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Soluble urokinase plasminogen activator receptor (suPAR) as a prognostic marker of mortality in healthy, general and patient populations: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Chronic inflammation is increasingly recognised as a major contributor to disease, disability and ultimately death, but measuring the levels of chronic inflammation remains non-canonised, making it difficult to relate chronic inflammation and mortality. Soluble urokinase plasminogen activator receptor (suPAR), an emerging biomarker of chronic inflammation, has been proposed as a prognostic biomarker associated with future incidence of chronic disease and mortality in general as well as patient populations. Proper prognostic biomarkers are important as they can help improve risk stratification in clinical settings and provide guidance in treatment or lifestyle decisions as well as in the design of randomised trials. Here, we wish to summarise the evidence about the overall association of the biomarker suPAR with mortality in healthy, general and patient populations across diseases.

Methods and analysis The search will be conducted using Medline, Embase and Scopus databases from their inception to 03 June 2020 to identify studies investigating 'suPAR' and 'mortality'. Observational studies and control groups from intervention studies written in English or Danish will be included. The 'Quality In Prognosis Studies' tool will be used to assess the risk of bias for the studies included. Unadjusted and adjusted mortality outcome measures (eg, risk ratios, ORs, HRs) with 95% CIs will be extracted for healthy individuals, general and patient populations. The primary outcome is all-cause mortality within any given follow-up. Subgroup analyses will be performed based on time of outcome, cause of death, population type, adjustments for conventional risk factors and inflammation markers.

Ethics and dissemination This systematic review will synthesise evidence on the use of suPAR as a prognostic marker for mortality. The results will be disseminated by publication in a peer-reviewed journal. Data used will be obtained from published studies, and ethics approval is therefore not necessary for this systematic review.

Trial registration number
PROSPERO CRD42020167401.

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review and meta-analysis that investigates the association between soluble urokinase plasminogen activator receptor (suPAR) and mortality across general and patient populations.
- This review will provide valuable new knowledge for researchers studying chronic inflammation's effect on both short- and long-term health, and for clinicians using suPAR in clinical settings to stratify patients.
- Study selection, data extraction and quality assessment will be performed independently by two reviewers.
- The results will be discussed in context with other studies in the field.
- Common to most meta-analyses, significant heterogeneity may exist, which will be investigated thoroughly with subgroup analyses and meta-regressions.

INTRODUCTION

Rationale

Chronic inflammation is increasingly recognised as a major contributor to disease, disability and ultimately death in industrialised and low/middle-income countries alike.[1–4] Chronic inflammation is related to multiple genetic and lifestyle factors, but measuring the levels of chronic inflammation remains non-canonised, making it difficult to relate chronic inflammation and death. Soluble urokinase plasminogen activator receptor (suPAR) is a protein present in the blood, and its concentration is thought to reflect a person's level of chronic inflammation and immune activation.[5 6] Thus, elevated suPAR is proposed as a prognostic biomarker associated with future incidence of chronic disease and mortality in general as well as patient populations,[7 8] including previous systematic reviews and meta-analyses showing suPAR to be elevated in focal segmental glomerulosclerosis[9 10] or to be associated with mortality in patients with bacterial infections and sepsis.[11–14] While healthy persons generally have a low level of suPAR in the blood,[15] the blood concentration of suPAR is increased in a wide range of diseases: acute and chronic, non-communicable and infectious, that is, suPAR has been shown to be elevated in cardiovascular diseases (stroke, ischaemic heart disease, venous thromboembolism, incident atrial fibrillation),[16–18] type 1 and type 2 diabetes,[19–21] various types of cancer,[22–36] rheumatic disease,[37 38] chronic pulmonary disease,[39] chronic liver disease (non-alcoholic fatty liver disease, cirrhosis),[40–42] chronic kidney disease[43 44] as well as infectious diseases caused by viruses,[42 45–47] bacteria[48–57] and parasites.[58 59] Together, these studies highlight the broad associations across patient groups and aetiologies—and even in general populations—between elevated blood levels of suPAR with general health, disease outcome, complications and mortality.

In contrast to common inflammatory biomarkers, such as the current gold-standard C-reactive protein (CRP), suPAR is not an acute-phase reactant, and suPAR levels in the blood are less rapidly affected by acute changes and short-term influences.[17 60] Additionally, suPAR was more reliably associated with early-life risk factors such as adverse childhood experiences, early-life stress and violence than CRP and interleukin-6 (IL-6), potentially because these more traditional biomarkers of inflammation as acute-phase reactants mix historical and acute effects.[61 62] This, along with its non-specific associations with pathologies in general, suggests that suPAR blood levels are an appropriate readout for chronic inflammation.

Prognostic biomarkers are important as they can help improve risk stratification in clinical settings or provide guidance in treatment or lifestyle decisions as well as in the design of randomised trials.[63] Here, we wish to summarise the evidence about the overall association of the biomarker suPAR with mortality in healthy, general and patient populations and across diseases. As suPAR is still a relatively new clinical biomarker, clinical guidelines and cut-offs are still lacking. Our findings will clarify the association between suPAR and mortality, and what value a biomarker reflecting chronic inflammation adds, compared with the current standard inflammatory biomarkers. The study will help development of future clinical guidelines, based on a better understanding of differences in the prognostic value of suPAR between and across healthy individuals and patient subgroups, which is critical in clinical decision making. Having an established accurate chronic inflammation biomarker with a well-described association with mortality is a vital tool in future efforts to combat major public health challenges.

Objective

In this systematic review, we aim to investigate the hypothesis that elevated suPAR is associated with increased risk of short-term and long-term mortality in healthy, general and patient populations, independent of conventional risk factors.

To this end, the proposed systematic review will answer the following questions:

Primary aim:

1. Do individuals with higher suPAR levels have a higher risk of mortality?

Secondary aims:

1. Is the association between suPAR and mortality present in healthy, general and various patient populations?
2. Is the association between suPAR and mortality independent of conventional risk factors, such as age, sex, smoking and chronic disease?
3. Is the association between suPAR and mortality independent of other inflammatory biomarkers?
4. What is the discrimination performance of suPAR for predicting mortality?
5. What clinical and study methodological characteristics explain heterogeneity in the results?

METHODS AND ANALYSIS

Review design

The study protocol for this systematic review and meta-analysis was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines[64 65] and was registered with PROSPERO (registration number CRD42020167401).

This study will follow the recommendations on conducting and reporting systematic reviews and meta-analyses set forth by the PRISMA[66] and Meta-analysis of Observational Studies in Epidemiology (MOOSE)[67] guidelines, as well as the updated CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) checklist for prognostic factors CHARMS-(PF).[63]

Eligibility criteria

Studies on suPAR and mortality will be selected according to the criteria outlined below.

Study designs

We will include prospective or retrospective observational studies (cohorts, case–control studies, nested case–control studies) and control groups from intervention studies. We will exclude animal experiments.

Participants

We will include studies examining healthy human individuals, general human populations or any human patient population. We will include studies of both children and adults without restrictions on ethnicity, sex or disease status.

Index prognostic factor

We will include studies with suPAR measured in plasma or serum, independent of assay type, manufacturer or sample storage time and conditions (whether suPAR was measured in fresh or frozen samples); this information will be collected for quality assessment and heterogeneity analysis (described below in detail). We will exclude studies where suPAR was not measured in blood (eg, urine samples).

Comparators

We will investigate the unadjusted and adjusted prognostic value of suPAR, that is, without and with adjustments for other PFs, for example, conventional risk factors (such as age, sex, smoking and chronic disease), inflammatory biomarkers (such as CRP, white blood cells and IL-6), or kidney function (such as creatinine and glomerular filtration rate).

Outcomes

We will investigate the outcome of mortality. We will include studies with outcomes reported as unadjusted or adjusted effect estimates of relative risk (eg, risk ratio (RR), OR, HR). In studies reporting mortality as part of a composite outcome measure, we will extract all individual outcomes as reported in the studies. We will extract the outcome in all data forms (for example, dichotomous—30 days mortality yes/no; continuous—time to death) as reported in the included studies. For studies reporting survival from time-to-event analyses, we will use this information to extract the number of deaths. Further, we will investigate the discriminative ability of suPAR as a secondary outcome, that is, area under the curves (AUCs) for receiver operating characteristics (ROC) curve analyses of suPAR and mortality. We will exclude studies of deaths due to external/unnatural causes, such as homicide, suicides, accidents, drug overdoses and medical errors.

Timing

We will investigate the association between suPAR and mortality during any given period of follow-up. We will exclude cross-sectional studies.

Setting

There will be no restrictions by type of setting.

Language and publication type

We will include peer-reviewed studies in English or Danish published through 03 June 2020. We will exclude reviews, commentaries, correspondence, case reports, conference abstracts, expert opinions, editorials, experimental studies and dissertations. A list of possibly relevant titles in other languages will be provided as an online supplementary appendix.

Information sources

The following databases will be searched from their inception forward for potentially eligible studies published on or before 03 June 2020: (1) Medline via PubMed, (2) Embase via Elsevier and (3) Scopus via Elsevier. The electronic database search will be supplemented with a hand search of reference lists of included studies. Finally, we will circulate a bibliography of the included articles to the systematic review team, as well as to suPAR experts identified by the team. The electronic databases search will be carried out by KDB (Biomedical Research Liaison Librarian), and the supplemental hand search will be carried out by JEVP and LJHR.

Search strategy

The specific search strategy was created by a Biomedical Research Liaison Librarian (KDB) with expertise in systematic review searching. The search strategy was developed with input from the project team. The search uses medical subject headings terms and keywords related to suPAR and mortality. No study design, date or language limits will be imposed on the search. The following terms will be used to search the electronic databases in addition to other related terms for the concepts of 'suPAR' and 'mortality':

"suPAR" or "soluble urokinase plasminogen activator receptor" or "soluble urokinase-type" or "soluble urokinase receptor" or "uPAR"

AND

"mortality" or "death" or "fatality".

The initial search will be performed on 03 June 2020. Searches will be repeated prior to publication. The full PubMed search and search terms are shown in online supplementary appendix 1.

Study records

Data management

Citations extracted from electronic databases will by imported to EndNote. The Covidence systematic review software will be used for the screening and review processes, including removal of duplicates. For the actual data extraction, a data codebook will be a priori developed in Microsoft Excel based on a pilot search, along with a manual describing the information to be entered under each data item in the codebook.

Selection process

Two reviewers (JEVP and LJHR) will independently screen titles and abstracts yielded by the search to identify eligible studies according to the inclusion criteria. Studies that do not meet the screening criteria will be excluded. We will obtain full reports for all titles that appear to meet the inclusion criteria or where there is any uncertainty. The same two reviewers (JEVP and LJHR) will independently review the full-text articles to assess for eligibility. The included and excluded studies will be checked and reasons for inclusion/exclusion will be verified. Disagreements will be resolved by consensus, or by a third author if necessary. Reasons for exclusion will be coded for both the initial screening and for the review of the full-text articles. The PRISMA flow diagram will be used to document the study selection process. An appendix with a reference list of all excluded studies will be included in the final manuscript. Neither of the reviewers will be blind to the article titles, study authors, or institutions. Multiple reports of a single study will be identified by juxtaposing author names, study names, institutions, study dates. To avoid double counting, in cases of duplicate publications or multiple reports from the same study that all meet the inclusion criteria, the reviewers will select publications based on the following prioritisation: reports with (1) adjusted analyses; (2) more covariates included; (3) bigger sample size. In cases where different reports from the same study provide unique data on different follow-up times, adjustments or subgroups, unique information from the individual reports will be extracted for the main analysis, subgroup analyses and meta-regressions.

Data collection process

Data will be extracted from reports and entered in the Excel codebook in duplicate by the two independent reviewers (JEVP and LJHR). As mentioned, the data extraction codebook is developed a priori with statistical consultancy from TK. To ensure consistency across reviewers, we will conduct calibration exercises before starting the data extraction. The extracted data will include all the necessary information to describe and characterise the studies, assess the quality, synthesise data for the meta-analyses and to assess heterogeneity. In case of missing data or insufficient reporting of details, the study's corresponding author will be contacted for clarification, if possible, by a maximum of three email attempts. When data extraction is completed, both authors will review the codebooks and resolve any discrepancies by consensus or by a third author if necessary. Prior to correcting disagreements, the overall inter-rater agreement rate will be calculated using Cohen's κ statistic (>0.80 is considered good). A list of extracted variables will be provided as an appendix in the final manuscript. For studies consisting of multiple groups of individuals (eg, healthy controls, patients with precancerous lesions and patients with cancer), individual group information will be extracted to assess the association between suPAR and mortality for each group.

Data items

The major categories of extracted data will be: (1) study characteristics (author, journal, year of publication, country/region, funding sources, etc); (2) study design (type of study, year of study start, duration of follow-up, etc); (3) study population (sample size at baseline, population characteristics (healthy individuals, general population, patient types), age, sex, sample size at follow-up, reasons for loss to follow-up, information about treatments, etc), (4) index suPAR (suPAR levels, distribution, assay type, manufacturer, comparison groups and cut-offs, etc); (5) outcomes (including mortality/survival rates; cause of death; suPAR levels stratified by survivors/non-survivors; unadjusted, minimally adjusted and most adjusted RR, OR and/or HR for short-term and long-term all-cause mortality; and true positive, false positive (FP), true negative, and false negative frequencies as well as AUCs for ROC curves); (6) control characteristics (conventional risk factors, eg, age, sex, smoking and chronic diseases; other inflammatory biomarkers, eg, CRP, white blood cell count, cytokines and fibrinogen; and kidney function, eg, creatinine (measured or estimated), creatinine clearance, glomerular filtration rate (measured or estimated)); (7) setting (general population, healthcare setting, eg, acute care, intensive care unit, outpatients, etc).

Outcomes and prioritisation

The primary outcome is all-cause mortality within any given follow-up period. Reports that are not indicating cause of deaths will be analysed under all-cause mortality.

When studies report mortality/survival rates at various time points of the follow-up, we have decided a priori to subdivide the mortality rates as follows:

1. Short-term mortality: Death within 30 days from baseline.
2. 30–365 days mortality: Death occurring between 30 days and 365 days from baseline.
3. Long-term mortality: Death occurring more than 365 days from baseline.

For the primary meta-analysis, the most long-term outcome will be used, that is, if a study reports associations between suPAR and mortality at multiple time points, the more long-term assessment of mortality will be used. Furthermore, we will conduct subgroup analyses stratifying studies reporting mortality within 30 days, between 30 and 365 days and more than 365 days, as described in detail in the 'Subgroup analyses and meta-regression' section.

Secondary outcomes will be:

1. Short-term mortality (within 30 days) of any cause (all-cause mortality).
2. Cardiovascular mortality.
3. Cancer mortality.
4. Discriminative ability of suPAR, that is, AUCs for ROC curves of suPAR and mortality for the most long-term outcome reported.

Risk of bias in individual studies (quality assessment)

To facilitate the assessment of possible risk of bias, the methodological quality of each study will be evaluated using the Quality in Prognosis Studies (QUIPS) tool, table 1.[68] The QUIPS tool assesses risk of bias across six domains in studies of PFs: (1) study participation (sampling bias); (2) study attrition (attrition bias); (3) PF measurement; (4) outcome measurement; (5) study confounding; and (6) statistical analysis and reporting. The QUIPS tool will be adapted to meet the specific needs of this systematic review. To ensure consistency across reviewers, we will conduct calibration exercises before starting the quality assessments. Neither of the reviewers will be blinded to

Table 1 The Hayden, Côté and Bombardier QUIPS risk of bias assessment instrument for prognostic factor (PF) studies

Biases	Issues to consider for judging overall rating of 'risk of bias'
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgement about the overall risk of bias within each of the six domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgement of potential bias for each of the six domains.
1. Study participation	**Goal: To judge the risk of selection bias (likelihood that relationship between PF and outcome is different for participants and eligible non-participants**).
Source of target population	The source population or population of interest is adequately described for key characteristics.
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, eg, referral patterns in healthcare).
Recruitment period	Period of recruitment is adequately described.
Place of recruitment	Place of recruitment (setting and geographical location) are adequately described.
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (eg, including explicit diagnostic criteria or 'zero time' description).
Adequate study participation	There is adequate participation in the study by eligible individuals.
Baseline characteristics	The baseline study sample (ie, individuals entering the study) is adequately described for key characteristics.
Study participation summary	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.
2. Study attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for completing and non-completing participants**).
Proportion of baseline sample available for analysis	Response rate (ie, proportion of study sample completing the study and providing outcome data) is adequate.
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.
Outcome and PF information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics. There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Study attrition summary	Loss to follow-up (from baseline sample to study population analysed) is not associated with key characteristics (ie, the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.
3. PF measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome**).
Definition of the PF	A clear definition or description of 'PF' is provided (eg, including dose, level, duration of exposure and clear specification of the method of measurement).
Valid and reliable measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (eg, may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). Continuous variables are reported or appropriate cut-points (ie, not data-dependent) are used.
Method and setting of PF measurement	The method and setting of measurement of PF is the same for all study participants.
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.
PF measurement summary	PF is adequately measured in study participants to sufficiently limit potential bias.
4. Outcome measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF**).
Definition of the outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.

Continued

Table 1 Continued

Biases	Issues to consider for judging overall rating of 'risk of bias'
Valid and reliable measurement of outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (eg, may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).
Method and setting of outcome measurement	The method and setting of outcome measurement is the same for all study participants.
Outcome measurement summary	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias.
5. Study confounding	**Goal: To judge the risk of bias due to confounding (ie, the effect of PF is distorted by another factor that is related to PF and outcome).**
Important confounders measured	All important confounders, including treatments (key variables in conceptual model), are measured.
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (eg, including dose, level and duration of exposures).
Valid and reliable measurement of confounders	Measurement of all important confounders is adequately valid and reliable (eg, may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).
Method and setting of confounding measurement	The method and setting of confounding measurement are the same for all study participants.
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.
Appropriate accounting for confounding	Important potential confounders are accounted for in the study design (eg, matching for key variables, stratification, or initial assembly of comparable groups). Important potential confounders are accounted for in the analysis (ie, appropriate adjustment).
Study confounding summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome.
6. Statistical analysis and reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.
Model development strategy	The strategy for model building (ie, inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model. The selected statistical model is adequate for the design of the study.
Reporting of results	There is no selective reporting of results.
Statistical analysis and reporting summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.

Modified from: Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144:427–37.

QUIPS, Quality in Prognosis Studies.

studies during the quality assessment. For each domain in the tool, we will describe the procedures undertaken for each study, including verbatim quotes. If there is insufficient detail reported in the study, we will judge the risk of bias as 'unclear' and the study's authors will be contacted for more information. Studies will be considered to have a low, moderate or high risk of bias according to the following scores of low risk across domains: 5–6, 3–4, 0–2. The two reviewers (JEVP and LJHR) will assess the risk of bias independent of each other. Any disagreements will be resolved by consensus, or if necessary by a third author, and a log of these will be included as an appendix in the final manuscript. No study will be excluded based on the results of risk of bias assessment. We will compute graphic representations of potential bias for the final manuscript. In the meta-analysis, subgroup analyses will be performed based on the risk of bias (QUIPS; low, moderate or high risk of bias). The adapted QUIPS tool will be provided as an appendix in the final manuscript along with the log of disagreements.

Data synthesis

Reported relative risks and their corresponding 95%–99% CIs will be used to assess the association between suPAR and most long-term mortality with random-effects meta-analyses to minimise between-study heterogeneity. A quantitative synthesis will be performed, and our outcomes will be studied separately in three pooled datasets: (1)

across all studies (despite a high degree of expected heterogeneity), (2) within studies of healthy/general populations and (3) within studies of patient populations.

Relative risks with 95%–99% CIs will be used as the common measure of association across studies. RRs, ORs and HRs will be assumed to approximate the same measure of relative risk. As previously described for CRP and albumin,[69 70] we will convert the reported study-specific relative risk estimates for suPAR onto a standardised scale of effect, comparing the highest third with the lowest third of the suPAR distribution, that is, providing an estimate per 2.18 times SD units of suPAR. 2.18 is the difference in the means of the top and bottom third of the standard normal distribution and is therefore used as the point estimate for the lower and upper third of the suPAR distribution when scaled with SD. This method assumes that suPAR follows a normal distribution, or a transformation of suPAR, such as the logarithm, follows a normal distribution. Additionally, it is assumed that the suPAR SD estimates within the studies are similar when scaling; if this is not the case additional adjustment to account for this will be done and differences between calculation methods will be reported. If we conclude that these assumptions cannot be made for the studies, separate relative risk estimates (per suPAR unit, log2(suPAR), Q1 vs Q4 suPAR, etc) analyses will be made instead of the standardised scale analysis.

For the primary analysis all study outcome measures (eg, RR, OR and HR) will be pooled as a single measure, and all available studies will be included, regardless of population. If a study has multiple versions of the same model with different adjustments, the model with most adjustments will be included. In addition, we will conduct separate subgroup analyses, as described below, to account for the heterogeneity across methods of reporting outcomes and variation in adjustments made.

As suggested by Riley *et al*,[63] in addition to the main analysis, we will conduct multiple meta-analyses separately based on the most long-term outcome stratified on the following levels: (1) population level: all data, healthy/general populations and patients; (2) model adjustment: unadjusted, minimally adjusted (age and sex), adjusted for some conventional risk factors (eg, age, sex, chronic disease/Charlson score, smoking) or inflammatory markers (eg, CRP, cytokines, fibrinogen) and maximally adjusted (most adjusted estimate from each study); (3) outcome measure: RR, OR and HR.

Statistical heterogeneity among studies will be evaluated using the τ^2 and I^2 statistic (where I^2 of 30%–60% will be interpreted to indicate moderate heterogeneity and I^2 >50% to indicate substantial heterogeneity across studies).[71] We will try to explain the source of heterogeneity by subgroup analysis or sensitivity analysis (see below).

Study characteristics of the included studies will be summarised in a table. To visually assess between-study variability, we will present the results and summary relative risks in forest plots.

Analysis of the predictive value of suPAR for mortality will be done by hierarchal summary ROC (HSROC) model curves. From this, SROC curves with AUCs, Qs and diagnostic ORs will be produced.

As described for CRP by Hemingway *et al*,[69] we will attempt to calculate the detection rate (sensitivity) at different FP rates from 0 to 100 by constructing the log-normal distributions of suPAR separately for those who survived and those who died. From this we will obtain a ROC curve and report the c-statistic. Pooled estimates of both the c-statistic and detection rate of suPAR's discriminative ability for predicting mortality will be obtained by random-effects meta-analysis of the study-specific c-statistics and detection rates. CIs and a 10% FP rate will be reported.

All statistical analyses will be performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) software.

Subgroup analyses and meta-regression

In addition to the primary analysis of the most long-term mortality, separate analyses will be made for the following mortality outcomes: mortality within 30 days, 30–365 days, and long-term mortality (more than 365 days). These analyses will be done as described for the primary analysis above.

Subgroup analyses will be used to explore possible sources of heterogeneity, and univariate random-effects meta-regression will be performed based on the following: study design (cohort, case–control, randomised controlled trials); year of study start; sex; age groups; time of outcome (within 30 days, 30–365 days, more than 365 days); reported relative risk estimates (eg, RR, OR, HR); population type (healthy/general population vs patient types, eg, cardiovascular disease, cancer, chronic kidney disease, infectious disease, critical illness, acute care); cause of death studied (all-cause, cardiovascular, cancer mortality, etc); methods of suPAR measurement; suPAR assay manufacturer; suPAR comparison group (continuous suPAR, equal sized groups, unequal sized groups); region (North America + Europe, Asia, Africa, South America); duration of follow-up; no. of adjustments; adjustment for CRP; adjustment for kidney function; no. of events; risk of bias (QUIPS; low, moderate, high risk of bias).

To explore other potential sources of heterogeneity, a random-effects meta-regression model will be employed, which includes study level continuous or categorical covariates.

Sensitivity analysis

Sensitivity analyses will be performed in which the pooled risk estimates are recalculated by removing the studies one by one and comparing the results. Furthermore, a sensitivity analysis of risk of bias will be performed by omitting studies that are judged to be at high risk of bias.

Meta-biases

Small study bias (including publication bias) will be assessed with contour-enhanced Funnel plots, by Begg's-adjusted rank correlation test and by Egger's regression asymmetry test.

Confidence in cumulative evidence

Reporting and interpretation of results will follow the reporting guidelines of PRISMA[66] and MOOSE.[67] Interpretation and translation of summary results will follow these guidelines as well as the steps recommended for PF studies by Riley *et al*.[63] The summary results will be discussed in terms of potential usefulness for clinical practice and need for future research.

Strength in the body of evidence will be further evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) assessment.[72 73] However, this approach was developed for the assessment of intervention effectiveness in reviews of interventions and not for assessing the certainty of summary results of systematic reviews of PFs; allowing for heterogeneity in the latter case may be more acceptable.[63]

Patient and public involvement

No patients involved.

DISCUSSION

The biomarker suPAR has been suggested to be a prognostic biomarker in the general population and various patient populations. However, clinical guidelines and cut-offs are still lacking, hampering the wide clinical utilisation of suPAR. Our findings in this systematic review and meta-analysis will clarify the association between suPAR and mortality, and establish its prognostic value across healthy and ill individuals, providing support for development of future clinical guidelines. Thus, we will discuss the usefulness of suPAR in clinical practice, in particular settings, or as a general marker of prognosis across populations.

Only few randomised studies have investigated the value of adding suPAR as a prognostic biomarker to inform clinical practice,[74 75] and most evidence is based on observational studies of suPAR, but many studies have reported an association between suPAR and mortality. Summarising this evidence is important to establish the prognostic role of suPAR. This protocol has been developed in compliance with recommended guidelines for PF studies,[63] including PRISMA-P,[64] and it provides a clear and structured protocol for maximising data extraction and summarising the relevant information on the importance of suPAR as a prognostic marker of mortality. suPAR is used as a marker of inflammation, and as such, many studies have compared it with CRP, although suPAR has been suggested to be a marker of chronic rather than acute inflammation while CRP is an acute phase reactant and potentially reflects a distinct aspect of inflammation. In adjusted analyses, suPAR has been shown to be associated with mortality independent of CRP.[8 76] In our analyses, we aim to investigate the associations between suPAR and mortality in studies adjusting for CRP to assess the effect over and above CRP. The advantage of using a chronic inflammation marker rather than an acute phase reactant for prognostication includes the lower variation and sensitivity towards acute, short-term influences and a better assessment of underlying health status.

Blood suPAR levels have been associated with kidney function[77] and proposed a causal factor of certain chronic kidney diseases.[78] The potential causal effect in kidney disease is outside the scope of this review. However, we will investigate whether suPAR is associated with mortality in individuals with and without chronic kidney disease.

Our primary aim of summarising all evidence of suPAR and mortality in one meta-analysis imposes a high degree of study population heterogeneity on this study; however, to establish an association between suPAR and mortality, it is important to summarise the information available on this issue and it will provide us with a general estimate of association. We will account for the heterogeneity by performing meta-regressions and stratified analyses to investigate the association in more homogeneous subsets of the literature.

This systematic review and meta-analysis will provide an up-to-date global overview of the current literature on suPAR and mortality. If our results indicate an association between suPAR level and mortality risk, suPAR may constitute an easily measurable, accurate chronic inflammation biomarker with a well-described association with mortality, which could be a vital tool in future efforts to combat major public health challenges, such as chronic disease prevention and premature mortality, and improve future research on this topic.

ETHICS AND DISSEMINATION

This systematic review will synthesise evidence on the use of suPAR as a prognostic marker for mortality based on published publicly available studies and data. The study will not obtain, store or report any individual-level personal information and there will be no concerns about privacy. Therefore, ethical approval is not necessary for this systematic review. The results will be disseminated by publication in a peer-reviewed journal.

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