., suPAR. Immunologically, suPAR levels have been suggested as a novel prognostic marker of disease severity in bacteremia, ventilator-associated pneumonia, SIRS, and sepsis. However, suPAR levels are not specific but can also be performed quickly and cost-effectively. Therefore, a need to identify biomarkers that not only are more sensitive and specific but can also be performed quickly and cost-effectively.

The diagnosis of bacterial infection in culture-negative patients was done based on the findings of a clinical focus of infection.

**Classification of Patient Groups**

Based on the criteria of SIRS and sepsis, patients were classified as:

- Group I (noninfectious SIRS): Patients with two or more signs of SIRS without any evidence of infection and diagnosed with recent onset of pancreatitis and trauma (within 24 hours) were included in this group.
- Group II (sepsis group): Patients with two or more signs of SIRS and clinical suspicion of infection or culture-proven infections.

Statistical Package for the Social Science (SPSS) version 17.0 was used to perform statistical testing. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR) for nonnormally distributed data. Student’s t test was performed to compare normally distributed continuous variables between the groups. Mann–Whitney U test was performed for nonnormal distribution continuous variables. For categorical variables, Chi-square test or Fisher’s exact test was used, and the results were expressed as frequencies and percentages as appropriate. A receiver–operating characteristic (ROC) analysis was calculated to determine the optimal cutoff value for suPAR and PCT. To analyze the diagnostic accuracy of the markers, AUC, sensitivity, specificity, positive predictive value (PPV), and NPV were calculated. For all statistical tests, a p value of <0.05 is indicative of significant difference.

Statistical Analysis

The study was conducted in 88 patients prospectively. As explained in the methodology, enrolled patients were classified into two groups, namely, noninfectious SIRS (n = 29) and sepsis (n = 59) (Flowchart 1). Of the total patients enrolled, nearly 33% patients were noninfectious SIRS and 67% were sepsis. The demographic characteristics of the patients enrolled are shown in Table 1.

Characteristics of Patients Enrolled

No significant age or gender difference was observed between the study groups (Table 1). Mean APACHE II score was significantly (p < 0.001) higher in sepsis group (25.3) as compared to SIRS.
A Comparative Study of the Diagnostic and Prognostic Utility of suPAR and PCT in Patients with Sepsis and SIRS

**Source of Infection**

The major sources of infection were respiratory tract (37.3%), abdominal (23.7%), bloodstream (17.9%), and urinary tract (11.9%) (Fig. 1). Ten percent of the patients had more than one source of infection.

**Table 1:** Demographics and outcome of the study patient groups

| Characteristics                  | Group I (SIRS) | Group II (Sepsis) | p value |
|----------------------------------|---------------|-------------------|---------|
| No. of patients                  | 29            | 59                | –       |
| Sex, M/F                         | 20/9          | 40/19             | –       |
| Mean age (years/min–max)         | 37 (20–64)    | 58 (38–84)        | NS      |
| Mortality, n (%)                 | 4 (13.8%)     | 24 (40.7%)        | 0.001   |
| APACHE II, mean (range)          | 15.8 (5–48)   | 25.3 (9–47)       | <0.001  |

**Flowchart 1:** Patients enrolled in the study

- Total admissions (n = 4829)
- Patients who fulfilled >2SIRS criteria (n = 2265)
- Excluded (n = 2177)
- Reason for exclusion
  - Transferred (n = 642)
  - Prior exposure to healthcare in last three months, (n = 832)
  - Postoperative cases, (n = 386)
  - Tropical illness, (n = 426)
  - Immuoncompromised, (n = 31)
  - Died within 24 hours, (n = 48)
- Samples Analyzed (n = 88)

**Serum Levels of suPAR and PCT in Study Groups**

The levels of suPAR and PCT were measured in all the enrolled patients on the day of admission (day 1), day 3, and day 7. The median PCT value on day 1 was significantly higher (p < 0.001) in the sepsis group (32.78 ng/mL) as compared to SIRS group (1.17 ng/mL). Similarly, day 1 median suPAR values were significantly higher in sepsis group (19.54 pg/mL) as compared to SIRS (4.2 pg/mL) (p = 0.05) (Fig. 2). Thus, both PCT and suPAR were able to distinguish between sepsis and SIRS on day 1.

**Discriminative Performance of suPAR and PCT to Diagnose Sepsis**

The ROC curve analysis was performed for suPAR and PCT for prediction of sepsis (Fig. 3). The AUC for suPAR (day 1) and PCT (day 1) were 0.89 and 0.82, respectively. For suPAR, the optimal cutoff point was 5.58 with a sensitivity of 96%, NPV of 90%, and accuracy of 82.05%. The best cutoff for PCT was 1.96 with a sensitivity of 93.1%, NPV of 73.4%, and accuracy of 79.4%. Both the markers were sensitive enough to predict sepsis; however, suPAR was statistically a more accurate marker for the diagnosis of sepsis. Similar trends were
A Comparative Study of the Diagnostic and Prognostic Utility of suPAR and PCT in Patients with Sepsis and SIRS

Table 2: Diagnostic performance of soluble urokinase-type plasminogen activator receptor and procalcitonin in differentiating sepsis and systemic inflammation response syndrome

| Variable       | Cutoff | AUC   | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | p value |
|----------------|--------|-------|----------------|-----------------|---------|---------|--------------|---------|
| PCT @ day 1    | 1.96   | 0.82  | 93.1           | 53.33           | 79.41   | 80.0    | 79.55        | 0.002   |
| suPAR @ day 1  | 5.58   | 0.89  | 96             | 60.00           | 79.31   | 90.00   | 82.05        |         |

Table 3: Prognostic values of soluble urokinase-type plasminogen activator receptor and procalcitonin in systemic inflammation response syndrome group

|      | Survivors | Nonsurvivors | p value |
|------|-----------|--------------|---------|
| PCT  | Median (IQR) | Median (IQR) |         |
| D1   | 1.18 (0.2–4.46) | 3.11 (0.31–5.99) | 0.793   |
| D3   | 0.80 (0.40–3.02) | 1.21 (0.09–2.38) | 0.431   |
| D7   | 0.5 (0.2–0.68) | 36.86 (3.45–70.07) | 0.003*  |
| suPAR| Median (IQR) | Median (IQR) |         |
| D1   | 4.20 (2.69–9.56) | 19.20 (2.48–36.15) | 0.470   |
| D3   | 3.73 (2.28–8.89) | 12.55 (2.42–21.22) | 0.280   |
| D7   | 4.21 (3.11–8.70) | 24.83 (15.65–25.90) | 0.009*  |
| p value | 0.276 | 0.607 |         |

*Highly significant

Table 4: Prognostic values of soluble urokinase-type plasminogen activator receptor and procalcitonin in sepsis group

|      | Survivors | Nonsurvivors | p value |
|------|-----------|--------------|---------|
| PCT  | Median (IQR) | Median (IQR) |         |
| D1   | 22.93 (7.11–47.56) | 36.24 (9.48–104.64) | 0.210   |
| D3   | 6.24 (2.23–20.96) | 33.45 (4.03–109.88) | 0.004** |
| D7   | 1.20 (0.65–3.68) | 28.04 (12.04–53.45) | <0.001**|
| suPAR| Median (IQR) | Median (IQR) |         |
| D1   | 12.20 (7.12–23.03) | 28.66 (14.84–38.55) | 0.003** |
| D3   | 9.55 (6.98–15.38) | 22.08 (13.24–21.94) | <0.001**|
| D7   | 13.19 (7.39–18.20) | 19.13 (10.19–28.83) | 0.022*  |
| p value | 0.452 | 0.104 |         |

**Highly significant

Table 5: Prognostic ability of soluble urokinase-type plasminogen activator receptor to distinguish between survivors and nonsurvivors in sepsis group

| Sepsis | AUC | suPAR Cut off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | p value |
|--------|-----|---------------|----------------|-----------------|---------|---------|--------------|---------|
| Day 1  | 0.741 | 30.2 | 50.0 | 88.6 | 73.3 | 73.8 | 73.7 | 0.002   |
| Day 3  | 0.805 | 9.77 | 100.0 | 52.80 | 54.05 | 100.0 | 69.6 | <0.001 |
| Day 7  | 0.684 | 18.36 | 55.0 | 80.0 | 61.1 | 75.7 | 70.9 | 0.008   |

observed in the levels of suPAR and PCT collected on day 3 (Table 2). On day 3, suPAR was statistically slightly better at differentiating sepsis from SIRS (Table 2).

**Prognostic Values of suPAR and PCT to Predict Mortality in SIRS**

On analyzing the suPAR values, we observed no difference in median values from day 1 to day 7 in both survivors (p = 0.276) and nonsurvivors (p = 0.607) (Table 3). A significant decrease in the median PCT levels was observed in survivors (p = 0.001) from day 1 (1.18 ng/mL; IQR = 0.2 to 4.46) to day 7 (0.5 ng/mL; IQR = 0.2 to 0.68) and a sharp increase (p = 0.05) in the median PCT values from day 1 (3.11 ng/mL; IQR = 0.31 to 5.99) to day 7 (36.86 ng/mL; IQR = 3.45 to 70.07) in nonsurvivors of SIRS group (p = 0.05). The trends of median values for both suPAR and PCT suggest that PCT had a better prognostic value for predicting nonsurvivors in SIRS group. On day 7, a significant increase in the median suPAR (p = 0.009) and PCT (p = 0.003) levels was observed in nonsurvivors as compared to survivors.

**Prognostic Values of suPAR and PCT to Predict Mortality in Sepsis**

In the case of sepsis, no significant difference (p = 0.45) was observed in the median suPAR values from day 1 (12.2 pg/mL; IQR = 7.12 to 23.03) to day 7 (13.19 pg/mL; IQR = 7.39 to 18.2) among survivors, whereas a decrease was observed in the median values of suPAR from 28.66 pg/mL (IQR = 14.84 to 38.55) on day 1 to 19.13 pg/mL (IQR = 10.19 to 28.83) on day 7 in nonsurvivors, though it did not reach statistical significance (Table 4). It was observed that the suPAR values were significantly higher at all three time points (day 1, p = 0.003; day 3, p < 0.001; and day 7, p = 0.022) in nonsurvivors as compared to survivors.

Similar trends in the median PCT values were observed in survivors and nonsurvivors. The median PCT levels decreased significantly from day 1 to day 7 in both survivors (p < 0.001) and nonsurvivors (p = 0.006), but the PCT levels remained significantly higher in nonsurvivors as compared to survivors on day 3 (p = 0.004) and day 7 (p < 0.001).

Median values of suPAR at all the time points (day 1, day 3, and day 7) were significant in distinguishing the nonsurvivors from the survivors. The accuracy of suPAR at day 1 (p = 0.002), day 3 (p < 0.001), and day 7 (p = 0.008) was 73.7%, 69.6%, and 70.9%, respectively. The NPV of suPAR was 73.8%, 100%, and 75.7% on day 1, day 3, and day 7, respectively (Table 5).

The median values of PCT on day 3 and day 7 were highly significant in identifying nonsurvivors in the sepsis groups. For PCT, a cutoff value of 16.93 ng/mL on day 3 (p = 0.001) had a specificity and NPV of 72.2% and 81.3%, respectively, to predict mortality. On day 7, at a cutoff value of 11.62 ng/mL, PCT (p < 0.001) had a specificity and NPV of 72.2% and 89.7%, respectively, to predict mortality (Table 6). Although there was a difference in the median values of PCT on day 1 to differentiate survivors from nonsurvivors among sepsis patients, it did not reach statistical significance.

**Discussion**

Sepsis is a life-threatening clinical syndrome characterized by a dysregulated host response to infections with nonspecific clinical symptoms.5 The dysregulated inflammatory responses involve the activation of proinflammatory and anti-inflammatory cellular
and humoral responses affecting organ function in sepsis. Early diagnosis of sepsis is important to rapidly implement appropriate therapy, which is directly associated with clinical outcomes.

The gold standard to diagnose infection is bacterial culture, which is positive in less than 50% of cases of sepsis (8) and it takes 24 to 48 hours. Despite adequate improvements in diagnostic techniques, it is still a challenge to differentiate between sepsis and SIRS early. These patients are primarily diagnosed by clinical acumen based on very subjective criteria. Thus, identifying a marker that can differentiate between sepsis, particularly culture-negative sepsis, and noninfectious SIRS is the need of the hour. Early and better diagnostic and prognostic markers will aid the clinicians in taking appropriate clinical decisions. As evidence has shown, giving early antibiotics (within 1 hour) in sepsis patients improves outcome significantly.20

Recently, many new biomarkers such as PCT, suPAR, interleukin (IL)-27, macrophage migration inhibitory factor (MIF), and galectin-3 have been evaluated for their diagnostic and prognostic ability in management of sepsis either as independent diagnostic/prognostic biomarkers or as a combination of biomarkers.9,21–23

Procalcitonin is a peptide precursor of hormone calcitonin consisting of 116 amino acids (molecular weight, 13 kD).24 It is synthesized by the C-cells of thyroid gland and remains undetectable in healthy individuals. Assicot et al. were the first to report abnormally raised PCT levels in patients with bacterial infections.25 In healthy volunteers, high PCT levels were detected in plasma 2 to 3 hours after endotoxin injection. The half-life of PCT in serum is 25 to 30 hours.26

The suPAR is the soluble form of the uPAR, a three-domain receptor mainly expressed on immune cells, including neutrophils, activated T-cells, and macrophages.14 The levels of suPAR were found to be elevated in several pathological conditions such as sepsis, bacteremia, malaria, tuberculosis, HIV infection, central nervous system infections, etc.15–18 Published literature has acknowledged suPAR as a marker to predict sepsis; however, it is also known to be relatively nonspecific. Our study evaluates the diagnostic and prognostic ability of serum PCT and suPAR in identifying sepsis patients and their value in prognostication.

The APACHE II score is an indicator of severity of illness and the risk of mortality in critically ill patients. In the current study, we observed that APACHE II scores were significantly higher in sepsis (p < 0.001) group as compared with SIRS. The mortality rate was also significantly higher in the sepsis group. This was similar to the results of Phua et al. and Kumar et al. who reported higher mortality in sepsis patients as compared to noninfective SIRS.20,27

We observed a significant increase in both suPAR and PCT in the sepsis group. Several immune cells are activated in sepsis, thereby resulting in a highly inflammatory condition. These activated immune cells release both suPAR and PCT which is reflected in our study. Our study results were in agreement with those reported by Mölkänen et al.28 and Sehestedt et al.29

The ROC analysis between sepsis and SIRS patients demonstrated a slightly superior AUC for suPAR in diagnosing sepsis than PCT on day 1. The sensitivity of suPAR at an optimum cutoff value of 5.58 pg/mL was 96% with an NPV of 90%. For PCT at a cutoff value of 1.96 ng/mL, the sensitivity and NPV were comparatively lower (93% and 80%, respectively). Kofod et al. and Sehestedt et al. found similar results, wherein suPAR showed higher sensitivity in patients with sepsis and SIRS.29,30

A clinical trial TRIAGE III was carried out to assess the prognostic value of suPAR. The trial did not find any significant correlation between increased level of suPAR and mortality.31 Our study correlates the declining trends in PCT (p < 0.001) with better prognostication than the trends in suPAR to predict survivors in SIRS (p = 0.276) and sepsis (p = 0.452).

Our data suggest suPAR to have a statistically better diagnostic ability in predicting sepsis over PCT. On the contrary, the PCT trend showed a better prognostic value to predict mortality in patients with sepsis and SIRS.

Hence, both suPAR and PCT can be used in addition to culture reports to improve outcome in sepsis by early initiation of antibiotics and resuscitation. On the contrary, both these biomarkers could reduce the inappropriate use of antibiotics in noninfective SIRS. Further, suPAR and PCT assays are simple to perform, provide quick results, and can be carried out in most modern healthcare establishments. The sensitivity and NPV of both suPAR and PCT suggest that they can be useful markers that can guide early, accurate, and rapid differentiation of sepsis from noninfective SIRS, much before the availability of culture reports. Further, a sequential analysis of PCT levels at various time points in sepsis can aid in understanding the severity and outcome of the disease.

The strength of our study was the stringent inclusion and exclusion criteria to enroll patients that clearly delineated the two groups under study. For sepsis, only those patients with fresh episodes having no history of previous hospital stay or antibiotic therapy in the last 3 months; and for SIRS, patients with trauma or pancreatitis in the last 24 hours were enrolled. The limitation of this study is that it is a single-center study without a very large number of patients. A multicenter study will enable validation of our findings.

### Conclusion

Our findings suggest that both suPAR and PCT can be used as potential test tools to differentiate between SIRS and sepsis. Both suPAR and PCT can help in the clinical setting by accurately and sensitively differentiating sepsis from SIRS, thereby improving outcomes in sepsis by early initiation of antibiotics and resuscitation. It would also help in reducing inappropriate antibiotic use in noninfective SIRS. Their ability to predict disease progression would help the clinicians to prognosticate outcomes. Larger multicenter trials are required to corroborate our findings.

### Clinical Significances

Surrogate biomarkers such as suPAR and PCT may aid in better distinction of sepsis from SIRS. Our study showed PCT to have a significant prognostic trend to identify nonsurvivors. This can help

---

**Table 6: Prognostic ability of procalcitonin to distinguish between survivors and nonsurvivors in sepsis group**

| Sepsis  | AUC   | PCT cutoff | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | p value |
|--------|-------|------------|----------------|-----------------|---------|---------|-------------|---------|
| Day 1  | 0.597 | 23.25      | 70.8           | 52.8            | 50.0    | 73.1    | 60.0        | 0.071   |
| Day 3  | 0.728 | 16.93      | 72.7           | 72.20           | 61.54   | 81.3    | 72.4        | 0.001   |
| Day 7  | 0.895 | 11.62      | 81.8           | 97.2            | 94.7    | 89.7    | 91.4        | <0.001  |
A Comparative Study of the Diagnostic and Prognostic Utility of suPAR and PCT in Patients with Sepsis and SIRS

clinchians to identify the patients at greater risk. Also, the use of biomarkers such as PCT and suPAR could reduce the inappropriate use of antibiotics in noninfective SIRS.

ACKNOWLEDGMENTS

We thank Mr Devinder Soni from ViroGates for providing us with the kits to perform suPAR. He had no role in planning, conducting and analyzing this study. We are grateful to Dr Seema Bhargava, Department of Biochemistry, Sir Ganga Ram Hospital, New Delhi, for helping us with the PCT results. A heartfelt thanks to the patients and the families of the enrolled patients for cooperating with the clinical and the research team.

REFERENCES

1. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2005;348(16):1546–1554. DOI: 10.1056/NEJMoa022139.

2. Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a prospective multicenter study. Intensive Care Med 2007;33(4):606–618. DOI: 10.1007/s00134-006-0517-7.

3. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med 2007;35(5):1244–1250. DOI: 10.1097/01.CCM.0000261890.41311.E9.

4. Hall MJ, Williams SN, DeFrances CJ, Goloshubsky I. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. NCHS Data Brief 2011;1(2):1–8.

5. Vincent JL, Rello J, Suter PM, Rubenfeld GD, Russell JA,6. Guidoboni G, et al. EPIC II group of investigators. International study of the prevalence and outcomes of infection in intensive care units. J Am Med Assoc 2009;302(21):2323–2329. DOI: 10.1001/jama.2009.1574.

6. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/society of critical care medicine. Chest 1992;101(6):1644–1655. DOI: 10.1378/chest.101.6.1644.

7. Anand D, Das S, Bhargava S, Srivastava LM, Garg A, Tyagi N, et al. Procalcitonin as a rapid diagnostic biomarker to discriminate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: a prospective, observational, cohort study. J Crit Care 2013;30(1):218–227. DOI: 10.1016/j.jcrc.2013.04.017.

8. Hayer-Hansen G, Remne E, Solberg H, Behrendt N, Ploug M, Lund LR, et al. Urokinase plasminogen activator receptor cleaves its cell surface receptor releasing the ligand-binding domain. J Biol Chem 1992;267(25):18224–18229.

9. Wilhelmi OG, Wilhelm S, Escott GM, Lutz V, Magdolen V, Schmitt M, et al. Cellular glycosylphosphatidylinositol-specific phospholipase D regulates urokinase receptor shedding and cell surface expression. J Cell Physiol 1999;180(2):225–235. DOI: 10.1002/(SICI)1077-4652(199908)180:2<225::AID-JCP2>3.0.CO;2-2.

10. 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). J Am Med Assoc 2016;315(8):801–810. DOI: 10.1001/jama.2016.0287.

11. Tsaklikidou E, Hansen TW, Ladelund S, Linneberg A, Andersen Ø, Haagard SB. Increased plasma soluble uPA receptor level is a risk marker of respiratory cancer in initially cancer-free individuals. Cancer Epidemiol Biomarkers Prev 2011;20(4):609–618. DOI: 10.1158/1055-9965.EPI-10-1009.

12. Sidinius N, Sier CF, Blasi F. Shedding and cleavage of the urokinase receptor (uPAR): identification and characterisation of uPAR fragments in vitro and in vivo. FEMS Lett 2000;475(1):52–56. DOI: 10.1111/j.1365-2958.2000.01624.x.

13. Jevdjic J, Surbatovic M, Milosavljevic S, Rondovic G, Stanojevic I, Eric J, et al. Galectin-3 in critically ill patients with sepsis and/or trauma: a good predictor of outcome or not? J Exp Clin Res 2013.

14. Le Mouel JC, Jullienne A, Chenais J, Lamasoilles F, Galiana JM, Milhaud G, et al. The complete sequence of human preprocalcitonin. FEBS Lett 1994;365(1):79–82. DOI: 10.1016/0014-5793(94)90335-9.

15. Wittenhagen P, Kronborg G, Weis N, Nielsen H, Obel N, Pedersen SS, et al. The plasma level of soluble urokinase receptor is elevated in patients with streptococcus pneumoniae bacteremia and predicts mortality. Clin Microbiol Infect 2004;10(5):409–415. DOI: 10.1111/j.1469-0691.2004.00850.x.

16. Huttunen R, Syrjänen J, Vuento R, Hurme M, Huhtala H, Laine J, et al. Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteremia: a prospective cohort study. J Intern Med 2011;270(1):32–40. DOI: 10.1111/j.1365-2696.2011.02363.x.

17. Engelen O, Van der Sluijs KF, Tacke F, Koch A, Polder PA, et al. Serum level of soluble urokinase receptor is elevated in tuberculosis patients and predicts mortality during treatment: a community study from guinea-Bissau. Int J Tuberc Lung Dis 2002;6(8):686–692.

18. Savva A, Raftogiannis M, Baziaka F, Antonopoulou A, Koutaoukas P, Tsaganos T, et al. Soluble urokinase plasminogen activator receptor (suPAR) for assessment of disease severity in ventilator-associated pneumonia and sepsis. J Infect 2011;63(5):344–350. DOI: 10.1016/j.jinf.2011.07.016.

19. Koch A, Voigt S, Kreuschinski C, Sanson E, Duckers H, Horn A, et al. Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. Crit Care 2011;15(1):R63. DOI: 10.1186/cc10037.

20. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589–1596. DOI: 10.1097/01.CCM.0000217961.75225.E9.

21. Backes Y, van der Sluijs KF, Mackie DP, Tacke F, Koch A, Tenhunen JJ, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review. Intensive Care Med 2012;38(9):1418–1428. DOI: 10.1007/s00134-012-2613-1.

22. Assicot M, Gendrel D, Carsin H, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis absence of bacteremia in adult patients with acute fever. Clin Infect Dis 2003;35(12):156–161. DOI: 10.1086/341023.

23. Tsalik EL, Jaggers LB, Glickman SW, Langley RJ, van Velkinburgh JA, et al. Usefulness of procalcitonin serum level for the diagnosis of bacteremia. Eur J Clin Microbiol Infect Dis 2003;22(8):524–527. DOI: 10.1023/A:1005096100548.

24. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, et al. uPAR for assessment of disease severity in ventilator-associated pneumonia and sepsis. J Infect 2011;63(5):344–350. DOI: 10.1016/j.jinf.2011.07.016.

25. Koopmans LM, Faes J, Tacke F, Koch A, Tenhunen JJ, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review. Intensive Care Med 2012;38(9):1418–1428. DOI: 10.1007/s00134-012-2613-1.

26. Loeb C, Schaffert C, Fritsch H, Exler J, Blasius H, Wieser W, et al. Serum level of soluble urokinase receptor is elevated in patients with sepsis absence of bacteremia in adult patients with acute fever. Clin Infect Dis 2003;35(12):156–161. DOI: 10.1086/341023.
29. Sehestedt T, Lyngbæk S, Eugen-Olsen J, Jeppesen J, Andersen O, Hansen TW, et al. Soluble urokinase plasminogen activator receptor is associated with subclinical organ damage and cardiovascular events. Atherosclerosis 2011;216(1):237–243. DOI: 10.1016/j.atherosclerosis.2011.01.049.

30. Kofoed K, Eugen-Olsen J, Petersen J, Larsen K, Andersen O. Predicting mortality in patients with systemic inflammatory response syndrome: an evaluation of two prognostic models, two soluble receptors, and a macrophage migration inhibitory factor. Eur J Clin Microbiol Infect Dis 2008;27(5):375–383. DOI: 10.1007/s10096-007-0447-5.

31. Schultz M, Rasmussen L, Andersen M, Stefansson J, Falkentoft A, Alstrup M, et al. Use of the prognostic biomarker suPAR in the emergency department improves risk stratification but has no effect on mortality: a cluster-randomized clinical trial (TRIAGE III). Scand J Trauma Resusc Emerg Med 2018;26(1):69. DOI: 10.1186/s13049-018-0539-5.