

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

Association of tissue factor expression with prognosis and clinical features in human pancreatic cancer: a systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037431
Article Type:	Protocol
Date Submitted by the Author:	03-Feb-2020
Complete List of Authors:	Li, Haiyuan ; The Department of Tumor Surgery, Lanzhou University Second Hospital, ; The Second Clinical Medical College, Lanzhou University, Yu, Yang ; The Second Clinical Medical College, Lanzhou University, Shi, Qianling ; The First Clinical Medical College, Lanzhou University, The First Clinical Medical College of Lanzhou University Chen, Xueping ; Sleep Medicine Center, Gansu Provincial Hospital Zhen, Peng ; The Second Clinical Medical College, Lanzhou University Wang, Dengfeng ; The Second Clinical Medical College, Lanzhou University Tao, Pengxian ; The Second Clinical Medical College, Lanzhou University Gu, Baohong ; The Second Clinical Medical College, Lanzhou University Li, Xuemei ; The Second Clinical Medical College, Lanzhou University Zhang, Tao Xiang, Lin ; The Second Clinical Medical College, Lanzhou University Xi, Dayong ; The Second Clinical Medical College, Lanzhou University Gao, Lei ; The Second Clinical Medical College, Lanzhou University Maswikiti Ewetse , Paul; The Second Clinical Medical College, Lanzhou University, Chen, Hao; Lanzhou University Second Hospital,
Keywords:	Gastrointestinal tumours < ONCOLOGY, Pancreatic disease < GASTROENTEROLOGY, Molecular biology < TROPICAL MEDICINE

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 **Association of tissue factor expression with prognosis**
5
6
7 **and clinical features in human pancreatic cancer: a**
8
9 **systematic review protocol**
10

11 Haiyuan Li^{1,2}, Yang Yu², Qianling Shi³, Xueping Chen⁴, Peng Zheng², Dengfeng

12 Wang², Pengxian Tao², Baohong Gu², Xuemei Li², Tao zhang², Lin Xiang², Dayong

13 Xi², Lei Gao², Maswikiti Ewetse Paul², Hao Chen^{1*}
14
15
16
17
18

19 1. The Department of Tumor Surgery, Lanzhou University Second Hospital, Lanzhou

20
21
22 730030, China;
23

24 2. The Second Clinical Medical College, Lanzhou University, Lanzhou 730030,

25
26
27 China;
28

29 3. The First Clinical Medical College, Lanzhou University, Lanzhou 730000, China;
30

31 4. Sleep Medicine Center, Gansu Provincial Hospital, Lanzhou 730000, China;
32

33
34
35 Haiyuan Li and Yang Yu contributed equally
36

37 * Corresponding Author: Hao Chen, MD, PhD, the Department of Tumor Surgery,
38

39
40 Lanzhou University Second Hospital, Lanzhou 730030, China;
41

42
43 Tel: +86-15009467790; E-mail: chenhaodrs@163.com.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Pancreatic cancer is a type of highly aggressive digestive system tumour with poor prognosis. Venous thromboembolism (VTE) is a well-known complication of pancreatic cancer. Tissue factor (TF) is an important factor which contributes to the generation of a hypercoagulable state and thrombotic disease in pancreatic cancer. Several studies showed that TF expression with different types was related to the clinicopathological features of pancreatic cancer and influenced the survival of patients with pancreatic cancer. We thus want to conduct a systematic review of the literature to clarify the association between TF expression and clinicopathological features/prognosis of pancreatic cancer patients.

Methods and analysis: Studies comparing the clinicopathological features and the prognosis between pancreatic cancer patients with high and low expression of TF in tissue, plasma and MVs levels are eligible for the review. The outcomes include survival endpoints and the relationship between TF expression and clinicopathological features, such as VTE, tumor embolus, tumour size, clinical stage, and differentiation. Primary studies of any type published in English are included. Two reviewers will search the Medline, EMBASE and Cochrane from inception to Jan 2020 and retrieve the relevant studies. The same reviewers independently select the literatures and extract the data of included studies. The quality of the each included study is assessed by the Newcastle-Ottawa Scale (NOS score). The HR and 95% CI of each study are pooled for the survival outcome, and the pooled odds ratio (OR) and 95% CI are used for other outcomes. If a meta-analysis is not appropriate,

1
2
3
4 the result will only be reported qualitatively. Subgroup and sensitivity analyses are
5
6 considered to identify the source of heterogeneity. The Grades of Recommendation,
7
8 Assessment, Development and Evaluation method is applied to assess the level of
9
10 evidence obtained from this systematic review.
11
12
13
14

15 **Ethics and dissemination:** There is no concerning ethical issue. The result will be
16
17 sought for publication.
18
19
20

21 **PROSPERO registration number:** CRD42019133665
22
23
24

25 **Key words:** pancreatic cancer; tissue factor; microvesicle; prognosis; systematic
26
27 review
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

Strengths and limitations of this study

- This is the first systematic review addressing the significance of the TF for pancreatic cancer from different levels.
- Multiple outcomes are collected and analysed in this systematic review.
- It may be difficult to combine the results due to a small number of studies and substantial heterogeneity.

Introduction

Pancreatic cancer is a type of highly aggressive digestive system tumor with poor prognosis.¹ It is estimated that pancreatic cancer will be the second largest cancer-related cause of death in the United States by 2030.² Pancreatic cancer has insidious onset, rapid progression, low rate of early diagnosis and radical resection.³ Most of the patients already have advanced or distant metastasis at the first diagnosis. Despite recent advances in surgical techniques as well as chemotherapy and radiation therapy, pancreatic cancer patients still has a dismal 5-year survival rate.³

Venous thromboembolism (VTE), associated with the generation of an intrinsic hypercoagulable state, is a well-known complication of malignant tumor. Spreau first discovered that pancreatic cancer patients are prone to VTE in 1938.⁴ Subsequently, the incidence of VTE in pancreatic cancer patients ranges from 17% to 57% by Khorana.⁵ Furthermore, several studies have found that thrombosis and diffuse intravascular coagulation are associated with poor prognosis in patients with pancreatic cancer.⁶⁻¹⁰ However, the relationship between VTE and pancreatic cancer and the biological significance of VTE are not completely understood.

Several factors may play an important part in the generation of a hypercoagulable state and VTE in pancreatic cancer. Of prime importance is tissue factor (TF), a single chain transmembrane-receptor glycoprotein with a molecular weight of approximately 47 kDa, which initiates the extrinsic pathway of coagulation.¹¹ In recent years, It was reported that TF is expressed in many malignant tumours tissues, including

1
2
3
4 pancreatic cancer, leading to increased blood coagulability and a high risk of
5
6 VTE.^{12,13} Similarly, the plasma TF concentration increased significantly in patients
7
8 with pancreatic cancer and thrombosis.¹⁴ Pancreatic cancer cells express TF and
9
10 release Tissue factor - positive(TF⁺) microvesicles (MVs) (TF⁺MVs)¹⁵ and circulating
11
12 TF⁺MVs can be detected in patients.¹⁶ Importantly, the levels TF⁺ MVs are associated
13
14 with VTE in patients with pancreatic cancer.¹⁷⁻¹⁹

21
22 Emerging data suggest that the hemostatic system has a regulatory role in tumour
23
24 invasion and metastasis. Therefore, the activation of the hemostatic system may not
25
26 only contribute to VTE but also promote tumor invasion and metastasis. In recent
27
28 studies found that TF was shown to promote angiogenesis²⁰, inflammatory reaction²¹,
29
30 tumour invasion²² and metastasis.²³ Some evidence showed that the expression of TF
31
32 in metastatic melanoma cells was significantly higher than in non-metastatic cells;²⁴
33
34 the expression of TF in metastatic cancer sublines was significantly higher than in
35
36 parental lines.²⁵ Similarly, studies have found that TF expression is related to the
37
38 invasion phenotype of pancreatic cancer.²⁶ In addition, compared with tumour cells
39
40 with a higher degree of differentiation in pancreatic cancer, tumour cells with lower
41
42 degree of differentiation seem to have higher TF expression and associated with
43
44 decreased overall survival.^{13,26-28} Therefore, there seem to be a significant association
45
46 between TF and pancreatic cancer, and TF may be a potential marker of disease
47
48 prognosis in patients with pancreatic cancer. We plan to undertake a systematic
49
50 review of the literature to summarize previous evidence regarding this topic and
51
52
53
54
55
56
57
58
59
60

1
2
3
4 clarify the prognostic significance of TF in pancreatic cancer.
5
6
7

8 **Why it is important to do this review**

9
10
11 Pancreatic cancer is one of the most aggressive malignant tumours in the clinic. The

12
13 3-year survival rate after surgical resection of primary tumours is only 17%.

14
15
16 Therefore, identifying markers that may predict poor prognosis will benefit patients
17
18 with radical or molecular targeted therapies. Some methods have been established to
19
20 study the TF in pancreatic cancer. However, to date, no systematic review has been
21
22 conducted to study the association between TF expression or activity and
23
24 clinicopathological features/prognosis of pancreatic cancer.
25
26
27
28
29
30

31 **Objectives**

32
33 To systematically clarify the relationship between TF expression/activity and
34
35 clinicopathological features in patients with pancreatic cancer and to explore the
36
37 prognostic value of TF as a marker for pancreatic cancer.
38
39
40
41
42
43

44 **Methods and analysis**

45 **Registration**

46
47
48 This protocol was registered with PROSPERO (International Prospective Register of
49
50 Systematic Reviews) (CRD42019133665)
51
52
53
54

55 **Eligibility criteria**

56 **Participants**

57
58
59
60

1
2
3
4 Patients with pancreatic cancer are eligible for the review. The diagnosis is
5
6 histologically confirmed. Surgery is performed by several surgeons in accordance
7
8 with the standard criteria for pancreatic cancer resection, but there are no restrictions
9
10 regarding the type of surgery. The resected specimens are histologically examined
11
12 according to the Union for International Cancer Control (UICC)
13
14 tumour-node-metastasis (TNM) classification. Patients are excluded if they are
15
16 unresectable, or have other malignancies, or receive preoperative therapy.
17
18
19
20
21
22
23

24 **Exposure**

25
26 The expression/activity of TF in tissue, plasma and MVs is the exposure variable of
27
28 this study. The TF is detected based on the resected specimens, plasma and MVs in
29
30 pancreatic cancer patients using the respective test methods. This review compares the
31
32 clinicopathological features and the prognosis between pancreatic cancer patients with
33
34 high and low level of TF expression or activity.
35
36
37
38
39
40
41

42 **Outcomes**

43
44 The study is included if it reports survival endpoints and provides the relationship
45
46 between TF and clinicopathological features, such as VTE, tumor embolus, primary
47
48 tumour size, clinical stage, and differentiation. The study should also provide
49
50 sufficient information to estimate the hazard ratio (HR).
51
52
53
54
55

56 **Studies**

57
58 Any prospective or retrospective published studies which evaluate the relationship
59
60

1
2
3
4 between TF and pancreatic cancer are included. There is no limitation regarding the
5
6 number of participants. Only studies published in English were included.
7
8
9

10 **Information sources**

11
12
13 We will search the Medline, Embase, and Cochrane Library from inception to Jan
14
15
16 2020.
17

18 **Search strategy**

19
20
21 Two reviewers search the Medline, EMBASE and Cochrane using a combination of
22
23
24 subject terms with free-text terms. The following search words are adopted for each
25
26
27 database: (pancreas or pancrea* or pancreas [MeSh]) and (carcinoma [MeSh] or
28
29
30 adenocarcinoma [MeSh] or carcinoma, ductal [MeSh] or neoplasms [MeSh] or
31
32
33 cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or
34
35
36 malig*) and (tissue factor or CD142 antigens or coagulation factor III or
37
38
39 thromboplastin [MeSh]). Reference lists of eligible studies and relevant review
40
41
42 articles are also hand-searched to identify any potentially eligible studies that are
43
44
45 recorded in the databases. We will also search in Google Scholar to identify any grey
46
47
48 literatures.
49

50 **Study records**

51 **Data management**

52
53
54 All study records are processed through EndNote X9, which can identify and remove
55
56
57 duplicates. All extracted data are stored in a Microsoft Excel spreadsheet.
58
59
60

Study selection and data collection process

Two reviewers independently screen first the titles and abstracts of all retrieved articles after removing duplicates, and then the full texts of the selected articles. Disagreements are resolved by face-to-face discussion, or in case of persistent disagreement, a third researcher will be consulted. The same reviewers extract the data of included studies based on a predefined data extraction form.

Data items

The data extracted include author, publication year, country, study design, number of participants, follow-up period, baseline and clinicopathological information of patients, survival outcomes, hazard ratio (HR), and 95% confidence interval (CI) related to TF expression. In addition, methods for statistical analysis, summary statistics, and items associated with a risk of bias are also summarized.

Risk of bias in individual studies

Two researchers will independently assess the quality of the each included study using the Newcastle-Ottawa Scale (NOS score).²⁹ Scores of the NOS are split into three aspects: object selection, inter-group comparability, and outcome measurement. It is generally considered that an article with a score 0–5 point(s) is of low quality, and the article with a score >6 is considered high-quality.

Data synthesis

All statistical tests are calculated with RevMan 5.3. The hazard ratio (HR) and 95%

1
2
3
4 CI of each study are used to assess the relationship between the expression of TF and
5
6 the prognosis. The association between TF expression and clinicopathological
7
8 features is calculated using the pooled odds ratio (OR) and 95% CI. The HR and 95%
9
10 CI of each study are directly extracted from the original published study. The method
11
12 from Tierney et al³⁰ is used to extract the data or conduct a variable transformation if
13
14 the studies do not directly provide HR and 95% CI. For example, some studies
15
16 provide only the survival curve. The HR and 95% CI of each study are finally
17
18 combined using the method of generic inverse variance in RevMan software, so the ln
19
20 (HR) and SEln (HR) will be calculated in advance based on the data extracted. The
21
22 level of statistical significance is set at the 5%. If a meta-analysis is not appropriate
23
24 because of small number of studies or concerns regarding substantial variability, the
25
26 result will only be reported qualitatively. The heterogeneity is assessed using the I²
27
28 statistic. We will utilize the fixed effect model when the effects are assumed to be
29
30 homogenous ($p > 0.05$, I² 50%) and the random effect model when they are
31
32 heterogeneous ($p < 0.05$, I² 50%). To explore the source of heterogeneity, subgroup
33
34 analysis is considered. Sensitivity analysis will also be conducted and will be focused
35
36 on studies with a low risk of bias.
37
38
39
40
41
42
43
44
45
46
47
48
49

50 **Meta-biases**

51
52 Reporting bias will be explored graphically by a funnel plot and statistically by the
53
54 Egger's test³¹ if 10 or more studies are available. $P < 0.05$ is considered to indicate
55
56 publication bias.
57
58
59
60

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation method is applied to assess the level of evidence obtained from this systematic review.³²

Patient and Public Involvement

No patient involved.

Discussion

Studies have shown that TF is closely related to the clinicopathological features and prognosis of pancreatic cancer.^{13,26,28} Nevertheless, no systematic review on the association of different types TF expression with pancreatic cancer patients have been published in English. Thus, we plan to conduct a systematic review and meta-analysis on this topic. We hope that the results of this review will provide researchers and clinicians with more convincing evidence on whether TF is a potential biomarker of thrombotic risk and prognostic factor, and thereby promote the development of individualized diagnosis and treatment of pancreatic cancer patients.

Funding

This study was supported by National Natural Science Foundation of China (No. 81670594, 81470791, 81376597), Gansu Basic Research Innovation Group Project (No. 1606RJIA328), Gansu Scientific Research of Health Services Project (No. GSWSKY2017-09), Talents Innovation and Entrepreneurship Program of Lanzhou City (No. 2017-RC-62), Talent Staff Fund of the Second Hospital of Lanzhou

1
2
3
4 University (No. ynyjrckyzx2015-1-01), Cuiying Scientific and Technological
5
6 Innovation Program of Lanzhou University Second Hospital (No. CY2017-ZD01,
7
8 CY2019-BJ09) and Fundamental Research Funds for the Central
9
10 Universities(lzujbky-2016-k16, lzujbky-2017-79).
11
12
13
14
15
16

17 **Competing interest**

18
19 None declared
20
21
22
23

24 **Authors' contribution**

25
26
27 HYL and HC conceived the idea and planned the entire methods to undertake it. HYL
28
29 and YY wrote the manuscript of this protocol. YY, QLS, XPC and PZ designed the
30
31 search strategy and planned the data extraction. DFW, PXT, BHG, XML, TZ, LX,
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
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

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-386.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921.
3. Chu LC, Goggins MG, Fishman EK. Diagnosis and Detection of Pancreatic Cancer. *Cancer J*. 2017;23(6):333-342.
4. Sproul EE. Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis. *American Journal of Cancer*. 1938;34.
5. Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. *Lancet Oncol*. 2004;5(11):655-663.
6. Unruh D, Sagin F, Adam M, et al. Levels of Alternatively Spliced Tissue Factor in the Plasma of Patients with Pancreatic Cancer May Help Predict Aggressive Tumor Phenotype. *Ann Surg Oncol*. 2015;22 Suppl 3:S1206-1211.
7. Davila M, Robles-Carrillo L, Unruh D, et al. Microparticle association and heterogeneity of tumor-derived tissue factor in plasma: is it important for coagulation activation? *J Thromb Haemost*. 2014;12(2):186-196.
8. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. *Thromb Res*. 2013;132(2):180-184.

- 1
2
3
4 9. Boone BA, Zenati MS, Rieser C, et al. Risk of Venous Thromboembolism for Patients with
5
6
7 Pancreatic Ductal Adenocarcinoma Undergoing Preoperative Chemotherapy Followed by Surgical
8
9
10 Resection. *Ann Surg Oncol*. 2019;26(5):1503-1511.
- 11
12 10. Mier-Hicks A, Raj M, Do RK, et al. Incidence, Management, and Implications of Visceral
13
14
15 Thrombosis in Pancreatic Ductal Adenocarcinoma. *Clin Colorectal Cancer*. 2018;17(2):121-128.
- 16
17 11. Nemerson Y. Tissue factor and hemostasis. *Blood*. 1988;71(1):1-8.
- 18
19 12. Haas SL, Jesnowski R, Steiner M, et al. Expression of tissue factor in pancreatic adenocarcinoma
20
21
22 is associated with activation of coagulation. *World J Gastroenterol*. 2006;12(30):4843-4849.
- 23
24 13. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis
25
26
27 in pancreatic cancer. *Clin Cancer Res*. 2007;13(10):2870-2875.
- 28
29 14. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous
30
31
32 thromboembolism in pancreatic cancer. *J Thromb Haemost*. 2008;6(11):1983-1985.
- 33
34 15. Wang JG, Geddings JE, Aleman MM, et al. Tumor-derived tissue factor activates coagulation and
35
36
37 enhances thrombosis in a mouse xenograft model of human pancreatic cancer.
38
39
40 *Blood*;119(23):5543-5552.
- 41
42 16. Tesselaar MET, ROMIJN FPHTM, LINDEN IKVD, PRINS FA, BERTINA RM, OSANTO S.
43
44
45 Microparticle-associated tissue factor activity: a link between cancer and thrombosis? *Journal of*
46
47
48 *Thrombosis & Haemostasis Jth*;5(3):520-527.
- 49
50 17. Thaler J, AY C, MACKMAN N, et al. Microparticle-associated tissue factor activity, venous
51
52
53 thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. *Journal of*
54
55
56 *Thrombosis & Haemostasis*;10(7):0-0.
- 57
58 18. Zwicker JI, Liebman HA, Neuberg D, et al. Tumor-Derived Tissue Factor-Bearing Microparticles
59
60

1
2
3
4 Are Associated With Venous Thromboembolic Events in Malignancy. *Clinical Cancer*
5
6
7 *Research*;15(22):6830-6840.

8
9 19. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor,
10
11 thromboembolism and survival in pancreaticobiliary cancers. *Thrombosis Research*;132(2):180-184.

12
13
14 20. Milsom CC, Yu JL, Mackman N, et al. Tissue factor regulation by epidermal growth factor
15
16
17 receptor and epithelial-to-mesenchymal transitions: effect on tumor initiation and angiogenesis. *Cancer*
18
19
20 *Res.* 2008;68(24):10068-10076.

21
22 21. Date K, Ettlai C, Maraveyas A. Tissue factor-bearing microparticles and inflammation: a
23
24
25 potential mechanism for the development of venous thromboembolism in cancer. *J Thromb Haemost.*
26
27
28 2017;15(12):2289-2299.

29
30 22. Hu C, Huang L, Gest C, et al. Opposite regulation by PI3K/Akt and MAPK/ERK pathways of
31
32
33 tissue factor expression, cell-associated procoagulant activity and invasiveness in MDA-MB-231 cells.
34
35
36 *J Hematol Oncol.* 2012;5:16.

37
38 23. Chanakira A, Westmark PR, Ong IM, Sheehan JP. Tissue factor-factor VIIa complex triggers
39
40
41 protease activated receptor 2-dependent growth factor release and migration in ovarian cancer. *Gynecol*
42
43
44 *Oncol.* 2017;145(1):167-175.

45
46 24. Mueller BM, Reisfeld RA, Edgington TS, Ruf W. Expression of tissue factor by melanoma cells
47
48
49 promotes efficient hematogenous metastasis. *Proc Natl Acad Sci U S A.* 1992;89(24):11832-11836.

50
51 25. Kataoka H, Uchino H, Asada Y, et al. Analysis of tissue factor and tissue factor pathway inhibitor
52
53
54 expression in human colorectal carcinoma cell lines and metastatic sublines to the liver. *Int J Cancer.*
55
56
57 1997;72(5):878-884.

58
59 26. Chen K, Li Z, Jiang P, et al. Co-expression of CD133, CD44v6 and human tissue factor is
60

1
2
3
4 associated with metastasis and poor prognosis in pancreatic carcinoma. *Oncol Rep.*
5
6 2014;32(2):755-763.
7

8
9 27. Kakkar AK, Lemoine NR, Scully MF, Tebbutt S, Williamson RCN. Tissue factor expression
10
11 correlates with histological grade in human pancreatic cancer. *British Journal of Surgery.*
12
13 1995;82(8):1101-1104.
14
15

16
17 28. Nitori N, Ino Y, Nakanishi Y, et al. Prognostic significance of tissue factor in pancreatic ductal
18
19 adenocarcinoma. *Clin Cancer Res.* 2005;11(7):2531-2539.
20
21

22
23 29. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of
24
25 nonrandomized studies in meta-analyses. *European journal of epidemiology.* 2010;25(9):603-605.
26
27

28
29 30. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating
30
31 summary time-to-event data into meta-analysis. *Trials.* 2007;8(1):16.
32
33

34
35 31. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for
36
37 publication bias in meta-analysis. *Biometrics.* 2000;56(2):455-463.
38
39

40
41 32. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about
42
43 prognosis: rating confidence in estimates of event rates in broad categories of patients. *bmj.*
44
45 2015;350:h870.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

Prognostic significance of tissue factor in patients with pancreatic cancer: a systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037431.R1
Article Type:	Protocol
Date Submitted by the Author:	11-May-2020
Complete List of Authors:	<p>Li, Haiyuan ; The Department of Tumor Surgery, Lanzhou University Second Hospital, ; The Second Clinical Medical College, Lanzhou University,</p> <p>Yu, Yang ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Shi, Qianling ; The First Clinical Medical College, Lanzhou University, The First Clinical Medical College of Lanzhou University</p> <p>Chen, Xueping ; Sleep Medicine Center, Gansu Provincial Hospital</p> <p>Zheng, Peng; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Wang, Dengfeng ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Tao, Pengxian ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Gu, Baohong ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Li, Xuemei ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Zhang, Tao; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Xiang, Lin ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Xi, Dayong ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Gao, Lei ; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Maswikiti Ewetse , Paul; The Department of Tumor Surgery, Lanzhou University Second Hospital; The Second Clinical Medical College, Lanzhou University,</p> <p>Chen, Hao; The Department of Tumor Surgery, Lanzhou University Second Hospital</p>

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

Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Oncology, Gastroenterology and hepatology, Patient-centred medicine
Keywords:	Gastrointestinal tumours < ONCOLOGY, Pancreatic disease < GASTROENTEROLOGY, Molecular biology < TROPICAL MEDICINE

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 **1 Prognostic significance of tissue factor in patients with**
5
6 **2 pancreatic cancer: a systematic review protocol**
7
8

9 Haiyuan Li^{1,2#}, Yang Yu^{1,2#}, Qianling Shi³, Xueping Chen⁴, Peng Zheng^{1,2}, Dengfeng
10
11 Wang^{1,2}, Pengxian Tao^{1,2}, Baohong Gu^{1,2}, Xuemei Li^{1,2}, Tao Zhang^{1,2}, Lin Xiang^{1,2},
12
13 Dayong Xi^{1,2}, Lei Gao^{1,2}, Paul Maswikiti Ewetse^{1,2}, Hao Chen^{1*}
14
15

16
17 1. The Department of Tumour Surgery, Lanzhou University Second Hospital,
18
19 Lanzhou 730030, China;
20
21

22 2. The Second Clinical Medical College, Lanzhou University, Lanzhou 730030,
23
24 China;
25
26

27 3. The First Clinical Medical College, Lanzhou University, Lanzhou 730000, China;
28
29

30 4. Sleep Medicine Center, Gansu Provincial Hospital, Lanzhou 730000, China;
31
32

33 # Haiyuan Li and Yang Yu contributed equally; Haiyuan Li and Yang Yu are joint
34
35 first authors
36
37

38 * Corresponding Author: Hao Chen, MD, PhD, the Department of Tumor Surgery,
39
40 Lanzhou University Second Hospital, Lanzhou 730030, China;
41
42 Tel: +86-15009467790; E-mail: chenhaodrs@163.com.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

23

Abstract

Introduction: Pancreatic cancer is a highly aggressive digestive system tumour with poor prognosis. Venous thromboembolism (VTE) is a well-known complication of pancreatic cancer, and tissue factor (TF) contributes to the generation of a hypercoagulable state and thrombotic disease in pancreatic cancer. Several studies showed that an elevated TF level was related to the development of VTE and influenced the survival of pancreatic cancer patients. Thus, we wish to conduct a systematic review of literature to clarify the prognostic significance of TF in pancreatic cancer.

Methods and analysis: Studies comparing the circulating microparticle-associated MP TF level between pancreatic cancer patients with and without VTE will be included to evaluate the roles of TF in VTE development. Studies comparing the survival data between patients with high TF expression and low TF expression will also be included to explore the association of TF expression with patient survival. The outcomes are plasma MP TF level and survival endpoints (overall and progression-free survival), respectively. Primary studies of any type published in English will be included. Two reviewers will search Medline, EMBASE and Cochrane databases from inception to June 2020, retrieve relevant studies, and independently select the literatures and extract data from the included studies. The quality of each included study will be assessed by the Newcastle-Ottawa Scale (NOS score). The HR and 95% CI of each study will be pooled for survival outcome, and

1
2
3
4 45 the standardized mean difference with 95% confidence intervals will be used for
5
6 46 continuous outcomes. If meta-analysis is inappropriate, the result will only be
7
8
9 47 reported qualitatively. Subgroup and sensitivity analyses will be considered to
10
11 48 identify sources of heterogeneity. The Grades of Recommendation, Assessment,
12
13
14 49 Development and Evaluation method will be applied to assess the level of evidence of
15
16
17 50 this systematic review.

18
19
20 51 **Ethics and dissemination:** There are no concerning ethical issues. The results will be
21
22
23 52 published.

24
25
26 53 **PROSPERO registration number:** CRD42019133665

27
28
29
30 54 **Key words:** pancreatic cancer; tissue factor; microvesicle; prognosis; systematic
31
32
33 55 review

34
35
36 56

37
38
39
40
41 57

42
43
44
45
46 58

47
48
49
50
51 59

52
53
54
55 60

56
57
58
59
60 61

1
2
3
4 62
5
6
7

8 **63 Strengths and limitations of this study**

- 9
10
11
12 64 ● A detailed and completed search strategy will be used to collect potentially
13
14 65 eligible studies.
15
16
17
18 66 ● Sources of heterogeneity will be carefully considered, and multiple solutions will
19
20
21 67 be considered.
22
23
24
25 68 ● The included literature will be limited to studies published in English.
26
27
28
29 69 ● Heterogeneity among the TF measuring methods may exist.
30
31
32
33
34 70 ● The findings are potentially subject to publication bias.
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

72 INTRODUCTION

73 Pancreatic cancer is a type of highly aggressive digestive system tumour with poor
74 prognosis.¹ It is estimated that pancreatic cancer will be the second largest
75 cancer-related cause of death in the United States by 2030.² Pancreatic cancer has
76 insidious onset, rapid progression, low rate of early diagnosis and radical resection.³
77 Most of the patients already have advanced or distant metastasis at the first diagnosis.
78 Despite recent advances in surgical techniques as well as chemotherapy and radiation
79 therapy, pancreatic cancer patients still has a dismal 5-year survival rate.³

80 Venous thromboembolism (VTE), associated with the generation of an intrinsic
81 hypercoagulable state, is a well-known complication of malignant tumour. Sproul first
82 discovered that pancreatic cancer patients are prone to VTE in 1938.⁴ Subsequently,
83 the reported incidence of VTE in pancreatic cancer patients ranges from 17% to 57%.⁵
84 Several factors and pathological mechanisms contribute to the generation of a
85 hypercoagulable state and VTE in pancreatic cancer.⁶ Of prime importance is tissue
86 factor (TF), a single chain transmembrane-receptor glycoprotein with a molecular
87 weight of approximately 47 kDa, which initiates the extrinsic pathway of
88 coagulation.⁷ In recent years, it was reported that TF is expressed in many malignant
89 tumour tissues, including pancreatic cancer, leading to increased blood coagulability
90 and a high risk of VTE.^{8,9} In addition, high level of the plasma TF was detected in
91 patients with pancreatic cancer.¹⁰ Pancreatic cancer cells express TF and release
92 microparticle-associated TF (MP TF) into blood.^{11,12}

1
2
3
4 93 Several studies have found that thrombosis and diffuse intravascular coagulation are
5
6 94 associated with poor prognosis in patients with pancreatic cancer.¹³⁻¹⁷ Meanwhile,
7
8
9 95 substantial evidence indicated that TF is of predictive value in the biologic features of
10
11
12 96 tumours and the survival of patients. It was found that TF plays an important role in
13
14 97 promoting angiogenesis,¹⁸ inflammatory reaction,¹⁹ tumour invasion,²⁰ and
15
16
17 98 metastasis.²¹ Compared with tumour cells with a higher degree of differentiation in
18
19
20 99 pancreatic cancer, tumour cells with lower degree of differentiation seem to have
21
22 100 higher TF expression and associated with decreased overall survival.^{9 22-24} Therefore,
23
24
25 101 we hypothesize that the elevated circulating TF level may contribute to the
26
27
28 102 development of VTE, and TF expression in tumour tissue may be associated with
29
30
31 103 poor prognosis in patients with pancreatic cancer. To test this hypothesis, we plan to
32
33
34 104 undertake a systematic review of previous studies assessing the association between
35
36
37 105 TF and pancreatic cancer.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

108 **METHODS AND ANALYSIS**

109 **Objective of the review**

110 This review aims to clarify the prognostic significance of TF in pancreatic cancer.
111 This review contains two sections. First, we will evaluate the association between
112 circulating MP TF level and VTE. Second, we will explore the impact of TF
113 expression on patients' survival.

114 **Registration**

1
2
3
4 115 This protocol was registered with PROSPERO (International Prospective Register of
5
6 116 Systematic Reviews) (CRD42019133665)
7
8
9

10
11 117 **Eligibility criteria**
12

13
14 118 **Participants**
15

16 119 Patients with pancreatic cancer are eligible for the review. The diagnosis will be
17
18 120 pathologically confirmed. There are no limitations on the stages, grades, and types of
19
20 121 pancreatic cancer. Patients will be excluded if they have primary haematological
21
22 122 system disease or other malignancies or receive transfusion therapy during the study
23
24 123 course.
25
26
27
28
29

30
31 124 **Exposure**
32

33
34 125 To evaluate the association between circulating MP TF level and VTE, pancreatic
35
36 126 cancer patients will be divided into two groups based on the presence or absence of
37
38 127 VTE. The MP TF level will be compared between two groups. There are no strict
39
40 128 restrictions on the diagnosis approach for VTE, and diagnosis by clinical assessment,
41
42 129 imaging, and D-dimer testing are all acceptable. To explore the impact of TF
43
44 130 expression on patients' survival, patients will be defined as groups of high TF
45
46 131 expression or low TF expression. Survival between different TF-expression groups
47
48 132 will be compared. The TF will be detected using immunohistochemistry analysis of
49
50 133 the tissue specimens.
51
52
53
54
55
56
57
58

59 134 **Outcomes**
60

1
2
3
4 135 According to different purpose, studies are eligible if they: a) individually report the
5
6 136 level of circulating MP TF of patients with VTE and without VTE; or b) report
7
8
9 137 survival endpoints (including overall survival [OS] and progression free survival
10
11
12 138 [PFS]) of patients in the groups of high TF expression and low TF expression. In
13
14 139 addition, the level of circulating MP TF is determined by flowcytometry or activity
15
16
17 140 tests. The studies reporting survival data should also provide sufficient information to
18
19
20 141 estimate the hazard ratio (HR).

21 22 23 24 142 **Studies**

25
26 143 Any prospective or retrospective published studies which evaluate the relationship
27
28
29 144 between TF and pancreatic cancer are included. There is no limitation regarding the
30
31
32 145 number of participants. Only studies published in English were included.

33 34 35 36 146 **Information sources**

37
38
39 147 We will search the Medline, Embase, and Cochrane Library from inception to June
40
41
42 148 2020.

43 44 45 46 149 **Search strategy**

47
48
49 150 Two reviewers search the Medline, EMBASE and Cochrane using a combination of
50
51
52 151 subject terms with free-text terms. The following search words are adopted for each
53
54
55 152 database: (pancreas or pancrea* or pancreas [MeSh]) and (carcinoma [MeSh] or
56
57
58 153 adenocarcinoma [MeSh] or carcinoma, ductal [MeSh] or neoplasms [MeSh] or
59
60 154 cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or

155 malig*) and (tissue factor or TF expression or microparticle or TF-positive MP or
156 TF+MP or TF-bearing MP or MP-associated or MP TF or microvesicle or TF-positive
157 MV or TF+MV or TF-bearing MV or MV-associated or MV TF or CD142 antigens
158 or coagulation factor III or thromboplastin [MeSh]). An example of the Medline
159 search strategy is provided in the supplementary file. Reference lists of eligible
160 studies and relevant review articles will also be hand-searched to identify any
161 potentially eligible studies that are recorded in the databases. We will also search
162 Google Scholar to identify any grey literature.

163 **Study records**

164 **Data management**

165 All study records will be processed through EndNote X9, which can identify and
166 remove duplicates. All extracted data will be stored in a Microsoft Excel spreadsheet.

167 **Study selection and data collection process**

168 Two reviewers will independently screen first the titles and abstracts of all retrieved
169 articles after removing duplicates, and then the full texts of the selected articles.

170 Disagreements will be resolved by face-to-face discussion, or in case of persistent
171 disagreement, a third researcher will be consulted. The same reviewers will extract the
172 data of included studies based on a predefined data extraction form.

173 **Data items**

174 The data extracted will include author, publication year, country, study design,

1
2
3
4 175 number of participants, follow-up period, baseline and clinicopathological
5
6 176 information of patients, methods used to measure TF, circulating MP TF level related
7
8
9 177 to VTE presence, OS and PFS (hazard ratio [HR], 95% confidence interval [CI])
10
11 178 related to TF expression. In addition, methods for statistical analysis, summary
12
13
14 179 statistics, and items associated with a risk of bias will also be summarized.
15
16
17
18

19 180 **Risk of bias in individual studies**

20
21 181 Two researchers will independently assess the quality of the each included study
22
23
24 182 using the Newcastle-Ottawa Scale (NOS score).²⁵ Scores of the NOS are split into
25
26
27 183 three aspects: object selection, inter-group comparability, and outcome measurement.
28
29 184 It is generally considered that an article with a score 0–5 point(s) is of low quality,
30
31
32 185 and an article with a score >6 is of high quality.
33
34
35

36 186 **Data synthesis**

37
38
39 187 All statistical tests are calculated with RevMan 5.3. The pooled standardized mean
40
41
42 188 difference (SMD) with 95% confidence intervals (CI) will be used to compare the
43
44
45 189 circulating MP TF level in VTE group and non-VTE group because the MP TF level
46
47
48 190 reported in studies may have inconsistent units. The hazard ratio (HR) and 95% CI of
49
50
51 191 each study will be used to evaluate the survival difference between groups with
52
53
54 192 different strength of TF expression. The case number and mean and standard
55
56
57 193 deviation (SD) of MP TF level are collected from included studies. The HR and 95%
58
59
60 194 CI will first be extracted from the original published study. The method from Tierney
195 et al²⁶ is used to extract the data or conduct a variable transformation if the studies do

1
2
3
4 196 not directly provide HR and 95% CI. For example, some studies provide only the
5
6 197 survival curve. The HR and 95% CI of each study are finally combined using the
7
8
9 198 method of generic inverse variance in RevMan software; therefore, the ln (HR) and
10
11 199 SEln (HR) will be calculated in advance based on the data extracted. The level of
12
13
14 200 statistical significance is set at 5%. If a meta-analysis is not appropriate because of
15
16
17 201 small number of studies or concerns regarding substantial variability, the result will
18
19 202 only be reported qualitatively. The heterogeneity will be assessed using the I^2 statistic.
20
21
22 203 We will utilize the fixed-effect model when the effects are assumed to be
23
24 204 homogenous ($p > 0.05$, $I^2 \leq 50\%$) and the random effect model when they are
25
26
27 205 heterogeneous ($p < 0.05$, $I^2 \geq 50\%$). To explore the source of heterogeneity, subgroup
28
29 206 analysis will be performed according to the same regions, study design, types of
30
31
32 207 tumour, and methods of measuring MP TF level. Sensitivity analysis will also be
33
34
35 208 conducted and focused on studies with a low risk of bias.
36
37
38
39

40 209 **Meta-biases**

41
42 210 Reporting bias will be explored graphically by a funnel plot and statistically by the
43
44 211 Egger's test²⁷ if 10 or more studies are available. $P < 0.05$ is considered to indicate
45
46
47 212 publication bias.
48
49
50
51

52 213 **Confidence in cumulative evidence**

53
54 214 The Grades of Recommendation, Assessment, Development and Evaluation method is
55
56
57 215 applied to assess the level of evidence obtained from this systematic review.²⁸
58
59
60

216 **Patient and Public Involvement**

217 No patients are involved.

218 **Discussion**

219 Studies have shown that TF is closely related to the VTE development and survival of
220 patients with pancreatic cancer.^{9 22 24 29} Nevertheless, no systematic review regarding
221 the predictive value of plasma MP TF level and tissue TF expression strength on
222 pancreatic cancer patients have been published in English. Thus, we plan to conduct a
223 systematic review and meta-analysis on this topic. We hope that the results of this
224 review will provide researchers and clinicians with more convincing evidence on
225 whether TF is a potential biomarker of thrombotic risk and prognostic factor, and
226 thereby promote the development of individualized diagnosis and treatment of
227 pancreatic cancer patients. This article provides a detailed and complete description of
228 the methodology of the review; however, some limitations may become apparent
229 during the course of this review. First, only studies published in English will be
230 included. The exclusion of non-English articles will negatively influence the
231 representativeness of the results to a global population. Second, the inclusion criteria
232 regarding the methods used to measure TF are not strict. Heterogeneity in the
233 measuring methods will reduce the accuracy of results. Third, as with all systematic
234 reviews and meta-analyses, there are potential risks of publication bias. Overall,
235 regardless of the potential methodological deficiencies, we believe that each aspect of
236 the review has been addressed and the protocol will help ensure study's integrity and

237 transparency.

238

239 **Ethics and dissemination**

240 This proposed systematic review and meta-analysis is based on published data, and no

241 information of an individual patient will be accessed and discussed in this review.

242 Therefore, ethical approval is not required. The results of this review will be sought

243 for publication in a peer-reviewed journal and relevant conference proceedings. Data

244 generated during the research will be available from the corresponding author on

245 reasonable request.

246

248 References

- 249 1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality
250 worldwide: sources, methods and major patterns in GLOBOCAN 2012.
251 *International journal of cancer* 2015;136:E359-86. doi: 10.1002/ijc.29210
- 252 2. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to
253 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the
254 United States. *Cancer research* 2014;74:2913-21. doi:
255 10.1158/0008-5472.can-14-0155
- 256 3. Chu LC, Goggins MG, Fishman EK. Diagnosis and Detection of Pancreatic
257 Cancer. *Cancer journal (Sudbury, Mass)* 2017;23:333-42. doi:
258 10.1097/ppo.0000000000000290
- 259 4. Sproul EE. Carcinoma and Venous Thrombosis: The Frequency of Association of
260 Carcinoma in the Body or Tail of the Pancreas with Multiple Venous
261 Thrombosis. *American Journal of Cancer* 1938;34
- 262 5. Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. *The Lancet*
263 *Oncology* 2004;5:655-63. doi: 10.1016/s1470-2045(04)01606-7
- 264 6. Campello E, Ilich A, Simioni P, et al. The relationship between pancreatic cancer
265 and hypercoagulability: a comprehensive review on epidemiological and
266 biological issues. *Br J Cancer* 2019;121:359-71. doi:
267 10.1038/s41416-019-0510-x
- 268 7. Nemerson Y. Tissue factor and hemostasis. *Blood* 1988;71:1-8.
- 269 8. Haas SL, Jesnowski R, Steiner M, et al. Expression of tissue factor in pancreatic

-
- 1
2
3
4 270 adenocarcinoma is associated with activation of coagulation. *World J*
5
6 271 *Gastroenterol* 2006;12:4843-9.
7
8
9 272 9. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis,
10
11 273 and thrombosis in pancreatic cancer. *Clinical cancer research : an official*
12
13 274 *journal of the American Association for Cancer Research* 2007;13:2870-5.
14
15 275 doi: 10.1158/1078-0432.ccr-06-2351
16
17
18
19 276 10. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be
20
21 277 predictive of venous thromboembolism in pancreatic cancer. *Journal of*
22
23 278 *thrombosis and haemostasis : JTH* 2008;6:1983-5. doi:
24
25 279 10.1111/j.1538-7836.2008.03156.x
26
27
28
29 30 11. Wang JG, Geddings JE, Aleman MM, et al. Tumor-derived tissue factor activates
31
32 301 coagulation and enhances thrombosis in a mouse xenograft model of human
33
34 302 pancreatic cancer. *Blood*;119:5543-52.
35
36
37 303 12. Tesselaar MET, ROMIJN FPHTM, LINDEN IKVD, et al.
38
39 304 Microparticle-associated tissue factor activity: a link between cancer and
40
41 305 thrombosis? *Journal of Thrombosis & Haemostasis Jth*;5:520-27.
42
43
44 306 13. Unruh D, Sagin F, Adam M, et al. Levels of Alternatively Spliced Tissue Factor in
45
46 307 the Plasma of Patients with Pancreatic Cancer May Help Predict Aggressive
47
48 308 Tumor Phenotype. *Annals of surgical oncology* 2015;22 Suppl 3:S1206-11.
49
50 309 doi: 10.1245/s10434-015-4592-2
51
52
53
54 310 14. Davila M, Robles-Carrillo L, Unruh D, et al. Microparticle association and
55
56 311 heterogeneity of tumor-derived tissue factor in plasma: is it important for
57
58
59
60

-
- 1
2
3
4 292 coagulation activation? *Journal of thrombosis and haemostasis : JTH*
5
6 293 2014;12:186-96. doi: 10.1111/jth.12475
7
8
9 294 15. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor,
10
11 295 thromboembolism and survival in pancreaticobiliary cancers. *Thrombosis*
12
13 296 *research* 2013;132:180-4. doi: 10.1016/j.thromres.2013.06.026
14
15
16
17 297 16. Boone BA, Zenati MS, Rieser C, et al. Risk of Venous Thromboembolism for
18
19 298 Patients with Pancreatic Ductal Adenocarcinoma Undergoing Preoperative
20
21 299 Chemotherapy Followed by Surgical Resection. *Annals of surgical oncology*
22
23 300 2019;26:1503-11. doi: 10.1245/s10434-018-07148-z
24
25
26
27 301 17. Mier-Hicks A, Raj M, Do RK, et al. Incidence, Management, and Implications of
28
29 302 Visceral Thrombosis in Pancreatic Ductal Adenocarcinoma. *Clinical*
30
31 303 *colorectal cancer* 2018;17:121-28. doi: 10.1016/j.clcc.2018.01.008
32
33
34
35 304 18. Milsom CC, Yu JL, Mackman N, et al. Tissue factor regulation by epidermal
36
37 305 growth factor receptor and epithelial-to-mesenchymal transitions: effect on
38
39 306 tumor initiation and angiogenesis. *Cancer research* 2008;68:10068-76. doi:
40
41 307 10.1158/0008-5472.can-08-2067
42
43
44
45 308 19. Date K, Ettelaie C, Maraveyas A. Tissue factor-bearing microparticles and
46
47 309 inflammation: a potential mechanism for the development of venous
48
49 310 thromboembolism in cancer. *Journal of thrombosis and haemostasis : JTH*
50
51 311 2017;15:2289-99. doi: 10.1111/jth.13871
52
53
54
55
56 312 20. Hu C, Huang L, Gest C, et al. Opposite regulation by PI3K/Akt and MAPK/ERK
57
58 313 pathways of tissue factor expression, cell-associated procoagulant activity and
59
60

-
- 1
2
3
4 314 invasiveness in MDA-MB-231 cells. *Journal of hematology & oncology*
5
6 315 2012;5:16. doi: 10.1186/1756-8722-5-16
7
8
9 316 21. Chanakira A, Westmark PR, Ong IM, et al. Tissue factor-factor VIIa complex
10
11 317 triggers protease activated receptor 2-dependent growth factor release and
12
13 318 migration in ovarian cancer. *Gynecologic oncology* 2017;145:167-75. doi:
14
15 319 10.1016/j.ygyno.2017.01.022
16
17
18 320 22. Chen K, Li Z, Jiang P, et al. Co-expression of CD133, CD44v6 and human tissue
19
20 321 factor is associated with metastasis and poor prognosis in pancreatic
21
22 322 carcinoma. *Oncology reports* 2014;32:755-63. doi: 10.3892/or.2014.3245
23
24
25 323 23. Kakkar AK, Lemoine NR, Scully MF, et al. Tissue factor expression correlates
26
27 324 with histological grade in human pancreatic cancer. *British Journal of Surgery*
28
29 325 1995;82:1101-04.
30
31
32 326 24. Nitori N, Ino Y, Nakanishi Y, et al. Prognostic significance of tissue factor in
33
34 327 pancreatic ductal adenocarcinoma. *Clinical cancer research : an official*
35
36 328 *journal of the American Association for Cancer Research* 2005;11:2531-9.
37
38 329 doi: 10.1158/1078-0432.ccr-04-0866
39
40
41 330 25. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of
42
43 331 the quality of nonrandomized studies in meta-analyses. *European journal of*
44
45 332 *epidemiology* 2010;25:603-05.
46
47
48 333 26. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating
49
50 334 summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
51
52
53 335 27. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing
54
55
56
57
58
59
60

336 and adjusting for publication bias in meta-analysis. *Biometrics*
337 2000;56:455-63.

338 28. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of
339 evidence about prognosis: rating confidence in estimates of event rates in
340 broad categories of patients. *bmj* 2015;350:h870.

341 29. Geddings JE, Mackman N. Tumor-derived tissue factor-positive microparticles
342 and venous thrombosis in cancer patients. *Blood* 2013;122:1873-80. doi:
343 10.1182/blood-2013-04-460139

346 **Authors' contribution**

347 HYL and HC conceived the idea and planned the entire method of undertaking this
348 study. HYL and YY wrote the protocol. YY, QLS, XPC and PZ designed the search
349 strategy and planned the data extraction. DFW, PXT, BHG, XML, TZ, LX, DYX, LG
350 and MEP made contributions in conceiving this research project. All authors revised
351 and approved the final version of the manuscript.

353 **Funding**

354 This work was supported by National Natural Science Foundation of China (No.
355 81670594, 81470791, 81376597), Gansu Basic Research Innovation Group Project
356 (No. 1606RJIA328), Gansu Scientific Research of Health Services Project (No.
357 GSWSKY2017-09), Talents Innovation and Entrepreneurship Program of Lanzhou

1
2
3
4 358 City (No. 2017-RC-62), Talent Staff Fund of the Second Hospital of Lanzhou
5
6 359 University (No. ynyjrckyzx2015-1-01), Cuiying Scientific and Technological
7
8
9 360 Innovation Program of Lanzhou University Second Hospital (No. CY2017-ZD01,
10
11 361 CY2019-BJ09), Fundamental Research Funds for the Central Universities (No.
12
13 362 lzujbky-2016-k16, lzujbky-2017-79) and Cuiying Scientific Training Program for
14
15 363 Undergraduates of Lanzhou University Second Hospital (No. 2018-12).
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

364

365 **Competing interest**

366 None declared

367

368 **Word count**

369 1782

The search strategy in Medline

#1	pancreas [MeSh]
#2	pancreas [Title/Abstract]
#3	pancrea* [Title/Abstract]
#4	#1-3 or
#5	carcinoma [MeSh]
#6	adenocarcinoma [MeSh]
#7	carcinoma, ductal [MeSh]
#8	neoplasms [MeSh]
#9	cancer* [Title/Abstract]
#10	carcin* [Title/Abstract]
#11	neoplas* [Title/Abstract]
#12	tumo* [Title/Abstract]
#13	cyst* [Title/Abstract]
#14	growth* [Title/Abstract]
#15	adenocarcin* [Title/Abstract]
#16	malig* [Title/Abstract]
#17	#5-16 or
#18	thromboplastin [MeSh]
#19	tissue factor [Title/Abstract]
#20	TF expression [Title/Abstract]
#21	TF-positive microparticle [Title/Abstract]
#22	TF-positive MP [Title/Abstract]
#23	TF+MP [Title/Abstract]
#24	TF-bearing microparticle [Title/Abstract]
#25	TF-bearing MP [Title/Abstract]
#26	microparticle-associated [Title/Abstract]
#27	MP-associated [Title/Abstract]
#28	MP TF [Title/Abstract]
#29	TF-positive microvesicle [Title/Abstract]
#30	TF-positive MV [Title/Abstract]
#31	TF+MV [Title/Abstract]
#32	TF-bearing microvesicle [Title/Abstract]
#33	TF-bearing MV [Title/Abstract]
#34	microvesicle-associated [Title/Abstract]
#35	MV-associated [Title/Abstract]
#36	MV TF [Title/Abstract]
#37	CD142 antigens [Title/Abstract]
#38	coagulation factor III [Title/Abstract]
#39	#18-38
#40	#4 and #17 and #39

PRISMA-P 2015 Checklist

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.

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not Applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3, line 53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, line 3-16
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 18, line 346-351
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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not Applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 18-19, line 353-363
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 18-19, line 353-363
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 18-19, line 353-363
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5-6, line 72-105
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, line 109-113
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 7-8, line 117-145
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, line 146-148
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8-9, line 149-162
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, line 164-166
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, line 167-172
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, line 167-172
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9-10, line 173-179
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 7-8, line 134-141
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, line 180-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10-11, line 186-208
	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 (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10-11, line 186-208
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10-11, line 186-208
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10-11, line 186-208
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 11, line 209-212
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 11, line 213-215