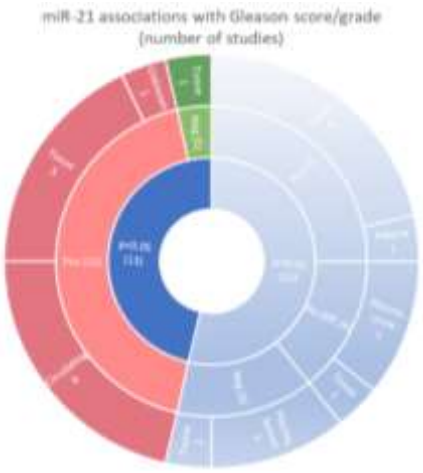
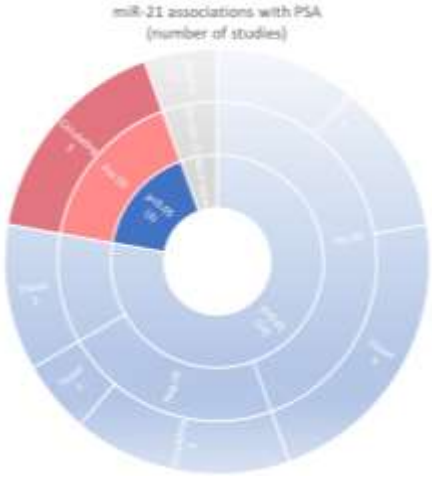
SUPPLEMENTARY FIGURES

a



b

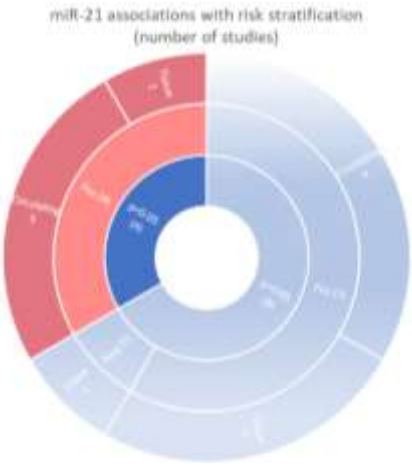
c



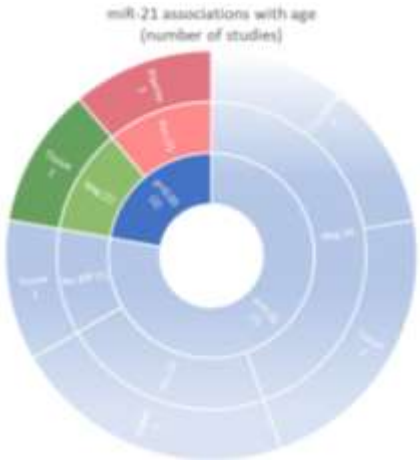
d

e

f



g



SF 1: Associations of miR-21 expression with clinicopathological measurements. (a) Gleason score/grade, (b) Stage, (c) PSA, (d) Recurrence, (e) Metastasis, (f) Risk stratification and (g) Age at diagnosis

ST 1: Search strategies in electronic databases

Medline (Ovid)

1. exp MicroRNAs/
2. (microRNA or miRNA or microRNA-21 or microRNA21 or miRNA-21 or miRNA21 or miR-21 or miR21)
3. exp Prostatic Neoplasms/
4. (prostat* cancer* or prostat* carcinoma* or prostat* tumo?r* or prostat* neoplasm* or prostat* adenocarcinoma* or PRAD)
5. exp Biomarkers/
6. exp Prognosis/
7. exp Survival Analysis/
8. (biomarker* or marker* or prognos* or survival)
9. 1 or 2
10. 3 or 4
11. 5 or 6 or 7 or 8
12. 9 and 10 and 11
13. limit 12 to yr="2010 -Current"
14. limit 13 to english language
15. limit 14 to (case reports or editorial or english abstract or letter or meta analysis or "review" or "systematic review")
16. 14 not 15

EMBASE

1. exp microRNA 21/
2. exp microRNA/
3. (microRNA or miRNA or microRNA-21 or microRNA21 or miRNA-21 or miRNA21 or miR-21 or miR21)
4. 1 or 3
5. exp prostate cancer/
6. (prostat* cancer* or prostat* carcinoma* or prostat* tumo?r* or prostat* neoplasm* or prostat* adenocarcinoma* or PRAD)
7. 5 or 6
8. exp prognosis/
9. exp biological marker/
10. exp survival/ or exp survival analysis/
11. (biomarker* or marker* or prognos* or survival)
12. 8 or 9 or 10 or 11
13. 4 and 7
14. 12 and 13
15. limit 14 to yr="2010 -Current"
16. limit 15 to english language
17. limit 16 to (meta analysis or "systematic review")
18. limit 16 to (books or chapter or conference abstract or editorial or letter or "review" or short survey)
19. 17 or 18
20. 16 not 19

Web of Science (Core Collection)

1. TOPIC: ("microRNA-21" OR "microRNA21" OR "miRNA-21" OR "miRNA21" OR "miR-21" OR "miR21" OR microRNA OR miRNA)
2. TOPIC: ("prostat* cancer*" or "prostat* carcinoma*" or "prostat* tumo?r*" or "prostat* neoplasm*" or "prostat* adenocarcinoma*" or PRAD)
3. TOPIC: (biomarker* or marker* or prognos* or survival)
4. #3 AND #2 AND #1 Refined by: [excluding] PUBLICATION YEARS: (2008 OR 2007 OR 2006 OR 2009) AND LANGUAGES: (ENGLISH) AND [excluding] DOCUMENT TYPES: (EDITORIAL MATERIAL OR LETTER OR REVIEW OR PROCEEDINGS PAPER OR RETRACTED PUBLICATION OR RETRACTION OR MEETING ABSTRACT OR BOOK CHAPTER)

Scopus

(TITLE-ABS-KEY (biomarker* OR marker* OR prognos* OR survival)) AND ((TITLE-ABS-KEY ("microRNA-21" OR "microRNA21" OR "miRNA-21" OR "miRNA21" OR "miR-21" OR "miR21" OR "circulating microRNA*")) AND (TITLE-ABS-KEY ("prostat* cancer*" OR "prostat* carcinoma*" OR "prostat* tumo?r*" OR "prostat* neoplasm*" OR "prostat* adenocarcinoma*" OR prad))) AND (EXCLUDE (PUBYEAR , 2009) OR EXCLUDE (PUBYEAR , 2008)) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "no")) AND (LIMIT-TO (DOCTYPE , "ar"))

Cochrane Library

microRNA-21 or microRNA21 or miRNA-21 or miRNA21 or miR-21 or miR21 or microRNA or miRNA or miR in All Text AND prostate or prostatic in Title Abstract Keyword AND cancer or carcinoma or tumour or tumor or neoplasm or adenocarcinoma or PRAD in Title Abstract Keyword AND biomarker or marker or prognostic or prognosis or survival in Title Abstract Keyword

ST 2: Data items included in Covidence data extraction form (Adapted from CHARMS-PF checklist [22])

General information
Study ID
Title
Lead author and contact details
Country in which the study conducted
Study funding sources
Possible conflicts of interest for study authors
Notes
Source of data
Source of data (e.g., cohort, case control, randomised trial or registry data)
Participants
Participant eligibility and recruitment method
Participant description
Details of treatments received (if relevant)
Study dates
Outcomes to be predicted
Definition and method for measurement of outcomes
Was the same outcome definition (and method for measurement) used in all participants?
Types of outcomes
Were the outcomes assessed without knowledge of the candidate prognostic factors (i.e., blinded)?
Were candidate prognostic factors part of the outcome?
Time of outcome occurrence or summary of duration of follow-up
Prognostic factors (index and comparator)
Number and type of prognostic factors
Definition and method for measurement of prognostic factors
Timing of prognostic factor measurement
Were prognostic factors assessed blinded for outcome, and for each other (if relevant)?
Handling of prognostic factors in the analysis
Sample size
Was a sample size calculation conducted and, if so, how?
Number of participants and number of outcomes or events
Number of outcomes or events in relation to the number of candidate prognostic factors (events per variable)
Missing data
Number of participants with any missing value
Number of participants with missing data for miR-21 expression
Details of attrition (loss to follow-up) and, for time-to-event outcomes, number of censored observations
Handling of missing data
Analysis (N/A for studies excluded from meta-analysis)
Modelling method
How modelling assumptions were checked; the method for assessing non-proportional hazards
Method for selection of prognostic factors for inclusion in multivariable modelling
Method for selection or exclusion of prognostic factors during multivariable modelling, and criteria used for any selection or exclusion
Method of handling each continuous prognostic factor, including values of any cut points used and their justification
Results of studies included in meta-analysis
Unadjusted and adjusted prognostic effect estimates for miR-21 expression, the corresponding 95% confidence interval with p-value.
For the extracted adjusted prognostic effect estimate of interest, the set of adjustment factors used
Results of studies excluded from meta-analysis
Prognostic factors or stratification used for association analysis
Type of association analysis and estimates with p-value
Interpretation and discussion
Interpretation of presented results
Comparison with other studies, discussion of generalisability, strengths and limitations

ST 3: Records of authors contacted (12 studies)

Study ID	Author contacted	Response	Additional data
Bryant2012 [36]	Freddie Hamdy <freddie.hamdy@nds.ox.ac.uk> Richard Bryant <richard.bryant@nds.ox.ac.uk>	Yes	miR-21 raw data excel file including 78 PCa patients
Fendler2011 [40]	Klaus Jung <klaus.jung@charite.de>	Yes	No (Communication stopped without useful data)
Huang2015a [46]	Liang Wang <liwang@mcw.edu>	No	
Kelly2015 [52]	Brian Kelly <drbriankelly@hotmail.com>	Yes	No (Communication stopped without useful data)
Leite2013 [59]	Katia Ramos Moreira Leite Updated: <katiaramos@usp.br>	Yes	Clarification on results reported
Leite2015 [60]			Details of multivariate analysis
Lin2014 [64]	Hui-Ming Lin <h.lin@garvan.org.au>	Yes	Clarification on analysis method
Lin2017 [65]			Results of univariate & multivariate analyses
McDonald2019 [67]	Alicia McDonald <amcdonald3@phs.psu.edu>	Yes	No (miR-21 measured but not analysed because it did not meet criteria)
Mortensen2014 [69]	Lars Dyrskjøt Andersen <lars@clin.au.dk>	Yes	Raw unanalysed data
Schubert2013 [76]	Maria Schubert <schubert_m@klinik.uni-wuerzburg.de> Burkhard Kneitz <kneitz_b@klinik.uni-wuerzburg.de>	No	
Stuopelyte2016 [81]	Sonata Jarmalaite <sonata.jarmalaite@gf.vu.lt> <sonata.jarmalaite@nvi.lt>	No	

ST 4: QUIPS (Quality in Prognostic Factor Studies) risk of bias classification tool [26]

	QUIPS domains		
Signalling items	**1. Study participation** (a) Adequate participation in the study by eligible persons (b) Description of the target population or population of interest (c) Description of the baseline study sample (d) Adequate description of the sampling frame and recruitment (e) Adequate description of the period and place of recruitment (f) Adequate description of inclusion and exclusion criteria		
Risk of bias ratings *	HIGH	MODERATE	LOW
	The relationship between the PF and outcome is very likely to be different for participants and eligible non-participants	The relationship between the PF and outcome may be different for participants and eligible non-participants	The relationship between the PF and outcome is unlikely to be different for participants and eligible non-participants
Signalling items	**2. Study attrition** (a) Adequate response rate for study participants (b) Description of attempts to collect information on participants who dropped out (c) Reasons for loss to follow-up are provided (d) Adequate description of participants lost to follow-up (e) There are no important differences between participants who completed the study and those who did not		
Risk of bias ratings *	HIGH	MODERATE	LOW
	The relationship between the PF and outcome is very likely to be different for completing and non-completing participants	The relationship between the PF and outcome may be different for completing and non-completing participants	The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants
Signalling items	**3. Prognostic factor measurement** (a) A clear definition or description of the PF is provided (b) Method of PF measurement is adequately valid and reliable (c) Continuous variables are reported or appropriate cut-points are used (d) The method and setting of measurement of PF is the same for all study participants (e) Adequate proportion of the study sample has complete data for the PF (f) Appropriate methods of imputation are used for missing PF data		
Risk of bias ratings *	HIGH	MODERATE	LOW
	The measurement of the PF is very likely to be different for different levels of the outcome of interest	The measurement of the PF may be different for different levels of the outcome of interest	The measurement of the PF is unlikely to be different for different levels of the outcome of interest
Signalling items	**4. Outcome measurement** (a) A clear definition of the outcome is provided (b) Method of outcome measurement used is adequately valid and reliable (c) The method and setting of outcome measurement is the same for all study participants		
Risk of bias ratings *	HIGH	MODERATE	LOW
	The measurement of the outcome is very likely to be different related to the baseline level of the PF	The measurement of the outcome may be different related to the baseline level of the PF	The measurement of the outcome is unlikely to be different related to the baseline level of the PF
Signalling items	**5. Adjustment for covariates** (a) All other important covariates are measured (b) Clear definitions of the important covariates measured are provided (c) Measurement of all important covariates is adequately valid and reliable (d) The method and setting of covariate measurement are the same for all study participants (e) Appropriate methods are used to deal with missing values of covariates, such as multiple imputation (f) Important covariates are accounted for in the study design (g) Important covariates are accounted for in the analysis		
Risk of bias ratings *	HIGH	MODERATE	LOW
	The observed effect of the covariate on the outcome is very likely to be distorted by another factor related to PF and outcome	The observed effect of the covariate on outcome may be distorted by another factor related to PF and outcome	The observed effect of the covariate on outcome is unlikely to be distorted by another factor related to PF and outcome
Signalling items	**6. Statistical analysis and reporting** (a) Sufficient presentation of data to assess the adequacy of the analytic strategy (b) Strategy for model building is appropriate and is based on a conceptual framework or model (c) The selected statistical model is adequate for the design of the study (d) There is no selective reporting of results		
Risk of bias ratings *	HIGH	MODERATE	LOW
	The reported results are very likely to be spurious or biased related to analysis or reporting	The reported results may be spurious or biased related to analysis or reporting	The reported results are unlikely to be spurious or biased related to analysis or reporting

***** Risk of bias is rated as **Unclear** when there is insufficient information to inform judgment.

PF: Prognostic factor

ST 5: Reasons for exclusion of 13 full-text articles

Reason for exclusion	Full-text articles
No prognostic data (n=8)	Benoist2020; Egidi2013; Li2015; Liu2018; Martens-Uzunova2012; Osipov2016; Valera2020; Yang2015
miR-21 not studied (n=4)	Haldrup2014; Knyazev2016; Moltzahn2011; Nam2015
Non-original human prognostic data (n=1)	Kumar2018

Benoist2020

Benoist, G.E., van Oort, I.M., Boerrigter, E., Verhaegh, G.W., van Hooij, O., Groen, L., Smit, F., de Mol, P., Hamberg, P., Dezentjé, V.O. and Mehra, N., 2020. Prognostic Value of Novel Liquid Biomarkers in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Enzalutamide: A Prospective Observational Study. *Clinical Chemistry*, *66*(6), pp.842-851.

Egidi2013

Egidi, M.G., Cochetti, G., Serva, M.R., Guelfi, G., Zampini, D., Mechelli, L. and Mearini, E., 2013. Circulating microRNAs and kallikreins before and after radical prostatectomy: are they really prostate cancer markers?. *BioMed research international*, *2013*.

Haldrup2014

Haldrup, C., Kosaka, N., Ochiya, T., Borre, M., Høyer, S., Orntoft, T.F. and Sorensen, K.D., 2014. Profiling of circulating microRNAs for prostate cancer biomarker discovery. *Drug delivery and translational research*, *4*(1), pp.19-30.

Knyazev2016

Knyazev, E., Samatov, T., Fomicheva, K., Nyushko, K., Alekseev, B. and Shkurnikov, M., 2016. MicroRNA hsa-miR-4674 in hemolysis-free blood plasma is associated with distant metastases of prostatic cancer. *Bulletin of Experimental Biology & Medicine*, *161*(1).

Kumar2018

Kumar, B., Rosenberg, A.Z., Choi, S.M., Fox-Talbot, K., De Marzo, A.M., Nonn, L., Brennen, W.N., Marchionni, L., Halushka, M.K. and Lupold, S.E., 2018. Cell-type specific expression of oncogenic and tumor suppressive microRNAs in the human prostate and prostate cancer. *Scientific reports*, *8*(1), pp.1-13.

Li2015

Li, M., Rai, A.J., DeCastro, G.J., Zeringer, E., Barta, T., Magdaleno, S., Setterquist, R. and Vlassov, A.V., 2015. An optimized procedure for exosome isolation and analysis using serum samples: application to cancer biomarker discovery. *Methods*, *87*, pp.26-30.

Liu2018

Liu, R.S., Olkhov-Mitsel, E., Jeyapala, R., Zhao, F., Commisso, K., Klotz, L., Loblaw, A., Liu, S.K., Vesprini, D., Fleshner, N.E. and Bapat, B., 2018. Assessment of serum microRNA biomarkers to predict reclassification of prostate cancer in patients on active surveillance. *The Journal of urology*, *199*(6), pp.1475-1481.

Martens-Uzunova2012

Martens-Uzunova, E.S., Jalava, S.E., Dits, N.F., Van Leenders, G.J.L.H., Møller, S., Trapman, J., Bangma, C.H., Litman, T., Visakorpi, T. and Jenster, G., 2012. Diagnostic and prognostic signatures from the small non-coding RNA transcriptome in prostate cancer. *Oncogene*, *31*(8), pp.978-991.

Moltzahn2011

Moltzahn, F., Olshen, A.B., Baehner, L., Peek, A., Fong, L., Stöppler, H., Simko, J., Hilton, J.F., Carroll, P. and Blelloch, R., 2011. Microfluidic-based multiplex qRT-PCR identifies diagnostic and prognostic microRNA signatures in the sera of prostate cancer patients. *Cancer research*, *71*(2), pp.550-560.

Nam2015

Nam, R.K., Amemiya, Y., Benatar, T., Wallis, C.J., Stojcic-Bendavid, J., Bacopulos, S., Sherman, C., Sugar, L., Naeim, M., Yang, W. and Zhang, A., 2015. Identification and validation of a five microRNA signature predictive of prostate cancer recurrence and metastasis: a cohort study. *Journal of Cancer*, *6*(11), p.1160.

Osipov2016

Osipov, I.D., Zaporozhchenko, I.A., Bondar, A.A., Zaripov, M.M., Voytsitskiy, V.E., Vlassov, V.V., Laktionov, P.P. and Morozkin, E.S., 2016. Cell-free miRNA-141 and miRNA-205 as prostate cancer biomarkers. In *Circulating Nucleic Acids in Serum and Plasma–CNAPS IX* (pp. 9-12). Springer, Cham.

Valera2020

Valera, V.A., Parra-Medina, R., Walter, B.A., Pinto, P. and Merino, M.J., 2020. microRNA expression profiling in young prostate cancer patients. *Journal of Cancer*, *11*(14), p.4106.

Yang2015

Yang, C.H., Pfeffer, S.R., Sims, M., Yue, J., Wang, Y., Linga, V.G., Paulus, E., Davidoff, A.M. and Pfeffer, L.M., 2015. The oncogenic microRNA-21 inhibits the tumor suppressive activity of FBXO11 to promote tumorigenesis. *Journal of Biological Chemistry*, *290*(10), pp.6037-6046.

ST 6: Characteristics of included studies and references (n=64)

Ref no.	Study ID	Study size	miR-21 source	miR-21 -5p/-3p	Comparator	Association
29	Agaoglu2011	51	plasma	Not specified	PSA, metastasis	Correlation, median diff
30	Al-Qatati2017	79	plasma	miR-21-5p	GS, pT, PSA, risk groups	FC
31	**Amankwah 2013**	65	tissue	Not specified	Aggressiveness (determined by GS or stage), recurrence (BCR/clinical metastasis/PCa death)	% diff
32	Arisan2020	40	tissue	Not specified	GS	% diff
33	Bell2015 *	43	tissue	Not specified	*(Raw data of m-R-21 in GEO not analysed. No other miR-21 data available.)*	
34	Bonci2016	15	tissue	Not specified	Metastasis	% diff
35	Brase2011	21	serum	Not specified	Metastasis	FC
36	Bryant2012 *	78	plasma	Not specified	*(Author provided miR-21 raw data excel file.)*	
37	Danarto2020	60	urine exosome	miR-21-5p	Metastasis	Mean diff
38	Endzeliņš 2017 *	50	plasma or exosome	miR-21-5p	*(Comparison and ROC curve of miR-21 expression between GS≥8 & ≤6 were done but not shown due to insignificant result.)*	
39	Farran2018	114	plasma	Not specified	Aggressiveness (determined by GS)	OR
40	Fendler2011 *	52	tissue	Not specified	*(Communication with authors failed to obtain full list of differentially expressed miRNAs.)*	
41	Foj2017	60	urine, urine exosome	miR-21-5p	GS, D'Amico risk groups	Mean diff
42	**Guan2016**	85	tissue	Not specified	GS, PSA, metastasis, age	Correlation
43	Gurbuz2020	65	whole blood	Not specified	GS, TNM, PSA	FC diff
44	Hart2014	20	tissue	Not specified	pT	FC diff
45	Hoey2019	75	serum	miR-21-5p	Risk groups	FC
46	Huang2015a *	Screening =23 Follow-up =100	plasma exosome	miR-21-5p	*(miR-21 raw data in supplemental materials; overall survival might have been analysed but contact author failed.)*	
47	Huang2015b	75	PBMC	Not specified	pT, cT, pN, metastasis, recurrence, age	Mean diff
48	Ibrahim2019a	100	plasma	Not specified	GS, pT, metastasis, DRE, prostate volume	Correlation, mean diff
49	Ibrahim2019b	80	plasma	Not specified	GS, pT, PSA, metastasis, DRE, prostate volume	Median diff
50	Ju2019	88	serum	Not specified	GS, pT, PSA, metastasis, BCR, risk groups	Mean diff
51	Katz2014	51	tissue	Not specified	GS, pT, PSA, BCR, risk groups	Mean diff
52	Kelly2015 *	75	whole blood	Not specified	*(miR-21 was among the 12 selected for expression profiling, but data wasn't presented. Author stopped communication.)*	
53	Kopcalic2019	15	PBMC	Not specified	Acute genitourinary radiotoxicity	Mean diff
54	Kotb2014	10	serum	Not specified	GS	Correlation
55	Kristensen 2016	Training =134 Validation	tissue	miR-21-3p	GS, BCR	FC, correlation

		=138				
56	Kurul2019	45	tissue	Not specified	Gleason upgrade, BCR	FC diff
57	Leite2011a	22	tissue	Not specified	Metastasis	Mean diff
58	Leite2011b	49	tissue	Not specified	BCR	Mean diff
59	Leite2013 **	48	tissue	Not specified	Risk groups (favourable vs non-favourable)	Mean diff
60	**Leite2015**	Discovery =53 Validation =127	tissue	miR-21-5p, miR-21-3p	BCR	FC, mean diff
61	**Li2012**	168	tissue	Not specified	GS, pT, PSA, pN, BCR, age, surgical margin, capsular invasion, organ confined disease	% diff
62	Lichner2013	Discovery =41 Validation =64	tissue	miR-21-5p, miR-21-3p	Risk groups	FC
63	Lichner2015	Discovery =45 Validation =60	tissue	miR-21-5p, miR-21-3p	GG	FC
64	**Lin2014 ***	97	plasma or serum	Not specified	*(Pre-docetaxel median diff and post-docetaxel median FC in responder vs non-responder compared. Results for miR-21 not shown due to insignificant p-values.)*	
65	**Lin2017 ***	87	plasma	Not specified	*(No association analysis with comparator.)*	
66	Long2011 *	Training =70 Validation =40	tissue	Not specified	*(miR-21 expression relating to BCR prediction raw data in supplemental materials.)*	
67	McDonald 2019 *	66	plasma	Not specified	*(miR-21 expression measured but not analysed because it did not meet study criteria.)*	
68	**Melbø-Jørgensen 2014**	535	tissue	miR-21-5p	GS, pT, BCR, perineural infiltration, vascular infiltration	Correlation, FC
69	Mortensen2014 *	36	tissue	Not specified	*(miR-21 expression measured but not analysed.)*	
70	Nam2018 *	38	tissue	miR-21-5p, miR-21-3p	*(miR-21 normalised read count available in GEO, not analysed.)*	
71	Ostano2020	48	tissue	miR-21-3p	Neuroendocrine-like vs Adeno PCa	FC
72	Reis2012	53	tissue	Not specified	GS, pT, PSA, BCR	Mean diff
73	Ren2014	204	tissue	Not specified	GS, pT, metastasis, BCR, age, ethnicity, survival, tissue type, hormone therapy	FC, mean diff
74	Samaan2014	95	Not stated	Not specified	GG	FC
75	Sapre2014	36	urine	Not specified	Risk groups	Ct FC
76	Schubert 2013 *	13	tissue	Not specified	*(miR-21 tested in microarray; raw data deposited in GEO (GSE18671); not included in further tests because of insignificant differential expression in high-risk PCa compared to BPH.)*	
77	Selth2013	Screening	serum	Not specified	BCR	FC

		=16 Validation =70				
78	**Sharova2021**	31	plasma	miR-21-5p	Haemoglobin; Neutrophil/lymphocyte ratio; PSA; Time to CRPC	Correlation
79	Shen2012	82	plasma	Not specified	GS, pT, PSA, BCR, risk groups (CAPRA, D'Amico), age, prostate volume, ethnicity, follow-up time, family history of PCa	Mean diff (copy number)
80	Singh2014	93	serum	Not specified	Biochemical progression	Mean diff (delta Ct)
81	Stuopelyte 2016	143	urine	Not specified	GS, pT, BCR	FC
82	Suer2019	40	tissue	miR-21-3p	BCR	FC
83	Watahiki2013	50	plasma	Not specified	mCRPC	Mean diff
84	**Yang2016**	92	PBMC	Not specified	GS, cT, PSA, metastasis (bone), BCR, age	Mean diff
85	**Zedan2017**	49	tissue	Not specified	GS, pT, PSA, risk groups (D'Amico, NCCN)	Correlation
86	Zedan2018	Screening =46 Validation =149	tissue or plasma	Not specified	GS, PSA	Mean diff
87	Zedan2019	149	plasma	Not specified	GS, cT, PSA, risk groups (EAU), age, prostate volume	Correlation
88	Zhang2011	50	serum	Not specified	Chemo-resistance	
89	**Zhao2019a**	206	tissue	miR-21-5p	ISUP (based on GS), pT, PSA, age, DRE, margin	Correlation
90	Zhao2019b	103	urine	Not specified	PSA, age, %core, reclassification	Correlation
91	Zheng2014	118	tissue	Not specified	Recurrence (BCR/local recurrence/systemic metastases/PCa death)	Mean diff, OR
92	Zhu2019	158	tissue	Not specified	Risk groups (identified by GAS5 SNPs)	FC

Studies in **bold** are eligible for meta-analyses (n=11).
Possible part overlap of participants between Ibrahim2019a [48] and Ibrahim2019b [49].
* miR-21 expression measured but no useful data for narrative summary (n=13).
** (Leite2013 [59]) A corrigendum would be published in *Urologic Oncology*.

ARTA: Androgen receptor-targeted agents; **BCR:** Biochemical recurrence; **BPH:** Benign prostate enlargement; **CAPRA:** Cancer of the Prostate Risk Assessment; **CRPC:** Castration-resistant prostate cancer; **cT:** Clinical tumour stage; **Ct:** Threshold cycle; **diff:** Difference; **DRE:** Digital rectal examination; **EAU:** European Association of Urology; **FC:** Fold change; **GAS5:** Growth Arrest Specific 5; **GEO:** Gene Expression Omnibus; **GG:** Gleason grade; **GS:** Gleason score; **ISUP:** International Society of Urological Pathology; **mCRPC:** Metastatic castration resistant prostate cancer; **miRNAs:** microRNAs; **NCCN:** National Comprehensive Cancer Network; **OR:** Odds ratio; **PBMC:** Peripheral blood mononuclear cell; **PCa:** Prostate cancer; **pN:** Lymph node metastasis; **PSA:** Prostate-specific antigen; **pT:** Pathological tumour stage; **ROC:** Receiver operating characteristic; **SNPs:** Single-nucleotide polymorphisms; **TNM:** Tumour, Node, Metastasis staging

Agaoglu2011
Agaoglu, F.Y., Kovancilar, M., Dizdar, Y., Darendeliler, E., Holdenrieder, S., Dalay, N. and Gezer, U., 2011. Investigation of miR-21, miR-141, and miR-221 in blood circulation of patients with prostate cancer. *Tumor Biology*, *32*(3), pp.583-588.

Al-Qatati2017
Al-Qatati, A., Akrong, C., Stevic, I., Pantel, K., Awe, J., Saranchuk, J., Drachenberg, D., Mai, S. and Schwarzenbach, H., 2017. Plasma microRNA signature is associated with risk stratification in prostate cancer patients. *International journal of cancer*, *141*(6), pp.1231-1239.

Amankwah2013 *(Analysis 1)*
Amankwah, E.K., Anegbe, E., Park, H., Pow-Sang, J., Hakam, A. and Park, J.Y., 2013. miR-21, miR-221 and miR-222 expression and prostate cancer recurrence among obese and non-obese cases. *Asian journal of andrology*, *15*(2), p.226.

Arisan2020
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ST 7: Rationales for rating down certainty of evidence - GRADE

Domains	Analysis 1.1	Analysis 1.2	Analysis 2	Analysis 3	Analysis 4.1	Analysis 4.2
RoB	Estimate was unadjusted but sensitivity analysis showed limited difference in HR, rate-down not necessary. High RoB in 3 studies (Amankwah2013 – Domain 1, Leite2015 & Li2012 – Domain 6), rate down 1 point.	Visual inspection of the point estimates and CI showed limited difference caused by difference in covariate adjustments, rate-down not necessary. High RoB in 3 studies (Amankwah2013 – Domain 1, Leite2015 & Li2012 – Domain 6), rate down 1 point.	Unadjusted estimate and high RoB in 1 study (Zhao2019a – Domain 5), rate down 1 point.	Unadjusted estimate and high RoB in 3 studies (Lin2014, Lin2017 & Sharova2021 – Domain 5), rate down 1 point.	High RoB in both studies (Domain 5), rate down 1 point.	High RoB in both studies (Domain 5), rate down 1 point.
Inconsistency	Amankwah2013 outlying but low weight (8.5%), rate-down not necessary.	Amankwah2013 outlying but low weight (8.5%), rate-down not necessary.	Both studies showed positive association and CI overlapped, no rate-down.	Sharova2021 outlying but low weight (8.2%), rate-down not necessary.	The two studies showed opposite direction results, rate down 1 point.	The two studies showed opposite direction results, rate down 1 point.
Indirectness	Amankwah2013 RFS endpoint included clinical metastasis and PCa death but low weight, rate-down not necessary.	Amankwah2013 RFS endpoint included clinical metastasis and PCa death but low weight, rate-down not necessary.	No rate-down.	Lin2014 & Lin2017 included CRPC patients, not representing entire PCa population; main aim was to address chemo-response, rate down 1 point.	No rate-down.	No rate-down.
Imprecision	Pooled CI well excluded HR of 1 but individual HRs were not reported and hence estimated from available data, rate down 1 point.	Pooled CI well excluded HR of 1, no rate-down.	Pooled CI close to HR of 1 (CI: 1.01-1.26), rate down 1 point.	HR was not reported and hence estimated from available data in Yang 2016. Pooled CI close to HR of 1 (CI: 1.06-2.01), rate down 1 point.	Wide pooled CI crossing HR of 1 (CI: 0.63-1.88), rate down 1 point.	Wide pooled CI crossing HR of 1 (CI: 0.70-2.27), rate down 1 point.
Publication bias	Publication bias was not assessed because there was inadequate number of studies for proper assessment by funnel plot and statistical tests.					
Overall certainty	LOW	MODERATE	LOW	VERY LOW	VERY LOW	VERY LOW

CI: Confidence interval; **CRPC:** Castration-resistant prostate cancer; **HR:** Hazard ratio; **mCRPC:** metastatic castration-resistant prostate cancer; **PCa:** Prostate cancer; **RFS:** Recurrence-free survival; **RoB:** Risk of bias