

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

suPAR as a prognostic marker of mortality in healthy, general, and patient populations: protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-036125
Article Type:	Protocol
Date Submitted by the Author:	01-Dec-2019
Complete List of Authors:	Petersen, Jens Emil; Duke University, Department of Infectious Diseases Kallemose, Thomas; Copenhagen University Hospital Hvidovre, Clinical Research Centre 056 Barton, Karen; Duke University, Duke University Medical Center Library & Archives Caspi, A; Duke University, Department of Psychology and Neuroscience; King's College London, Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience Rasmussen, Line Jee Hartmann; Duke University, Department of Psychology and Neuroscience; Copenhagen University Hospital Hvidovre, Clinical Research Centre 056
Keywords:	Clinical chemistry < PATHOLOGY, PREVENTIVE MEDICINE, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, IMMUNOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 **suPAR as a prognostic marker of mortality in healthy, general, and patient populations:**
5
6
7 **protocol for a systematic review and meta-analysis**
8
9

10
11 **Authors:**
12
13

14
15 Jens Emil Vang Petersen,¹ Thomas Kalleemose,² Karen D. Barton,³ Avshalom Caspi,^{4,5,6,7} Line
16

17
18 Jee Hartmann Rasmussen^{2,4}
19
20

21
22 ¹Department of Infectious Diseases, Duke University, Durham, NC, USA
23
24

25 ²Clinical Research Centre, Copenhagen University Hospital Amager and Hvidovre, Hvidovre,
26
27
28 Denmark
29
30

31 ³Duke University Medical Center Library & Archives, Duke University, Durham, NC, USA
32
33

34 ⁴Department of Psychology and Neuroscience, Duke University, Durham, NC, USA
35
36

37
38 ⁵Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine,
39
40
41 Durham, NC, USA
42
43

44 ⁶Center for Genomic and Computational Biology, Duke University, Durham, NC, USA
45
46

47 ⁷Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and
48
49
50 Neuroscience, King's College London, London, UK
51
52
53

1
2
3 E-mail: Jens E V Petersen jensemilvang.petersen@duke.edu – Thomas Kallelose

4
5
6 thomas.kallelose@regionh.dk – Karen Barton karen.d.barton@duke.edu – Avshalom Caspi

7
8
9 avshalom.caspi@duke.edu – Line J H Rasmussen line.jee.hartmann.rasmussen@duke.edu

10
11
12
13 **Corresponding author:**

14
15
16 Line Jee Hartmann Rasmussen

17
18
19 Dept. of Psychology and Neuroscience

20
21
22 2020 W Main St, Suite 201

23
24
25
26
27 Durham, NC 27705, USA

28
29
30
31 Clinical Research Centre

32
33
34 Hvidovre Hospital

35
36
37 Kettegård Allé 30

38
39
40 DK-2650 Hvidovre, Denmark

41
42
43
44 **Word count: 3,982**

45
46
47
48 **Registration:**

1
2
3 In accordance with the guidelines, our systematic review protocol was registered with the
4
5
6 International Prospective Registry of Systematic Reviews (PROSPERO) on [DATE] (registration
7
8
9 number CRDXXX).

10
11
12
13
14
15
16
17 [Notes regarding protocol registration at PROSPERO:
18

19
20
21 This study will be registered at PROSPERO, however, as PROSPERO has the following
22
23 recommendation: "*Ensure that your review protocol is in its (near) final form and that no major*
24
25 *changes are anticipated at this stage - e.g. if your protocol will be peer reviewed it will usually be*
26
27 *sensible to wait until this is complete before registering*" we will wait with the registration until the
28
29
30
31
32
33
34 protocol has been peer-reviewed.

35
36
37
38 Moreover, from 1st of October, 2019, PROSPERO only accept reviews provided that data
39
40
41 extraction has not yet started. We have therefore not begun the search or data extraction yet,
42
43
44 and all instances requiring a "date of search" in the protocol have been marked as "[search
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
[date]". This date will be completed after peer review but before publication of this protocol
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

Source: <https://www.crd.york.ac.uk/PROSPERO/>]

Contributions:

JEVP and LJHR are the guarantors of the review. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. LJHR and JEVF conceived the study. JEVF, KB, and LJHR developed the search strategy. TK provided statistical expertise. JEVF and LJHR drafted the protocol. All authors read, provided feedback, and approved the final protocol.

Amendments:

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale for the change in this section. An updated protocol will be identified with a new version number and a list of the specific amendments that were made to the previous version, in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Funding statement:

1
2
3 This research received no specific grant from any funding agency in the public, commercial, or
4
5
6 not-for-profit sectors. JEVP is supported by an international postdoc fellowship from the Alfred
7
8
9 Benzon Foundation (grant no. ABF-2018-91). LJHR is supported by an international postdoc
10
11
12 fellowship from the Lundbeck Foundation (grant no. R288-2018-380). The funders had no role
13
14
15 in designing the project or developing the protocol, neither will they have any role in the review
16
17
18 conduct, data analysis and interpretation, or publication of the study results.
19
20
21
22

23 **Competing interests:**

24
25
26
27 LJHR has received funding from travel outside the submitted work from ViroGates A/S. The
28
29
30 remaining authors report no conflicts of interest.
31
32
33

34 **ABSTRACT**

35
36
37
38 **Introduction:** Chronic inflammation is increasingly recognized as a major contributor to disease,
39
40
41 disability, and ultimately death, but measuring the levels of chronic inflammation remains non-
42
43
44 canonized, making it difficult to relate chronic inflammation and mortality. *Soluble urokinase*
45
46
47 *plasminogen activator receptor* (suPAR), an emerging biomarker of chronic inflammation, has
48
49
50 been proposed as a prognostic biomarker associated with future incidence of chronic disease
51
52
53 and mortality in general as well as patient populations. Proper prognostic biomarkers are
54
55
56
57
58
59
60

1
2
3 important as they can help improve risk stratification in clinical settings and provide guidance in
4
5
6 treatment or lifestyle decisions as well as in the design of randomized trials. Here, we wish to
7
8
9
10 summarize the evidence about the overall association of the biomarker suPAR with mortality in
11
12
13 healthy, general, and patient populations across diseases.

14
15
16
17 **Methods and analysis:** The search will be conducted using Medline, Embase, and Scopus

18
19
20 databases from their inception to identify studies investigating “suPAR” and “mortality”.

21
22
23 Observational studies and control groups from intervention studies written in English or Danish
24
25
26 will be included. The “Quality In Prognosis Studies” tool will be used to assess the risk of bias
27
28
29 for the studies included. Unadjusted and adjusted mortality outcome measures (e.g., risk ratios,
30
31
32 odds ratios, hazard ratios) with 95% CIs will be extracted for healthy individuals, general and
33
34
35 patient populations. The primary outcome is all-cause mortality within any given follow-up.
36
37

38
39 Subgroup analyses will be performed based on time of outcome, cause of death, population
40
41
42 type, adjustments for conventional risk factors and inflammation markers, etc.
43
44

45
46 **Ethics and dissemination:** This systematic review will synthesize evidence on the use of suPAR
47
48
49 as a prognostic marker for mortality. The results will be disseminated by publication in a peer-
50
51

1
2
3 reviewed journal. Data used will be obtained from published studies, and ethics approval is
4
5
6 therefore not necessary for this systematic review.
7
8
9

10 **Trial registration number:** PROSPERO [CRDXXX].
11
12
13

14 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

15
16
17

- 18 - To the best of our knowledge, this is the first systematic review and meta-analysis that
19
20
21 investigates the association between suPAR and mortality across general and patient
22
23
24 populations.
25
26
- 27 - This review will provide valuable new knowledge for researchers studying chronic
28
29
30 inflammation's effect on both short- and long-term health, and for clinicians using suPAR
31
32
33 in clinical settings to stratify patients.
34
35
- 36 - Study selection, data extraction, and quality assessment will be performed
37
38
39 independently by two reviewers.
40
41
42
- 43 - The results will be discussed in context with other studies in the field.
44
45
- 46 - Common to most meta-analyses, significant heterogeneity may exist, which will be
47
48
49 investigated thoroughly with subgroup analyses and meta-regressions.
50
51
52
53
54
55
56
57

INTRODUCTION

Rationale:

Chronic inflammation is increasingly recognized as a major contributor to disease, disability, and ultimately death in industrialized and developing countries alike.¹⁻⁴ Chronic inflammation is related to multiple genetic and lifestyle factors, but measuring the levels of chronic inflammation remains non-canonized, 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, i.e., suPAR has been shown to be elevated in cardiovascular diseases (stroke, ischemic heart disease, venous thromboembolism, incident

1
2
3 atrial fibrillation),^{16–18} type 1 and type 2 diabetes,^{19–21} various types of cancer,^{22–36} rheumatic
4
5
6 disease,^{37,38} chronic pulmonary disease,³⁹ chronic liver disease (non-alcoholic fatty liver
7
8
9 disease, cirrhosis),^{40–42} chronic kidney disease^{43,44} as well as infectious diseases caused by
10
11
12 viruses^{42,45–47}, bacteria^{48–57}, and parasites^{58,59}. Together, these studies highlight the broad
13
14
15
16 associations across patient groups and etiologies—and even in general populations—between
17
18
19 elevated blood levels of suPAR with general health, disease outcome, complications, and
20
21
22
23 mortality.

24
25
26 In contrast to common inflammatory biomarkers, such as the current gold standard C-reactive
27
28
29 protein (CRP), suPAR is not an acute-phase reactant, and suPAR levels in the blood are less
30
31
32 rapidly affected by acute changes and short-term influences.^{17,60} Additionally suPAR was more
33
34
35
36 reliably associated with early-life risk factors such as adverse childhood experiences, early-life
37
38
39 stress, and violence than CRP and interleukin-6 (IL-6), potentially because these more
40
41
42 traditional biomarkers of inflammation as acute-phase reactants mix historical and acute
43
44
45 effects.^{61,62} This, along with its non-specific associations with pathologies in general, suggests
46
47
48
49 that suPAR blood levels are an appropriate readout for chronic inflammation.

1
2
3 Prognostic biomarkers are important as they can help improve risk stratification in clinical
4
5
6 settings or provide guidance in treatment or lifestyle decisions as well as in the design of
7
8
9 randomized trials.⁶³ Here, we wish to summarize the evidence about the overall association of
10
11
12 the biomarker suPAR with mortality in healthy, general, and patient populations and across
13
14
15 diseases. As suPAR is still a relatively new clinical biomarker, clinical guidelines and cut-offs are
16
17
18 still lacking. Our findings will clarify the association between suPAR and mortality, and what
19
20
21 value a biomarker reflecting chronic inflammation adds, compared to the current standard
22
23
24 inflammatory biomarkers. The study will help development of future clinical guidelines, based on
25
26
27 a better understanding of differences in the prognostic value of suPAR between and across
28
29
30 healthy individuals and patient subgroups, which is critical in clinical decision-making. Having an
31
32
33 established accurate chronic inflammation biomarker with a well-described association with
34
35
36 mortality is a vital tool in future efforts to combat major public health challenges.
37
38
39
40
41

42 **Objective:**

43
44
45
46 In this systematic review, we aim to investigate the hypothesis that elevated suPAR is
47
48
49 associated with increased risk of short-term and long-term mortality in healthy, general, and
50
51
52 patient populations, independent of conventional risk factors.
53
54
55
56
57

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:

2. Is the association between suPAR and mortality present in healthy, general, and various patient populations?
3. Is the association between suPAR and mortality independent of conventional risk factors, such as age, sex, smoking, and chronic disease?
4. Is the association between suPAR and mortality independent of other inflammatory biomarkers?
5. What is the discrimination performance of suPAR for predicting mortality?
6. 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 PRISMA-P guidelines^{64,65} and was registered with PROSPERO (registration number CRDXXX).

This study will follow the recommendations on conducting and reporting systematic reviews and meta-analyses set forth by the PRISMA⁶⁶ and Meta-analysis of observational studies in epidemiology (MOOSE)⁶⁷ guidelines, as well as the updated 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.

1
2
3 Participants: We will include studies examining healthy human individuals, general human
4
5
6 populations, or any human patient population. We will include studies of both children and
7
8
9 adults without restrictions on ethnicity, sex, or disease status.
10
11

12
13 Index prognostic factor: We will include studies with suPAR measured in plasma or serum,
14
15
16 independent of assay type, manufacturer, or sample storage time and conditions (whether
17
18
19 suPAR was measured in fresh or frozen samples); this information will be collected for quality
20
21
22 assessment and heterogeneity analysis (described below in detail). We will exclude studies
23
24
25 where suPAR was not measured in blood (e.g., urine samples).
26
27
28

29
30 Comparators: We will investigate the unadjusted and adjusted prognostic value of suPAR, i.e.,
31
32
33 without and with adjustments for other prognostic factors, e.g., conventional risk factors (such
34
35
36 as age, sex, smoking, and chronic disease) or inflammatory biomarkers (such as CRP, white
37
38
39 blood cells, and IL-6).
40
41
42

43
44 Outcomes: We will investigate the outcome of mortality. We will include studies with outcomes
45
46
47 reported as unadjusted or adjusted effect estimates of relative risk (e.g., risk ratio [RR], odds
48
49
50 ratio [OR], hazard ratio [HR]). In studies reporting mortality as part of a composite outcome
51
52
53 measure, we will extract all individual outcomes as reported in the studies. We will extract the
54
55
56

1
2
3 outcome in all data forms (for example, dichotomous—30-day mortality yes/no; continuous—
4
5
6 time to death) as reported in the included studies. For studies reporting survival from time-to-
7
8
9 event analyses, we will use this information to extract the number of deaths. Further, we will
10
11
12 investigate the discriminative ability of suPAR as a secondary outcome, i.e., area under the
13
14
15 curves (AUCs) for receiver operating characteristics (ROC) curve analyses of suPAR and
16
17
18 mortality. We will exclude studies of deaths due to external/unnatural causes, such as homicide,
19
20
21 suicides, accidents, drug overdoses, and medical errors.
22
23

24
25
26 Timing: We will investigate the association between suPAR and mortality during any given
27
28
29 period of follow-up. We will exclude cross-sectional studies.
30
31

32
33
34 Setting: There will be no restrictions by type of setting.
35
36

37
38 Language and publication type: We will include peer-reviewed studies in English or Danish
39
40 published up to [search date]. We will exclude reviews, commentaries, correspondence, case
41
42
43 reports, conference abstracts, expert opinions, editorials, experimental studies, and
44
45
46 dissertations. A list of possibly relevant titles in other languages will be provided as an appendix.
47
48
49

50
51 **Information sources:**
52
53
54
55
56
57
58
59
60

1
2
3 The following databases will be searched from their inception forward for potentially eligible
4
5
6 studies published on or before [search date]: 1) Medline via PubMed, 2) Embase via Elsevier,
7
8
9 and 3) Scopus via Elsevier. The electronic database search will be supplemented with a hand
10
11
12 search of reference lists of included studies, etc. Finally, we will circulate a bibliography of the
13
14
15 included articles to the systematic review team, as well as to suPAR experts identified by the
16
17
18 team. The electronic databases search will be carried out by KB (Biomedical Research Liaison
19
20
21 Librarian), and the supplemental hand search will be carried out by JEVF and LJHR.
22
23
24
25

26 **Search strategy:**

27
28
29
30 The specific search strategy was created by a Biomedical Research Liaison Librarian (KB) with
31
32
33 expertise in systematic review searching. The search strategy was developed with input from
34
35
36 the project team. The search uses medical subject headings (MeSH) terms and keywords
37
38
39 related to suPAR and mortality. No study design, date, or language limits will be imposed on the
40
41
42 search. The following terms will be used to search the electronic databases in addition to other
43
44
45 related terms for the concepts of “suPAR” and “mortality”:
46
47
48
49

50 “suPAR” or “soluble urokinase plasminogen activator receptor” or “soluble urokinase-type” or
51
52
53 “uPAR”
54
55
56
57

1
2
3 AND
4
5

6
7 “mortality” or “death” or “fatality”
8
9

10
11 The initial search will be performed in [search date; tentatively December 2019]. Searches will
12
13 be repeated prior to publication. An example of the PubMed search and search terms is shown
14
15 in **Appendix 1**.
16
17
18
19

20
21 **Study records:**
22

23
24
25 *Data management:*
26

27
28
29 Citations extracted from electronic databases will be imported to EndNote. The Covidence
30
31 systematic review software will be used for the screening and review processes, including
32
33 removal of duplicates. For the actual data extraction, a data codebook will be a priori developed
34
35 in Microsoft Excel based on a pilot search, along with a manual describing the information to be
36
37 entered under each data item in the codebook.
38
39
40
41
42
43

44
45
46 *Selection process:*
47

48
49 Two reviewers (JEVP, LJHR) will independently screen titles and abstracts yielded by the
50
51 search to identify eligible studies according to the inclusion criteria. Studies that do not meet the
52
53
54
55
56
57

1
2
3 screening criteria will be excluded. We will obtain full reports for all titles that appear to meet the
4
5
6 inclusion criteria or where there is any uncertainty. The same two reviewers (JEVP, LJHR) will
7
8
9 independently review the full-text articles to assess for eligibility. The included and excluded
10
11
12 studies will be checked and reasons for inclusion/exclusion will be verified. Disagreements will
13
14
15 be resolved by consensus, or by a third author if necessary. Reasons for exclusion will be
16
17
18 coded for both the initial screening and for the review of the full-text articles. The PRISMA flow
19
20
21 diagram will be used to document the study selection process. An appendix with a reference list
22
23
24 of all excluded studies will be included in the final manuscript. Neither of the reviewers will be
25
26
27 blind to the article titles, study authors, or institutions. Multiple reports of a single study will be
28
29
30 identified by juxtaposing author names, study names, institutions, study dates, etc. To avoid
31
32
33 double counting, in cases of duplicate publications or multiple reports from the same study that
34
35
36 all meet the inclusion criteria, the reviewers will select publications based on the following
37
38
39 prioritization: reports with 1) adjusted analyses; 2) more covariates included; 3) bigger sample
40
41
42 size. In cases where different reports from the same study provide unique data on different
43
44
45 follow-up times, adjustments, or subgroups, unique information from the individual reports will
46
47
48 be extracted for the main analysis, subgroup analyses, and meta-regressions.
49
50
51
52
53
54

55 ***Data collection process:***
56
57

1
2
3 Data will be extracted from reports and entered in the Excel codebook in duplicate by the two
4
5
6 independent reviewers (JEVP, LJHR). As mentioned, the data extraction codebook is developed
7
8
9 a priori with statistical consultancy from TK. To ensure consistency across reviewers, we will
10
11
12 conduct calibration exercises before starting the review. The extracted data will include all the
13
14
15 necessary information to describe and characterize the studies, assess the quality, synthesize
16
17
18 data for the meta-analyses, and to assess heterogeneity. In case of missing data or insufficient
19
20
21 reporting of details, the study's corresponding author will be contacted for clarification, if
22
23
24 possible, by a maximum of three e-mail attempts. When data extraction is completed, both
25
26
27 authors will review the codebooks and resolve any discrepancies by consensus or by a third
28
29
30 author if necessary. Prior to correcting disagreements, the overall inter-rater agreement rate will
31
32
33 be calculated using Cohen's κ statistic (>0.80 is considered good). A list of extracted variables
34
35
36 will be provided as an appendix in the final manuscript. For studies consisting of multiple groups
37
38
39 of individuals (for example, healthy controls, patients with precancerous lesions, and patients
40
41
42 with cancer), individual group information will be extracted to assess the association between
43
44
45 suPAR and mortality for each group.
46
47
48
49
50

51
52 **Data items:**
53
54
55
56
57

1
2
3 The major categories of extracted data will be: (1) study characteristics (author, journal, year of
4
5
6 publication, country/region, funding sources, etc.); (2) study design (type of study, year of study
7
8
9 start, duration of follow-up, etc.); (3) study population (sample size at baseline, population
10
11
12 characteristics (healthy individuals, general population, patient types), age, sex, sample size at
13
14
15 follow-up, reasons for loss to follow-up, information about treatments, etc.), (4) index suPAR
16
17
18 (suPAR levels, distribution, assay type, manufacturer, comparison groups and cut-offs, etc.); (5)
19
20
21 outcomes (including mortality/survival rates; cause of death; suPAR levels stratified by
22
23
24 survivors/non-survivors; unadjusted, minimally adjusted, and most adjusted RR, OR and/or HR
25
26
27 for short-term and long-term all-cause mortality; and AUCs for ROC curves); (6) control
28
29
30 characteristics (conventional risk factors, e.g., age, sex, smoking, and chronic diseases, and
31
32
33 other inflammatory biomarkers, e.g., C-reactive protein (CRP), white blood cells, cytokines,
34
35
36 fibrinogen, etc.); (7) setting (general population, healthcare setting, e.g., acute care, ICU,
37
38
39 outpatients, etc.).
40
41
42
43
44
45

46 **Outcomes and prioritization:**

47
48

49 The primary outcome is all-cause mortality within any given follow-up period. Reports that are
50
51
52 not indicating cause of deaths will be analyzed under all-cause mortality.
53
54
55
56
57

1
2
3
4 When studies report mortality/survival rates at various time points of the follow-up, we have
5
6 decided a priori to subdivide the mortality rates as follows:
7

- 10 1. Short-term mortality: Death within 30 days from baseline.
- 12 2. 30-365-day mortality: Death occurring between 30 days and 365 days from baseline.
- 14 3. Long-term mortality: Death occurring more than 365 days from baseline.

18
19
20 For the primary meta-analysis, the most long-term outcome will be used, i.e., if a study reports
21
22 associations between suPAR and mortality at multiple timepoints, the more long-term
23
24 assessment of mortality will be used. Furthermore, we will conduct subgroup analyses
25
26 stratifying studies reporting mortality within 30 days, between 30-365 days, and more than 365
27
28 days, as described in detail in the "*Subgroup analyses and meta-regression*" section below.
29
30
31
32
33
34
35
36
37

38 Secondary outcomes will be:

- 40 1. Short-term mortality (within 30 days) of any cause (all-cause mortality)
- 42 2. Cardiovascular mortality
- 44 3. Cancer mortality
- 46 4. Discriminative ability of suPAR, i.e., AUCs for ROC curves of suPAR and mortality for
48
49
50
51
52
53
54 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 prognostic factors: (1) study participation (sampling bias); (2) study attrition (attrition bias); (3) prognostic factor 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 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, 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. 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.

1
2
3 In the meta-analysis, subgroup analyses will be performed based on the risk of bias (QUIPS;
4
5
6 low, moderate, or high risk of bias). The adapted QUIPS tool will be provided as an appendix in
7
8
9
10 the final manuscript.

11 12 13 **Data synthesis:**

14
15
16
17 Reported relative risks and their corresponding 95-99% confidence intervals will be used to
18
19
20 assess the association between suPAR and most long-term mortality with random-effects meta-
21
22
23 analyses to minimize between-study heterogeneity. A quantitative synthesis will be performed,
24
25
26 and our outcomes will be studied separately in three pooled datasets: i) across all studies
27
28
29 (despite a high degree of expected heterogeneity), ii) within studies of healthy/general
30
31
32 populations, and iii) within studies of patient populations.
33
34
35

36
37 As previously described for CRP and albumin,^{69,70} we will convert the reported study-specific
38
39
40 relative risk estimates for suPAR onto a standardized scale of effect, comparing the highest
41
42
43 third with the lowest third of the suPAR distribution, i.e., providing an estimate per 2.18 times
44
45
46 standard deviation (SD) units of suPAR. 2.18 is the difference in the means of the top and
47
48
49 bottom third of the standard normal distribution and is therefore used as the point estimate for
50
51
52
53 the lower and upper third of the suPAR distribution when scaled with SD. This method assumes
54
55
56
57
58
59
60

1
2
3 that suPAR follows a normal distribution, or a transformation of suPAR, such as the logarithm,
4
5
6 follows a normal distribution. Additionally, it is assumed that the suPAR SD estimates within the
7
8
9 studies are similar when scaling; if this is not the case additional adjustment to account for this
10
11
12 will be done and differences between calculation methods will be reported. If we conclude that
13
14
15 these assumptions cannot be made for the studies, separate relative risk estimates (per suPAR
16
17
18 unit, $\log_2(\text{suPAR})$, Q1 vs Q4 suPAR, etc.) analysis will be made instead of the standardized
19
20
21 scale analysis.
22
23

24
25
26 For the primary analysis all study outcome measures (e.g., RR, OR, and HR) will be pooled as a
27
28
29 single measure, and all available studies will be included, regardless of population. If a study
30
31
32 has multiple versions of the same model with different adjustments, the model with most
33
34
35 adjustments will be included. In addition, we will conduct separate subgroup analyses, as
36
37
38 described below, to account for the heterogeneity across methods of reporting outcomes and
39
40
41 variation in adjustments made.
42
43

44
45
46 As suggested by Riley et al. 2019,⁶³ in addition to the main analysis, we will conduct multiple
47
48
49 meta-analyses separately based on the most long-term outcome stratified on the following
50
51
52 levels: (1) population level: all data, healthy/general populations, and patients; (2) model
53
54
55

1
2
3 adjustment: unadjusted, minimally adjusted (age and sex), adjusted for some conventional risk
4
5
6 factors (e.g., age, sex, chronic disease/Charlson score, smoking) or inflammatory markers (e.g.,
7
8
9 CRP, cytokines, fibrinogen), and maximally adjusted (most adjusted estimate from each study);
10
11
12
13 (3) outcome measure: RR, OR, and HR.
14
15

16
17 Statistical heterogeneity among studies will be evaluated using the Chi² test (significance level:
18
19 0.1) and I² statistic (I² >50% indicates significant heterogeneity across studies). We will try to
20
21
22 explain the source of heterogeneity by subgroup analysis or sensitivity analysis (see below).
23
24
25

26
27 Study characteristics of the included studies will be summarized in a table. To visually assess
28
29
30 between-study variability, we will present the results and summary relative risks in Forest plots.
31
32
33

34 Pooled estimates of AUCs for ROC curve analyses or equivalent c-statistics of suPAR's
35
36
37 discriminative ability for predicting mortality will be obtained by random effects meta-analysis of
38
39
40 the study-specific AUC's and detection rates (only for studies reporting AUCs).
41
42
43

44 All statistical analyses will be performed using SAS Enterprise Guide (SAS Institute, Cary, NC)
45
46
47 and R (R Foundation for Statistical Computing, Vienna, Austria) software.
48
49
50

51 ***Subgroup analyses and meta-regression:***
52
53
54
55
56
57

1
2
3 In addition to the primary analysis of the most long-term mortality, separate analyses will be
4
5
6 made for the following mortality outcomes: mortality within 30 days, 30-365 days, and long-term
7
8
9 mortality (more than 365 days). These analyses will be done as described for the primary
10
11
12 analysis above.
13
14
15

16
17 Subgroup analyses will be used to explore possible sources of heterogeneity, and univariate
18
19 random effects meta-regression will be performed based on the following: study design (cohort,
20
21 case-control); year of study start; sex; age groups; time of outcome (within 30 days, 30-365
22
23 days, more than 365 days); population type (healthy/general population vs. patient types, e.g.,
24
25 cardiovascular disease, cancer, chronic kidney disease, infectious disease, critical illness, acute
26
27 care); cause of death studied (all-cause, cardiovascular, cancer mortality, etc.); methods of
28
29 suPAR measurement; suPAR assay manufacturer; suPAR comparison group (continuous
30
31 suPAR, equal sized groups, unequal sized groups); region (North America + Europe, Asia,
32
33 Africa, South America); duration of follow-up; no. of adjustments; adjustment for CRP; no. of
34
35 events; risk of bias (QUIPS; low, moderate, high risk of bias).
36
37
38
39
40
41
42
43
44
45
46
47
48

49 To explore other potential sources of heterogeneity, a random effects meta-regression model
50
51
52 will be employed, which includes study level continuous or categorical covariates.
53
54
55
56
57

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 PRISMA⁶⁶ and MOOSE.⁶⁷ Interpretation and translation of summary results will follow these guidelines as well as the steps recommended for prognostic factor studies by Riley et al. 2019.⁶³ 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 GRADE assessment (Grades of Recommendation, Assessment, Development, and Evaluation).^{71,72} However, this approach was developed for the assessment of intervention effectiveness in reviews of

1
2
3 interventions and not for assessing the certainty of summary results of systematic reviews of
4
5
6 prognostic factors; allowing for heterogeneity in the latter case may be more acceptable.⁶³
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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 utilization 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 randomized studies have investigated the value of adding suPAR as a prognostic biomarker to inform clinical practice,^{73,74} and most evidence is based on observational studies of suPAR, but many studies have reported an association between suPAR and mortality.

Summarizing this evidence is important to establish the prognostic role of suPAR. This protocol has been developed in compliance with recommended guidelines for prognostic factor studies,⁶³ including PRISMA-P,⁶⁴ and it provides a clear and structured protocol for maximizing data extraction and summarizing the relevant information on the importance of suPAR as a prognostic marker of mortality.

1
2
3 suPAR is used as a marker of inflammation, and as such, many studies have compared it with
4
5
6
7 CRP, although suPAR has been suggested to be a marker of chronic rather than acute
8
9
10 inflammation while CRP is an acute-phase reactant and potentially reflects a distinct aspect of
11
12
13 inflammation. In adjusted analyses, suPAR has been shown to be associated with mortality
14
15
16 independent of CRP.^{8,75} In our analyses, we aim to investigate the associations between suPAR
17
18
19 and mortality in studies adjusting for CRP to assess the effect over and above CRP. The
20
21
22 advantage of using a chronic inflammation marker rather than an acute-phase reactant for
23
24
25 prognostication includes the lower variation and sensitivity towards acute, short-term influences
26
27
28 and a better assessment of underlying health status.
29
30
31
32
33 Blood suPAR levels have been associated with kidney function⁷⁶ and proposed a causal factor
34
35
36 of certain chronic kidney diseases.⁷⁷ The potential causal effect in kidney disease is outside the
37
38
39 scope of this review. However, we will investigate whether suPAR is associated with mortality in
40
41
42 individuals with and without chronic kidney disease.
43
44
45

46 Our primary aim of summarizing all evidence of suPAR and mortality in one meta-analysis
47
48
49 imposes a high degree of study population heterogeneity on this study; however, to establish an
50
51
52 association between suPAR and mortality, it is important to summarize the information available
53
54
55
56
57

1
2
3 on this issue and it will provide us with a general estimate of association. We will account for the
4
5
6 heterogeneity by performing meta-regressions and stratified analyses to investigate the
7
8
9 association in more homogeneous subsets of the literature.
10
11

12
13 This systematic review and meta-analysis will provide an up-to-date global overview of the
14
15 current literature on suPAR and mortality. If our results indicate an association between suPAR
16
17 level and mortality risk, suPAR may constitute an easily measurable, accurate chronic
18
19 inflammation biomarker with a well described association with mortality, which could be a vital
20
21 tool in future efforts to combat major public health challenges, such as chronic disease
22
23 prevention and premature mortality, and improve future research on this topic.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Hunter P. The inflammation theory of disease. The growing realization that chronic inflammation is crucial in many diseases opens new avenues for treatment. *EMBO Rep.* 2012;13(11):968-970.
2. Medzhitov R. Inflammation 2010: New Adventures of an Old Flame. *Cell.* 2010;140(6):771-776.
3. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci.* 2014;69 Suppl 1:S4-9.
4. Michaud M, Balardy L, Moulis G, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc.* 2013;14(12):877-882.
5. Thunø M, Macho B, Eugen-Olsen J. suPAR: The molecular crystal ball. *Dis Markers.* 2009;27(3):157-172.
6. Desmedt S, Desmedt V, Delanghe JR, Speeckaert R, Speeckaert MM. The intriguing role of soluble urokinase receptor in inflammatory diseases. *Crit Rev Clin Lab Sci.* 2017;54(2):117-133.
7. Eugen-Olsen J, Andersen O, Linneberg A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. *J Intern Med.* 2010;268(3):296-308.
8. Rasmussen LJH, Ladelund S, Haupt TH, et al. Soluble urokinase plasminogen activator receptor (suPAR) in acute care: A strong marker of disease presence and severity, readmission and mortality. A retrospective cohort study. *Emerg Med J.* 2016;33(11):769-775.
9. Shuai T, Pei Jing Y, Huang Q, et al. Serum soluble urokinase type plasminogen activated receptor

- 1
2
3 and focal segmental glomerulosclerosis: A systematic review and meta-analysis. *BMJ Open*.
4
5
6 2019;9(10):e031812.
7
8
9 10. Lee JM, Yang JW, Kronbichler A, et al. Increased serum soluble urokinase-type plasminogen
10
11 activator receptor (suPAR) Levels in FSGS: A Meta-Analysis. *J Immunol Res*.
12
13 2019;2019:5679518.
14
15
16 11. Pregernig A, Müller M, Held U, Beck-Schimmer B. Prediction of mortality in adult patients with
17
18 sepsis using six biomarkers: a systematic review and meta-analysis. *Ann Intensive Care*.
19
20 2019;9(1):125.
21
22
23 12. Backes Y, Van Der Sluijs KF, Mackie DP, et al. Usefulness of suPAR as a biological marker in
24
25 patients with systemic inflammation or infection: A systematic review. *Intensive Care Med*.
26
27 2012;38(9):1418-1428.
28
29
30 13. Ni W, Han Y, Zhao J, et al. Serum soluble urokinase-type plasminogen activator receptor as a
31
32 biological marker of bacterial infection in adults: A systematic review and meta-Analysis. *Sci Rep*.
33
34 2016;6:39481.
35
36
37 14. Huang Q, Xiong H, Yan P, et al. The Diagnostic and Prognostic Value of Supar in Patients with
38
39 Sepsis: A Systematic Review and Meta-Analysis. *Shock*. September 2019.
40
41 doi:10.1097/SHK.0000000000001434
42
43
44 15. Hastrup E, Grau K, Eugen-Olsen J, Thorball C, Kessing LV, Ullum H. Soluble urokinase
45
46 plasminogen activator receptor as a marker for use of antidepressants. *PLoS One*.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 2014;9(10):e110555.
16. Persson M, Östling G, Smith G, et al. Soluble Urokinase Plasminogen Activator Receptor: A Risk Factor for Carotid Plaque, Stroke, and Coronary Artery Disease. *Stroke*. 2014;45(1):18-23.
17. Lyngbæk S, Marott JL, Møller D V, et al. Usefulness of soluble urokinase plasminogen activator receptor to predict repeat myocardial infarction and mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous intervention. *Am J Cardiol*. 2012;110(12):1756-1763.
18. Westin O, Rasmussen LJH, Andersen O, Buch E, Eugen-Olsen J, Friberg J. Soluble Urokinase Plasminogen Activator Receptor (suPAR) as a Predictor of Incident Atrial Fibrillation. *J Atr Fibrillation*. 2018;10(6):1801.
19. Theilade S, Lyngbaek S, Hansen TW, et al. Soluble urokinase plasminogen activator receptor levels are elevated and associated with complications in patients with type 1 diabetes. *J Intern Med*. 2015;277(3):362-371.
20. Heraclides A, Jensen TM, Rasmussen SS, et al. The pro-inflammatory biomarker soluble urokinase plasminogen activator receptor (suPAR) is associated with incident type 2 diabetes among overweight but not obese individuals with impaired glucose regulation: Effect modification by smoking and body weight. *Diabetologia*. 2013;56(7):1542-1546.
21. Guthoff M, Wagner R, Randrianarisoa E, et al. Soluble urokinase receptor (suPAR) predicts microalbuminuria in patients at risk for type 2 diabetes mellitus. *Sci Rep*. 2017;7:40627.

- 1
2
3
4 22. Mustjoki S, Sidenius N, Sier CF, et al. Soluble urokinase receptor levels correlate with number of
5
6 circulating tumor cells in acute myeloid leukemia and decrease rapidly during chemotherapy.
7
8
9 *Cancer Res.* 2000;60(24):7126-7132.
10
11
12 23. Mustjoki S, Alitalo R, Stephens RW, Vaeheri A. Blast cell-surface and plasma soluble urokinase
13
14 receptor in acute leukemia patients: relationship to classification and response to therapy. *Thromb*
15
16 *Haemost.* 1999;81(5):705-710.
17
18
19
20 24. Wach S, Al-Janabi O, Weigelt K, et al. The combined serum levels of miR-375 and urokinase
21
22 plasminogen activator receptor are suggested as diagnostic and prognostic biomarkers in prostate
23
24 cancer. *Int J Cancer.* 2015;137(6):1406-1416.
25
26
27
28
29 25. Cobos E, Jumper C, Lox C. Pretreatment Determination of the Serum Urokinase Plasminogen
30
31 Activator and its Soluble Receptor in Advanced Small-Cell Lung Cancer or Non-Small-Cell Lung
32
33 Cancer. *Clin Appl Thromb.* 2003;9(3):241-246.
34
35
36
37
38 26. Miyake H, Hara I, Yamanaka K, Gohji K, Arakawa S, Kamidono S. Elevation of serum levels of
39
40 urokinase-type plasminogen activator and its receptor is associated with disease progression and
41
42 prognosis in patients with prostate cancer. *Prostate.* 1999;39(2):123-129.
43
44
45
46
47 27. Rigolin GM, Tieghi A, Ciccone M, et al. Soluble urokinase-type plasminogen activator receptor
48
49 (suPAR) as an independent factor predicting worse prognosis and extra-bone marrow involvement
50
51 in multiple myeloma patients. *Br J Haematol.* 2003;120(6):953-959.
52
53
54
55
56 28. Riisbro R, Christensen IJ, Piironen T, et al. Prognostic significance of soluble urokinase
57
58
59
60

- 1
2
3 plasminogen activator receptor in serum and cytosol of tumor tissue from patients with primary
4
5
6 breast cancer. *Clin Cancer Res.* 2002;8(5):1132-1141.
7
8
- 9 29. Jing J, Zheng S, Han C, Du L, Guo Y, Wang P. Evaluating the value of uPAR of serum and tissue
10
11 on patients with cervical cancer. *J Clin Lab Anal.* 2012;26(1):16-21.
12
13
- 14 30. Riisbro R, Stephens RW, Brünner N, et al. Soluble urokinase plasminogen activator receptor in
15
16 preoperatively obtained plasma from patients with gynecological cancer or benign gynecological
17
18 diseases. *Gynecol Oncol.* 2001;82(3):523-531.
19
20
21
- 22 31. Lomholt AF, Høyer-Hansen G, Nielsen HJ, Christensen IJ. Intact and cleaved forms of the
23
24 urokinase receptor enhance discrimination of cancer from non-malignant conditions in patients
25
26 presenting with symptoms related to colorectal cancer. *Br J Cancer.* 2009;101(6):992-997.
27
28
29
- 30 32. Usnarska-Zubkiewicz L, Strutyńska-Karpińska M, Zubkiewicz-Kucharska A, Zarębski P,
31
32 Grabowski K. Soluble urokinase-type plasminogen activator receptor and ferritin concentration in
33
34 patients with advanced alimentary tract carcinoma. Relationship to localization, surgical treatment
35
36 and the stage of the disease - Preliminary report. *Adv Clin Exp Med.* 2014;23(6):959-967.
37
38
39
- 40 33. Fidan E, Mentese A, Ozdemir F, et al. Diagnostic and prognostic significance of CA IX and suPAR
41
42 in gastric cancer. *Med Oncol.* 2013;30(2):540.
43
44
45
- 46 34. Chounta A, Ellinas C, Tzanetakou V, et al. Serum soluble urokinase plasminogen activator
47
48 receptor as a screening test for the early diagnosis of hepatocellular carcinoma. *Liver Int.*
49
50
51
52
53
54
55
56 2015;35(2):601-607.
57

- 1
2
3 35. Rubio-Jurado B, Tello-González A, Bustamante-Chávez L, de la Peña A, Riebeling-Navarro C,
4
5
6 Nava-Zavala AH. Circulating Levels of Urokinase-Type Plasminogen Activator Receptor and D-
7
8
9 Dimer in Patients With Hematological Malignancies. *Clin Lymphoma Myeloma Leuk*.
10
11
12 2015;15(10):621-626.
13
14
15 36. Henic E, Borgfeldt C, Christensen IJ, Casslén B, Høyer-Hansen G. Cleaved forms of the
16
17
18 urokinase plasminogen activator receptor in plasma have diagnostic potential and predict
19
20
21 postoperative survival in patients with ovarian cancer. *Clin Cancer Res*. 2008;14(18):5785-5793.
22
23
24 37. Enocsson H, Wetterö J, Skogh T, Sjöwall C. Soluble urokinase plasminogen activator receptor
25
26
27 levels reflect organ damage in systemic lupus erythematosus. *Transl Res*. 2013;162(5):287-296.
28
29
30 38. Toldi G, Bekő G, Kádár G, et al. Soluble urokinase plasminogen activator receptor (suPAR) in the
31
32
33 assessment of inflammatory activity of rheumatoid arthritis patients in remission. *Clin Chem Lab*
34
35
36 *Med*. 2013;51(2):327-332.
37
38
39 39. Portelli MA, Siedlinski M, Stewart CE, et al. Genome-wide protein QTL mapping identifies human
40
41
42 plasma kallikrein as a post-translational regulator of serum uPAR levels. *FASEB J*.
43
44
45 2014;28(2):923-934.
46
47
48 40. Zimmermann HW, Koch A, Seidler S, Trautwein C, Tacke F. Circulating soluble urokinase
49
50
51 plasminogen activator is elevated in patients with chronic liver disease, discriminates stage and
52
53
54 aetiology of cirrhosis and predicts prognosis. *Liver Int*. 2012;32(3):500-509.
55
56
57 41. Wiese S, Mortensen C, Gøtze JP, et al. Cardiac and proinflammatory markers predict prognosis in

- 1
2
3 cirrhosis. *Liver Int.* 2014;34(6):e19-30.
4
5
6
7 42. Sjöwall C, Martinsson K, Cardell K, Ekstedt M, Kechagias S. Soluble urokinase plasminogen
8
9 activator receptor levels are associated with severity of fibrosis in nonalcoholic fatty liver disease.
10
11
12 *Transl Res.* 2015;165(6):658-666.
13
14
15 43. Meijers B, Poesen R, Claes K, et al. Soluble urokinase receptor is a biomarker of cardiovascular
16
17 disease in chronic kidney disease. *Kidney Int.* 2015;87(1):210-216.
18
19
20
21 44. Schaefer F, Trachtman H, Wühl E, et al. Association of serum soluble urokinase receptor levels
22
23 with progression of kidney disease in children. *JAMA Pediatr.* 2017;171(11):e172914.
24
25
26 45. Sevgi DY, Bayraktar B, Gündüz A, et al. Serum soluble urokinase-type plasminogen activator
27
28 receptor and interferon- γ -induced protein 10 levels correlate with significant fibrosis in chronic
29
30 hepatitis B. *Wien Klin Wochenschr.* 2016;128(1-2):28-33.
31
32
33
34
35 46. Sidenius N, Sier CF, Ullum H, et al. Serum level of soluble urokinase-type plasminogen activator
36
37 receptor is a strong and independent predictor of survival in human immunodeficiency virus
38
39 infection. *Blood.* 2000;96(13):4091-4095.
40
41
42
43
44 47. Kirkegaard-Klitbo DM, Langkilde A, Mejer N, Andersen O, Eugen-Olsen J, Benfield T. Soluble
45
46 Urokinase Plasminogen Activator Receptor Is a Predictor of Incident Non-AIDS Comorbidity and
47
48 All-Cause Mortality in Human Immunodeficiency Virus Type 1 Infection. *J Infect Dis.*
49
50 2017;216(7):819-823.
51
52
53
54
55 48. Hoenigl M, Raggam RB, Wagner J, et al. Diagnostic accuracy of soluble urokinase plasminogen
56
57

- 1
2
3 activator receptor (suPAR) for prediction of bacteremia in patients with systemic inflammatory
4
5
6 response syndrome. *Clin Biochem.* 2013;46(3):225-229.
7
8
9 49. Wittenhagen P, Kronborg G, Weis N, et al. The plasma level of soluble urokinase receptor is
10
11 elevated in patients with *Streptococcus pneumoniae* bacteraemia and predicts mortality. *Clin*
12
13 *Microbiol Infect.* 2004;10(5):409-415.
14
15
16 50. Donadello K, Scolletta S, Taccone FS, et al. Soluble urokinase-type plasminogen activator
17
18 receptor as a prognostic biomarker in critically ill patients. *J Crit Care.* 2014;29(1):144-149.
19
20
21 51. Koch A, Voigt S, Kruschinski C, et al. Circulating soluble urokinase plasminogen activator receptor
22
23 is stably elevated during the first week of treatment in the intensive care unit and predicts mortality
24
25 in critically ill patients. *Crit Care.* 2011;15(1):R63.
26
27
28 52. Tzanakaki G, Paparoupa M, Kyprianou M, Barbouni A, Eugen-Olsen J, Kourea-Kremastinou J.
29
30 Elevated soluble urokinase receptor values in CSF, age and bacterial meningitis infection are
31
32 independent and additive risk factors of fatal outcome. *Eur J Clin Microbiol Infect Dis.*
33
34 2012;31(6):1157-1162.
35
36
37 53. Østergaard C, Benfield T, Lundgren JD, Eugen-Olsen J. Soluble urokinase receptor is elevated in
38
39 cerebrospinal fluid from patients with purulent meningitis and is associated with fatal outcome.
40
41 *Scand J Infect Dis.* 2004;36(1):14-19.
42
43
44 54. Wittenhagen P, Andersen JB, Hansen A, et al. Plasma soluble urokinase plasminogen activator
45
46 receptor in children with urinary tract infection. *Biomark Insights.* 2011;6:79-82.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 55. Wrotek A, Jackowska T, Pawlik K. Soluble urokinase plasminogen activator receptor: an indicator
4
5
6 of pneumonia severity in children. *Adv Exp Med Biol.* 2015;835:1-7.
7
8
9 56. Savva A, Raftogiannis M, Baziaka F, et al. Soluble urokinase plasminogen activator receptor
10
11 (suPAR) for assessment of disease severity in ventilator-associated pneumonia and sepsis. *J*
12
13 *Infect.* 2011;63(5):344-350.
14
15
16
17 57. Rabna P, Andersen A, Wejse C, et al. Utility of the plasma level of suPAR in monitoring risk of
18
19 mortality during TB treatment. *PLoS One.* 2012;7(8):e43933.
20
21
22
23 58. Perch M, Kofoed P, Fischer TK, et al. Serum levels of soluble urokinase plasminogen activator
24
25 receptor is associated with parasitemia in children with acute Plasmodium falciparum malaria
26
27 infection. *Parasite Immunol.* 2004;26(5):207-211.
28
29
30
31
32 59. Plewes K, Royakkers AA, Hanson J, et al. Correlation of biomarkers for parasite burden and
33
34 immune activation with acute kidney injury in severe falciparum malaria. *Malar J.* 2014;13:91.
35
36
37
38 60. Andersen O, Eugen-Olsen J, Kofoed K, Iversen J, Haugaard SB. Soluble Urokinase Plasminogen
39
40 Activator Receptor is a Marker of Dysmetabolism in HIV-Infected Patients Receiving Highly Active
41
42 Antiretroviral Therapy. *J Med Virol.* 2008;80(2):209-216.
43
44
45
46
47 61. Rasmussen LJH, Moffitt TE, Arseneault L, et al. Association of Adverse Experiences and
48
49 Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People.
50
51
52 *JAMA Pediatr.* 2019;Nov 4:1-11. doi:10.1001/jamapediatrics.2019.3875
53
54
55
56 62. Rasmussen LJH, Moffitt TE, Eugen-Olsen J, et al. Cumulative childhood risk is associated with a
57
58
59
60

- 1
2
3 new measure of chronic inflammation in adulthood. *J Child Psychol Psychiatry*. 2019;60(2):199-
4
5
6 208.
7
8
9 63. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of
10
11 prognostic factor studies. *BMJ*. 2019;364:k4597.
12
13
14
15 64. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-
16
17 analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ*. 2015;350:g7647.
18
19
20
21 65. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-
22
23 analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
24
25
26
27 66. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for
28
29 systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
30
31
32
33 67. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology - a
34
35 proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.
36
37 *JAMA*. 2000;283(15):2008-2012.
38
39
40
41 68. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of
42
43 prognostic factors. *Ann Intern Med*. 2013;158(4):280-286.
44
45
46
47 69. Hemingway H, Philipson P, Chen R, et al. Evaluating the quality of research into a single
48
49 prognostic biomarker: A systematic review and meta-analysis of 83 studies of C-reactive protein in
50
51 stable coronary artery disease. *PLoS Med*. 2010;7(6):e1000286.
52
53
54
55 70. Chêne G, Thompson SG. Methods for summarizing the risk associations of quantitative variables
56
57

- 1
2
3 in epidemiologic studies in a consistent form. *Am J Epidemiol.* 1996;144(6):610-621.
4
5
6
7 71. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of
8
9 evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.
10
11
12 72. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic
13
14 factor research: Adapting the GRADE framework. *Syst Rev.* 2013;2:71.
15
16
17
18 73. Schultz M, Rasmussen LJH, Andersen MH, et al. Use of the prognostic biomarker suPAR in the
19
20 emergency department improves risk stratification but has no effect on mortality: a cluster-
21
22 randomized clinical trial (TRIAGE III). *Scand J Trauma Resusc Emerg Med.* 2018;26(1):69.
23
24
25
26
27 74. Schultz M, Rasmussen LJH, Kallemose T, et al. Availability of suPAR in emergency departments
28
29 may improve risk stratification: A secondary analysis of the TRIAGE III trial. *Scand J Trauma*
30
31 *Resusc Emerg Med.* 2019;27(1):43.
32
33
34
35 75. Botha S, Fourie CM, Schutte R, Eugen-Olsen J, Pretorius R, Schutte AE. Soluble urokinase
36
37 plasminogen activator receptor as a prognostic marker of all-cause and cardiovascular mortality in
38
39 a black population. *Int J Cardiol.* 2015;184:631-636.
40
41
42
43
44 76. Hayek SS, Sever S, Ko YA, et al. Soluble Urokinase Receptor and Chronic Kidney Disease. *N*
45
46 *Engl J Med.* 2015;373(20):1916-1925.
47
48
49
50 77. Wei C, El Hindi S, Li J, et al. Circulating urokinase receptor as a cause of focal segmental
51
52 glomerulosclerosis. *Nat Med.* 2011;17(8):952-960.
53
54
55
56
57
58
59
60

Table 1. 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 judgment about the overall risk of bias within each of the 6 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 judgment of potential bias for each of the 6 domains.
1. Study Participation	Goal: To judge the risk of selection bias (likelihood that relationship between <i>PF</i> and <i>outcome</i> is different for participants and eligible non-participants).
<i>Source of target population</i>	The source population or population of interest is adequately described for key characteristics.
<i>Method used to identify population</i>	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)
<i>Recruitment period</i>	Period of recruitment is adequately described
<i>Place of recruitment</i>	Place of recruitment (setting and geographic location) are adequately described
<i>Inclusion and exclusion criteria</i>	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).
<i>Adequate study participation</i>	There is adequate participation in the study by eligible individuals
<i>Baseline characteristics</i>	The baseline study sample (i.e., 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 <i>PF</i> and <i>outcome</i> are different for completing and non-completing participants).

<i>Proportion of baseline sample available for analysis</i>	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.
<i>Attempts to collect information on participants who dropped out</i>	Attempts to collect information on participants who dropped out of the study are described.
<i>Reasons and potential impact of subjects lost to follow-up</i>	Reasons for loss to follow-up are provided.
<i>Outcome and prognostic factor information on those lost to follow-up</i>	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 analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.
3. Prognostic Factor 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).
<i>Definition of the PF</i>	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).
<i>Valid and Reliable Measurement of PF</i>	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., 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 (i.e., not data-dependent) are used.
<i>Method and Setting of PF Measurement</i>	The method and setting of measurement of PF is the same for all study participants.
<i>Proportion of data on PF available for analysis</i>	Adequate proportion of the study sample has complete data for PF variable.

<i>Method used for missing data</i>	Appropriate methods of imputation are used for missing 'PF' data.
PF Measurement Summary	<i>PF</i> 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).
<i>Definition of the Outcome</i>	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.
<i>Valid and Reliable Measurement of Outcome</i>	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., 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).
<i>Method and Setting of Outcome Measurement</i>	The method and setting of outcome measurement is the same for all study participants.
Outcome Measurement Summary	<i>Outcome of interest</i> is adequately measured in study participants to sufficiently limit potential bias.
5. Study Confounding	Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).
<i>Important Confounders Measured</i>	All important confounders, including treatments (key variables in conceptual model), are measured.
<i>Definition of the confounding factor</i>	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).
<i>Valid and Reliable Measurement of Confounders</i>	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).
<i>Method and Setting of Confounding Measurement</i>	The method and setting of confounding measurement are the same for all study participants.
<i>Method used for missing data</i>	Appropriate methods are used if imputation is used for missing confounder data.

<i>Appropriate Accounting for Confounding</i>	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Study Confounding Summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between <i>PF</i> and <i>outcome</i> .
6. Statistical Analysis and Reporting	Goal: To judge the risk of bias related to the statistical analysis and presentation of results.
<i>Presentation of analytical strategy</i>	There is sufficient presentation of data to assess the adequacy of the analysis.
<i>Model development strategy</i>	The strategy for model building (i.e., 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.
<i>Reporting of results</i>	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. <i>Annals of Internal Medicine</i> . 2006;144:427-437.	

Appendix 1. Example of planned PubMed search.

Search	Query
#1	"Receptors, Urokinase Plasminogen Activator"[Mesh] OR "Soluble urokinase plasminogen activator receptor"[tiab] OR "Soluble urokinase plasminogen activator receptors"[tiab] OR "soluble urokinase-type plasminogen activator receptor"[tiab] OR "soluble urokinase-type plasminogen activator receptors"[tiab] OR "soluble urokinase receptor"[tiab] OR "soluble urokinase receptors"[tiab] OR "plasminogen activator receptor"[tiab] OR "plasminogen activator receptors"[tiab] OR suPAR[tiab] OR uPAR[tiab]
#2	"Mortality"[Mesh] OR mortality[tiab] OR mortalities[tiab] OR "death"[Mesh] OR death[tiab] OR deaths[tiab] OR fatality[tiab] OR fatalities[tiab] OR "fatal outcome"[tiab] OR "fatal outcomes"[tiab] OR "prognosis"[Mesh] OR prognosis[tiab] OR prognostic[tiab] OR "survival"[Mesh] OR "survival analysis"[Mesh] OR "survival rate"[Mesh] OR survival[tiab] OR "life expectancy"[Mesh] OR "life expectancy"[tiab] OR "hazard ratio"[tiab] OR "hazard ratios"[tiab] OR "risk assessment"[Mesh] OR risk[tiab] OR "severity of illness index"[Mesh] OR "severity of illness"[tiab]
#3	#1 AND #2
#4	#3 NOT ("animals"[mh] NOT "humans"[mh])
#5	#4 NOT (case reports[ptyp] OR editorial[ptyp] OR comment[ptyp])

Full PubMed search term:

(((((("Receptors, Urokinase Plasminogen Activator"[Mesh] OR "Soluble urokinase plasminogen activator receptor"[tiab] OR "Soluble urokinase plasminogen activator receptors"[tiab] OR "soluble urokinase-type plasminogen activator receptor"[tiab] OR "soluble urokinase-type plasminogen activator receptors"[tiab] OR "soluble urokinase receptor"[tiab] OR "soluble urokinase receptors"[tiab] OR "plasminogen activator receptor"[tiab] OR "plasminogen activator receptors"[tiab] OR suPAR[tiab] OR uPAR[tiab])) AND (("Mortality"[Mesh] OR mortality[tiab] OR mortalities[tiab] OR "death"[Mesh] OR death[tiab] OR deaths[tiab] OR fatality[tiab] OR fatalities[tiab] OR "fatal outcome"[tiab] OR "fatal outcomes"[tiab] OR "prognosis"[Mesh] OR prognosis[tiab] OR prognostic[tiab] OR "survival"[Mesh] OR "survival analysis"[Mesh] OR

1
2
3 "survival rate"[Mesh] OR survival[tiab] OR "life expectancy"[Mesh] OR "life expectancy"[tiab] OR
4 "hazard ratio"[tiab] OR "hazard ratios"[tiab] OR "risk assessment"[Mesh] OR risk[tiab] OR
5 "severity of illness index"[Mesh] OR "severity of illness"[tiab]))) NOT ("animals"[mh] NOT
6 "humans"[mh])) NOT (case reports[ptyp] OR editorial[ptyp] OR comment[ptyp])
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review. Included in title, p. 1.
Update	1b	If the protocol is for an update of a previous systematic review, identify as such. N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number. See p. 2-3; the protocol will be registered at PROSPERO, however, PROSPERO has the following recommendation: "Ensure that your review protocol is in its (near) final form and that no major changes are anticipated at this stage - e.g. if your protocol will be peer reviewed it will usually be sensible to wait until this is complete before registering". Therefore, we will wait with the registration at PROSPERO until the protocol has been peer-reviewed.
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author. p. 1-2.
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review. p. 4.
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments. The plan for documenting protocol amendments is presented on p. 4.
Support:		
Sources	5a	Indicate sources of financial or other support for the review. p. 4-5.
Sponsor	5b	Provide name for the review funder and/or sponsor. p. 4-5.
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol. p. 4-5.
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known. p. 8-10.
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO). p. 10-11.
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review. p. 12-14.
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage. p. 14-15.

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated. p. 15-16 + Appendix 1.
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review. p. 16.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis). p. 16-17.
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators. p. 17-18.
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications. p. 18-19.
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale. p. 19-20.
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis. p. 21-22.
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised. p. 22-23
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ). p. 22-24.
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression). p. 24-26.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned. p. 23.
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies). p. 26.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE). p. 26-27.

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015 Jan 2;349(jan02 1):g7647.*

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-036125.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Feb-2020
Complete List of Authors:	Petersen, Jens Emil; Duke University, Department of Infectious Diseases Kallemose, Thomas; Copenhagen University Hospital Hvidovre, Clinical Research Centre 056 Barton, Karen; Duke University, Duke University Medical Center Library & Archives Caspi, A; Duke University, Department of Psychology and Neuroscience; King's College London, Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience Rasmussen, Line Jee Hartmann; Duke University, Department of Psychology and Neuroscience; Copenhagen University Hospital Hvidovre, Clinical Research Centre 056
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Immunology (including allergy)
Keywords:	Clinical chemistry < PATHOLOGY, PREVENTIVE MEDICINE, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, IMMUNOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Soluble urokinase plasminogen activator receptor (suPAR) as a prognostic marker of**
4
5
6
7 **mortality in healthy, general, and patient populations: protocol for a systematic review**
8
9
10 **and meta-analysis**
11
12
13

14 **Authors:**

15
16
17
18 Jens Emil Vang Petersen,¹ Thomas Kalleose,² Karen D. Barton,³ Avshalom Caspi,^{4,5,6,7} Line

19
20
21 Jee Hartmann Rasmussen^{2,4}
22
23

24
25 ¹Department of Infectious Diseases, Duke University, Durham, NC, USA
26
27

28 ²Clinical Research Centre, Copenhagen University Hospital Amager and Hvidovre, Hvidovre,
29
30
31 Denmark
32
33

34
35 ³Duke University Medical Center Library & Archives, Duke University, Durham, NC, USA
36
37

38 ⁴Department of Psychology and Neuroscience, Duke University, Durham, NC, USA
39
40

41 ⁵Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine,
42
43
44 Durham, NC, USA
45
46

47 ⁶Center for Genomic and Computational Biology, Duke University, Durham, NC, USA
48
49

50
51 ⁷Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and
52
53
54 Neuroscience, King's College London, London, UK
55
56

1
2
3 E-mail: Jens E V Petersen jensemilvang.petersen@duke.edu – Thomas Kallelose

4
5
6 thomas.kallelose@regionh.dk – Karen Barton karen.d.barton@duke.edu – Avshalom Caspi

7
8
9 avshalom.caspi@duke.edu – Line J H Rasmussen line.jee.hartmann.rasmussen@duke.edu

10
11
12
13 **Corresponding author:**

14
15
16 Line Jee Hartmann Rasmussen

17
18
19 Dept. of Psychology and Neuroscience

20
21
22 2020 W Main St, Suite 201

23
24
25
26
27 Durham, NC 27705, USA

28
29
30
31 Clinical Research Centre

32
33
34 Hvidovre Hospital

35
36
37 Kettegård Allé 30

38
39
40 DK-2650 Hvidovre, Denmark

41
42
43
44 **Word count: 4,224**

Contributions:

JEVP and LJHR are the guarantors of the review. All authors (JEVP, TK, KDB, AC, LJHR) contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. LJHR and JEVV conceived the study. JEVV, KDB, and LJHR developed the search strategy. TK provided statistical expertise. JEVV and LJHR drafted the protocol. All authors (JEVP, TK, KDB, AC, LJHR) read, provided feedback, and approved the final protocol.

Amendments:

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale for the change in this section. An updated protocol will be identified with a new version number and a list of the specific amendments that were made to the previous version, in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Funding statement:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. JEVV is supported by an international postdoc fellowship from the Alfred

1
2
3 Benzon Foundation (grant no. ABF-2018-91). LJHR is supported by an international postdoc
4
5
6 fellowship from the Lundbeck Foundation (grant no. R288-2018-380). The funders had no role
7
8
9 in designing the project or developing the protocol, neither will they have any role in the review
10
11
12
13 conduct, data analysis and interpretation, or publication of the study results.
14
15

16
17 **Competing interests:**

18
19
20 LJHR has received funding for travel outside the submitted work from ViroGates A/S. The
21
22
23
24 remaining authors report no conflicts of interest.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction: Chronic inflammation is increasingly recognized as a major contributor to disease, disability, and ultimately death, but measuring the levels of chronic inflammation remains non-canonized, 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 randomized trials. Here, we wish to summarize 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 through 28 February 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

1
2
3 measures (e.g., risk ratios, odds ratios, hazard ratios) with 95% CIs will be extracted for healthy
4
5
6 individuals, general and patient populations. The primary outcome is all-cause mortality within
7
8
9 any given follow-up. Subgroup analyses will be performed based on time of outcome, cause of
10
11
12 death, population type, adjustments for conventional risk factors and inflammation markers, etc.
13
14
15

16
17 **Ethics and dissemination:** This systematic review will synthesize evidence on the use of suPAR
18
19 as a prognostic marker for mortality. The results will be disseminated by publication in a peer-
20
21
22 reviewed journal. Data used will be obtained from published studies, and ethics approval is
23
24
25 therefore not necessary for this systematic review.
26
27
28
29

30 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 31
32
- 33 - To the best of our knowledge, this is the first systematic review and meta-analysis that
34
35 investigates the association between suPAR and mortality across general and patient
36
37 populations.
38
39
 - 40 - This review will provide valuable new knowledge for researchers studying chronic
41
42 inflammation's effect on both short- and long-term health, and for clinicians using suPAR
43
44 in clinical settings to stratify patients.
45
46
47
 - 48 - Study selection, data extraction, and quality assessment will be performed
49
50
51 independently by two reviewers.
52
53
54
55
56
57

- 1
2
3
4 - The results will be discussed in context with other studies in the field.
5
6
7 - Common to most meta-analyses, significant heterogeneity may exist, which will be
8
9
10 investigated thoroughly with subgroup analyses and meta-regressions.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 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.

For peer review only

INTRODUCTION

Rationale:

Chronic inflammation is increasingly recognized as a major contributor to disease, disability, and ultimately death in industrialized and developing countries alike.¹⁻⁴ Chronic inflammation is related to multiple genetic and lifestyle factors, but measuring the levels of chronic inflammation remains non-canonized, 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, i.e., suPAR has been shown to be elevated in cardiovascular diseases (stroke, ischemic heart disease, venous thromboembolism, incident

1
2
3 atrial fibrillation),^{16–18} type 1 and type 2 diabetes,^{19–21} various types of cancer,^{22–36} rheumatic
4
5
6 disease,^{37,38} chronic pulmonary disease,³⁹ chronic liver disease (non-alcoholic fatty liver
7
8
9 disease, cirrhosis),^{40–42} chronic kidney disease^{43,44} as well as infectious diseases caused by
10
11
12 viruses^{42,45–47}, bacteria^{48–57}, and parasites^{58,59}. Together, these studies highlight the broad
13
14
15
16 associations across patient groups and etiologies—and even in general populations—between
17
18
19 elevated blood levels of suPAR with general health, disease outcome, complications, and
20
21
22
23 mortality.

24
25
26 In contrast to common inflammatory biomarkers, such as the current gold standard C-reactive
27
28
29 protein (CRP), suPAR is not an acute-phase reactant, and suPAR levels in the blood are less
30
31
32 rapidly affected by acute changes and short-term influences.^{17,60} Additionally suPAR was more
33
34
35
36 reliably associated with early-life risk factors such as adverse childhood experiences, early-life
37
38
39 stress, and violence than CRP and interleukin-6 (IL-6), potentially because these more
40
41
42 traditional biomarkers of inflammation as acute-phase reactants mix historical and acute
43
44
45 effects.^{61,62} This, along with its non-specific associations with pathologies in general, suggests
46
47
48
49 that suPAR blood levels are an appropriate readout for chronic inflammation.

1
2
3 Prognostic biomarkers are important as they can help improve risk stratification in clinical
4
5
6 settings or provide guidance in treatment or lifestyle decisions as well as in the design of
7
8
9 randomized trials.⁶³ Here, we wish to summarize the evidence about the overall association of
10
11
12 the biomarker suPAR with mortality in healthy, general, and patient populations and across
13
14
15 diseases. As suPAR is still a relatively new clinical biomarker, clinical guidelines and cut-offs are
16
17
18 still lacking. Our findings will clarify the association between suPAR and mortality, and what
19
20
21 value a biomarker reflecting chronic inflammation adds, compared to the current standard
22
23
24 inflammatory biomarkers. The study will help development of future clinical guidelines, based on
25
26
27 a better understanding of differences in the prognostic value of suPAR between and across
28
29
30 healthy individuals and patient subgroups, which is critical in clinical decision-making. Having an
31
32
33 established accurate chronic inflammation biomarker with a well-described association with
34
35
36 mortality is a vital tool in future efforts to combat major public health challenges.
37
38
39
40
41

42 **Objective:**
43
44
45

46 In this systematic review, we aim to investigate the hypothesis that elevated suPAR is
47
48
49 associated with increased risk of short-term and long-term mortality in healthy, general, and
50
51
52 patient populations, independent of conventional risk factors.
53
54
55
56
57

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:

2. Is the association between suPAR and mortality present in healthy, general, and various patient populations?
3. Is the association between suPAR and mortality independent of conventional risk factors, such as age, sex, smoking, and chronic disease?
4. Is the association between suPAR and mortality independent of other inflammatory biomarkers?
5. What is the discrimination performance of suPAR for predicting mortality?
6. 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 PRISMA-P guidelines^{64,65}.

This study will follow the recommendations on conducting and reporting systematic reviews and meta-analyses set forth by the PRISMA⁶⁶ and Meta-analysis of observational studies in epidemiology (MOOSE)⁶⁷ guidelines, as well as the updated 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.

1
2
3
4 Participants: We will include studies examining healthy human individuals, general human
5
6
7 populations, or any human patient population. We will include studies of both children and
8
9
10 adults without restrictions on ethnicity, sex, or disease status.

11
12
13 Index prognostic factor: We will include studies with suPAR measured in plasma or serum,
14
15
16 independent of assay type, manufacturer, or sample storage time and conditions (whether
17
18
19 suPAR was measured in fresh or frozen samples); this information will be collected for quality
20
21
22 assessment and heterogeneity analysis (described below in detail). We will exclude studies
23
24
25 where suPAR was not measured in blood (e.g., urine samples).
26
27

28
29
30 Comparators: We will investigate the unadjusted and adjusted prognostic value of suPAR, i.e.,
31
32
33 without and with adjustments for other prognostic factors, e.g., conventional risk factors (such
34
35
36 as age, sex, smoking, and chronic disease), inflammatory biomarkers (such as CRP, white
37
38
39 blood cells, and IL-6), or kidney function (such as creatinine and glomerular filtration rate).
40
41
42

43
44 Outcomes: We will investigate the outcome of mortality. We will include studies with outcomes
45
46
47 reported as unadjusted or adjusted effect estimates of relative risk (e.g., risk ratio [RR], odds
48
49
50 ratio [OR], hazard ratio [HR]). In studies reporting mortality as part of a composite outcome
51
52
53 measure, we will extract all individual outcomes as reported in the studies. We will extract the
54
55
56

1
2
3 outcome in all data forms (for example, dichotomous—30-day mortality yes/no; continuous—
4
5
6 time to death) as reported in the included studies. For studies reporting survival from time-to-
7
8
9 event analyses, we will use this information to extract the number of deaths. Further, we will
10
11
12 investigate the discriminative ability of suPAR as a secondary outcome, i.e., area under the
13
14
15 curves (AUCs) for receiver operating characteristics (ROC) curve analyses of suPAR and
16
17
18 mortality. We will exclude studies of deaths due to external/unnatural causes, such as homicide,
19
20
21 suicides, accidents, drug overdoses, and medical errors.
22
23

24
25
26 Timing: We will investigate the association between suPAR and mortality during any given
27
28
29 period of follow-up. We will exclude cross-sectional studies.
30
31

32
33
34 Setting: There will be no restrictions by type of setting.
35
36

37
38 Language and publication type: We will include peer-reviewed studies in English or Danish
39
40
41 published through 28 February 2020. We will exclude reviews, commentaries, correspondence,
42
43
44 case reports, conference abstracts, expert opinions, editorials, experimental studies, and
45
46
47 dissertations. A list of possibly relevant titles in other languages will be provided as an appendix.
48
49

50
51 **Information sources:**
52
53
54
55
56
57

1
2
3 The following databases will be searched from their inception forward for potentially eligible
4
5
6 studies published on or before 28 February 2020: 1) Medline via PubMed, 2) Embase via
7
8
9 Elsevier, and 3) Scopus via Elsevier. The electronic database search will be supplemented with
10
11
12 a hand search of reference lists of included studies, etc. Finally, we will circulate a bibliography
13
14
15 of the included articles to the systematic review team, as well as to suPAR experts identified by
16
17
18 the team. The electronic databases search will be carried out by KB (Biomedical Research
19
20
21 Liaison Librarian), and the supplemental hand search will be carried out by J EVP and LJHR.
22
23
24
25

26 **Search strategy:**

27
28
29
30 The specific search strategy was created by a Biomedical Research Liaison Librarian (KB) with
31
32
33 expertise in systematic review searching. The search strategy was developed with input from
34
35
36 the project team. The search uses medical subject headings (MeSH) terms and keywords
37
38
39 related to suPAR and mortality. No study design, date, or language limits will be imposed on the
40
41
42 search. The following terms will be used to search the electronic databases in addition to other
43
44
45 related terms for the concepts of “suPAR” and “mortality”:
46
47
48
49

50 “suPAR” or “soluble urokinase plasminogen activator receptor” or “soluble urokinase-type” or
51
52
53 “soluble urokinase receptor” or “uPAR”
54
55
56
57

1
2
3 AND
4
5

6
7 “mortality” or “death” or “fatality”
8
9

10
11 The initial search will be performed on 28 February 2020. Searches will be repeated prior to
12
13 publication. The full PubMed search and search terms are shown in **Appendix 1**.
14
15

16
17
18 **Study records:**
19

20
21
22 *Data management:*
23

24
25
26 Citations extracted from electronic databases will be imported to EndNote. The Covidence
27
28 systematic review software will be used for the screening and review processes, including
29
30 removal of duplicates. For the actual data extraction, a data codebook will be a priori developed
31
32 in Microsoft Excel based on a pilot search, along with a manual describing the information to be
33
34 entered under each data item in the codebook.
35
36
37
38
39
40

41
42
43 *Selection process:*
44

45
46 Two reviewers (JEVP, LJHR) will independently screen titles and abstracts yielded by the
47
48 search to identify eligible studies according to the inclusion criteria. Studies that do not meet the
49
50 screening criteria will be excluded. We will obtain full reports for all titles that appear to meet the
51
52
53
54
55
56
57

1
2
3 inclusion criteria or where there is any uncertainty. The same two reviewers (JEVP, LJHR) will
4
5
6 independently review the full-text articles to assess for eligibility. The included and excluded
7
8
9 studies will be checked and reasons for inclusion/exclusion will be verified. Disagreements will
10
11
12 be resolved by consensus, or by a third author if necessary. Reasons for exclusion will be
13
14
15 coded for both the initial screening and for the review of the full-text articles. The PRISMA flow
16
17
18 diagram will be used to document the study selection process. An appendix with a reference list
19
20
21 of all excluded studies will be included in the final manuscript. Neither of the reviewers will be
22
23
24 blind to the article titles, study authors, or institutions. Multiple reports of a single study will be
25
26
27 identified by juxtaposing author names, study names, institutions, study dates, etc. To avoid
28
29
30 double counting, in cases of duplicate publications or multiple reports from the same study that
31
32
33 all meet the inclusion criteria, the reviewers will select publications based on the following
34
35
36 prioritization: reports with 1) adjusted analyses; 2) more covariates included; 3) bigger sample
37
38
39 size. In cases where different reports from the same study provide unique data on different
40
41
42 follow-up times, adjustments, or subgroups, unique information from the individual reports will
43
44
45 be extracted for the main analysis, subgroup analyses, and meta-regressions.
46
47
48
49
50

51
52 ***Data collection process:***
53
54
55
56
57

1
2
3 Data will be extracted from reports and entered in the Excel codebook in duplicate by the two
4
5
6 independent reviewers (JEVP, LJHR). As mentioned, the data extraction codebook is developed
7
8
9 a priori with statistical consultancy from TK. To ensure consistency across reviewers, we will
10
11
12 conduct calibration exercises before starting the data extraction. The extracted data will include
13
14
15 all the necessary information to describe and characterize the studies, assess the quality,
16
17
18 synthesize data for the meta-analyses, and to assess heterogeneity. In case of missing data or
19
20
21 insufficient reporting of details, the study's corresponding author will be contacted for
22
23
24 clarification, if possible, by a maximum of three e-mail attempts. When data extraction is
25
26
27 completed, both authors will review the codebooks and resolve any discrepancies by consensus
28
29
30 or by a third author if necessary. Prior to correcting disagreements, the overall inter-rater
31
32
33 agreement rate will be calculated using Cohen's κ statistic (>0.80 is considered good). A list of
34
35
36 extracted variables will be provided as an appendix in the final manuscript. For studies
37
38
39 consisting of multiple groups of individuals (for example, healthy controls, patients with
40
41
42 precancerous lesions, and patients with cancer), individual group information will be extracted to
43
44
45 assess the association between suPAR and mortality for each group.
46
47
48
49
50

51
52 **Data items:**
53
54
55
56
57

1
2
3 The major categories of extracted data will be: (1) study characteristics (author, journal, year of
4
5
6 publication, country/region, funding sources, etc.); (2) study design (type of study, year of study
7
8
9 start, duration of follow-up, etc.); (3) study population (sample size at baseline, population
10
11
12 characteristics (healthy individuals, general population, patient types), age, sex, sample size at
13
14
15 follow-up, reasons for loss to follow-up, information about treatments, etc.), (4) index suPAR
16
17
18 (suPAR levels, distribution, assay type, manufacturer, comparison groups and cut-offs, etc.); (5)
19
20
21 outcomes (including mortality/survival rates; cause of death; suPAR levels stratified by
22
23
24 survivors/non-survivors; unadjusted, minimally adjusted, and most adjusted RR, OR and/or HR
25
26
27 for short-term and long-term all-cause mortality; and true positive (TP), false positive (FP), true
28
29
30 negative (TN), and false negative (FN) frequencies as well as AUCs for ROC curves); (6)
31
32
33 control characteristics (conventional risk factors, e.g., age, sex, smoking, and chronic diseases;
34
35
36 other inflammatory biomarkers, e.g., C-reactive protein (CRP), white blood cells, cytokines,
37
38
39 fibrinogen; and kidney function, e.g., creatinine (measured or estimated), creatinine clearance,
40
41
42 glomerular filtration rate (measured or estimated)); (7) setting (general population, healthcare
43
44
45 setting, e.g., acute care, ICU, outpatients, etc.).
46
47
48
49
50
51

52 **Outcomes and prioritization:**

53
54
55
56
57

1
2
3 The primary outcome is all-cause mortality within any given follow-up period. Reports that are
4
5
6 not indicating cause of deaths will be analyzed under all-cause mortality.
7
8
9

10 When studies report mortality/survival rates at various time points of the follow-up, we have
11
12
13 decided a priori to subdivide the mortality rates as follows:
14
15

- 16 1. Short-term mortality: Death within 30 days from baseline.
- 17
- 18 2. 30-365-day mortality: Death occurring between 30 days and 365 days from baseline.
- 19
- 20
- 21 3. Long-term mortality: Death occurring more than 365 days from baseline.
- 22
- 23
- 24
- 25
- 26
- 27

28 For the primary meta-analysis, the most long-term outcome will be used, i.e., if a study reports
29
30
31 associations between suPAR and mortality at multiple time-points, the more long-term
32
33
34 assessment of mortality will be used. Furthermore, we will conduct subgroup analyses
35
36
37 stratifying studies reporting mortality within 30 days, between 30-365 days, and more than 365
38
39
40 days, as described in detail in the *"Subgroup analyses and meta-regression"* section below.
41
42
43

44 Secondary outcomes will be:

- 45
- 46
- 47
- 48 1. Short-term mortality (within 30 days) of any cause (all-cause mortality)
- 49
- 50
- 51 2. Cardiovascular mortality
- 52
- 53
- 54 3. Cancer mortality
- 55
- 56
- 57

- 1
2
3 4. Discriminative ability of suPAR, i.e., AUCs for ROC curves of suPAR and mortality for
4
5
6 the most long-term outcome reported
7
8
9

10 **Risk of bias in individual studies (quality assessment):**
11
12

13
14 To facilitate the assessment of possible risk of bias, the methodological quality of each study will
15
16 be evaluated using the Quality in Prognosis Studies (QUIPS) tool, **Table 1**.⁶⁸ The QUIPS tool
17
18 assesses risk of bias across six domains in studies of prognostic factors: (1) study participation
19
20 (sampling bias); (2) study attrition (attrition bias); (3) prognostic factor measurement; (4)
21
22 outcome measurement; (5) study confounding; and (6) statistical analysis and reporting. The
23
24 QUIPS tool will be adapted to meet the specific needs of this systematic review. To ensure
25
26 consistency across reviewers, we will conduct calibration exercises before starting the quality
27
28 assessments. Neither of the reviewers will be blinded to studies during the quality assessment.
29
30 For each domain in the tool, we will describe the procedures undertaken for each study,
31
32 including verbatim quotes. If there is insufficient detail reported in the study, we will judge the
33
34 risk of bias as “unclear” and the study’s authors will be contacted for more information. Studies
35
36 will be considered to have a low, moderate, or high risk of bias according to the following scores
37
38 of low risk across domains: 5-6, 3-4, 0-2. The two reviewers (JEVP, LJHR) will assess the risk
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 of bias independent of each other. Any disagreements will be resolved by consensus, or if
4
5
6 necessary by a third author, and a log of these will be included as an appendix in the final
7
8
9 manuscript. No study will be excluded based on the results of risk of bias assessment. We will
10
11
12 compute graphic representations of potential bias for the final manuscript. In the meta-analysis,
13
14
15 subgroup analyses will be performed based on the risk of bias (QUIPS; low, moderate, or high
16
17
18 risk of bias). The adapted QUIPS tool will be provided as an appendix in the final manuscript
19
20
21 along with the log of disagreements.
22
23
24
25

26 **Data synthesis:**

27
28
29
30 Reported relative risks and their corresponding 95-99% confidence intervals will be used to
31
32
33 assess the association between suPAR and most long-term mortality with random-effects meta-
34
35
36 analyses to minimize between-study heterogeneity. A quantitative synthesis will be performed,
37
38
39 and our outcomes will be studied separately in three pooled datasets: i) across all studies
40
41
42 (despite a high degree of expected heterogeneity), ii) within studies of healthy/general
43
44
45 populations, and iii) within studies of patient populations.
46
47
48
49

50 Relative risks with 95-99% CIs will be used as the common measure of association across
51
52
53 studies. RRs, ORs, and HRs will be assumed to approximate the same measure of relative risk.
54
55
56
57

1
2
3 As previously described for CRP and albumin,^{69,70} we will convert the reported study-specific
4
5
6 relative risk estimates for suPAR onto a standardized scale of effect, comparing the highest
7
8
9 third with the lowest third of the suPAR distribution, i.e., providing an estimate per 2.18 times
10
11
12 standard deviation (SD) units of suPAR. 2.18 is the difference in the means of the top and
13
14
15 bottom third of the standard normal distribution and is therefore used as the point estimate for
16
17
18 the lower and upper third of the suPAR distribution when scaled with SD. This method assumes
19
20
21 that suPAR follows a normal distribution, or a transformation of suPAR, such as the logarithm,
22
23
24 follows a normal distribution. Additionally, it is assumed that the suPAR SD estimates within the
25
26
27 studies are similar when scaling; if this is not the case additional adjustment to account for this
28
29
30 will be done and differences between calculation methods will be reported. If we conclude that
31
32
33 these assumptions cannot be made for the studies, separate relative risk estimates (per suPAR
34
35
36 unit, log₂(suPAR), Q1 vs Q4 suPAR, etc.) analyses will be made instead of the standardized
37
38
39 scale analysis.
40
41
42
43
44

45 For the primary analysis all study outcome measures (e.g., RR, OR, and HR) will be pooled as a
46
47
48 single measure, and all available studies will be included, regardless of population. If a study
49
50
51 has multiple versions of the same model with different adjustments, the model with most
52
53
54 adjustments will be included. In addition, we will conduct separate subgroup analyses, as
55
56
57

1
2
3 described below, to account for the heterogeneity across methods of reporting outcomes and
4
5
6 variation in adjustments made.
7

8
9
10 As suggested by Riley et al. 2019,⁶³ in addition to the main analysis, we will conduct multiple
11
12
13 meta-analyses separately based on the most long-term outcome stratified on the following
14
15
16 levels: (1) population level: all data, healthy/general populations, and patients; (2) model
17
18
19 adjustment: unadjusted, minimally adjusted (age and sex), adjusted for some conventional risk
20
21
22 factors (e.g., age, sex, chronic disease/Charlson score, smoking) or inflammatory markers (e.g.,
23
24
25 CRP, cytokines, fibrinogen), and maximally adjusted (most adjusted estimate from each study);
26
27
28 (3) outcome measure: RR, OR, and HR.
29
30
31

32
33 Statistical heterogeneity among studies will be evaluated using the τ^2 and I^2 statistic (where I^2
34
35
36 of 30-60% will be interpreted to indicate moderate heterogeneity and $I^2 > 50\%$ to indicate
37
38
39 substantial heterogeneity across studies⁷¹). We will try to explain the source of heterogeneity by
40
41
42 subgroup analysis or sensitivity analysis (see below).
43
44
45

46
47 Study characteristics of the included studies will be summarized in a table. To visually assess
48
49
50 between-study variability, we will present the results and summary relative risks in Forest plots.
51
52
53

1
2
3 Analysis of the predictive value of suPAR for mortality will be done by hierarchal summary
4
5
6 receiver operation characteristic (HSROC) model curves. From this, SROC curves with AUCs,
7
8
9
10 Qs, and diagnostic odds ratios (DORs) will be produced.

11
12
13 As described for CRP by Hemingway et al.,⁶⁹ we will attempt to calculate the detection rate
14
15
16 (sensitivity) at different false positive rates from 0 to 100 by constructing the log-normal
17
18
19 distributions of suPAR separately for those who survived and those who died. From this we will
20
21
22 obtain a ROC curve and report the c-statistic. Pooled estimates of both the c-statistic and
23
24
25 detection rate of suPAR's discriminative ability for predicting mortality will be obtained by
26
27
28 random effects meta-analysis of the study-specific c-statistics and detection rates. Confidence
29
30
31 intervals and a 10% false positive rate will be reported.
32
33
34
35
36

37 All statistical analyses will be performed using SAS Enterprise Guide (SAS Institute, Cary, NC)
38
39
40 and R (R Foundation for Statistical Computing, Vienna, Austria) software.
41
42
43

44 ***Subgroup analyses and meta-regression:***

45
46
47 In addition to the primary analysis of the most long-term mortality, separate analyses will be
48
49
50 made for the following mortality outcomes: mortality within 30 days, 30-365 days, and long-term
51
52
53
54
55
56
57

1
2
3 mortality (more than 365 days). These analyses will be done as described for the primary
4
5
6 analysis above.
7
8
9

10 Subgroup analyses will be used to explore possible sources of heterogeneity, and univariate
11
12 random effects meta-regression will be performed based on the following: study design (cohort,
13
14 case-control, randomized controlled trials); year of study start; sex; age groups; time of outcome
15
16 (within 30 days, 30-365 days, more than 365 days); reported relative risk estimates (e.g., RR,
17
18 OR, HR); population type (healthy/general population vs. patient types, e.g., cardiovascular
19
20 disease, cancer, chronic kidney disease, infectious disease, critical illness, acute care); cause of
21
22 death studied (all-cause, cardiovascular, cancer mortality, etc.); methods of suPAR
23
24 measurement; suPAR assay manufacturer; suPAR comparison group (continuous suPAR,
25
26 equal sized groups, unequal sized groups); region (North America + Europe, Asia, Africa, South
27
28 America); duration of follow-up; no. of adjustments; adjustment for CRP; adjustment for kidney
29
30 function; no. of events; risk of bias (QUIPS; low, moderate, high risk of bias).
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 To explore other potential sources of heterogeneity, a random effects meta-regression model
47
48 will be employed, which includes study level continuous or categorical covariates.
49
50
51
52

53 ***Sensitivity analysis:***
54
55
56
57

1
2
3 Sensitivity analyses will be performed in which the pooled risk estimates are recalculated by
4
5
6 removing the studies one by one and comparing the results. Furthermore, a sensitivity analysis
7
8
9 of risk of bias will be performed by omitting studies that are judged to be at high risk of bias.
10
11
12

13 **Meta-biases:**

14
15
16
17 Small study bias (including publication bias) will be assessed with contour-enhanced Funnel
18
19
20 plots, by Begg's adjusted rank correlation test, and by Egger's regression asymmetry test.
21
22
23

24 **Confidence in cumulative evidence:**

25
26
27
28 Reporting and interpretation of results will follow the reporting guidelines of PRISMA⁶⁶ and
29
30
31 MOOSE.⁶⁷ Interpretation and translation of summary results will follow these guidelines as well
32
33
34 as the steps recommended for prognostic factor studies by Riley et al. 2019.⁶³ The summary
35
36
37 results will be discussed in terms of potential usefulness for clinical practice and need for future
38
39
40 research.
41
42
43

44
45 Strength in the body of evidence will be further evaluated using the GRADE assessment
46
47
48 (Grades of Recommendation, Assessment, Development, and Evaluation).^{72,73} However, this
49
50
51 approach was developed for the assessment of intervention effectiveness in reviews of
52
53
54
55
56
57
58
59
60

1
2
3 interventions and not for assessing the certainty of summary results of systematic reviews of
4
5
6 prognostic factors; allowing for heterogeneity in the latter case may be more acceptable.⁶³
7
8
9

10 **Patient and public involvement:**
11
12

13
14 No patients involved.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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 utilization 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 randomized 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.

Summarizing this evidence is important to establish the prognostic role of suPAR. This protocol has been developed in compliance with recommended guidelines for prognostic factor studies,⁶³ including PRISMA-P,⁶⁴ and it provides a clear and structured protocol for maximizing data extraction and summarizing the relevant information on the importance of suPAR as a prognostic marker of mortality.

1
2
3 suPAR is used as a marker of inflammation, and as such, many studies have compared it with
4
5
6
7 CRP, although suPAR has been suggested to be a marker of chronic rather than acute
8
9
10 inflammation while CRP is an acute-phase reactant and potentially reflects a distinct aspect of
11
12
13 inflammation. In adjusted analyses, suPAR has been shown to be associated with mortality
14
15
16 independent of CRP.^{8,76} In our analyses, we aim to investigate the associations between suPAR
17
18
19 and mortality in studies adjusting for CRP to assess the effect over and above CRP. The
20
21
22 advantage of using a chronic inflammation marker rather than an acute-phase reactant for
23
24
25 prognostication includes the lower variation and sensitivity towards acute, short-term influences
26
27
28 and a better assessment of underlying health status.
29
30
31
32
33 Blood suPAR levels have been associated with kidney function⁷⁷ and proposed a causal factor
34
35
36 of certain chronic kidney diseases.⁷⁸ The potential causal effect in kidney disease is outside the
37
38
39 scope of this review. However, we will investigate whether suPAR is associated with mortality in
40
41
42 individuals with and without chronic kidney disease.
43
44
45

46 Our primary aim of summarizing all evidence of suPAR and mortality in one meta-analysis
47
48
49 imposes a high degree of study population heterogeneity on this study; however, to establish an
50
51
52 association between suPAR and mortality, it is important to summarize the information available
53
54
55
56
57
58
59
60

1
2
3 on this issue and it will provide us with a general estimate of association. We will account for the
4
5
6 heterogeneity by performing meta-regressions and stratified analyses to investigate the
7
8
9 association in more homogeneous subsets of the literature.
10
11

12
13 This systematic review and meta-analysis will provide an up-to-date global overview of the
14
15 current literature on suPAR and mortality. If our results indicate an association between suPAR
16
17 level and mortality risk, suPAR may constitute an easily measurable, accurate chronic
18
19 inflammation biomarker with a well described association with mortality, which could be a vital
20
21 tool in future efforts to combat major public health challenges, such as chronic disease
22
23 prevention and premature mortality, and improve future research on this topic.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **ETHICS AND DISSEMINATION:**
4
5

6
7 This systematic review will synthesize evidence on the use of suPAR as a prognostic marker for
8 mortality based on published publicly available studies and data. The study will not obtain, store,
9
10
11 or report any individual-level personal information and there will be no concerns about privacy.
12
13
14

15
16 Therefore ethical approval is not necessary for this systematic review. The results will be
17
18
19
20 disseminated by publication in a peer-reviewed journal.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Hunter P. The inflammation theory of disease. The growing realization that chronic inflammation is crucial in many diseases opens new avenues for treatment. *EMBO Rep.* 2012;13(11):968-970.
doi:10.1038/embor.2012.142
2. Medzhitov R. Inflammation 2010: New Adventures of an Old Flame. *Cell.* 2010;140(6):771-776.
doi:10.1016/j.cell.2010.03.006
3. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci.* 2014;69 Suppl 1:S4-9.
doi:10.1093/gerona/glu057
4. Michaud M, Balardy L, Moulis G, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc.* 2013;14(12):877-882. doi:10.1016/j.jamda.2013.05.009
5. Thunø M, Macho B, Eugen-Olsen J. suPAR: The molecular crystal ball. *Dis Markers.* 2009;27(3):157-172.
6. Desmedt S, Desmedt V, Delanghe JR, Speeckaert R, Speeckaert MM. The intriguing role of soluble urokinase receptor in inflammatory diseases. *Crit Rev Clin Lab Sci.* 2017;54(2):117-133.
doi:10.1080/10408363.2016.1269310
7. Eugen-Olsen J, Andersen O, Linneberg A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. *J Intern Med.* 2010;268(3):296-308.

- 1
2
3
4 8. Rasmussen LJH, Ladelund S, Haupt TH, et al. Soluble urokinase plasminogen activator receptor
5
6 (suPAR) in acute care: A strong marker of disease presence and severity, readmission and
7
8 mortality. A retrospective cohort study. *Emerg Med J*. 2016;33(11):769-775.
9
10
11
12 doi:10.1136/emered-2015-205444
13
14
15 9. Shuai T, Pei Jing Y, Huang Q, et al. Serum soluble urokinase type plasminogen activated receptor
16
17 and focal segmental glomerulosclerosis: A systematic review and meta-analysis. *BMJ Open*.
18
19
20 2019;9(10):e031812. doi:10.1136/bmjopen-2019-031812
21
22
23
24 10. Lee JM, Yang JW, Kronbichler A, et al. Increased serum soluble urokinase-type plasminogen
25
26 activator receptor (suPAR) Levels in FSGS: A Meta-Analysis. *J Immunol Res*.
27
28
29 2019;2019:5679518. doi:10.1155/2019/5679518
30
31
32
33 11. Pregernig A, Müller M, Held U, Beck-Schimmer B. Prediction of mortality in adult patients with
34
35 sepsis using six biomarkers: a systematic review and meta-analysis. *Ann Intensive Care*.
36
37
38 2019;9(1):125. doi:10.1186/s13613-019-0600-1
39
40
41
42 12. Backes Y, Van Der Sluijs KF, Mackie DP, et al. Usefulness of suPAR as a biological marker in
43
44 patients with systemic inflammation or infection: A systematic review. *Intensive Care Med*.
45
46
47 2012;38(9):1418-1428. doi:10.1007/s00134-012-2613-1
48
49
50
51 13. Ni W, Han Y, Zhao J, et al. Serum soluble urokinase-type plasminogen activator receptor as a
52
53 biological marker of bacterial infection in adults: A systematic review and meta-Analysis. *Sci Rep*.
54
55
56 2016;6:39481. doi:10.1038/srep39481
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
14. Huang Q, Xiong H, Yan P, et al. The Diagnostic and Prognostic Value of Supar in Patients with Sepsis: A Systematic Review and Meta-Analysis. *Shock*. September 2019.
doi:10.1097/SHK.0000000000001434
 15. Haastrup E, Grau K, Eugen-Olsen J, Thorball C, Kessing LV, Ullum H. Soluble urokinase plasminogen activator receptor as a marker for use of antidepressants. *PLoS One*. 2014;9(10):e110555. doi:10.1371/journal.pone.0110555
 16. Persson M, Östling G, Smith G, et al. Soluble Urokinase Plasminogen Activator Receptor: A Risk Factor for Carotid Plaque, Stroke, and Coronary Artery Disease. *Stroke*. 2014;45(1):18-23.
 17. Lyngbæk S, Marott JL, Møller D V, et al. Usefulness of soluble urokinase plasminogen activator receptor to predict repeat myocardial infarction and mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous intervention. *Am J Cardiol*. 2012;110(12):1756-1763. doi:10.1016/j.amjcard.2012.08.008
 18. Westin O, Rasmussen LJH, Andersen O, Buch E, Eugen-Olsen J, Friberg J. Soluble Urokinase Plasminogen Activator Receptor (suPAR) as a Predictor of Incident Atrial Fibrillation. *J Atr Fibrillation*. 2018;10(6):1801.
 19. Theilade S, Lyngbaek S, Hansen TW, et al. Soluble urokinase plasminogen activator receptor levels are elevated and associated with complications in patients with type 1 diabetes. *J Intern Med*. 2015;277(3):362-371.
 20. Heraclides A, Jensen TM, Rasmussen SS, et al. The pro-inflammatory biomarker soluble

- 1
2
3 urokinase plasminogen activator receptor (suPAR) is associated with incident type 2 diabetes
4
5
6 among overweight but not obese individuals with impaired glucose regulation: Effect modification
7
8
9 by smoking and body weight. *Diabetologia*. 2013;56(7):1542-1546. doi:10.1007/s00125-013-2914-
10
11
12 0
13
14
15 21. Guthoff M, Wagner R, Randrianarisoa E, et al. Soluble urokinase receptor (suPAR) predicts
16
17 microalbuminuria in patients at risk for type 2 diabetes mellitus. *Sci Rep*. 2017;7:40627.
18
19
20
21 doi:10.1038/srep40627
22
23
24 22. Mustjoki S, Sidenius N, Sier CF, et al. Soluble urokinase receptor levels correlate with number of
25
26 circulating tumor cells in acute myeloid leukemia and decrease rapidly during chemotherapy.
27
28
29
30
31
32
33 23. Mustjoki S, Alitalo R, Stephens RW, Vaheri A. Blast cell-surface and plasma soluble urokinase
34
35 receptor in acute leukemia patients: relationship to classification and response to therapy. *Thromb*
36
37
38
39
40
41
42 24. Jing J, Zheng S, Han C, Du L, Guo Y, Wang P. Evaluating the value of uPAR of serum and tissue
43
44 on patients with cervical cancer. *J Clin Lab Anal*. 2012;26(1):16-21. doi:10.1002/jcla.20499
45
46
47
48
49
50
51
52
53 25. Riisbro R, Stephens RW, Brünner N, et al. Soluble urokinase plasminogen activator receptor in
54
55 preoperatively obtained plasma from patients with gynecological cancer or benign gynecological
56
57 diseases. *Gynecol Oncol*. 2001;82(3):523-531. doi:10.1006/gyno.2001.6324
58
59
60 26. Lomholt AF, Høyer-Hansen G, Nielsen HJ, Christensen IJ. Intact and cleaved forms of the

- 1
2
3 urokinase receptor enhance discrimination of cancer from non-malignant conditions in patients
4
5
6 presenting with symptoms related to colorectal cancer. *Br J Cancer*. 2009;101(6):992-997.
7
8
9 doi:10.1038/sj.bjc.6605228
10
11
12 27. Usnarska-Zubkiewicz L, Strutyńska-Karpińska M, Zubkiewicz-Kucharska A, Zarębski P,
13
14 Grabowski K. Soluble urokinase-type plasminogen activator receptor and ferritin concentration in
15
16 patients with advanced alimentary tract carcinoma. Relationship to localization, surgical treatment
17
18 and the stage of the disease - Preliminary report. *Adv Clin Exp Med*. 2014;23(6):959-967.
19
20
21 doi:10.17219/acem/30817
22
23
24
25
26 28. Fidan E, Mentese A, Ozdemir F, et al. Diagnostic and prognostic significance of CA IX and suPAR
27
28 in gastric cancer. *Med Oncol*. 2013;30(2):540. doi:10.1007/s12032-013-0540-9
29
30
31
32 29. Chounta A, Ellinas C, Tzanetakou V, et al. Serum soluble urokinase plasminogen activator
33
34 receptor as a screening test for the early diagnosis of hepatocellular carcinoma. *Liver Int*.
35
36 2015;35(2):601-607. doi:10.1111/liv.12705
37
38
39
40
41 30. Rubio-Jurado B, Tello-González A, Bustamante-Chávez L, de la Peña A, Riebeling-Navarro C,
42
43 Nava-Zavala AH. Circulating Levels of Urokinase-Type Plasminogen Activator Receptor and D-
44
45 Dimer in Patients With Hematological Malignancies. *Clin Lymphoma Myeloma Leuk*.
46
47 2015;15(10):621-626. doi:10.1016/j.clml.2015.07.632
48
49
50
51
52 31. Henic E, Borgfeldt C, Christensen IJ, Casslén B, Høyer-Hansen G. Cleaved forms of the
53
54 urokinase plasminogen activator receptor in plasma have diagnostic potential and predict
55
56
57
58
59
60

- 1
2
3 postoperative survival in patients with ovarian cancer. *Clin Cancer Res.* 2008;14(18):5785-5793.
4
5
6 doi:10.1158/1078-0432.CCR-08-0096
7
8
- 9 32. Wach S, Al-Janabi O, Weigelt K, et al. The combined serum levels of miR-375 and urokinase
10
11 plasminogen activator receptor are suggested as diagnostic and prognostic biomarkers in prostate
12
13 cancer. *Int J Cancer.* 2015;137(6):1406-1416. doi:10.1002/ijc.29505
14
15
16
- 17 33. Cobos E, Jumper C, Lox C. Pretreatment Determination of the Serum Urokinase Plasminogen
18
19 Activator and its Soluble Receptor in Advanced Small-Cell Lung Cancer or Non-Small-Cell Lung
20
21 Cancer. *Clin Appl Thromb.* 2003;9(3):241-246. doi:10.1177/107602960300900309
22
23
24
25
- 26 34. Miyake H, Hara I, Yamanaka K, Gohji K, Arakawa S, Kamidono S. Elevation of serum levels of
27
28 urokinase-type plasminogen activator and its receptor is associated with disease progression and
29
30 prognosis in patients with prostate cancer. *Prostate.* 1999;39(2):123-129. doi:10.1002/(SICI)1097-
31
32 0045(19990501)39:2<123::AID-PROS7>3.0.CO;2-2
33
34
35
36
- 37 35. Rigolin GM, Tieghi A, Ciccone M, et al. Soluble urokinase-type plasminogen activator receptor
38
39 (suPAR) as an independent factor predicting worse prognosis and extra-bone marrow involvement
40
41 in multiple myeloma patients. *Br J Haematol.* 2003;120(6):953-959. doi:10.1046/j.1365-
42
43 2141.2003.04176.x
44
45
46
47
- 48 36. Riisbro R, Christensen IJ, Piironen T, et al. Prognostic significance of soluble urokinase
49
50 plasminogen activator receptor in serum and cytosol of tumor tissue from patients with primary
51
52 breast cancer. *Clin Cancer Res.* 2002;8(5):1132-1141.
53
54
55
56
57

- 1
2
3
4 37. Enocsson H, Wetterö J, Skogh T, Sjöwall C. Soluble urokinase plasminogen activator receptor
5
6 levels reflect organ damage in systemic lupus erythematosus. *Transl Res*. 2013;162(5):287-296.
7
8
9 doi:10.1016/j.trsl.2013.07.003
10
11
12 38. Toldi G, Bekő G, Kádár G, et al. Soluble urokinase plasminogen activator receptor (suPAR) in the
13
14 assessment of inflammatory activity of rheumatoid arthritis patients in remission. *Clin Chem Lab*
15
16
17
18 *Med*. 2013;51(2):327-332. doi:10.1515/cclm-2012-0221
19
20
21 39. Portelli MA, Siedlinski M, Stewart CE, et al. Genome-wide protein QTL mapping identifies human
22
23 plasma kallikrein as a post-translational regulator of serum uPAR levels. *FASEB J*.
24
25
26 2014;28(2):923-934. doi:10.1096/fj.13-240879
27
28
29 40. Zimmermann HW, Koch A, Seidler S, Trautwein C, Tacke F. Circulating soluble urokinase
30
31 plasminogen activator is elevated in patients with chronic liver disease, discriminates stage and
32
33 aetiology of cirrhosis and predicts prognosis. *Liver Int*. 2012;32(3):500-509.
34
35
36
37
38 41. Wiese S, Mortensen C, Gøtze JP, et al. Cardiac and proinflammatory markers predict prognosis in
39
40 cirrhosis. *Liver Int*. 2014;34(6):e19-30. doi:10.1111/liv.12428
41
42
43
44 42. Sjöwall C, Martinsson K, Cardell K, Ekstedt M, Kechagias S. Soluble urokinase plasminogen
45
46 activator receptor levels are associated with severity of fibrosis in nonalcoholic fatty liver disease.
47
48
49
50 *Transl Res*. 2015;165(6):658-666. doi:10.1016/j.trsl.2014.09.007
51
52
53 43. Meijers B, Poesen R, Claes K, et al. Soluble urokinase receptor is a biomarker of cardiovascular
54
55 disease in chronic kidney disease. *Kidney Int*. 2015;87(1):210-216.
56
57

- 1
2
3 44. Schaefer F, Trachtman H, Wühl E, et al. Association of serum soluble urokinase receptor levels
4
5
6 with progression of kidney disease in children. *JAMA Pediatr.* 2017;171(11):e172914.
7
8
9 doi:10.1001/jamapediatrics.2017.2914
10
11
12 45. Sevgi DY, Bayraktar B, Gündüz A, et al. Serum soluble urokinase-type plasminogen activator
13
14
15 receptor and interferon- γ -induced protein 10 levels correlate with significant fibrosis in chronic
16
17
18 hepatitis B. *Wien Klin Wochenschr.* 2016;128(1-2):28-33. doi:10.1007/s00508-015-0886-4
19
20
21 46. Sidenius N, Sier C, Ullum H, et al. Serum level of soluble urokinase-type plasminogen activator
22
23
24 receptor is a strong and independent predictor of survival in human immunodeficiency virus
25
26
27 infection. *Blood.* 2000;96(13):4091-4095.
28
29
30 47. Kirkegaard-Klitbo DM, Langkilde A, Mejer N, Andersen O, Eugen-Olsen J, Benfield T. Soluble
31
32
33 Urokinase Plasminogen Activator Receptor Is a Predictor of Incident Non-AIDS Comorbidity and
34
35
36 All-Cause Mortality in Human Immunodeficiency Virus Type 1 Infection. *J Infect Dis.*
37
38
39 2017;216(7):819-823. doi:10.1093/infdis/jix266
40
41
42 48. Hoenigl M, Raggam RB, Wagner J, et al. Diagnostic accuracy of soluble urokinase plasminogen
43
44
45 activator receptor (suPAR) for prediction of bacteremia in patients with systemic inflammatory
46
47
48 response syndrome. *Clin Biochem.* 2013;46(3):225-229. doi:10.1016/j.clinbiochem.2012.11.004
49
50
51 49. Wittenhagen P, Kronborg G, Weis N, et al. The plasma level of soluble urokinase receptor is
52
53
54 elevated in patients with *Streptococcus pneumoniae* bacteraemia and predicts mortality. *Clin*
55
56
57 *Microbiol Infect.* 2004;10(5):409-415. doi:10.1111/j.1469-0691.2004.00850.x
58
59
60

- 1
2
3 50. Donadello K, Scolletta S, Taccone FS, et al. Soluble urokinase-type plasminogen activator
4
5
6 receptor as a prognostic biomarker in critically ill patients. *J Crit Care*. 2014;29(1):144-149.
7
8
9 doi:10.1016/j.jcrc.2013.08.005
10
11
12 51. Koch A, Voigt S, Kruschinski C, et al. Circulating soluble urokinase plasminogen activator receptor
13
14
15 is stably elevated during the first week of treatment in the intensive care unit and predicts mortality
16
17
18 in critically ill patients. *Crit Care*. 2011;15(1):R63. doi:10.1186/cc10037
19
20
21 52. Tzanakaki G, Paparoupa M, Kyprianou M, Barbouni A, Eugen-Olsen J, Kourea-Kremastinou J.
22
23
24 Elevated soluble urokinase receptor values in CSF, age and bacterial meningitis infection are
25
26
27 independent and additive risk factors of fatal outcome. *Eur J Clin Microbiol Infect Dis*.
28
29
30 2012;31(6):1157-1162. doi:10.1007/s10096-011-1423-7
31
32
33 53. Østergaard C, Benfield T, Lundgren JD, Eugen-Olsen J. Soluble urokinase receptor is elevated in
34
35
36 cerebrospinal fluid from patients with purulent meningitis and is associated with fatal outcome.
37
38
39 *Scand J Infect Dis*. 2004;36(1):14-19. doi:10.1080/00365540310017366
40
41
42 54. Wittenhagen P, Andersen JB, Hansen A, et al. Plasma soluble urokinase plasminogen activator
43
44
45 receptor in children with urinary tract infection. *Biomark Insights*. 2011;6:79-82.
46
47
48 doi:10.4137/BMI.S6876
49
50
51 55. Wrotek A, Jackowska T, Pawlik K. Soluble urokinase plasminogen activator receptor: an indicator
52
53
54 of pneumonia severity in children. *Adv Exp Med Biol*. 2015;835:1-7. doi:10.1007/5584_2014_40
55
56
57 56. Savva A, Raftogiannis M, Baziaka F, et al. Soluble urokinase plasminogen activator receptor

- 1
2
3 (suPAR) for assessment of disease severity in ventilator-associated pneumonia and sepsis. *J*
4
5
6 *Infect.* 2011;63(5):344-350. doi:10.1016/j.jinf.2011.07.016
7
8
9 57. Rabna P, Andersen A, Wejse C, et al. Utility of the plasma level of suPAR in monitoring risk of
10
11 mortality during TB treatment. *PLoS One.* 2012;7(8):e43933. doi:10.1371/journal.pone.0043933
12
13
14
15 58. Perch M, Kofoed P, Fischer TK, et al. Serum levels of soluble urokinase plasminogen activator
16
17 receptor is associated with parasitemia in children with acute *Plasmodium falciparum* malaria
18
19 infection. *Parasite Immunol.* 2004;26(5):207-211.
20
21
22
23
24 59. Plewes K, Royakkers AA, Hanson J, et al. Correlation of biomarkers for parasite burden and
25
26 immune activation with acute kidney injury in severe *falciparum* malaria. *Malar J.* 2014;13:91.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41 60. Andersen O, Eugen-Olsen J, Kofoed K, Iversen J, Haugaard SB. Soluble Urokinase Plasminogen
42
43 Activator Receptor is a Marker of Dysmetabolism in HIV-Infected Patients Receiving Highly Active
44
45 Antiretroviral Therapy. *J Med Virol.* 2008;80(2):209-216.
46
47
48
49
50 61. Rasmussen LJH, Moffitt TE, Arseneault L, et al. Association of Adverse Experiences and
51
52 Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People.
53
54
55
56
57
58
59
60
61
62 62. Rasmussen LJH, Moffitt TE, Eugen-Olsen J, et al. Cumulative childhood risk is associated with a
63
64 new measure of chronic inflammation in adulthood. *J Child Psychol Psychiatry.* 2019;60(2):199-
65
66
67
68
69
70
208. doi:10.1111/jcpp.12928

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
63. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ*. 2019;364:k4597. doi:10.1136/bmj.k4597
64. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ*. 2015;350:g7647. doi:10.1136/bmj.g7647
65. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi:10.1186/2046-4053-4-1
66. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535
67. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology - a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1007/978-94-007-3024-3_10
68. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158(4):280-286. doi:10.7326/0003-4819-158-4-201302190-00009
69. Hemingway H, Philipson P, Chen R, et al. Evaluating the quality of research into a single prognostic biomarker: A systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. *PLoS Med*. 2010;7(6):e1000286.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- doi:10.1371/journal.pmed.1000286
70. Chêne G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. *Am J Epidemiol.* 1996;144(6):610-621.
- doi:10.1093/oxfordjournals.aje.a008971
71. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ WV (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.
72. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926. doi:doi:10.1136/bmj.39489.470347.AD
73. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: Adapting the GRADE framework. *Syst Rev.* 2013;2:71. doi:10.1186/2046-4053-2-71
74. Schultz M, Rasmussen LJH, Andersen MH, 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.
75. Schultz M, Rasmussen LJH, Kallemose T, et al. Availability of suPAR in emergency departments may improve risk stratification: A secondary analysis of the TRIAGE III trial. *Scand J Trauma Resusc Emerg Med.* 2019;27(1):43. doi:10.1186/s13049-019-0621-7

- 1
2
3
4 76. Botha S, Fourie CM, Schutte R, Eugen-Olsen J, Pretorius R, Schutte AE. Soluble urokinase
5
6 plasminogen activator receptor as a prognostic marker of all-cause and cardiovascular mortality in
7
8 a black population. *Int J Cardiol.* 2015;184:631-636. doi:10.1016/j.ijcard.2015.03.041
9
10
11
12 77. Hayek SS, Sever S, Ko YA, et al. Soluble Urokinase Receptor and Chronic Kidney Disease. *N*
13
14
15 *Engl J Med.* 2015;373(20):1916-1925. doi:10.1056/NEJMoa1506362
16
17
18 78. Wei C, El Hindi S, Li J, et al. Circulating urokinase receptor as a cause of focal segmental
19
20
21 glomerulosclerosis. *Nat Med.* 2011;17(8):952-960. doi:10.1038/nm.2411
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. 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 judgment about the overall risk of bias within each of the 6 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 judgment of potential bias for each of the 6 domains.
1. Study Participation	Goal: To judge the risk of selection bias (likelihood that relationship between <i>PF</i> and <i>outcome</i> is different for participants and eligible non-participants).
<i>Source of target population</i>	The source population or population of interest is adequately described for key characteristics.
<i>Method used to identify population</i>	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)
<i>Recruitment period</i>	Period of recruitment is adequately described
<i>Place of recruitment</i>	Place of recruitment (setting and geographic location) are adequately described
<i>Inclusion and exclusion criteria</i>	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).
<i>Adequate study participation</i>	There is adequate participation in the study by eligible individuals
<i>Baseline characteristics</i>	The baseline study sample (i.e., 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 <i>PF</i> and <i>outcome</i> are different for completing and non-completing participants).

<i>Proportion of baseline sample available for analysis</i>	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.
<i>Attempts to collect information on participants who dropped out</i>	Attempts to collect information on participants who dropped out of the study are described.
<i>Reasons and potential impact of subjects lost to follow-up</i>	Reasons for loss to follow-up are provided.
<i>Outcome and prognostic factor information on those lost to follow-up</i>	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 analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.
3. Prognostic Factor 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).
<i>Definition of the PF</i>	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).
<i>Valid and Reliable Measurement of PF</i>	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., 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 (i.e., not data-dependent) are used.
<i>Method and Setting of PF Measurement</i>	The method and setting of measurement of PF is the same for all study participants.
<i>Proportion of data on PF available for analysis</i>	Adequate proportion of the study sample has complete data for PF variable.

<i>Method used for missing data</i>	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).
<i>Definition of the Outcome</i>	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.
<i>Valid and Reliable Measurement of Outcome</i>	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., 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).
<i>Method and Setting of Outcome Measurement</i>	The method and setting of outcome measurement is the same for all study participants.
Outcome Measurement Summary	<i>Outcome of interest</i> is adequately measured in study participants to sufficiently limit potential bias.
5. Study Confounding	Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).
<i>Important Confounders Measured</i>	All important confounders, including treatments (key variables in conceptual model), are measured.
<i>Definition of the confounding factor</i>	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).
<i>Valid and Reliable Measurement of Confounders</i>	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).
<i>Method and Setting of Confounding Measurement</i>	The method and setting of confounding measurement are the same for all study participants.
<i>Method used for missing data</i>	Appropriate methods are used if imputation is used for missing confounder data.

<i>Appropriate Accounting for Confounding</i>	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Study Confounding Summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between <i>PF</i> and <i>outcome</i> .
6. Statistical Analysis and Reporting	Goal: To judge the risk of bias related to the statistical analysis and presentation of results.
<i>Presentation of analytical strategy</i>	There is sufficient presentation of data to assess the adequacy of the analysis.
<i>Model development strategy</i>	The strategy for model building (i.e., 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.
<i>Reporting of results</i>	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. <i>Annals of Internal Medicine</i> . 2006;144:427-437.	

Appendix 1. Example of planned PubMed search.

Search	Query
#1	"Receptors, Urokinase Plasminogen Activator"[Mesh] OR "Soluble urokinase plasminogen activator receptor"[tiab] OR "Soluble urokinase plasminogen activator receptors"[tiab] OR "soluble urokinase-type plasminogen activator receptor"[tiab] OR "soluble urokinase-type plasminogen activator receptors"[tiab] OR "soluble urokinase receptor"[tiab] OR "soluble urokinase receptors"[tiab] OR "plasminogen activator receptor"[tiab] OR "plasminogen activator receptors"[tiab] OR suPAR[tiab] OR uPAR[tiab]
#2	"Mortality"[Mesh] OR mortality[tiab] OR mortalities[tiab] OR "death"[Mesh] OR death[tiab] OR deaths[tiab] OR fatality[tiab] OR fatalities[tiab] OR "fatal outcome"[tiab] OR "fatal outcomes"[tiab] OR "prognosis"[Mesh] OR prognosis[tiab] OR prognostic[tiab] OR "survival"[Mesh] OR "survival analysis"[Mesh] OR "survival rate"[Mesh] OR survival[tiab] OR "life expectancy"[Mesh] OR "life expectancy"[tiab] OR "hazard ratio"[tiab] OR "hazard ratios"[tiab] OR "risk assessment"[Mesh] OR risk[tiab] OR "severity of illness index"[Mesh] OR "severity of illness"[tiab]
#3	#1 AND #2
#4	#3 NOT ("animals"[mh] NOT "humans"[mh])
#5	#4 NOT (case reports[ptyp] OR editorial[ptyp] OR comment[ptyp])

Full PubMed search term:

((((("Receptors, Urokinase Plasminogen Activator"[Mesh] OR "Soluble urokinase plasminogen activator receptor"[tiab] OR "Soluble urokinase plasminogen activator receptors"[tiab] OR "soluble urokinase-type plasminogen activator receptor"[tiab] OR "soluble urokinase-type plasminogen activator receptors"[tiab] OR "soluble urokinase receptor"[tiab] OR "soluble urokinase receptors"[tiab] OR "plasminogen activator receptor"[tiab] OR "plasminogen activator receptors"[tiab] OR suPAR[tiab] OR uPAR[tiab])) AND ("Mortality"[Mesh] OR mortality[tiab] OR mortalities[tiab] OR "death"[Mesh] OR death[tiab] OR deaths[tiab] OR fatality[tiab] OR fatalities[tiab] OR "fatal outcome"[tiab] OR "fatal outcomes"[tiab] OR "prognosis"[Mesh] OR prognosis[tiab] OR prognostic[tiab] OR "survival"[Mesh] OR "survival analysis"[Mesh] OR "survival rate"[Mesh] OR survival[tiab] OR "life expectancy"[Mesh] OR "life expectancy"[tiab] OR "hazard ratio"[tiab] OR "hazard ratios"[tiab] OR "risk assessment"[Mesh] OR risk[tiab] OR "severity of illness index"[Mesh] OR "severity of illness"[tiab]))) NOT ("animals"[mh] NOT "humans"[mh])) NOT (case reports[ptyp] OR editorial[ptyp] OR comment[ptyp])

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review. Included in title, p. 1.
Update	1b	If the protocol is for an update of a previous systematic review, identify as such. N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number. The protocol has been submitted at PROSPERO and is awaiting approval. The Registration statement and registration number will be added to the manuscript as soon as available.
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author. p. 1-2.
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review. p. 3.
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments. The plan for documenting protocol amendments is presented on p. 3.
Support:		
Sources	5a	Indicate sources of financial or other support for the review. p. 3-4.
Sponsor	5b	Provide name for the review funder and/or sponsor. p. 3-4.
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol. p. 3-4.
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known. p. 8-10.
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO). p. 10-11.
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review. p. 12-14.
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage. p. 14-15.
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be

		repeated. p. 15-16 + Appendix 1.
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review. p. 16.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis). p. 16-17.
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators. p. 17-18.
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications. p. 18-19.
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale. p. 19-21.
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis. p. 21-22.
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised. p. 22-25
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ). p. 24-25.
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression). p. 25-26.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned. p. 23.
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies). p. 27.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE). p. 27-28.

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015 Jan 2;349(jan02 1):g7647.*