Original Article

Evaluation of soluble urokinase-type plasminogen activator receptor (suPAR) quick test for triage in the emergency department

Pratyush Kumar[1], Atul Kakar[2], Atul Gogia[2], NIamatullah Waziri[2]

[1]Departments of Family Medicine and [2]Medicine, Sir Gangaram Hospital, Rajinder Nagar, New Delhi, India

Abstract

Background: *Soluble urokinase-type plasminogen activator receptor (suPAR) is a new biomarker, which is increased in conditions associated with inflammatory immune cell activation. In low resource, densely populated countries, there is a need for a quick test for triage and prognosticating in the emergency department. **Materials and Methods:** *A pilot, observational study was conducted wherein all consenting adult patients (>18 years) presented to casualty with acute medical illnesses were included. Detailed clinical history, examination, and suPAR quick tests were done and patients were categorized into five groups based on the emergency severity index (ESI) triage algorithm. Patients with suPAR level more than 5.5 ng/mL were advised hospitalization and those below were advised follow-up. All patients were followed-up after 3 days. **Results:** Total 190 patients (20–80 years), 80 males and 110 females participated. ESI triage 1, 2, and 3 had suPAR levels > 5.5 ng/mL and ESI triage 4 and 5 had suPAR level of <5.5 ng/mL. In ESI-1, 29 patients were admitted in ICU and 16 left against medical advice (LAMA) and on follow-up mortality was 96% (P = <0.05). In ESI-2, all patients were admitted in high dependency units and on follow-up they still needed hospitalization. In ESI-3, 22 patients admitted in ward and 24 went LAMA, on follow-up all improved except LAMA patients who required hospitalization (P – <0.05). Patients in ESI-4 and 5 did not require admission (P = <0.001).**Conclusion:** *suPAR can reliably be used in the emergency department to prognosticate and triage.

Keywords: Emergency, primary care, suPAR, triage

Introduction

Soluble urokinase-type plasminogen activator receptor (suPAR) is a new biomarker, which is increased in conditions associated with inflammatory immune cell activation. Hence, the receptor has been identified as a potential novel biomarker indicating prognosis in several clinical settings[1]

The emergency department (ED) plays a very important role in providing acute health care and triage to the public, especially in a limited resource setting and densely populated country like India. A large proportion of the total acute admissions to ICU and inpatient wards are via ED. In the ED, it is very difficult to abruptly categorize individuals according to their disease severity. They may come with acute or chronic disorders but priority is always given to the patients with critical or life-threatening conditions. This process of categorization is called triage.[2] Primary care settings in rural and remote areas needs to be better equipped with point of care testing for triage. In low and middle-income countries (LMICs), where there are huge health workforce shortage, resource constraints and increased patient load on tertiary centers, an effective referral strategy will help reduce morbidity and unnecessary load on the higher centers.

Address for correspondence: Dr. Pratyush Kumar, Department of Family Medicine, Sir Gangaram Hospital, Rajinder Nagar, New Delhi - 110 060, India.
E-mail: pratyush410@yahoo.co.in

Received: 08-02-2019 **Revised:** 10-02-2019
Accepted: 17-09-2019 **Published:** 10-12-2019

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_116_19

How to cite this article: Kumar P, Kakar A, Gogia A, Waziri N. Evaluation of soluble urokinase-type plasminogen activator receptor (suPAR) quick test for triage in the emergency department. J Family Med Prim Care 2019;8:3871-5.

The introduction of structured triage by specially trained nursing staff in the emergency department helps to accurately identify patients whose lives are endangered, especially at times of insufficient treatment capacity. Five-level triage systems are therefore recommended by national and international societies for emergency medicine.[3,4]

As suPAR serum level can give a very important clue to the clinician especially for medically ill patients coming to the ED with suspected infection and may provide a direct benefit for triage in such patients to determine the requirement for more intensive monitoring and care. As there are few studies done on suPAR and its comparison with emergency department triage scale, our aim in the present study was to evaluate the value of suPAR and compare it with Emergency Severity Index (ESI) scoring scale.

Subjects and Methods

This was a pilot, observational, noninterventional study conducted at a tertiary care hospital (675-bed) located in the northern part of India from March 1st 2015 to March 31st 2015. The data of 190 patients were collected after obtaining clearance from the Institutional Ethics committee and informed consent was taken from all participants before sample collection.

All adult patients (>18 years) presented to casualty with acute medical illnesses and those who were willing to give consent were included in this study and patients with trauma and requiring surgical intervention were excluded from the study.

Detailed clinical history and examination were recorded as per clinical proforma. In the case of unconscious patients' history was taken from their near kin. Patients were categorized according to Emergency Severity Index (ESI),[4] which is a five-level emergency department (ED) triage algorithm that provides clinically relevant stratification of patients into five groups from one (most urgent) to five (least urgent) on the basis of acuity and resource needs.

1. ESI level 1: The patient requires immediate lifesaving intervention.
2. ESI level 2: The patient is confused, lethargic, or disoriented or in severe pain i.e. high-risk situation. (HR > 100, RR > 20, SaO2 <92%).
3. ESI level 3: The patient is confused, lethargic, or disoriented or in severe pain but vital signs are normal. The patient is predicted to require two or more resources (ECG, X-ray, USG, MRI etc.,).
4. ESI level 4: The patient is predicted to require one resource.
5. ESI level 5: The patient is predicted to require no resources.

About 2 mL of blood was collected in EDTA tube for suPAR at the time of admission after giving consent. suPAR quick test was done using suPARnostic® kits.

Patients with a suPAR level of more than 5.5 ng/mL were advised hospitalization and those below the cutoff of 5.5 ng/mL were asked to follow up on an outpatient basis. In case they were not willing for admission, they were categorized from casualty as LAMA (leave against medical advice).

All the admitted patients were assessed to look for the severity of their illness after 3 days and a telephonic call was made to confirm the condition of the patient who went LAMA or were being discharged from the emergency department.

Statistical analysis with the statistical package for the social science system version SPSS 17.0 was done. Continuous variables were presented as mean ± SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages.

Results

A total of 1250 patients were screened for this study. Out of 1250 patients, 190 patients gave consent for participation in the study.

The study group comprised of 80 (42.1%) males and 110 (57.9%) female patients. The age of the patients ranged from 20 years to 80 years. The median age of the patients was 58 years old, 42.1% of the patients were 60 years of age or older.

A total of 79.9% of the patients had one or more coexisting medical conditions. The most common underlying comorbidities in our study were hypertension, diabetes, cardiovascular disease, and chronic kidney disease. They were found to have a prevalence of 40.5%, 27.4%, 18.4%, and 16.8%, respectively among all the patients. Mortality observed was 23.7% during the study.

Those patients whose suPAR levels were more than 5.5 ng/mL were advised hospitalization and those whose suPAR levels were less than 5.5 ng/mL and clinically stable were discharged.

Patients were categorized according to Emergency Severity Index. Out of 190 patients 126 patients (66.3%) had suPAR >5.5 and 64 patients (33.7%) had suPAR <5.5 ng/mL [Table 1]. ESI triage 1, 2, and 3 had suPAR levels > 5.5 ng/mL and ESI triage 4 and 5 had suPAR level of <5.5 ng/mL. Out of 190 patients, 45 patients (23.7%) were in ESI-1, 35 patients (18.4%) in ESI-2, 46 patients (24.2%) in ESI-3, 33 patients (17.4%) in ESI-4, and 31 patients (16.3%) in ESI-5 [Table 2].

Among patients in ESI-1, 29 patients were admitted in ICU and 16 went LAMA and on follow up mortality was 96% (P = <0.001).

In ESI-2, all patients were admitted in high dependency units and on follow up they still needed a hospital stay whereas in ESI-3, 22 patients were admitted inward and 24 went LAMA, on follow up all patients who were admitted improved and those who went LAMA required hospitalization (P = <0.001).

Table 1: suPAR level

		suPAR level		*P*
		>5.5 ng/mL	<5.5 ng/mL	
Number of patients	190	126	64	
ESI				
1	Expired (*n*=43)	43 (96%)	0 (0%)	<0.001
2	Expired (*n*=0)	0	0	
3	Expired (*n*=0)	0	0	
4	Expired (*n*=0)	0	0	
5	Expired (*n*=0)	0	0	

Table 2: Level of suPAR and patient outcome

		suPAR level		*P*
		>5.5 ng/mL	<5.5 ng/mL	
Number of patients	190	126	64	
ESI				
1	45	45	0	<0.001
2	35	35	0	
3	46	46	0	
4	33	0	33	
5	31	0	31	
PATIENT STATUS DAY 1				
ICU	29	29	0	<0.001
LAMA	40	40	0	
WARD	22	22	0	
HDU	35	35	0	
Discharged	64	0	64	
F/U After 3 days				
Expired	43	43	0	<0.001
HDU	35	35	0	
WARD	22	22	0	
IMPROVED	86	22	64	
Need further HOSPITALIZATION	24	24	0	

Patients in ESI-4 and 5 did not require admission and on follow up, they improved without hospitalization (P = <0.001).

Discussion

suPAR, the soluble form of urokinase-type plasminogen activator receptor (uPAR), is an endothelial based new biological marker of immunological activation. suPAR has a secondary structure of 17 anti-parallel β sheets with 3 short α helices. It exists in three homologous domains: D1, D2, and D3.[1]

Different biological markers have been used in acute medical settings. Biological markers have proved to play an important role in early stratification and prognosis of diseases. suPAR is a nonspecific biomarker reflecting inflammation and is a strong prognostic marker for several diseases.[1]

Urokinase-type plasminogen activator receptor (uPAR) is a glycoprotein released during infection and inflammation[5] which interacts with several molecules mediating immune system signals. uPAR is upregulated in various cells, including neutrophils, macrophages, lymphocytes, endothelial cells, and malignant cells in response to chemotaxis-inducing stimuli (e.g. interleukins).[1,5] uPAR and its ligand, urokinase plasminogen activator (uPA), promote the migration and adhesion of leucocytes by binding to β-integrins. uPAR also has a pivotal role in cell proliferation, angiogenesis, and fibrinolysis.[6-8] The soluble form of the receptor (suPAR) is formatted by proteases, which cleave uPAR from the cell surface. Thus, plasma suPAR levels are believed to represent the degree of immune activation.[3] Elevated circulating suPAR levels have proved to be risk markers even in the general population, of type-2 diabetes, cardiovascular disease, cancer, and overall mortality, probably through low-grade inflammation. Patients with bacteremia have been found to have increased plasma suPAR levels,[7] and high suPAR levels predict disease severity and outcome in various infections such as bacteremia,[9] human immunodeficiency virus infection (HIV),[10,11] bacterial meningitis,[12] and active pulmonary tuberculosis.[13] High suPAR levels have been linked to admission to the intensive care unit (ICU) and overall survival in critically ill patients.[3]

Several countries have developed and introduced different triage scales. ED triage[14,15] being designed as a five-level scale. Among these, the Australian Triage Scale (ATS), Canadian Emergency Department Triage and Acuity Scale (CTAS), Manchester Triage Scale (MTS), and Emergency Severity Index (ESI) have been proposed and introduced. The ESI[4] is a five-level triage algorithm that was developed in the USA in the late 1990s.

Clinically, the ESI[4] provides relevant stratification of patients into five levels from level one (most urgent) to five (least urgent) on the basis of acuity and resource needs.

We conducted this study to evaluate the role of suPAR. Patients were categorized according to the ESI and correlated with suPAR levels.

Various biomarkers are in clinical use for sepsis, inflammation, or infection, which includes: C-reactive protein (CRP), procalcitonin (PTC), interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), soluble triggering receptor expressed on myeloid cells (STREMI-1), macrophage migration inhibition factor (MIF), proadrenomedullin (ProADM), and presepsin.

Moreover, various laboratory biomarkers are routinely used in medical patients in the ED. However, many of these tools require specific diagnosis, which may not be obtained immediately, or may have limitations in predicting the expected course of disease including the case fatality rate.[16]

Among 190 patients a total of 79.9% patients had one or more coexisting medical conditions. Hypertension, diabetes, cardiovascular disease, and chronic kidney disease were found to have a prevalence of 40.5%, 27.4%, 18.4%, and 16.8%, respectively among all the patients. Mortality observed was 23.7%

in overall patients. In western literature, several studies have been done and showed that suPAR levels are not only related to the presence and severity of infection but its concentration can also show the presence and severity of organ dysfunction. Patients who have chronic liver disease have elevated suPAR levels and it can directly reflect the extent of liver dysfunction cirrhosis and its prognosis. suPAR levels can show the presence and severity of hepatic and renal failure in critically ill patients.[17] Other comorbidities seen were CAD; including acute MI, ACS, stroke, and so on, kidney disease especially focal segmental glomerulosclerosis (FSGS), liver biosynthesis, and cirrhosis.[17,18]

In our study, we compared suPAR level with ESI and found that those patients with positive suPAR value i.e. >5.5 ng/mL and who came in ESI-1 were either admitted in ICU or went LAMA. On follow up after 3 days, mortality was seen 96%. Katia *et al.* who conducted a prospective observational study to assess the role of blood soluble urokinase-type plasminogen activator receptor (suPAR) levels in the diagnosis and prognostication of sepsis in critically ill patients found that those patients having positive blood culture and critically ill had higher suPAR levels and hence it could help in prognostication of disease severity.[19]

We measured suPAR levels upon admission to the emergency department and did not conduct follow-up measurements of suPAR concentrations in those who survived beyond 3 days. Previous studies have shown that suPAR levels are elevated in acute infection and decreased towards recovery.[20] It would be useful in primary health care as a biomarker for diagnosis and prognosis of sepsis.[21]

Our aim was to establish whether suPAR could be used as an early diagnostic and/or prognostic marker in patients with suspected infection or underlying comorbidity in an emergency department setting.

This study has several limitations. First, no blinding was done as part of the study. Patients were followed only after 3 days and no further follow-up was done. Serial measurements of suPAR were not done. To further analyze the benefits, a randomized control study along with quantification of suPAR needs to be done for better stratification.

Conclusion

To conclude there is no previous data from India to compare the suPAR level with ESI. It is the first report giving fair information regarding the prognosis of critically ill patients upon coming to ED.

suPAR can reliably discriminate between survivors and nonsurvivors and may be used in the emergency department to prognosticate and triage. It can be a point of care test at the primary care level for assessing severity and triage. It would be useful in primary health care as biomarker for diagnosis and prognosis of sepsis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Thuno M, Macho B, Eugen-Olsen J. suPAR: The molecular crystal ball. Dis Markers 2009;27:157-72.
2. Lerner EB, Schwartz RB, Coule PL, Weinstein ES, Cone DC, Hunt RC, *et al.* Mass casualty triage: An evaluation of the data and development of a proposed national guideline. Disaster Med Public Health Prep 2008;2:S25-34.
3. Koch A, Voigt S, Kruschinski C. 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;15:63.
4. Tanabe P, Gimbel R, Yarnold PR, Kyariacou DN, Adams JG. Reliability and validity of scores on the emergency severity index version 3. Acad Emerg Med 2004;11:59-65.
5. Ossowski L, Aguirre-Ghiso JA. Urokinase receptor and integrin partnership: Coordination of signaling for cell adhesion, migration and growth. Curr Opin Cell Biol 2000;12:613-20.
6. Gyetko MR, Sud S, Kendall T, Fuller JA, Newstead MW, Standiford TJ. Urokinase receptor-deficient mice have impaired neutrophil recruitment in response to pulmonary Pseudomonas aeruginosa infection. J Immunol 2000;165:1513-9.
7. Rijneveld AW, Levi M, Florquin S, Speelman P, Carmeliet P, VanDer Poll T. Urokinase receptor is necessary for adequate host defense against pneumococcal pneumonia. J Immunol 2002;168:3507-11.
8. Wiersinga WJ, Kager LM, Hovius JW. Urokinase receptor is necessary for bacterial defense against pneumonia-derived septic melioidosis by facilitating phagocytosis. J Immunol 2010;184:3079-86.
9. Huttunen R, Syrjanen J, Vuento R. Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteraemia: A prospective cohort study. J Intern Med 2011;270:32-40.
10. Sidenius N, Sier CF, Ullum H. Serum level of soluble urokinase-type plasminogen activator receptor is a strong and independent predictor of survival in human immunodeficiency virus infection. Blood 2000;96:4091-5.
11. Lawn SD, Myer L, Bangani N, Vogt M, Wood R. Plasma levels of soluble urokinase-type plasminogen activator receptor (suPAR) and early mortality risk among patients

enrolling for antiretroviral treatment in South Africa. BMC Infect Dis 2007;7:41.

12. Østergaard C, Benfield T, Lundgren JD, Eugen-Olsen J. Soluble urokinase receptor is elevated in cerebrospinal fluid from patients with purulent meningitis and is associated with fatal outcome. Scand J Infect Dis 2004;36:14-9.
13. Eugen-Olsen J, Gustafson P, Sidenius N. The 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;6:686-92.
14. Fernandes CM, Tanabe P, Gilboy N, Johnson LA, McNair RS, Rosenau AM, *et al.* Five-level triage: A report from the ACEP/ENA Five-level Triage Task Force. J Emerg Nurs. 2005;31:39-50.
15. Shelton R. The emergency severity index 5-level triage system. Dimens Crit Care Nurs 2009;28:9-12.
16. Challen K, Goodacre SW. Predictive scoring in non-trauma emergency patients: A scoring review. Emerg Med J 2011;28:827-37.
17. Zimmermann HW, Koch A, Seidler S, Trautwein C, Tacke F. Circulating soluble urokinase plasminogen activator is elevated in patients with chronic liver disease, discriminates stage and aetiology of cirrhosis and predicts prognosis. Liver Int 2011;32:500-9.
18. Wei C, El Hindi S, Li J, Fornoni A, Goes N, Sageshima J, *et al.* Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat Med 2011;17:952-60.
19. Katia D, Sabino S, Cecilia C, Jean-Louis V. suPAR as a prognostic biomarker in sepsis. BMC Med 2012;10:2-6.
20. Snjezana M, Rusmir B. The importance of serum procalcitonin in diagnosis and treatment of serious bacterial infections and sepsis. Mater Sociomed 2013;25:277-81.
21. Huang Q, Xiong H, Yan P, Shuai T, Liu J, Zhu L, *et al.* The diagnostic and prognostic value of supar in patients with sepsis: A systematic review and meta-analysis. Shock 2019:1. doi: 10.1097/SHK.0000000000001434.