ORIGINAL ARTICLE

The role of soluble urokinase plasminogen activator receptor (suPAR) in patients with cancer: a review of the current literature

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ABSTRACT

Aim Several biomarkers are currently used as diagnostic and prognostic tools in patients with cancer. Soluble urokinase plasminogen activator receptor (suPAR) is elevated in acute and chronic inflammatory procedures and several observational studies during the last 20 years have investigated its role in oncology. The purpose of this article was to review the current literature regarding suPAR's role in clinical practice.

Methods A systematic literature search of PubMed, Scopus, OpenGrey and Cochrane Library databases through September 2021 was conducted using the following search terms: "supar"or "soluble urokinase plasminogen receptor" and "cancer" or "malignancy". Original articles reporting on suPAR's role in the diagnosis, prognosis and prediction of therapeutic outcomes in patients with confirmed or suspected cancer were included.

Results Among 45 found articles, the most were observational cohort studies. The included studies were further categorized by cancer site. SuPAR level was higher in patients with cancer compared to healthy controls, but its diagnostic and prognostic accuracy differs depending on the site of cancer.

Conclusion SuPAR has promising aspects in the field of oncology and public health and future research should further investigate its use in clinical practice. As it is elevated in different types of cancer, it could potentially serve as an adjunctive tool for the mass screening of patients with non-specific signs of cancer, but larger cohort studies that support these findings must be conducted.

Key words: biomarker, diagnosis, neoplasms, prognosis

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Original submission:
30 November 2021;
Revised submission:
18 January 2022;
Accepted:
24 January 2022
doi: 10.17392/1456-22

Med Glas (Zenica) 2022; 19(2): 197-206

INTRODUCTION

Even during this era of expansion of new technologies, tools and data in clinical practice, cancer is still an unsolved issue. In 2020, 19.3 million new cancer cases were diagnosed, and 10 million cancer related deaths occurred (1).

Biomarkers have been successfully used in oncology, and prostate specific antigen (PSA) is a great example of a biomarker that has shaped the clinical approach in that respective field (2). Thus, there is a rapid development of new biomarkers for cancer, which must be rigorously evaluated and analysed before they can be used in clinical settings (3).

Soluble urokinase plasminogen activator receptor (suPAR) is a urokinase type receptor, whose function is to bind plasminogen activator, while its soluble form can be measured in several biological fluids (4). SuPAR is a molecule that has been studied in acute and chronic inflammatory procedures, including sepsis and cancer (5).

In this article we have reviewed the current literature regarding suPAR's role in clinical practice.

MATERIALS AND METHODS

Materials and study design

A systematic literature search of PubMed, Scopus, OpenGrey and Cochrane Library databases was conducted through September 2021 using the following search terms: "supar" or "soluble urokinase plasminogen receptor" and "cancer" or "malignancy".

Methods

Inclusion criteria were observational and interventional studies who referred on the clinical significance of suPAR on adult patients with malignancy. More precisely, we included studies based on the diagnosis, prognosis and prediction of therapeutic outcomes in patients with confirmed or suspected cancer. Exclusion criteria were studies on paediatric malignancy, case reports, conference abstracts, thesis, review articles, editorials, duplicate studies, studies in a language other than English and studies published before 1 January 2000.

Two independent authors (TP and CM) performed title and abstract screening, after that conducted a full-text screening for eligibility. Any disagreements were solved by a referee (DV). For all the studies the following data were extracted: author, publication year, cancer type and main findings.

RESULTS

The systematic search yielded a total of 513 results; 192 were rejected as duplicated leaving 321 articles for screening based on their title and abstract. Out of 92 reports for retrieval, 85 were successfully retrieved and were assessed for eligibility. A total of 45 studies were included in this analysis and further categorized by site of cancer (Table 1, 2).

General

There are some studies that reported the clinical use of suPAR in general, including various types of cancer. Three of them concluded that cancer patients have higher suPAR levels than healthy individuals, a finding described also in other specific cancer type studies (6-8). Rasmussen et al. found that patients with nonspecific symptoms and signs of cancer who finally died had higher suPAR levels from those who survived (6). In a smaller cohort (n=197) of patients with nonspecific symptoms and signs of cancer that investigated various inflammatory and immunological biomarkers, the combination of CRP and suPAR were significantly associated with the diagnosis of cancer (9). Eugen-Olsen et al. reported a high risk of developing cancer for individuals having increased plasma suPAR (10). Loosen et al. examined suPAR levels as an evaluation tool for Immune Checkpoint Inhibitors therapy in patients with solid tumours. They found a positive correlation between suPAR and neutrophil/lymphocyte ratio, which could be a predictor of treatment response. The most interesting finding was that low pretreatment levels of suPAR were related with more frequent immune related side effects and ultimately better disease control and higher overall survival, insinuating a trend of those individuals to respond better to immune checkpoint inhibitors therapy (7). Gao et al. found that suPAR levels in patients with lymph node involvement were lower than in patients with distant metastasis and higher than in cancer patients without such a disease progression (8).

Neuroendocrine cancer

We identified one study that enrolled patients with neuroendocrine tumours and neuroendocrine carcinomas (11). SuPAR levels were higher

Table 1. Studies with general information on suPAR and cancer, neuroendocrine, prostate, respiratory tract, breast, ovarian and haematological malignancies

First author, publication year	Cancer type	Main finding
Rasmussen, 2020	General	Among patients with non-specific symptoms and signs of cancer, suPAR was lower in disease free patients compared to patients with malignancy or other non-malignant disease.
Loosen, 2021	General	SuPAR level was lower in healthy controls than in patients with solid tumours and predictive of the response to immune checkpoint inhibitor therapy.
Gao, 2021	General	SuPAR level was higher in patients with malignant tumours compared to healthy controls and correlated with tumour invasion, metastasis and surgical intervention.
Rasmussen, 2017	General	Among patients with non-specific symptoms and signs of cancer, suPAR was significantly associated with cancer diagnosis.
Eugen-olsen, 2010	General	In the general population elevated baseline suPAR was associated with increased risk of cancer.
Ozdirik, 2020	Neuroendocrine	In patients with neuroendocrine neoplasia, suPAR was higher compared to controls but could not identify between neuroendocrine tumours and malignancies.
Wach, 2015	Prostate	In patients with prostate cancer, suPAR was higher compared to controls and patients with benign prostate hyperplasia and was associated with mortality.
Mccabe, 2000	Prostate	Compared to controls, SuPAR was elevated in patients with prostate cancer and to a lesser degree in patients with benign prostate hyperplasia.
Piironen, 2006	Prostate	Cleaved forms of suPAR were elevated in patients with cancer compared to benign disease.
Steuber, 2007	Prostate	Measurement of suPAR can increase the accuracy of a PSA-based model for the diagnosis of prostate cancer.
Shariat, 2007	Prostate	Among patients with prostate cancer, preoperative levels of suPAR were associated with disease severity and survival.
Al-janabi, 2014	Prostate	Among patients with prostate cancer, increased levels of suPAR were associated with poor survival.
Kjellman, 2011	Prostate	Among patients with prostate cancer, increased levels of suPAR were associated with poor overall survival and death from cardiovascular disease.
Langkilde, 2011	Respiratory	In the general population, elevated suPAR levels were associated with increased incident of respiratory and other types of cancer, but not gastrointestinal cancer.
Yalcin, 2020	Respiratory	Among patients with lung cancer, elevated suPAR levels were associated with increased mortality.
Riisbro, 2003	Breast	SuPAR levels were higher in patients with breast cancer compared to controls and were associated with overall survival and relapse-free survival.
Nijziel, 2003	Breast	SuPAR levels were higher in patients with breast cancer compared to controls, but suPAR could not discriminate between patients with and without metastasis.
Leandersson, 2016	Ovarian	In premenopausal women, suPAR in combination with human epididymis protein 4 and cancer antigen 125 could discriminate epithelial ovarian cancer and borderline tumours from benign tumours.
Henic, 2008	Ovarian	SuPAR and CA125 accurately discriminated malignant ovarian tumors and borderline tumours from benign tumours and elevated suPAR levels were associated with poor prognosis.
Begum, 2004	Ovarian	Preoperative levels of suPAR did not have significant prognostic value in patients with stage III ovarian cancer.
Begum, 2006	Ovarian	Pro-chemotherapeutic levels of suPAR did not have significant prognostic value in patients with recurrent epithelial ovarian cancer.
Ljuca, 2007	Ovarian	SuPAR had significant prognostic value and could predict chemotherapy successfulness in patients with ovarian carcinoma FIGO II and III stage.
Lane, 2015	Ovarian	SuPAR levels in the ascitic fluid did not differ between patients with serous epithelial ovarian carcinoma and controls.
Riisbro, 2001	Ovarian	In patients with different gynaecological cancers, suPAR levels were significantly increased compared to patients with benign diseases and healthy controls.
Shen, 2015	Haematological	In patients with multiple myeloma, suPAR levels predicted 2-years survival and were associated with disease progression and early extramedullary infiltration.
Erkut, 2016	Haematological	SuPAR levels were higher in patients with Acute Myeloid Leukemia compared to healthy controls and were associated with overall survival.
Guo, 2017	Haematological	SuPAR levels were higher in patients with Leukemia compared to healthy controls and significantly differed between subtypes of Leukemia.
Fujimura, 2014	Haematological	SuPAR in combination with the novel biomarker sLR11 could identify patients with early-stage Follicular Lymphoma and Diffuse Large B-Cell Lymphoma.

compared to healthy controls, but suPAR could not distinguish between the two groups. Additionally, contrary to other malignancies, suPAR did not have prognostic value or correlate with tumour-related factors in these patients.

Table 2. Studies with general information on gastrointestinal, hepatic and pancreatic malignancies

First author, publication year	Cancer type	Main finding
Liu, 2017	Gastrointestinal	SuPAR levels were higher in patients with colorectal cancer compared to healthy controls.
Usnarska-zubkiewicz, 2014	Gastrointestinal	SuPAR levels were higher in patients with gastrointestinal cancer compared to healthy controls.
Fidan, 2013	Gastrointestinal	SuPAR levels were higher in patients with gastric cancer compared to healthy controls and were associated with metastatic disease and survival.
Lomholt, 2009	Gastrointestinal	Among patients with colorectal cancer-related symptoms, suPAR levels associated with cancer diagnosis.
Loosen, 2018	Gastrointestinal	Among patients with colorectal cancer and liver metastases, elevated suPAR levels were associated with poor overall survival after resection.
Lomholt, 2010	Gastrointestinal	SuPAR and its cleaved forms were independent prognostic factors for overall survival in patients with colorectal cancer.
Fernebro, 2001	Gastrointestinal	Among patients with rectal cancer preoperative, suPAR levels were an independent prognostic marker for survival.
Riisbro, 2005	Gastrointestinal	In patients with rectal cancer preoperative, suPAR levels were an independent prognostic marker for survival.
Hogdall, 2002	Gastrointestinal	In patients with colorectal cancer a prognostic model that combines suPAR with tetranectin, plasminogen-activator inhibitor-1 (PAI-1) and carcinoembryonic antigen detects high-risk patients.
Tarpgaard, 2015	Gastrointestinal	Among patients with metastatic colorectal cancer higher baseline suPAR levels were associated with shorter progression-free survival and overall survival.
Rollf, 2019	Gastrointestinal	In patients with colorectal cancer preoperative and postoperative suPAR levels provided prognostic information.
Chounta, 2015	Hepatic	SuPAR levels were higher in patients with hepatocellular carcinoma compared with patients with minimal liver inflammation.
Loosen, 2021	Hepatic	SuPAR levels were higher in patients with hepatocellular carcinoma compared to healthy controls and were associated with mortality following transarterial chemoembolization.
Loosen, 2020	Hepatic	SuPAR levels were higher in patients with biliary tract cancer compared to healthy controls and were associated with outcome after resection.
Aronen, 2021	Pancreatic	SuPAR levels were higher in patients with pancreatic cancer compared to patients with chronic pancreatitis.
Sorio, 2011	Pancreatic	Urine suPAR/creatinine ratio was higher in patients with pancreatic cancer compared to patients with chronic pancreatitis and healthy controls.
Loosen, 2019	Pancreatic	Among patients with pancreatic adenocarcinoma undergoing resection, high preoperative suPAR levels were associated with poor survival.

Prostate cancer

We identified seven studies reporting on the clinical significance of suPAR in patients with prostate cancer. According to two of them, suPAR was significantly elevated in patients with prostate cancer or benign prostate hyperplasia compared to healthy controls, but the results of these studies differ numerically (12,13). In a study by Piironen et al, cleaved suPAR forms were higher in patients with prostate cancer and increased the diagnostic accuracy of PSA measurements, but this study does not discriminate between BPH and healthy patients (14). A study by Steuber et al. supports these results concluding that the measurement of cleaved suPAR forms can decrease the number of unnecessary biopsies (15). In preoperative serum samples of patients who underwent radical prostatectomy, suPAR increased with the severity of the disease. Additionally, higher preoperative suPAR levels were associated with worse clinical and pathological characteristics, biochemical progression, and aggressive disease (16).

Regarding prognosis, two studies report that elevated suPAR levels indicate poor prognosis, while a study in patients participating in prostate cancer screening contradicts these results (12,17,18). The latter included a small number of patients with prostate cancer (n=63) compared to those with positive results (n=146 and n=132) and used nationwide healthcare registers for a long-term follow-up.

Gastrointentestinal cancer

SuPAR has been evaluated for the diagnosis, prognosis and response to therapy of colorectal cancer and GI tract. Some studies asserted that it could be an effective screening test or a possible early detection biomarker due to its ability to discriminate colorectal cancer from colorectal adenomas and healthy volunteers (19-22). Esophageal cancer was related with higher levels than colorectal and gastric cancer, which is important because of the absence of early symptoms in this cancer type. Additionally, Loosen et al. described the combination of suPAR and CEA as a diagnostic tool for colorectal liver metastasis (23).

As a prognostic marker, high levels of suPAR are described as independent factor of reduced overall survival (21, 23-27) and progression-free survival

(28). These studies evaluated the preoperative status in patients scheduled for surgery, while Rolff et al. compared pre- and post-operative (6 months after resection) levels and found that the breadth of the decrease is associated with a better prognosis (29). Most studies confirmed an upgoing trend of suPAR levels, parallel to cancer stage by Duke, while Fidan et al. and Riisbro et al. related even higher suPAR levels with metastasis and Duke's stage D respectively (21,24,26,27). Hogdall et al. found that the combination of low plasminogen activator inhibitor 1 and tetranectin plus high suPAR and CEA is indicative of high-risk patients (27). Tarpgraad et al. claimed a statistically insignificant trend that patients with low suPAR levels could benefit more from the addition of cetuximab to their adjuvant therapy (28).

Hepatobiliary cancer

Regarding hepatic and biliary cancer, there are three articles that investigated the clinical importance of suPAR. All three studies are in line that cancer patients have greater plasma levels than healthy volunteers (30-32). Chounta et al. stated that suPAR levels can predict the development of hepatic cancer within 1-7 years among high-risk patients with hepatic disorders (30). Loosen et al. confirm the findings of other studies on hepatic cancer that high suPAR levels reduce overall survival (31). The third study demonstrates that low preoperative suPAR levels are associated with better outcome and high suPAR levels are related with decreased overall survival and increased incidence of acute kidney injury in patients who underwent surgery for biliary cancer (32).

Pancreatic cancer

There are three studies discussing the role of suPAR in pancreatic cancer management. Aronen et al. stated that plasma suPAR may help in differential diagnosis between pancreatic cancer, where they found elevated levels, and chronic pancreatitis, where levels were decreased even after acute alcoholic pancreatitis (5). Sorio et al. examined urinary suPAR/Creatinine ratio which was greater in cancer than in adenoma and healthy volunteers (4). Furthermore, non-resected patients and patients with metastasis had decreased overall survival if that ratio was high. Loosen et al. found that high preoperative plasma suPAR entrained poor overall survival after surgery and more complications (33).

Respiratory tract cancer

We included two studies on suPAR and respiratory cancer. Langkilde et al. enrolled 2656 patients in a nationwide study in Denmark and found that elevated suPAR was an independent risk factor for the diagnosis of respiratory cancer and other cancer types, but not GI tract cancer during the follow-up (median 12.4 years) (34). In a case-control study with 40 patients with lung cancer, suPAR was significantly elevated in cases vs controls, and was prognostic of mortality (35).

Breast cancer

We identified two studies on the prognostic value of suPAR in patients with breast cancer with contradicting results. Riisbro et al. reported that elevated suPAR levels are associated with increased morbidity and mortality and that preoperative levels of suPAR are a prognostic factor for relapse free survival and overall survival independent of established risk factors (36). On the other hand, in a small prospective study that followed up 50 breast cancer patients with and without metastases and a healthy control group for 3 years, found that suPAR is of limited prognostic significance in these patients (37). It is of note that, in the latter study, the samples were collected after the completion of the primary treatment.

Ovarian cancer

In a cohort of 350 patients undergoing surgery of adnexal masses, the researchers found that a panel of three biomarkers (cleaved form of suPAR, human epididymis 4 and CA125) could discriminate malignant from benign tumours more accurately compared to the Risk of Ovarian Malignancy Algorithm (ROMA) in premenopausal women (38). Additionally, high preoperative levels of suPAR are associated with poor prognosis. Similar results are reported by an older study, which did not account for menopausal status (39). On the contrary, in a cohort of 108 patients with late stage (stage III) ovarian cancer and a cohort of 71 patients with recurrent epithelial ovarian cancer, preoperative suPAR could not identify patients with poor prognosis (40,41).

An observational study by Ljuca et al. enrolled 27 patients with stage II and III ovarian carcinoma that were treated with platina/taxol chemotherapy after tumour resection (42). SuPAR measured before and after chemotherapy cycles could successfully monitor the succession of the treatment, and with better accuracy compared to two other biomarkers considered by the study (uPA and CEA).

One study assessed the levels of suPAR in ascitic fluid of patients with ovarian cancer compared to benign controls, and although its median levels were much higher in patients with malignancy (29-folds), it has shown no statistically significant difference (43).

A comparative study by Riisbro et al. that enrolled a smaller and more heterogeneous cohort (53 ovarian, 34 endometrial, and 30 cervical cancer patients, 17 patients with benign ovarian tumours, 28 patients with benign endometrial diseases and 31 female blood donors) concluded that preoperative levels of suPAR can differentiate between patients with malignancy and healthy control or patients with benign diseases) (44).

Haematological cancer

In addition to solid tumours, there is evidence that suPAR may have prognostic value in haematological malignancies. More precisely, Shen et al. enrolled 40 patients with multiple myeloma and 30 controls, and found that suPAR levels are correlated with clinical and laboratory markers of disease severity, and that suPAR is an independent prognostic factor for mortality and associated with disease progression and extramedullary infiltration (45). Erkut et al. reported similar findings regarding suPAR's prognostic value for newly diagnosed patients with Acute Myeloid Leukemia (46). In a study that included patients (n=86) with different types of leukemia, it was reported that suPAR levels differ between these types (higher levels are associated with AML) and thus may be useful for leukemia classification (47).

Fujimura et al., studied a population of 175 patients with newly diagnosed non-Hodgkin lymphoma, and concluded that suPAR in combination with the novel biomarker sLR11 could identify patients with early-stage follicular lymphoma and diffuse large B-cell lymphoma (48).

DISCUSSION

SuPAR is derived from the cleavage and release of urokinase-type plasminogen activator receptor (uPAR) and can be detected in several body fluids such as urine, cerebrospinal fluid, plasma and serum – hence being called the soluble form of uPAR. As a GPI-linked membrane protein, uPAR is central within the plasminogen activator (PA) system that has been found to play a pivotal role in cell migration, adhesion and chemotaxis, all of which are pivotal in inflammation response, immune cell mobilization, and cancer cell invasion (49-51). Among other characteristics, uPAR activation was also found to be crucial in the activation of several metalloproteinases that resulted in proteolysis of extracellular matter in a direction-specific manner (51). The uPAR-vitronectin interaction is another well-known molecular mechanism that is hypothesized to play a central role in cellular adhesion. Cancerous cells have also been described to alter their cytoskeletal structure in order to facilitate migration when exposed to uPA-uPAR complexes (49,52). Through numerous similar laboratory observations, suPAR has been found to be a key molecule in carcinogenesis and metastasis and has been further studied in a number of malignancy types as showcased here.

In the past few years, suPAR has been studied as a possible prognostic factor with promising results in a variety of malignancies. Our literature search suggests that several carcinomas exhibit a positive correlation between lessened survival and higher suPAR levels. In contrast, lower suPAR plasma levels seem to be related to better survival outcomes as well as response to treatment. One of the most studied cancer groups for possible suPAR correlations is the various gastrointestinal and colorectal carcinomas. In colorectal cancer, a significant difference in suPAR levels was not only observed between patients and healthy controls, but measurement of suPAR could also delineate patients with advanced adenocarcinoma from those with early-stage disease (19,22,29). Such studies provide evidence that suPAR levels have the potential to act not only as a screening tool, but additionally as an indicator of disease progression and treatment effect. Patients with ovarian tumours also exhibit a strong correlation between increased suPAR levels and probability of malignancy (7,39,42). Additionally, suPAR was found to be an independent prognostic marker

that was strongly correlated with worse prognosis in multivariate analysis as well as an indicator of successful chemotherapy treatment (42). Studies on prostate cancer patients described a slightly more complex image, as suPAR levels were not independently correlated with cancer presence, however suPAR measurements when utilized as an adjunct to PSA levels (15). The observation that BPH and prostatic carcinoma were not distinguished by serum suPAR levels alone can likely be attributed to the commonly activated PA-based inflammation cascade that results in elevated suPAR levels. Studying literature on hepatobiliary cancers also revealed a positive association between higher suPAR levels and impaired survival. In patients with hepatocellular carcinoma (HCC) suPAR levels was able to predict the risk of carcinoma incurrence and can be of potential value if validated in larger studies, since most markers currently in use for HCC aim towards the diagnosis of early-stage carcinomas instead of prediction of the incurrence risk (5,30,32). Observations in haematological malignancies follow closely those in other cancer types, as researchers have showcased that elevated suPAR levels are closely related to disease presence, as well as other malignancy markers (46,47).

Apart from the aforementioned role in cancer, suPAR has also been studied as an indicator of disease severity in infectious disease, as well as several inflammation-based syndromes. While it is no surprise that the inflammatory process and underlying malignancy can both cause elevated serum levels of suPAR (through activation of the PA cascade) (52,53), there is evidence that suPAR can still be used as a reliable malignancy marker that will differentiate between inflammation process and carcinoma, once appropriate cut-off values are implemented, as shown in studies regarding pancreatic and hepatocellular carcinomas (5,30). While the value of suPAR as a screening and prognostic indicator seems to be apparent and at the same time not confined to any single site of cancer, further validation studies with mass recruitment of affected individuals and healthy controls are needed before this tool is routinely implemented in clinical practice, mainly to accurately calculate appropriate cut-off values that seem to differ for each type of malignancy.

The main limitation of this study is the heterogeneity of the included studies, as we did not focus on a single cancer type or a prespecified measure of outcome, such as the biomarker's sensitivity for prognosing mortality. Nevertheless, we implemented a systematic strategy for the selection of the studies and categorized the current literature regarding suPAR and its clinical utility in patients with cancer.

Current literature suggests that suPAR is a potential biomarker for the diagnosis, prognosis, and prediction of therapy outcomes in patients with cancer. The most studied cancer group are cancers of the gastrointestinal tract. The accuracy of suPAR differs depending on the site of cancer, but studies suggest that it could also be used for the evaluation of patients with non-specific symptoms and signs of cancer. SuPAR has promising aspects in the field of oncology and public health and future research should further investigate its use in clinical practice.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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