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# Retrospective cohort study evaluating clinical, biochemical and pharmacological prognostic factors for prostate cancer progression using primary care data

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3 4	3	
5 6 7	4	Retrospective cohort study evaluating clinical, biochemical and
8 9 10	5	pharmacological prognostic factors for prostate cancer
11 12 13	6	progression using primary care data
14 15	7	
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1	1	Abstract
2 3	2	<b>Objectives</b> – To confirm the association of previously reported prognostic factors with future
4 5	3	progression of localised prostate cancer using primary care data and identify new potential
6 7	4	prognostic factors for further assessment in prognostic model development and validation.
8	5	Design – Retrospective cohort study, employing Cox proportional hazards regression controlling
9 10	6	for age, PSA, and Gleason score, stratified by diagnostic stage.
11 12	7	Setting – Primary care
13 14	8	Participants – Males with localised prostate cancer diagnosed between 01/01/1987 and
15 16	9	31/12/2016 within the Clinical Practice Research Datalink database, with linked data from the
17	10	National Cancer Registration and Analysis Service and Office for National Statistics.
19	11	Primary and Secondary outcomes – Primary outcome measure was prostate cancer mortality.
20 21	12	Secondary outcomes measures were all-cause mortality and commencing systematic therapy. Up-
22 23	13	staging after diagnosis was not used as a secondary outcome in the final analysis owing to
24 25	14	significant missing data.
26 27	15	Results
28 29	16	10,901 males (mean age 74.38 +/- 9.03 years) with localised prostate cancer were followed up for
30	17	a mean of 14.12 (+/- 6.36) years. 2,331 (21.38%) men underwent systemic therapy and 3,250
32	18	(31.65%) died, including 1,250 (11.47%) from prostate cancer. Factors associated with an
33 34	19	increased risk of prostate cancer mortality included age; high PSA; current or ex-smoker;
35 36	20	ischaemic heart disease; high C-Reactive Protein; high ferritin; low haemoglobin; high blood
37 38	21	glucose; and low albumin.
39 40	22	Conclusions
41	23	This study identified several new potential prognostic factors for prostate cancer progression, as
42	24	well as confirming some known prognostic factors, in an independent primary care data set.
44 45	25	Further research is needed to develop and validate a prognostic model for prostate cancer
46 47	26	progression.
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1	1	Article summary
2 3	2	Strengths and limitations of this study
4 5	3	- Large retrospective cohort study of men with localised prostate cancer
5 6	4	- Mean follow-up 14.12 years
7 8	5	- Data available on a wide range of potential prognostic factors for prostate cancer
9 10	6	progression
11 12	7	- Missing cancer stage and grade data from NCRAS cancer registry excluded a proportion of
13	8	the cohort
14 15 16 17 18 19 20 22 23 22 26 27 28 20 31 23 34 35 36 37 8 9 0 41 23 44 50 51 52 34 55 67 89 00		tor peer teriew only

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#### Main text

#### Introduction

Prostate cancer prognosis and treatment decisions remain a challenging clinical area for clinicians and patients, particularly for men with localised disease at the time of diagnosis. In recent decades, prostate cancer detection rates in many countries have increased markedly, in part as a result of the rising use of asymptomatic prostate specific antigen (PSA) testing[1]. However, more intensive PSA-based detection of prostate cancer has not been convincingly directly correlated with reductions in prostate cancer mortality for all men[2], implying increasing over-detection of clinically insignificant tumours[3]. Treatments for prostate cancer carry a significant risk of morbidity for men[4,5], underlining the importance of being able to identify which men with tumours confined to the prostate at diagnosis are at higher risk of prostate cancer progression and mortality to inform discussions about management options. 

Defining and measuring cancer progression with respect to treatment studies is outlined in the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, which was originally published by the World Health Organisation in 2000[6] and most recently updated in 2009[7]. Evidence of 30 17 tumour shrinkage on imaging and time to development of disease progression are used to <sub>32</sub> 18 measure treatment response. Definitions of cancer progression that are relevant to prognostic studies are less well defined, and numerous clinical, biological and surrogate markers of progression have been proposed in various studies. Prostate cancer mortality appears to be the logical ultimate endpoint of prostate cancer progression, but other measures such as development of metastases[8], biochemical recurrence[9], commencing systemic therapy[10], and 41 23 protein expression[11] have also been reported. 

There are a plethora of prognostic factor studies and prediction tools for prostate cancer risk[12] and prognosis[13] in the published literature. The vast majority are not externally calibrated or validated, and very few are established for use in clinical practice[12]. Initiatives such as the MRC PROGnosis RESearch Strategy Partnership (PROGRESS) partnership highlight the importance of **29** high quality prognostic research to help inform clinical practice[14], and outline methodologically rigorous approaches to achieve this aim[15–17]. Developing clinically useful risk-prediction rules 

starts with identifying potentially important prognostic factors which could be incorporated into a prediction model. The aim of the current study is to confirm the association of previously reported prognostic factors with future progression of localised prostate cancer using primary care data and identify new potential prognostic factors for further assessment in prognostic model development and validation. 

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#### **Materials and Methods**

The protocol for this study has been published previously in BMJ Open[18]. In summary, we undertook a retrospective cohort study using a longitudinal dataset of prospectively collected electronic primary care medical records from the Clinical Practice Research Datalink (CPRD)[19]. This dataset was linked with cancer registry data from the National Cancer Research and Analysis Service (NCRAS)[20] and mortality data from the Office for National Statistics (ONS)[21]. Men were included if they had a diagnosis of prostate cancer entered into their medical record during the 20-year study period (01/01/1987 – 31/12/2016). Localised prostate cancer was defined as T1-2/N0/M0 based on staging data entered into the NCRAS registry, which is determined from a combination of clinical, pathological and radiological data[22]. 

Potentially relevant clinical, biochemical and pharmacological factors measured in CPRD were identified from a review of the existing published literature (See BMJ Open protocol paper[18] for more information about the prognostic factors assessed). The primary outcome of the study was prostate cancer mortality. Secondary outcomes were all-cause mortality and commencing systemic prostate cancer therapy (a measurable proxy for progression and metastatic spread of prostate cancer). Surgery, radiotherapy and brachytherapy were classified as localised therapy, with chemotherapy, hormone treatments (primary or neo adjuvant), and immunotherapy considered systemic therapy. In our published protocol[18], up-staging after diagnosis was proposed as a secondary outcome indicating spread of disease; however, this was not used in the final analysis as repeat staging was rarely recorded in the cancer registry (see Table 2). 

#### Statistical analysis

Descriptive statistics were used to summarise the basic demographic details of the men, and the prevalence of the pre-selected putative prognostic factors. Cox proportional hazards regression was used to estimate crude and mutually adjusted hazard ratios (with 95% confidence intervals) for prostate cancer specific and all-cause mortality according to the prognostic factors, controlling for variables currently used in clinical practice (age, PSA level, Gleason score). Regression analyses of continuous prognostic factors were standardised using hazard ratios per change in one standard deviation. A Proportional Hazards test was performed to confirm modelling met

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1	1	regression assumptions. The analysis was also stratified by stage at diagnosis (T1/2N0M0 vs T3+
2 3	2	and/or N1 and/or M1). Sensitivity analysis was performed, assuming all men in the overall sample
4	3	with unknown tumour location had localised disease. In order to achieve 95% power and detect a
6	4	difference of 0.1 in prostate cancer mortality for a binary risk factor using an alpha of 0.05, a
/ 8	5	sample of at least 6,046 men with prostate cancer would be required, assuming that 10% die over
9 10	6	a median 10-year follow-up.
11 12	7	
13 14	8	Patient and public involvement
15	9	No patients were involved in the development or design of this study.
10	10	
18 19	11	Ethical approval
20 21	12	This study received ethical approval through the MHRA ISAC process (reference 17_041). The
22 23	13	funder had no role in the planning or undertaking of this study, or the preparation of this
$\begin{array}{c} 24\\ 25\\ 26\\ 27\\ 28\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 41\\ 42\\ 44\\ 45\\ 46\\ 47\\ 48\\ 90\\ 51\\ 52\\ 53\\ 55\\ 56\\ 78\\ 59\\ 60\\ \end{array}$	14	manuscript.

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#### **Results**

54,500 men within CPRD had a diagnosis of prostate cancer entered into their primary care medical record during the study period. Tumour-Node-Metastases (TNM) staging data from the linked cancer registry were available for 7,646 (14.03%) of the sample population and treatment data were available for 22,766 (41.77%) men. Missing TNM staging data from the cancer registry was lower for men diagnosed in more recent years: there were no TNM stage data for men diagnosed before 1993, rising to 37.2% with TNM stage data (1,064/2,836) in 2015. This is consistent with a recent validation study of the NCRAS prostate cancer registry that showed low levels of completeness of TNM stage and Gleason score data prior to 2010[23]. Using the available staging and treatment data, 10,901 (20%) men were identified as having localised prostate cancer at the time of diagnosis and were included in the final cohort for analysis, with a mean follow-up of 14.12 (+/-6.36) years. Levels of missing data for selected prognostic factors within CPRD varied (see Tables 3 and 4). Baseline participant data are shown in Table 1. 

1,250 men with localised disease died of prostate cancer over the course of follow-up, giving a prostate cancer mortality rate of 8.1 per 1,000 person-years. The total number of deaths for included men was 3,250 (21.11 deaths per 1,000 person-years). 2,331 (21.38%) men with localised disease received systemic therapy in the follow-up period after diagnosis. For over 90% of the men it was unknown whether they were re-investigated for cancer staging after diagnosis or not (see Table 2). 

Raised acute phase reactants (C-Reactive Protein [CRP] [adjusted HR per SD 1.35 95% CI 1.02, 1.77]), ferritin (adjusted HR per SD 2.03 95% CI 1.21, 3.39) and random glucose (adjusted HR per SD 1.27 95% CI 1.06, 1.54) were associated with prostate cancer mortality. Anaemia (adjusted HR per SD 0.72 95% CI 0.59, 0.88) and low albumin (adjusted HR per SD 0.81 95% CI 0.67, 0.97) were also associated with this outcome. No medications assessed were associated with prostate cancer mortality. Current and ex-smokers (adjusted HR 1.47 95% CI 1.05, 2.05), and patients with a history of ischaemic heart disease (adjusted HR 1.79 95% CI 1.20, 2.66) had a higher risk of prostate cancer mortality over the study period.

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Raised CRP, anaemia, and low albumin were biochemical factors associated with all-cause mortality; with anaemia and low albumin also being associated with commencing systemic therapy. A number of other factors were also associated with all-cause mortality, including age, raised PSA, smoking and smoking-related disease, cardiovascular diseases, as well as current use of aspirin or beta blockers. Smoking and beta blockers were also associated with increased risk of systemic therapy, as were vitamin D supplements. Benign prostatic hyperplasia and alpha blocker prescription were associated with a reduced risk of commencing systemic therapy (See Tables 3 & 4 for adjusted analysis results, and Supplementary Tables S1 & S2 for unadjusted results). 

Sensitivity analysis including all participants with unknown tumour location showed a relationship between a history of stroke and all-cause mortality (adjusted HR 1.47 95% CI 1.12, 1.93 p = 0.006). The relationship between aspirin and prostate cancer mortality altered to very weak evidence for association (adjusted HR 1.55 95% CI 0.79, 3.02 p = 0.2). For all other factors measured and for all three outcomes in the analysis, the direction of relationship did not change and the magnitude of relationship stayed relatively stable (see Supplementary Tables S3-6). 26 15 

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#### Discussion

This retrospective cohort study utilised primary care medical records data for men with localised prostate cancer from CPRD to confirm prognostic factors associated with prostate cancer progression. Well-known factors already incorporated into clinical guidelines, such as age and PSA, were confirmed as being individual prognostic factors. In addition, further clinical (history of smoking or ischaemic heart disease) and biochemical (anaemia or high ferritin) factors were found to be strongly associated with prostate cancer mortality. Anaemia, low albumin, raised PSA, history of ischaemic heart disease, and smoking were also strongly associated with all-cause mortality, as were peripheral vascular disease, COPD, and beta blocker use. Smoking history was strongly associated with future systemic therapy, as were recent prescriptions of alpha blockers, or vitamin D supplements. 

This analysis confirms the prognostic associations of some factors in prostate cancer progression. Smoking has also been found to be a risk factor for prostate cancer progression and mortality in cohort studies[24] and systematic reviews[8]. Low albumin was associated with prostate cancer mortality in the AMORIS cohort[25] and, along with anaemia[26], is a more widely accepted predictor of poor cancer outcomes[27]. The published literature around the prognostic effect of beta blockers for prostate cancer patients has been more mixed[28], with this study lending weight to the evidence of increased mortality in cancer patients. BMI was not shown to be associated with prostate cancer and overall mortality in this study. Whilst some observational studies of prostate cancer have suggested an association may exist[8,29,30], reviews of trial data have demonstrated higher BMI may actually improve the prognosis for men with cancer[31]. 

This study attempted to confirm prognostic factors in a primary care dataset that could be used in a model to predict prostate cancer progression at the time of diagnosis, prior to any treatment being initiated. This approach could allow the identified prognostic factors to be used to develop a new prognostic tool to inform treatment decisions between a patient and their treating team. There are already examples of similar prognostic tools available for use, including Predict Prostate (https://prostate.predict.nhs.uk/). However, these tools have only been developed using secondary care data[32], which may not capture all important prognostic factors or have 

equivalent length of follow-up of patients in their development or calibration cohorts. In the
 context of on-going challenges with prognostication for men with localised prostate cancer, and
 the increasing numbers of men being diagnosed every year, getting the most accurate information
 to inform treatment discussions between patients and their treating physicians is vital.

# 6 Strengths and limitations

This study has a number of unique features. This is the first study that the authors are aware of to utilise a primary care dataset to identify and confirm prognostic factors associated with prostate cancer progression. CPRD contains all data held in the primary care records of millions of UK patients, allowing the inclusion of a range of potentially important prognostic factors. Using a primary care dataset from the NHS also provided long-term data for included patients, with a mean follow-up of over 14 years. Prolonged follow-up for men with prostate cancer is important as many patients can live for years before their cancer progresses. The lack of high quality prognostic research discussed in the introduction is not limited to prostate cancer, with many other prognostic factor studies being conducted in similarly flawed ways[33–35]. This study sought to take a confirmatory approach to postulated prognostic factors in prostate cancer in a rigorous manner, following the methodological recommendations of the REMARK guidelines[36] and the PROGRESS partnership[14–17]. 

There are some limitations of this study that need to be considered. Previous research has shown that the prostate cancer registry in England has strong case completeness, but significant missing TNM stage and Gleason score data up until recent years[23]. Data completeness and quality within NCRAS continues to improve, and there is no equivalent UK cancer registry dataset with more complete data available at this present time[22]. This level of missing data meant it was unknown whether the majority of potentially included men had localised disease or not. Even so, the study was still powered to answer the research question, and sensitivity analyses showed minimal changes to almost all relationships between the prognostic factors of interest and the study outcomes. This study uses a retrospective design interrogating electronic primary care records. It relies on accurate coding from GPs[37], and there was significant missing data for some prognostic factors. 

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This study took a confirmatory approach to identify which prognostic factors for prostate cancer
progression may be relevant, and some new prognostic factors not currently recommended for
use in clinical practice were identified. These prognostic factors could be used to generate a more
robust clinical risk prediction tool to guide treatment decision-making. Developing an accurate
prediction tool for prostate cancer progression, not just mortality, could be more useful for
informing management discussions between patients and clinicians.
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**Ethical approval** 

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#### This study received ethical approval from the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Authority (MHRA) - Protocol reference 17 041. It was conducted in accordance with the Declaration of Helsinki. **Funding statement** This work was supported from an Academic Clinical Fellowship in Primary Care for SWDM, funded by the National Institute for Health Research and Health Education England. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health. RMM was supported by a CRUK programme grant, the Integrative Cancer Epidemiology Programme (C18281/A19169). MTM was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. **Author statement** SWDM conceived and designed the work that has led to this submission. He acquired the data and performed the analysis. He drafted the manuscript and approves the final version. He agrees to be accountable for all aspects of the work. As corresponding author, he also confirms he has full access to the data in the study and has taken final responsibility for the decision to submit for publication. SMI played an important role in the data analysis and interpretation of the results. She revised the manuscript and approved the final version. She agrees to be accountable for all aspects of the work. MTM helped design the work that has led to this submission, and supported interpretation of the results. She also provided study supervision to SWDM. She has revised the manuscript and approved the final version. She agrees to be accountable for all aspects of the work. RMM helped to conceive and design the work that has led to this submission. He also provided study supervision to SWDM He has revised the manuscript and approved the final version. He agrees to be accountable for all aspects of the work.

1	1	Conflict of interest disclosure statement – The authors declare no potential conflicts of interest
2	2	
4	3	Data statement
5 6	4	This study analysed a CPRD dataset, with linked NCRAS and ONS data. Permission was not sought
7 8	5	to share the dataset publicly.
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59 60		

1	1	Refer	ences
2	2	1	Collin SM, Martin RM, Metcalfe C, et al. Prostate-cancer mortality in the USA and UK in
4 5	3		1975-2004: an ecological study. <i>Lancet Oncol</i> 2008; <b>9</b> :445–52. doi:10.1016/S1470-
5 6	4		2045(08)70104-9
7 8	5	2	Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and
9 10	6		Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Int. Agency Res. Cancer.
11 12	7		2013.http://globocan.iarc.fr (accessed 24 May 2018).
13 14	8	3	Sandhu GS, Andriole GL. Overdiagnosis of prostate cancer. J Natl Cancer Inst - Monogr
15	9		2012; <b>2012</b> :146–51. doi:10.1093/jncimonographs/lgs031
16 17	10	4	Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring,
18 19	11		Surgery, or Radiotherapy for Prostate Cancer. <i>N Engl J Med</i> 2016; <b>375</b> :1425–37.
20 21	12		doi:10.1056/NEJMoa1606221
22 23	13	5	Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or
24 25	14		Radiotherapy for Localized Prostate Cancer. N Engl J Med 2016;:NEJMoa1606220-
26	15		10.http://www.nejm.org/doi/10.1056/NEJMoa1606220
27	16	6	Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to
29 30	17		treatment in solid tumors. European Organization for Research and Treatment of Cancer,
31 32	18		National Cancer Institute of the United States, National Cancer Institute of Canada. JNCI J.
33 34	19		Natl. Cancer Inst. 2000;92:205–
35 36	20		16.http://jnci.oxfordjournals.org/cgi/doi/10.1093/jnci/92.3.205
37	21	7	Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid
39	22		tumours: Revised RECIST guideline (version 1.1). 2009;45:228–
40 41	23		47.http://dx.doi.org/10.1016/j.ejca.2008.10.026
42 43	24	8	Peisch SF, Blarigan EL Van, Chan JM, et al. Prostate cancer progression and mortality: a
44 45	25		review of diet and lifestyle factors. World J Urol 2017;35:867–74. doi:10.1007/s00345-016-
46 47	26		1914-3.Prostate
48 40	27	9	Bianco-Miotto T, Chiam K, Buchanan G, et al. Global levels of specific histone modifications
50	28		and an epigenetic gene signature predict prostate cancer progression and development.
51 52	29		Cancer Epidemiol Biomarkers Prev 2010; <b>19</b> :2611–22. doi:10.1158/1055-9965.EPI-10-0555
53 54	30	10	Fleshner N, Lucia MS, Melich K, et al. Effect of dutasteride on prostate cancer progression
55 56			
57 58			
59 60			

Page 17 of 29

1	1		and cancer diagnosis on rebiopsy in the REDEEM active surveillance study. J Clin Oncol
2 3	2		2011; <b>29</b> :no pagination. doi:10.1200/jco.2011.29.7
4 5	3	11	Cullen J, Young D, Chen Y, et al. Predicting Prostate Cancer Progression as a Function of ETS-
5 6	4		related Gene Status, Race, and Obesity in a Longitudinal Patient Cohort. Eur Urol Focus
7 8	5		2017; <b>1</b> :1–7. doi:10.1016/j.euf.2017.02.016
9 10	6	12	Louie KS, Seigneurin A, Cathcart P, et al. Do prostate cancer risk models improve the
11 12	7		predictive accuracy of PSA screening? A meta-analysis. Ann Oncol 2015; <b>26</b> :848–64.
13 14	8		doi:10.1093/annonc/mdu525
15	9	13	Shariat SF, Kattan MW, Vickers AJ, et al. Critical review of prostate cancer predictive tools.
16 17	10		<i>Futur Oncol</i> 2009; <b>5</b> :1555–84.http://www.futuremedicine.com/doi/10.2217/fon.09.121
18 19	11	14	Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: A
20 21	12		framework for researching clinical outcomes. BMJ 2013; <b>346</b> :e5595–
22 23	13		e5595.http://www.bmj.com/cgi/doi/10.1136/bmj.e5595
24 25	14	15	Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2:
26	15		Prognostic Factor Research. PLoS Med 2013;10:e1001380-
27	16		9.http://dx.plos.org/10.1371/journal.pmed.1001380
29 30	17	16	Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis Research Strategy
31 32	18		(PROGRESS) 3: Prognostic Model Research. PLoS Med 2013;10:e1001381-
33 34	19		9.http://dx.plos.org/10.1371/journal.pmed.1001381
35	20	17	Hingorani AD, Windt DA v d, Riley RD, et al. Prognosis research strategy (PROGRESS) 4:
37	21		Stratified medicine research. BMJ 2013; <b>346</b> :e5793–
30 39	22		e5793.http://www.bmj.com/cgi/doi/10.1136/bmj.e5793
40 41	23	18	Merriel SWD, May MT, Martin RM. Predicting prostate cancer progression: protocol for a
42 43	24		retrospective cohort study to identify prognostic factors for prostate cancer outcomes using
44 45	25		routine primary care data. <i>BMJ Open</i> 2018; <b>8</b> :e019409. doi:10.1136/ bmjopen-2017-019409
46 47	26	19	CPRD. Welcome to the Clinical Practice Research Datalink. https://www.cprd.com/home/
48	27	20	NCRAS. National Cancer Research and Analysis Service.
49 50	28		papers3://publication/uuid/CBEF1C52-AEBE-4B92-A099-2BC799944207
51 52	29	21	ONS. Deaths Registered in England and Wales (Series DR), 2016. London: 2017.
53 54	30		http://www.ons.gov.uk/ons/rel/vsob1/mortality-statisticsdeaths-registered-in-england-
55 56			
57 58			
59 60			

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1	1		and-walesseries-dr-/2014/stb-mortality-stats-2014.html
2	2	22	Henson KE, Elliss-Brookes L, Coupland VH, et al. Data Resource Profile: National Cancer
3 4 5	3		Registration Dataset in England. Int J Epidemiol 2020;49:16-16h. doi:10.1093/ije/dyz076
5 6	4	23	Merriel SWD, Turner EL, Walsh E, et al. Cross-sectional study evaluating data quality of the
7 8	5		National Cancer Registration and Analysis Service (NCRAS) prostate cancer registry data
9 10	6		using the Cluster randomised trial of PSA testing for Prostate cancer (CAP). BMJ Open
11 12	7		2017; <b>7</b> :e015994. doi:10.1136/bmjopen-2017-015994
13 14	8	24	Rohrmann S, Genkinger JM, Burke A, et al. Smoking and Risk of Fatal Prostate Cancer in a
15	9		Prospective U.S. Study. Urology 2007;69:721-
17	10		5.http://linkinghub.elsevier.com/retrieve/pii/S0090429506026446
18 19	11	25	Arthur R, Williams R, Garmo H, et al. Serum inflammatory markers in relation to prostate
20 21	12		cancer severity and death in the Swedish AMORIS study. Int J Cancer 2018;142:2254–62.
22 23	13		doi:10.1002/ijc.31256
24 25	14	26	Van Belle SJP. What is the value of hemoglobin as a prognostic and predictive factor in
26	15		cancer? Eur J Cancer, Suppl 2004;2:11–9. doi:10.1016/S1359-6349(03)00103-4
27	16	27	Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: A systematic
29 30	17		review of the epidemiological literature. <i>Nutr J</i> 2010; <b>9</b> :1–16. doi:10.1186/1475-2891-9-69
31 32	18	28	Assayag J, Pollak MN, Azoulay L. Post-diagnostic use of beta-blockers and the risk of death
33 34	19		in patients with prostate cancer. Eur J Cancer 2014;50:2838–
35 36	20		45.http://dx.doi.org/10.1016/j.ejca.2014.08.006
37	21	29	Cantarutti A, Bonn SE, Adami H-O, et al. Body mass index and mortality in men with
38 39	22		prostate cancer. <i>Prostate</i> 2015; <b>75</b> :1129–36. doi:10.1002/pros.23001
40 41	23	30	Haque R, Van Den Eeden SK, Wallner LP, et al. Association of body mass index and prostate
42 43	24		cancer mortality. Obes Res Clin Pract 2014;8:e374-81. doi:10.1016/j.orcp.2013.06.002
44 45	25	31	Greenlee H, Unger JM, LeBlanc M, et al. Association between body mass index and cancer
46	26		survival in a pooled analysis of 22 clinical trials. Cancer Epidemiol Biomarkers Prev
48	27		2017; <b>26</b> :21–9. doi:10.1158/1055-9965.EPI-15-1336
49 50	28	32	Gnanapragasam VJ, Lophatananon A, Wright KA, et al. Improving Clinical Risk Stratification
51 52	29		at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study. PLoS Med
53 54	30		2016; <b>13</b> :1–18. doi:10.1371/journal.pmed.1002063
55 56			
57 52			
59			
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Page 19 of 29

1	1	33	Kyzas PA, Denaxa-Kyza D, Ioannidis JPA. Almost all articles on cancer prognostic markers
2 3	2		report statistically significant results. <i>Eur J Cancer</i> 2007; <b>43</b> :2559–79.
4	3		doi:10.1016/j.ejca.2007.08.030
5 6	4	34	Kyzas PA, Loizou KT, Ioannidis JPA. Selective reporting biases in cancer prognostic factor
7 8	5		studies. <i>J Natl Cancer Inst</i> 2005; <b>97</b> :1043–55. doi:10.1093/jnci/dji184
9 10	6	35	Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. BMJ
11 12	7		2010; <b>340</b> :410–4. doi:10.1136/bmj.b4184
13	8	36	McShane LM, Altman DG, Sauerbrei W, et al. Reporting Recommendations for Tumor
14 15	9		Marker Prognostic Studies (REMARK). JNCI J Natl Cancer Inst 2005;97:1180–
16 17	10		4.https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/dji237
18 19	11	37	Reeves D, Springate DA, Ashcroft DM, et al. Can analyses of electronic patient records be
20 21	12		independently and externally validated? The effect of statins on the mortality of patients
22 23	13		with ischaemic heart disease: a cohort study with nest case-control analysis. BMJ Open
24 25	14		2014; <b>4</b> :1–11.http://dx.doi.org/10.1136/bmjopen-2014-004952
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n = 10,901         Mean (SD)         ge (yrs)       74.38 (+/- 9.03)       0%         MI (kg/m²)       27.43 (+/- 4.48)       5.64%         ollow-up (yrs)       14.12 (+/- 6.36)       0%         Median (IQR)       8.4 (5.55, 14.6)       30.66%
Mean (SD)         Age (yrs)       74.38 (+/- 9.03)       0%         BMI (kg/m²)       27.43 (+/- 4.48)       5.64%         Sollow-up (yrs)       14.12 (+/- 6.36)       0%         Median (IQR)       2SA (ng/mL)       8.4 (5.55, 14.6)       30.66%
Age (yrs)74.38 (+/- 9.03)0%BMI (kg/m²)27.43 (+/- 4.48)5.64%Follow-up (yrs)14.12 (+/- 6.36)0%Median (IQR)SA (ng/mL)8.4 (5.55, 14.6)30.66%
BMI (kg/m²)       27.43 (+/- 4.48)       5.64%         Follow-up (yrs)       14.12 (+/- 6.36)       0%         Median (IQR)       PSA (ng/mL)       8.4 (5.55, 14.6)       30.66%
Follow-up (yrs) 14.12 (+/- 6.36) 0% Median (IQR) PSA (ng/mL) 8.4 (5.55, 14.6) 30.66%
Median (IQR) PSA (ng/mL) 8.4 (5.55, 14.6) 30.66%
PSA (ng/mL) 8.4 (5.55, 14.6) 30.66%
n (%)
Gleason score
6 3,655 (33.53%)
7+ 4,420 (40.55%)
Family history of 70 (0 64%) 55 11%
prostate cancer
Ethnicity
White 7,361 (67.53%)
Mixed 21 (0.19%)
Asian 75 (0.69%) 29.79%
Black 156 (1.43%)
Other 41 (0.38%)

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**BMJ** Open

		Prostate cancer	All-cause	Systemic	Upstaging <sup>a</sup>
		mortality	mortality	therapy	
Included	Localised (T1/2 N0 M0) n = 10,901	1,250 (11.47%)	3,450 (31.65%)	2,331 (21.38%)	45 (0.41%)
uded	Invasive (T3+ / N1 / M1) n = 12,318	3,894 (31.61%)	6,916 (56.15%)	10,881 (88.33%)	28 (0.23%)
Excl	Unknown n = 31,281	1,540 (4.92%)	5,420 (17.33%)	31,954 (58.63%)	19 (0.06%)

Table 2 - Primary and Secondary outcomes for included and excluded participants

ια<sub>α</sub>, g for 50,119 (91.9ο~, <sup>a</sup> Repeat staging data missing for 50,119 (91.96%) of sample

n = 10,901			Prost	ate cancer mor	tality	AI	l-cause mortali	ty	,# 5' Sy	Stemic therapy	/
Factor	Mean (SD)	Missing [n (%)]	HR per	95% CI	р	HR per	95% CI	р	HR per SD <sup>®</sup> g	0 4495% CI	p
Age	74.39 (9.03)	0	1.70	1.40, 2.06	<0.01	1.92	1.74, 2.12	<0.01		<b>9</b> 0.95, 1.06	0.98
BMI	27.43 (4.48)	394 (3.61%)	1.05	0.90, 1.08	0.52	0.97	0.90, 1.05	0.51	1.0 <b>4</b>	<b>g</b> 0.99, 1.09	0.10
Triglycerides	1.45 (0.80)	3,856 (35.37%)	0.83	0.64, 1.08	0.16	1.00 <sup>b</sup>	0.90, 1.13	0.93	1.088 T	0.97, 1.09	0.37
HDL cholesterol	1.35 (0.43)	3,954 (36.27%)	1.05	0.89, 1.23	0.56	1.01 <sup>b</sup>	0.91, 1.12	0.86		<b>č</b> 0.95, 1.07	0.75
LDL cholesterol	2.95 (0.99)	4,698 (43.10%)	0.86	0.69, 1.07	0.18	0.92 <sup>b</sup>	0.82, 1.02	0.12		<b>2</b> 0.94, 1.05	0.86
Hb	144.28 (14.35)	2,696 (24.73%)	0.72	0.59, 0.88	<0.01	0.74	0.67, 0.82	<0.01		0.86, 0.98	0.01
Albumin	41.83 (3.94)	2,954 (27.10%)	0.81	0.67, 0.97	0.02	0.83	0.76, 0.91	<0.01	0.940	0.89, 0.99	0.04
Random glucose	5.70 (2.11)	4,525 (41.51%)	1.27	1.06, 1.54	0.01	1.12	0.99, 1.25	0.06	1.02	<b>6</b> 0.95, 1.09	0.66
	Median (IQR)	Missing [n (%)]							ing,		
PSA	8.4 (5.55, 14.60)	2,352 (21.58%)	1.71	1.32, 2.23	<0.01	1.46	1.19, 1.78	< 0.01	1.34	1.06, 1.68	0.01
CRP	3.9 (2, 8)	8,061 (73.95%)	1.35 <sup>b</sup>	1.02, 1.77	0.03	1.23 <sup>b</sup>	1.05, 1.45	0.01	1.07	0.95, 1.20	0.24
Ferritin	108.6 (47, 196)	9,495 (87.10%)	2.03	1.21, 3.39	<0.01	0.98 b	0.60, 1.59	0.93	1.05	0.85, 1.31	0.64
Adjusted for age Proportional Haz IR – Hazard Ratio	, PSA, Gleason score, ards assumption tes ; SD – Standard Devi	, TNM stage It not met ation; BMI – Body I	Mass Index	;; PSA – Prostate	e Specific	Antigen; H	IDL – High Dens	ity Lipopi	milar technolog	on May 1	

n = 10,901       Protate cancer with level       All-case mortality       N       Section (herein)         Factor       n (%)       Mising (n(%)       HR*       95% CL       p       HR*       95% CL       p       HR*       95% CL       109,133         Smoker (current/ex)       5,112 (46.89%)       777 (7.13%)       1.47       1.05,2.05       0.02       1.66       1.39,1.98       0.01       1.47       0.91%       0.71,1.18       0.47       0.98       109,1.33         Excess alcohol       1,829 (16.78%)       4,370 (40.09%)       0.61       0.36,1.01       0.11       0.81       0.62,1.05       0.11       0.48       0.47       0.53       0.44       0.491       0.44       0.491       0.44       1.91       0.41       0.41       0.41       0.41       0.47       0.53       1.64       1.29,2.09       0.01       1.48       0.499       0.41       0.41       0.44       1.49,1.09       0.44       0.41       1.91       0.85,1.68       0.30       0.97       0.42,1.94       0.79       1.19       0.85,1.68       0.30       0.97       0.41       1.42       0.40       1.42       0.40       1.42       0.40       1.42       0.40       1.42       0.40       1.42       <	,
Factor         n (%)         Missing [n(%)]         HR*         95% CL         p         HR*         95% CL         D         <	
Smoker (current/ ex-)       5,112 (46.89%)       777 (7.13%)       1.47       1.05, 2.05       0.02       1.66       1.39, 1.98       <0.01	р
Excess alcohol       1,829 (16.78%)       4,370 (40.09%)       0.61       0.36, 1.04       0.07       0.91 b       0.71, 1.18       0.47       0.99 b       0.87, 1.13         BPH       1,169 (10.72%)       3,526 (32.35%)       0.64       0.36, 1.11       0.11       0.81       0.62, 1.05       0.11       0.97 b       0.65, 1.05       0.11       0.97 b       0.97 b       0.65, 1.05       0.11       0.97 b       0.99 1.41         CVA       553 (5.07%)       3,584 (32.88%)       0.90       0.42, 1,94       0.79       1.19       0.85, 1.68       0.30       0.99 1.41         CVA       553 (5.07%)       3,582 (32.86%)       1.79       1.20, 2.66       <0.01	<0.0
BPH       1,169 (10.72%)       3,526 (32.35%)       0.64       0.36, 1.11       0.11       0.81       0.62, 1.05       0.11       0.%       0.65, 0.90         COPD       862 (7.91%)       3,583 (32.87%)       0.86       0.47, 1.57       0.63       1.64       1.29, 2.09       <0.01	0.88
COPD       862 (7.91%)       3,583 (32.87%)       0.86       0.47, 1.57       0.63       1.64       1.29, 2.09       <0.01       1.86 m f       0.99, 1.41         CVA       553 (5.07%)       3,584 (32.88%)       0.90       0.42, 1,94       0.79       1.19       0.85, 1.68       0.30       0.99, 1.41         HD       1,548 (14.20%)       3,405 (31.24%)       1.79       1.20, 2.66       <0.01	<0.0
CVA         553 (5.07%)         3,584 (32.88%)         0.90         0.42, 1,94         0.79         1.19         0.85, 1.68         0.30         0.98         0.72, 1.17           IHD         1,548 (14.20%)         3,405 (31.24%)         1.79         1.20, 2.66         <0.01	0.06
IHD       1,548 (14.20%)       3,405 (31.24%)       1.79       1.20, 2.66       <0.01       1.25       1.02, 1.55       0.04       1.86       0.87, 1.18         PVD       202 (1.85%)       3,582 (32.86%)       2.24       0.98, 5.12       0.06       1.91       1.24, 2.95       <0.01	0.49
PVD       202 (1.85%)       3,582 (32.86%)       2.24       0.98, 5.12       0.06       1.91       1.24, 2.95       <0.01       1.64 (0,0)       0.71, 1.51         T2DM       1,508 (13.83%)       3,448 (31.63%)       0.97       0.62, 1.51       0.89       0.95       0.76, 1.19       0.68       0.990       0.86, 1.14         Aspirin       426 (3.91%)       426 (3.91%)       1.88       0.96, 3.70       0.06       1.58       1.09, 2.29       0.02       1.24       0.95, 1.60         Metformin       33 (0.30%)       166 (0.15%)       1.55       0.72, 3.35       0.26       1.15       0.76, 1.73       0.52       0.37       0.39, 0.82         Beta blockers       265 (2.43%)       16 (0.15%)       1.55       0.72, 3.35       0.26       1.15       0.76, 1.73       0.52       0.37       0.39, 0.82         Statins       339 (3.11%)       16 (0.15%)       1.65       0.87, 3.15       0.13       1.01       0.66, 1.53       0.97       1.09, 1.99         Statins       339 (3.11%)       1.33       0.65, 2.71       0.44       1.13       0.78, 1.65       0.51       1.95       0.90       0.90         able 4 - Prognostic factors for men with localised disease assciated with outcomes       Adjusted for age,	0.86
T2DM       1,508 (13.83%)       3,448 (31.63%)       0.97       0.62, 1.51       0.89       0.95       0.76, 1.19       0.68       0.95       0.88       0.95       0.89       0.95       0.76, 1.19       0.68       0.95       0.89       0.95       0.76, 1.19       0.68       0.95       0.89       0.95       0.76, 1.19       0.68       0.95       0.86, 1.14         Aspirin       426 (3.91%)       1.88       0.96, 3.70       0.06       1.58       1.09, 2.29       0.02       1.91       0.95, 1.60         Metformin       33 (0.30%)       16 (0.15%)       1.55       0.72, 3.35       0.26       1.15       0.76, 1.73       0.52       0.97       0.39, 0.82         Beta blockers       265 (2.43%)       16 (0.15%)       1.55       0.72, 3.35       0.26       1.15       0.76, 1.73       0.52       0.97       0.39, 0.82       0.39, 0.82         Statins       339 (3.11%)       1.65       0.87, 3.15       0.13       1.01       0.66, 1.53       0.97       1.09       0.84, 1.34         Vitamin D       465 (4.27%)       1.33       0.65, 2.71       0.44       1.13       0.78, 1.65       0.51       1.99       0.91       1.99       1.99       1.99       1.99       1.9	0.85
Aspirin       426 (3.91%)         Metformin       33 (0.30%)         Alpha blockers       305 (2.80%)         Beta blockers       265 (2.43%)         16 (0.15%)       1.55       0.72, 3.35       0.26       1.15       0.76, 1.73       0.52       0.37       0.39, 0.82         2.03       0.89, 4.60       0.09       1.79       1.18, 2.72       <0.01	0.91
Metformin       33 (0.30%)         Alpha blockers       305 (2.80%)         Beta blockers       265 (2.43%)         16 (0.15%)       1.55       0.72, 3.35       0.26       1.15       0.76, 1.73       0.52       0.57       0.39, 0.82         2.03       0.89, 4.60       0.09       1.79       1.18, 2.72       <0.01	0.11
Alpha blockers       305 (2.80%)         Beta blockers       265 (2.43%)         Statins       339 (3.11%)         Vitamin D       465 (4.27%)         1.33       0.65, 2.71         0.44       1.13         0.78, 1.65       0.51         1.90, 1.99         1.33       0.65, 2.71         0.44       1.13         0.78, 1.65       0.51         1.90, 1.68         able 4 – Prognostic factors for men with localised disease associated with outcomes         Adjusted for age, PSA, Gleason score, TNM stage         Proportional Hazards assumption test not met	0.18
Beta blockers       265 (2.43%)       16 (0.15%)       2.03       0.89, 4.60       0.09       1.79       1.18, 2.72       <0.01       1.48       0.109, 1.99         Statins       339 (3.11%)       1.65       0.87, 3.15       0.13       1.01       0.66, 1.53       0.97       1.06       0.84, 1.34         Vitamin D       465 (4.27%)       1.33       0.65, 2.71       0.44       1.13       0.78, 1.65       0.51       1.35       1.09, 1.68         able 4 – Prognostic factors for men with localised disease associated with outcomes       Adjusted for age, PSA, Gleason score, TNM stage       Image: state of the sta	<0.0
Statins       339 (3.11%)       1.65       0.87, 3.15       0.13       1.01       0.66, 1.53       0.97       1.066       0.84, 1.34         Vitamin D       465 (4.27%)       1.33       0.65, 2.71       0.44       1.13       0.78, 1.65       0.51       1.35       1.09, 1.68         able 4 – Prognostic factors for men with localised disease associated with outcomes       4djusted for age, PSA, Gleason score, TNM stage       9       9       9       9         Proportional Hazards assumption test not met       4djusted for age, PSA, Gleason score, TNM stage       1       1       1       1       1       1       1       1       1       1       1       0       1       1       1       0       1       1       0       1       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0       1       0	0.01
Vitamin D       465 (4.27%)       1.33       0.65, 2.71       0.44       1.13       0.78, 1.65       0.51       1.35       1.09, 1.68         able 4 – Prognostic factors for men with localised disease associated with outcomes       Adjusted for age, PSA, Gleason score, TNM stage       Image: Constraint of the standard stan	0.61
able 4 – Prognostic factors for men with localised disease associated with outcomes Adjusted for age, PSA, Gleason score, TNM stage	<0.0
R – Hazard Ratio; BPH – Benign Prostatic Hypertrophy; COPD – Chronic Obstructive Pulmonary Disease; CVA – Cerebrovascular Accient ald – Ischaemic isease; PVD – Peripheral Vascular Disease; T2DM – Type 2 Diabetes Mellitus	: Heai

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Mean (SD)	Missing [n (%)]	HR per	95% CI	р	HR per	95% CI	p ding	∯R per	95% CI	р
		SD			SD		for u	SD ND		
74.39 (9.03)	0	1.66	1.56, 1.76	<0.01	1.82	1.76, 1.89	<0.0	<b>6</b> 0.81	0.77, 0.84	<0.01
27.43 (4.48)	394 (3.61%)	0.96	0.91, 1.02	0.19	0.97	0.94, 1.01	0.1	<b>n</b> a 1.07	1.03, 1.12	<0.01
1.45 (0.80)	3,856 (35.37%)	0.93	0.84, 1.02	0.12	0.97	0.92, 1.02	0.28		0.95, 1.04	0.82
1.35 (0.43)	3,954 (36.27%)	0.98	0.88, 1.09	0.66	0.98	0.92, 1.04	0.455		0.98, 1.08	0.23
2.95 (0.99)	4,698 (43.10%)	0.90	0.81, 0.99	0.03	0.87	0.82, 0.92	<0.0	<b>G o</b> 0.95	0.91, 0.99	0.03
144.28 (14.35)	2,696 (24.73%)	0.55	0.51, 0.58	<0.01	0.62	0.59, 0.64	<0.0		0.89, 0.99	0.03
41.83 (3.94)	2,954 (27.10%)	0.71	0.67, 0.74	<0.01	0.74	0.71, 0.77	<0.0	• <b>å</b> 0.96	0.91, 1.00	0.06
5.70 (2.11)	4,525 (41.51%)	1.18	1.10, 1.27	<0.01	1.14	1.09, 1.20	<0.0	<b>B</b> 1.02	0.97, 1.07	0.48
Median (IQR)	Missing [n (%)]			9,			Alt	http:/		
8.4 (5.55, 14.60)	2,352 (21.58%)	1.45	1.39, 1.51	<0.01	1.36	1.31, 1.41	<0.0	1.01	0.86, 1.18	0.90
3.9 (2, 8)	8,061 (73.95%)	1.27	1.19, 1.36	<0.01	1.22	1.16, 1.28	<0.69	<b>8</b> 1.01	0.92, 1.10	0.90
108.6 (47, 196)	9,495 (87.10%)	1.48	1.25, 1.75	<0.01	1.13	0.97, 1.31	0.1	<b>1</b> .02	0.89, 1.16	0.79
ted HRs for progno	stic factors for men iation; BMI – Body I	with local Mass Index	ised disease asso ; PSA – Prostate	ociated v Specific	vith outcor Antigen; H	nes IDL – High Dens	ity Lipop	protein; LDL	– Low Density I	ipoproteir
;; CRP – C-Reactive	Protein; Hb – Haem	ioglobin					nnologie	May 15,		
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	74.39 (9.03) 27.43 (4.48) 1.45 (0.80) 1.35 (0.43) 2.95 (0.99) 144.28 (14.35) 41.83 (3.94) 5.70 (2.11) Median (IQR) 8.4 (5.55, 14.60) 3.9 (2, 8) 108.6 (47, 196) ced HRs for progno SD – Standard Dev ; CRP – C-Reactive	74.39 (9.03)       0         27.43 (4.48)       394 (3.61%)         1.45 (0.80)       3,856 (35.37%)         1.35 (0.43)       3,954 (36.27%)         2.95 (0.99)       4,698 (43.10%)         144.28 (14.35)       2,696 (24.73%)         41.83 (3.94)       2,954 (27.10%)         5.70 (2.11)       4,525 (41.51%)         Median (IQR)       Missing [n (%)]         8.4 (5.55, 14.60)       2,352 (21.58%)         3.9 (2, 8)       8,061 (73.95%)         108.6 (47, 196)       9,495 (87.10%)         :ed HRs for prognostic factors for men         SD – Standard Deviation; BMI – Body I         ; CRP – C-Reactive Protein; Hb – Haem	Integer       Integer         74.39 (9.03)       0       1.66         27.43 (4.48)       394 (3.61%)       0.96         1.45 (0.80)       3,856 (35.37%)       0.93         1.35 (0.43)       3,954 (36.27%)       0.98         2.95 (0.99)       4,698 (43.10%)       0.90         144.28 (14.35)       2,696 (24.73%)       0.55         41.83 (3.94)       2,954 (27.10%)       0.71         5.70 (2.11)       4,525 (41.51%)       1.18         Median (IQR)       Missing [n (%)]       1.45         3.9 (2, 8)       8,061 (73.95%)       1.27         108.6 (47, 196)       9,495 (87.10%)       1.48         SD       2.95 (2.12.58%)       1.48         SD       8,061 (73.95%)       1.27         108.6 (47, 196)       9,495 (87.10%)       1.48         SD       SD       Standard Deviation; BMI – Body Mass Index         ; CRP – C-Reactive Protein; Hb – Haemoglobin       ; CRP – C-Reactive Protein; Hb – Haemoglobin	Millioning [H (N)]       Milliper       Joint Jec.       Joint Jec.         74.39 (9.03)       0       1.66       1.56, 1.76         27.43 (4.48)       394 (3.61%)       0.96       0.91, 1.02         1.45 (0.80)       3,856 (35.37%)       0.93       0.84, 1.02         1.35 (0.43)       3,954 (36.27%)       0.98       0.88, 1.09         2.95 (0.99)       4,698 (43.10%)       0.90       0.81, 0.99         144.28 (14.35)       2,696 (24.73%)       0.55       0.51, 0.58         41.83 (3.94)       2,954 (27.10%)       0.71       0.67, 0.74         5.70 (2.11)       4,525 (41.51%)       1.18       1.10, 1.27         Median (IQR)       Missing [n (%)]       1.45       1.39, 1.51         3.9 (2, 8)       8,061 (73.95%)       1.27       1.19, 1.36         108.6 (47, 196)       9,495 (87.10%)       1.48       1.25, 1.75         red HRs for prognostic factors for men with localised disease asses       SD – Standard Deviation; BMI – Body Mass Index; PSA – Prostate         ; CRP – C-Reactive Protein; Hb – Haemoglobin       CRP – C-Reactive Protein; Hb – Haemoglobin	Initial (1, (x))       Init periods       355 Cell       p         74.39 (9.03)       0       1.66       1.56, 1.76       <0.01	International (ICR)       International (ICR)       International (ICR)       International (ICR)         144.83       3.94 (3.61%)       0.96       0.91, 1.02       0.19       0.97         1.45 (0.80)       3.856 (35.37%)       0.93       0.84, 1.02       0.12       0.97         1.35 (0.43)       3.954 (36.27%)       0.98       0.88, 1.09       0.66       0.98         2.95 (0.99)       4,698 (43.10%)       0.90       0.81, 0.99       0.03       0.87         144.28 (14.35)       2,696 (24.73%)       0.55       0.51, 0.58       <0.01	Intern (EP)       Integer       Solution       p       Integer       Solution         74.39 (9.03)       0       1.66       1.56, 1.76       <0.01	Intern (b)       Intern (b)       SD       SD       Intern (b)       SD       SD       Intern (b)       SD       SD       SD       Intern (b)       SD       SD <th< td=""><td>Internet (b)       Internet (b)       SD       Internet (b)       Internet (b</td><td>Intern (pb)       Intern (pb)       <thintern (pb)<="" th=""> <thintern (pb)<="" th=""></thintern></thintern></td></th<>	Internet (b)       Internet (b)       SD       Internet (b)       Internet (b	Intern (pb)       Intern (pb) <thintern (pb)<="" th=""> <thintern (pb)<="" th=""></thintern></thintern>

n = 10.901			Prosta	te cancer mo	rtality	Α	ll-cause mortal	ity C		Systemic therai	ov
Factor	n (%)	Missing [n(%)]	HR	95% CI	p	HR	95% CI	ping	HR C	95% Cl	р р
Smoker (current/ ex-)	5,112 (46.89%)	777 (7.13%)	1.24	1.09, 1.40	<0.01	1.36	1.26, 1.46	<0.01	<b>9</b> 1.20	1.10, 1.30	<0.01
Excess alcohol	1,829 (16.78%)	4,370 (40.09%)	0.75	0.62, 0.91	<0.01	0.67	0.60, 0.74	<0 <b>9</b> 1	<b>0</b> .92	0.80, 1.06	0.26
BPH	1,169 (10.72%)	3,526 (32.35%)	0.61	0.49, 0.76	<0.01	0.79	0.70, 0.88	<0 <b>⊉1</b>	0.70	0.61, 0.80	<0.01
COPD	862 (7.91%)	3,583 (32.87%)	0.95	0.77, 1.18	0.67	1.41	1.26, 1.58	<0.015	< 8 1.08	0.94, 1.25	0.26
CVA	553 (5.07%)	3,584 (32.88%)	1.48	1.18, 1.85	<0.01	1.89	1.67, 2.13	<0.60	<u>9</u> 0.78	0.64, 0.96	0.02
HD	1,548 (14.20%)	3,405 (31.24%)	1.62	1.39, 1.88	<0.01	1.79	1.64, 1.95	<0.916	<b>6</b> 0.89	0.79, 1.00	0.05
PVD	202 (1.85%)	3,582 (32.86%)	1.80	1.31, 2.49	<0.01	1.87	1.55, 2.25	<0.210	0.84	0.62, 1.14	0.26
r2dm	1,508 (13.83%)	3,448 (31.63%)	1.13	0.96, 1.33	0.16	1.03	0.94, 1.14	0.459'	0.93	0.83, 1.04	0.20
Aspirin	426 (3.91%)		2.33	1.88, 2.90	<0.01	2.18	1.90, 2.49	<0 <b>,2</b>	1.24	0.99, 1.54	0.06
Metformin	33 (0.30%)		1.99	0.90, 4.46	0.09	2.63	1.71, 4.04	<0.≹1	2.59	1.47, 4.57	<0.01
Alpha blockers	305 (2.80%)	16 (0 15%)	1.24	0.92, 1.67	0.16	1.17	0.97, 1.41	0.000	0.51	0.37, 0.71	<0.01
Beta blockers	265 (2.43%)	10 (0.1570)	2.15	1.65, 2.81	<0.01	1.76	1.48, 2.10	<0 <del>,0</del> 1 ລ	1.11	0.85, 1.46	0.43
Statins	339 (3.11%)		1.34	1.01, 1.77	0.04	0.93	0.76, 1.13	0.455 S	1.42	1.16, 1.73	<0.01
Vitamin D	465 (4.27%)		1.63	1.29, 2.05	<0.01	1.24	1.06, 1.46	<0.101	<b>1.52</b>	1.27, 1.82	<0.01
R – Hazard Ratio; BPH – VD – Peripheral Vascula	- Benign Prostatic Hy ır Disease; T2DM – T	/pertrophy; COPD	– Chronic ellitus	Obstructive P	ulmonar	y Disease	; CVA – Cerebro	ovascoogies.	on May 15. 2025 at Department GEZ-L	; IHD – Ischaem	ic Heart

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n = 42, 182			Prost	ate cancer mor	tality	Al	l-cause mortali	ty Clu	044 S	ystemic therap	ру
Factor	Mean (SD)	Missing [n (%)]	HR per	95% CI	р	HR per	95% CI	p p	HR per	95% CI	р
			SD			SD		for u	on A		
Age	76.70 (9.42)	0	1.55	1.49, 1.62	<0.01	1.78	1.74, 1.82	<0.0	<b>6</b> 0.67	0.65, 0.70	<0.01
BMI	27.37 (4.49)	394 (3.61%)	0.96	0.92, 0.99	0.05	0.96	0.94, 0.98	<0.0	ມີ ສູ່ 1.06	1.02, 1.10	<0.01
Triglycerides	1.48 (0.82)	3,856 (35.37%)	0.92	0.87, 0.99	0.02	0.95	0.91, 0.98	<0.0	8 <sup>0.96</sup>	0.91, 1.00	0.06
HDL cholesterol	1.34 (0.53)	3,954 (36.27%)	1	0.94, 1.07	0.60	1	0.97, 1.04	0.86		0.99, 1.06	0.12
LDL cholesterol	2.84 (0.99)	4,698 (43.10%)	0.93	0.86, 0.99	0.03	0.89	0.86, 0.93	<0.0	<b>§</b> 1.05	1, 1.10	0.03
Hb	141.81 (16.58)	2,696 (24.73%)	0.61	0.58, 0.63	<0.01	0.66	0.64, 0.67	<0.0	a 1.07	1.02, 1.13	<0.01
Albumin	41.41 (4.31)	2,954 (27.10%)	1.71	0.99, 2.96	0.06	1.33	0.91, 1.94	0.15	<b>ã</b> 0.75 <b>1</b>	0.46, 1.21	0.24
Random glucose	5.92 (2.11)	4,525 (41.51%)	1.06	1.01, 1.10	0.01	1.07	1.04, 1.09	<0.0	<b>8</b> 0.92	0.87, 0.98	0.01
	Median (IQR)	Missing [n (%)]			0,			Alt	http:/		
PSA	10.4 (6.11, 24.6)	2,352 (21.58%)	1.28	0.96, 1.71	0.10	0.84	0.73, 0.98	0.0	2.37	1.88, 2.99	<0.01
CRP	5 (2, 10)	8,061 (73.95%)	2.50	1.03, 6.08	0.04	2.55	1.47, 4.42	<0.69	<b>1</b> .03	0.51, 2.06	0.94
Ferritin	101.5 (45, 197)	9,495 (87.10%)	1.10	1.06, 1.15	<0.01	1.04	0.99, 1.09	0.1	<b>9</b> 0.99	0.90, 1.09	.089
IR – Hazard Ratio; Haemoglobin A1	SD – Standard Devi c; CRP – C-Reactive	ation; BMI – Body I Protein; Hb – Haem	Vass Index	; PSA – Prostate	e Specific	Antigen; H	IDL – High Dens	ity Lipæchnologies.	omæin; in; omæin May 15, 2025 at Department GEZ-	. – Low Density	/ Lipoprote

n = 42, 182			Prosta	te cancer mo	rtality	A	ll-cause mortali	ty מַ	<u>с</u> , 0 ог	Systemic thera	у
Factor	n (%)	Missing [n(%)]	HR	95% CI	р	HR	95% CI	p us	ਹ ਹੋ <sup>HR</sup>	95% CI	р
Smoker (current/ ex-)	19,215 (45.56%)	777 (7.13%)	1.24	1.09, 1.40	<0.01	1.36	1.26, 1.46	<0.001	<b>e</b> 1.20	1.10, 1.30	<0.01
Excess alcohol	5,926 (14.05%)	4,370 (40.09%)	0.75	0.62, 0.90	<0.01	0.79 <sup>b</sup>	0.71, 0.88	<0.001	1.01	0.90, 1.13	0.86
ВРН	4,318 (10.24%)	3,526 (32.35%)	0.61	0.49, 0.76	<0.01	0.79	0.70, 0.89	<0.012	<b>8</b> 0.70	0.61, 0.80	<0.01
COPD	3,866 (9.17%)	3,583 (32.87%)	0.95	0.77, 1.19	0.66	1.41	1.26, 1.58	<0.50 100 100 100 100 100 100 100 100 100 1	1.08	0.94, 1.25	0.26
CVA	2,973 (7.05%)	3,584 (32.88%)	1.48	1.19, 1.85	<0.01	1.89	1.67, 2.12	<0.315	0.78	0.64, 0.96	0.02
IHD	7,512 (17.81%)	3,405 (31.24%)	1.62	1.39, 1.88	<0.01	1.79	1.64, 1.95	<0 ឆ្នាំ <u>6</u>	0.89	0.79, 1.00	0.05
PVD	1,138 (2.70%)	3,582 (32.86%)	1.8	1.31, 2.49	<0.01	1.89	1.55, 2.25	<0₽1	<b>e</b> fr 0.84	0.62, 1.14	0.26
T2DM	6,233 (14.78%)	3,448 (31.63%)	1.13	0.96, 1.33	0.16	1.04	0.94, 1.14	0.	0.93	0.83, 1.04	0.20
Aspirin	2,022 (4.79%)		2.33	1.88, 2.90	<0.01	2.18	1.90, 2.49	<0.11	1.24	0.99, 1.54	0.06
Metformin	220 (0.52%)		1.99	0.90, 4.46	0.09	2.63	1.71, 4.04	<0.91	2.59	1.47, 4.57	<0.01
Alpha blockers	1,025 (2.43%)	16 (0 15%)	1.24	0.92, 1.67	0.16	1.17	0.98, 1.41	0.09	<b>0</b> .51	0.37, 0.71	<0.01
Beta blockers	1,127 (2.67%)	10 (0.1570)	2.15	1.65, 2.81	<0.01	1.76	1.48, 2.10	<0.01	1.11	0.85, 1.46	0.43
Statins	1,299 (3.08%)		1.34	1.01, 1.77	0.04	0.93	0.78, 1.13	0. <b>4</b>	<b>6</b> 1.42	1.16, 1.73	<0.01
Vitamin D	2,093 (4.96%)		1.63	1.29, 2.05	<0.01	1.24	1.06, 1.46	0.6	<b>g</b> 1.52	1.27, 1.88	<0.01
R – Hazard Ratio; BPH – VD – Peripheral Vascula	- Benign Prostatic Hy nr Disease; T2DM – T	vpertrophy; COPD	– Chronic	Obstructive P	ulmonar	y Disease	; CVA – Cerebro	ovascælar s	ay 14, 2025 at Department GEZ-L	t; IHD – Ischaen	nic Heart C

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n = 42, 182			Prosta	ate cancer mort	ality	All	-cause mortali	ty Clu	4 Systemic therapy			
Factor	Mean (SD)	Missing [n (%)]	HR per	95% CI	p	HR per	95% CI	p iding	₩ A Per	per 95% Cl p		
			SD <sup>a</sup>			SD <sup>a</sup>		for	ong			
Age	76.70 (9.42)	0	1.82	1.54, 2.16	<0.01	2.00	1.84, 2.19	<0.0	<b>E</b> 0.96	0.90, 1.01	0.01	
BMI	27.37 (4.49)	394 (3.61%)	1.07	0.93, 1.23	0.36	0.96	0.89, 1.03	0.2	ច្រុំ រុំឆ្នាំ 1.04	0.99, 1.09	0.10	
Triglycerides	1.48 (0.82)	3,856 (35.37%)	0.89	0.70, 1.12	0.31	1.02 <sup>b</sup>	0.92, 1.13	0.72	≥ ≥1.03	0.97, 1.09	0.38	
HDL cholesterol	1.34 (0.53)	3,954 (36.27%)	1.04	0.88, 1.23	0.67	0.97 <sup>b</sup>	0.86, 1.09	0.585	<u>1.01</u>	0.95, 1.07	0.79	
LDL cholesterol	2.84 (0.99)	4,698 (43.10%)	0.84	0.68, 1.03	0.09	0.90 <sup>b</sup>	0.82, 1.01	0.0	<b>9</b> 0.99	0.94, 1.05	0.81	
Hb	141.81 (16.58)	2,696 (24.73%)	0.71	0.59, 0.85	<0.01	0.74	0.67, 0.80	<0.0	<b>a</b> 0.90	0.85, 0.96	<0.01	
Albumin	41.41 (4.31)	2,954 (27.10%)	0.76	0.65, 0.89	<0.01	0.81	0.75, 0.88	<0.0	<b>å</b> 0.92	0.87, 0.97	<0.01	
Random glucose	5.92 (2.11)	4,525 (41.51%)	1.28	1.08, 1.53	<0.01	1.11	0.99, 1.24	0.0	<b>3</b> 1.02 <sup>b</sup>	0.95, 1.09	0.58	
	Median (IQR)	Missing [n (%)]			0.			, ∧It	http:/			
PSA	10.4 (6.11, 24.6)	2,352 (21.58%)	1.19	1.04, 1.35	0.01	1.14	1.02, 1.28	0.0	<b>1</b> .09	0.92, 1.30	0.33	
CRP	5 (2, 10)	8,061 (73.95%)	1.41 <sup>b</sup>	1.12, 1.77	<0.01	1.28 <sup>b</sup>	1.11, 1.47	<0.691	<b>1</b> .07	0.95, 1.20	0.25	
Ferritin	101.5 (45, 197)	9,495 (87.10%)	1.80	1.08, 3.00	0.02	1.02 <sup>b</sup>	0.67, 1.56	0.9	<b>9</b> 1.06	0.85, 1.32	0.62	
Adjusted for age, F Proportional Haza IR – Hazard Ratio; S - Haemoglobin A1c	PSA, Gleason score, rds assumption tes SD – Standard Devi ;; CRP – C-Reactive	. TNM stage t not met ation; BMI – Body I Protein; Hb – Haem	Mass Index	; PSA – Prostate	e Specific	Antigen; H	DL – High Dens	ilar technologies.	om/ on May #5, 202	.– Low Density	/ Lipopro	

n = 42, 182			Prosta	te cancer mo	rtality	Α	ll-cause mortal	ity L	<b>•</b> 44.	Systemic therap	ру
Factor	n (%)	Missing [n(%)]	HRª	95% CI	р	HR <sup>a</sup>	95% CI	p		95% CI	р
Smoker (current/ ex-)	19,215 (45.56%)	777 (7.13%)	1.41	1.04, 1.90	0.03	1.67	1.43, 1.96	<0.01	1.22	1.10, 1.34	<0.01
Excess alcohol	5,926 (14.05%)	4,370 (40.09%)	0.65	0.40, 1.05	0.08	0.89 <sup>b</sup>	0.71, 1.13	0.\$	<b>e</b> 0.99	0.86, 1.13	0.85
врн	4,318 (10.24%)	3,526 (32.35%)	0.63	0.38, 1.05	0.08	0.82	0.65, 1.03	0.	uar 0.73	0.62, 0.86	<0.01
COPD	3,866 (9.17%)	3,583 (32.87%)	0.99	0.58, 1.66	0.96	1.68	1.35, 2.09		× 201.18	0.99, 1.40	0.06
CVA	2,973 (7.05%)	3,584 (32.88%)	0.64	0.30, 1.38	0.26	1.47	1.12, 1.93		0.90	0.71, 1.15	0.41
IHD	7,512 (17.81%)	3,405 (31.24%)	1.70	1.19, 2.44	<0.01	1.31	1.08, 1.58		<b>§</b> 1.01	0.87, 1.00	0.9
PVD	1,138 (2.70%)	3,582 (32.86%)	2.52	1.23, 5.16	0.01	1.91	1.27, 2.85	<0.210	<b>ad</b> 1.09	0.75, 1.59	0.64
T2DM	6,233 (14.78%)	3,448 (31.63%)	1.06	0.72, 1.58	0.76	0.97	0.79, 1.19	0.25.	<b>0</b> 1.02	0.88, 1.17	0.83
Aspirin	2,022 (4.79%)		1.55	0.79, 3.02	0.20	1.41	0.99, 2.00	0.86	<b>8</b> 1.23	0.95, 1.60	0.12
Metformin	220 (0.52%)				),	2.76	1.03, 7.38	0.24	1.43	0.64, 3.20	0.38
Alpha blockers	1,025 (2.43%)	16 (0 15%)	1.28	0.59, 2.75	0.53	1.19	0.85, 1.67	0.352	0.55	0.38, 0.79	<0.01
Beta blockers	1,127 (2.67%)	10 (0.15%)	1.76	0.82, 3.75	0.15	1.82	1.27, 2.62	<0,01 °	1.43	1.06, 1.93	0.02
Statins	1,299 (3.08%)		1.42	0.75, 2.69	0.28	0.87	0.57, 1.32	0.54 s	1.09	0.86, 1.37	0.48
Vitamin D	2,093 (4.96%)		1.13	0.55, 2.30	0.74	1.13	0.78, 1.65	0.5	<mark>8</mark> 1.38	1.12, 1.72	<0.01
able S6 – Prognostic fac Adjusted for age, PSA, G Proportional Hazards as R – Hazard Ratio; BPH – VD – Peripheral Vascula	tors for men with Io Gleason score, TNM s ssumption test not n - Benign Prostatic Hy n Disease; T2DM – T	calised disease an stage net pertrophy; COPD ype 2 Diabetes Me	d unknow – Chronic ellitus	n location ass Obstructive P	ociated v ulmonar	vith outco	omes ;; CVA – Cerebro	bvasc@lar	on May 15, 2025 at Department GEZ-L	; IHD – Ischaem	iic Heart Di

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## **BMJ** Open

# TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction	1	1	, , ,	
Background	За	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4-5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3, 5
Methods	I			
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participante	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	50	D;V	Give details of treatments received, if relevant. Clearly define the outcome that is predicted by the prediction model, including how and	6
Outcome	6a 6b	D;V	when assessed. Report any actions to blind assessment of the outcome to be predicted	0 n/a
	7a		Clearly define all predictors used in developing the multivariable prediction model,	6.8
Predictors	74		including how and when they were measured. Report any actions to blind assessment of predictors for the outcome and other	0,0
Comple size	/D	D;V	predictors.	n/a
Sample size	8	D;v	Explain now the study size was arrived at. Describe how missing data were handled (e.g. complete-case analysis, single	1
Missing data	9	D;V	imputation, multiple imputation) with details of any imputation method.	6-7
	10a		Specify type of model, all model-building procedures (including any predictor selection).	6-7
Statistical	10b	D	and method for internal validation.	6-7
analysis	10c	V	For validation, describe how the predictions were calculated.	n/a
methodo	10d	D;V	multiple models.	n/a
Piek groupe	10e		Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Development	12	V	For validation, identify any differences from the development data in setting, eligibility	n/a
vs. validation	<u> </u>		criteria, outcome, and predictors.	
Results	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8
Participants	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a
Model	14a	D	Specify the number of participants and outcome events in each analysis.	8
development	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	S1-2
Model	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	n/a
specification	15b	D	Explain how to use the prediction model.	n/a
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	n/a
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion	r T			
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11
Interprotation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	n/a
merpretation	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-12
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	12
Other information			Provide information about the availability of supplementary resources, such as study	
information	21	D;V	protocol, Web calculator, and data sets.	6
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2

\*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

# Retrospective cohort study evaluating clinical, biochemical and pharmacological prognostic factors for prostate cancer progression using primary care data

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Keywords:	Prostate disease < UROLOGY, Epidemiology < ONCOLOGY, PRIMARY CARE





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2	2	
3 4	3	
5 6 7	4	Retrospective cohort study evaluating clinical, biochemical and
8 9 10	5	pharmacological prognostic factors for prostate cancer
11 12 13	6	progression using primary care data
14 15	7	
16	8	Samuel W D Merriel <sup>1, 2</sup>
17 18	9	Suzanne M Ingle <sup>2</sup>
19 20	10	Margaret T May <sup>2, 3</sup>
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1	1	Abstract
2 3	2	<b>Objectives</b> – To confirm the association of previously reported prognostic factors with future
4 5	3	progression of localised prostate cancer using primary care data and identify new potential
6 7	4	prognostic factors for further assessment in prognostic model development and validation.
8	5	Design – Retrospective cohort study, employing Cox proportional hazards regression controlling
9 10	6	for age, PSA, and Gleason score, stratified by diagnostic stage.
11 12	7	Setting – Primary care in England
13 14	8	Participants – Males with localised prostate cancer diagnosed between 01/01/1987 and
15 16	9	31/12/2016 within the Clinical Practice Research Datalink database, with linked data from the
17	10	National Cancer Registration and Analysis Service and Office for National Statistics.
19	11	Primary and Secondary outcomes – Primary outcome measure was prostate cancer mortality.
20 21	12	Secondary outcomes measures were all-cause mortality and commencing systematic therapy. Up-
22 23	13	staging after diagnosis was not used as a secondary outcome owing to significant missing data.
24 25	14	Results
26 27	15	10,901 males (mean age 74.38 +/- 9.03 years) with localised prostate cancer were followed up for
28 20	16	a mean of 14.12 (+/- 6.36) years. 2,331 (21.38%) men underwent systemic therapy and 3,250
30	17	(31.65%) died, including 1,250 (11.47%) from prostate cancer. Factors associated with an
32	18	increased risk of prostate cancer mortality included age; high PSA; current or ex-smoker;
33 34	19	ischaemic heart disease; high C-Reactive Protein; high ferritin; low haemoglobin; high blood
35 36	20	glucose; and low albumin.
37 38	21	Conclusions
39 40	22	This study identified several new potential prognostic factors for prostate cancer progression, as
41	23	well as confirming some known prognostic factors, in an independent primary care data set.
42 43	24	Further research is needed to develop and validate a prognostic model for prostate cancer
44 45	25	progression.
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1	1	Article summary
2 3	2	Strengths and limitations of this study
4	3	- Large retrospective cohort study of men with localised prostate cancer
6	4	- Mean follow-up 14.12 years
/ 8	5	- Data available on a wide range of potential prognostic factors for prostate cancer
9 10	6	progression
11 12	7	- Missing cancer stage and grade data from NCRAS cancer registry excluded a proportion of
13 14	8	the cohort
14 15 16 17 18 20 21 22 23 24 25 26 27 28 20 31 23 34 35 36 37 38 90 41 23 44 45 46 47 89 50 152 35 45 56 78 90		

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#### Main text

#### Introduction

Prostate cancer prognosis and treatment decisions remain a challenging clinical area for clinicians and patients, particularly for men with localised disease at the time of diagnosis. In recent decades, prostate cancer detection rates in many countries have increased markedly, in part as a result of the rising use of asymptomatic prostate specific antigen (PSA) testing[1]. However, more intensive PSA-based detection of prostate cancer has not been convincingly directly correlated with reductions in prostate cancer mortality for all men[2], implying increasing over-detection of clinically insignificant tumours[3]. Treatments for prostate cancer carry a significant risk of morbidity for men[4,5], underlining the importance of being able to identify which men with tumours confined to the prostate at diagnosis are at higher risk of prostate cancer progression and mortality to inform discussions about management options. 

Defining and measuring cancer progression with respect to treatment studies is outlined in the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, which was originally published by the World Health Organisation in 2000[6] and most recently updated in 2009[7]. Evidence of 30 17 tumour shrinkage on imaging and time to development of disease progression are used to <sub>32</sub> 18 measure treatment response. Definitions of cancer progression that are relevant to prognostic studies are less well defined, and numerous clinical, biological and surrogate markers of progression have been proposed in various studies. Prostate cancer mortality appears to be the logical ultimate endpoint of prostate cancer progression, but other measures such as development of metastases[8], biochemical recurrence[9], commencing systemic therapy[10], and 41 23 protein expression[11] have also been reported. 

There are a plethora of prognostic factor studies and prediction tools for prostate cancer risk[12] and prognosis[13] in the published literature. The vast majority are not externally calibrated or validated, and very few are established for use in clinical practice[12]. Initiatives such as the MRC PROGnosis RESearch Strategy Partnership (PROGRESS) partnership highlight the importance of **29** high quality prognostic research to help inform clinical practice[14], and outline methodologically rigorous approaches to achieve this aim[15–17]. Developing clinically useful risk-prediction rules 

starts with identifying potentially important prognostic factors which could be incorporated into a prediction model. The aim of the current study is to confirm the association of previously reported prognostic factors with future progression of localised prostate cancer using primary care data and identify new potential prognostic factors for further assessment in prognostic model development and validation. 

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#### **Materials and Methods**

The protocol for this study has been published previously in BMJ Open[18]. In summary, we undertook a retrospective cohort study using a longitudinal dataset of prospectively collected electronic primary care medical records from General Practices (GPs) in England for the Clinical Practice Research Datalink (CPRD)[19]. This dataset was linked with cancer registry data from the National Cancer Research and Analysis Service (NCRAS)[20] and mortality data from the Office for National Statistics (ONS)[21]. Men were included if they had a diagnosis of prostate cancer entered into their medical record during the 20-year study period (01/01/1987 – 31/12/2016). Localised prostate cancer was defined as T1-2/N0/M0 based on staging data entered into the NCRAS registry, which is determined from a combination of clinical, pathological and radiological data[22]. 

Potentially relevant clinical, biochemical and pharmacological factors measured in CPRD were identified from a review of the existing published literature (See BMJ Open protocol paper[18] for more information about the prognostic factors assessed). The primary outcome of the study was prostate cancer mortality. Secondary outcomes were all-cause mortality and commencing systemic prostate cancer therapy (a measurable proxy for progression and metastatic spread of prostate cancer). Surgery, radiotherapy and brachytherapy were classified as localised therapy, with chemotherapy, hormone treatments (primary or neo adjuvant), and immunotherapy considered systemic therapy. Mortality outcomes were based on primary/immediate cause of death reported in death certification information from the ONS, and therapy outcomes from NCRAS data. In our published protocol[18], up-staging after diagnosis was proposed as a secondary outcome indicating spread of disease; however, this was not used in the final analysis as repeat staging was rarely recorded in the cancer registry. 

Descriptive statistics were used to summarise the basic demographic details of the men, and the prevalence of the pre-selected putative prognostic factors. Cox proportional hazards regression was used to estimate crude and mutually adjusted hazard ratios (with 95% confidence intervals) for prostate cancer specific and all-cause mortality according to the prognostic factors, controlling for variables currently used in clinical practice (age, PSA level, Gleason score). Regression analyses

of continuous prognostic factors were standardised using hazard ratios per change in one standard deviation. A Proportional Hazards test was performed to confirm modelling met regression assumptions. The analysis was also stratified by stage at diagnosis (T1/2N0M0 vs T3+ and/or N1 and/or M1). Sensitivity analysis was performed, assuming all men in the overall sample with unknown tumour location had localised disease. In order to achieve 95% power and detect a difference of 0.1 in prostate cancer mortality for a binary risk factor using an alpha of 0.05, a sample of at least 6,046 men with prostate cancer would be required, assuming that 10% die over a median 10-year follow-up. 

.hroug. This study received ethical approval through the MHRA ISAC process (reference 17 041). The funder had no role in the planning or undertaking of this study, or the preparation of this 

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#### **Results**

54,500 men within CPRD had a diagnosis of prostate cancer entered into their primary care medical record during the study period. Baseline participant data are shown in Table 1. Tumour-Node-Metastases (TNM) staging data from the linked cancer registry were available for 7,646 (14.03%) of the sample population and treatment data were available for 22,766 (41.77%) men. Missing TNM staging data from the cancer registry was lower for men diagnosed in more recent years: there were no TNM stage data for men diagnosed before 1993, rising to 37.2% with TNM stage data (1,064/2,836) in 2015. This is consistent with a recent validation study of the NCRAS prostate cancer registry that showed low levels of completeness of TNM stage and Gleason score data prior to 2010[23]. Using the available staging and treatment data, 10,901 (20%) men were identified as having localised prostate cancer at the time of diagnosis and were included in the final cohort for analysis, with a mean follow-up of 14.12 (+/-6.36) years. Levels of missing data for selected prognostic factors within CPRD varied. 

1,250 men with localised disease died of prostate cancer over the course of follow-up, giving a prostate cancer mortality rate of 8.1 per 1,000 person-years. The total number of deaths for included men was 3,250 (21.11 deaths per 1,000 person-years). 2,331 (21.38%) men with localised disease received systemic therapy in the follow-up period after diagnosis. For over 90% of the men it was unknown whether they were re-investigated for cancer staging after diagnosis or not (see Table 2). 

Raised acute phase reactants (C-Reactive Protein [CRP] [adjusted HR per SD 1.35 95% CI 1.02, 1.77]), ferritin (adjusted HR per SD 2.03 95% CI 1.21, 3.39) and random glucose (adjusted HR per SD 1.27 95% CI 1.06, 1.54) were associated with prostate cancer mortality. Anaemia (adjusted HR per SD 0.72 95% CI 0.59, 0.88) and low albumin (adjusted HR per SD 0.81 95% CI 0.67, 0.97) were also associated with this outcome. No medications assessed were associated with prostate cancer mortality. Current and ex-smokers (adjusted HR 1.47 95% CI 1.05, 2.05), and patients with a history of ischaemic heart disease (adjusted HR 1.79 95% CI 1.20, 2.66) had a higher risk of prostate cancer mortality over the study period.

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Raised CRP, anaemia, and low albumin were biochemical factors associated with all-cause mortality; with anaemia and low albumin also being associated with commencing systemic therapy. A number of other factors were also associated with all-cause mortality, including age, raised PSA, smoking and smoking-related disease, cardiovascular diseases, as well as current use of aspirin or beta blockers. Smoking and beta blockers were also associated with increased risk of systemic therapy, as were vitamin D supplements. Benign prostatic hyperplasia and alpha blocker prescription were associated with a reduced risk of commencing systemic therapy (See Tables 3 & 4 for adjusted analysis results, and Supplementary Tables S1 & S2 for unadjusted results). 

Sensitivity analysis including all participants with unknown tumour location showed a relationship between a history of stroke and all-cause mortality (adjusted HR 1.47 95% CI 1.12, 1.93 p = 0.006). The relationship between aspirin and prostate cancer mortality altered to very weak evidence for association (adjusted HR 1.55 95% CI 0.79, 3.02 p = 0.2). For all other factors measured and for all three outcomes in the analysis, the direction of relationship did not change and the magnitude of relationship stayed relatively stable (see Supplementary Tables S3-6). 26 15 

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#### Discussion

This retrospective cohort study utilised primary care medical records data for men with localised prostate cancer from CPRD to confirm prognostic factors associated with prostate cancer progression. Well-known factors already incorporated into clinical guidelines, such as age and PSA, were confirmed as being individual prognostic factors. In addition, further clinical (history of smoking or ischaemic heart disease) and biochemical (anaemia or high ferritin) factors were found to be strongly associated with prostate cancer mortality. Anaemia, low albumin, raised PSA, history of ischaemic heart disease, and smoking were also strongly associated with all-cause mortality, as were peripheral vascular disease, COPD, and beta blocker use. Smoking history was strongly associated with future systemic therapy, as were recent prescriptions of alpha blockers, or vitamin D supplements. 

This analysis confirms the prognostic associations of some factors in prostate cancer progression. Smoking has also been found to be a risk factor for prostate cancer progression and mortality in cohort studies[24] and systematic reviews[8]. Low albumin was associated with prostate cancer mortality in the AMORIS cohort[25] and, along with anaemia[26], is a more widely accepted predictor of poor cancer outcomes[27]. The published literature around the prognostic effect of beta blockers for prostate cancer patients has been more mixed[28], with this study lending weight to the evidence of increased mortality in cancer patients. BMI was not shown to be associated with prostate cancer and overall mortality in this study. Whilst some observational studies of prostate cancer have suggested an association may exist[8,29,30], reviews of trial data have demonstrated higher BMI may actually improve the prognosis for men with cancer[31]. 

This study attempted to confirm prognostic factors in a primary care dataset that could be used in a model to predict prostate cancer progression at the time of diagnosis, prior to any treatment being initiated. This approach could allow the identified prognostic factors to be used to develop a new prognostic tool to inform treatment decisions between a patient and their treating team. There are already examples of similar prognostic tools available for use, including Predict Prostate (https://prostate.predict.nhs.uk/). However, these tools have only been developed using secondary care data[32], which may not capture all important prognostic factors or have 

equivalent length of follow-up of patients in their development or calibration cohorts. In the
 context of on-going challenges with prognostication for men with localised prostate cancer, and
 the increasing numbers of men being diagnosed every year, getting the most accurate information
 to inform treatment discussions between patients and their treating physicians is vital.

# 6 Strengths and limitations

This study has a number of unique features. This is the first study that the authors are aware of to utilise a primary care dataset to identify and confirm prognostic factors associated with prostate cancer progression. CPRD contains all data held in the primary care records of millions of UK patients, allowing the inclusion of a range of potentially important prognostic factors. Using a primary care dataset from the NHS also provided long-term data for included patients, with a mean follow-up of over 14 years. Prolonged follow-up for men with prostate cancer is important as many patients can live for years before their cancer progresses. The lack of high quality prognostic research discussed in the introduction is not limited to prostate cancer, with many other prognostic factor studies being conducted in similarly flawed ways[33–35]. This study sought to take a confirmatory approach to postulated prognostic factors in prostate cancer in a rigorous manner, following the methodological recommendations of the REMARK guidelines[36] and the PROGRESS partnership[14–17]. 

There are some limitations of this study that need to be considered. Previous research has shown that the prostate cancer registry in England has strong case completeness, but significant missing TNM stage and Gleason score data up until recent years[23]. Data completeness and quality within NCRAS continues to improve, and there is no equivalent UK cancer registry dataset with more complete data available at this present time[22]. This level of missing data meant it was unknown whether the majority of potentially included men had localised disease or not. Even so, the study was still powered to answer the research question, and sensitivity analyses showed minimal changes to almost all relationships between the prognostic factors of interest and the study outcomes. Misattribution of prostate cancer as the primary cause of death may occur in some frail, elderly patients or patients with multimorbidity, affecting the primary outcome of this study. There is evidence of misattribution of prostate cancer as a cause of death in other high-

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income countries[37,38], however an English study comparing death certification to a blinded, independent panel showed that ONS data on prostate cancer mortality classification is highly accurate[39]. This study uses a retrospective design interrogating electronic primary care records. It relies on accurate coding from GPs[40], and there was significant missing data for some prognostic factors. 

This study took a confirmatory approach to identify which prognostic factors for prostate cancer progression may be relevant, and some new prognostic factors not currently recommended for use in clinical practice were identified. These prognostic factors could be used to generate a more guid. progressic. Ins between pat. robust clinical risk prediction tool to guide treatment decision-making. Developing an accurate prediction tool for prostate cancer progression, not just mortality, could be more useful for informing management discussions between patients and clinicians. 

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### **Ethical approval** This study received ethical approval from the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Authority (MHRA) - Protocol reference 17 041. It was conducted in accordance with the Declaration of Helsinki. **Funding statement** SWDM is supported by the Can Test Collaborative, which is funded by CRUK (C8640/A23385). This work was supported from an Academic Clinical Fellowship in Primary Care for SWDM, funded by the National Institute for Health Research and Health Education England. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health. RMM was supported by a CRUK programme grant, the Integrative Cancer Epidemiology Programme (C18281/A19169). MTM was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. 26 15 Author statement SWDM conceived and designed the work that has led to this submission. He acquired the data and performed the analysis. He drafted the manuscript and approves the final version. He agrees to be accountable for all aspects of the work. As corresponding author, he also confirms he has full access to the data in the study and has taken final responsibility for the decision to submit for publication. SMI played an important role in the data analysis and interpretation of the results. She revised the manuscript and approved the final version. She agrees to be accountable for all aspects of the work. MTM helped design the work that has led to this submission, and supported interpretation of the results. She also provided study supervision to SWDM. She has revised the manuscript and approved the final version. She agrees to be accountable for all aspects of the work. RMM helped to conceive and design the work that has led to this submission. He also provided study supervision to SWDM He has revised the manuscript and approved the final version. He agrees to be accountable for all aspects of the work.

1 2 2	2	Confl	ict of interest disclosure statement – The authors declare no potential conflicts of interest
3 4	3		
5 6	4	Data	statement
7 8	5	This s	tudy analysed a CPRD dataset, with linked NCRAS and ONS data. Permission was not sought
9 10	6	to sha	are the dataset publicly.
11 12	7		
13	8	Patie	nt and Public Involvement
14 15 16	9	Patie	nts and the public were not involved in the design or conduct of this research.
17 18 19	11	Refer	ences
20 21	12	1	Collin SM, Martin RM, Metcalfe C, et al. Prostate-cancer mortality in the USA and UK in
22	13		1975-2004: an ecological study. <i>Lancet Oncol</i> 2008; <b>9</b> :445–52. doi:10.1016/S1470-
24	14		2045(08)70104-9
26	15	2	Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and
27 28	16		Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Int. Agency Res. Cancer.
29 30	17		2013.http://globocan.iarc.fr (accessed 24 May 2018).
31 32	18	3	Sandhu GS, Andriole GL. Overdiagnosis of prostate cancer. J Natl Cancer Inst - Monogr
33 34	19		2012; <b>2012</b> :146–51. doi:10.1093/jncimonographs/lgs031
35	20	4	Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring,
37	21		Surgery, or Radiotherapy for Prostate Cancer. <i>N Engl J Med</i> 2016; <b>375</b> :1425–37.
30 39	22		doi:10.1056/NEJMoa1606221
40 41	23	5	Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or
42 43	24		Radiotherapy for Localized Prostate Cancer. N Engl J Med 2016;:NEJMoa1606220-
44 45	25		10.http://www.nejm.org/doi/10.1056/NEJMoa1606220
46 47	26	6	Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to
48 40	27		treatment in solid tumors. European Organization for Research and Treatment of Cancer,
50	28		National Cancer Institute of the United States, National Cancer Institute of Canada. JNCI J.
51 52	29		Natl. Cancer Inst. 2000;92:205-
53 54	30		16.http://jnci.oxfordjournals.org/cgi/doi/10.1093/jnci/92.3.205
55 56			
57 58			
59 60			

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1	1	7	Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid
2	2		tumours: Revised RECIST guideline (version 1.1). 2009;45:228–
4 5	3		47.http://dx.doi.org/10.1016/j.ejca.2008.10.026
5 6	4	8	Peisch SF, Blarigan EL Van, Chan JM, et al. Prostate cancer progression and mortality: a
7 8	5		review of diet and lifestyle factors. World J Urol 2017;35:867–74. doi:10.1007/s00345-016-
9 10	6		1914-3.Prostate
11 12	7	9	Bianco-Miotto T, Chiam K, Buchanan G, et al. Global levels of specific histone modifications
13 14	8		and an epigenetic gene signature predict prostate cancer progression and development.
15	9		Cancer Epidemiol Biomarkers Prev 2010;19:2611–22. doi:10.1158/1055-9965.EPI-10-0555
10	10	10	Fleshner N, Lucia MS, Melich K, et al. Effect of dutasteride on prostate cancer progression
18 19	11		and cancer diagnosis on rebiopsy in the REDEEM active surveillance study. J Clin Oncol
20 21	12		2011; <b>29</b> :no pagination. doi:10.1200/jco.2011.29.7
22 23	13	11	Cullen J, Young D, Chen Y, et al. Predicting Prostate Cancer Progression as a Function of ETS-
24 25	14		related Gene Status, Race, and Obesity in a Longitudinal Patient Cohort. Eur Urol Focus
26	15		2017; <b>1</b> :1–7. doi:10.1016/j.euf.2017.02.016
27	16	12	Louie KS, Seigneurin A, Cathcart P, et al. Do prostate cancer risk models improve the
29 30	17		predictive accuracy of PSA screening? A meta-analysis. Ann Oncol 2015;26:848–64.
31 32	18		doi:10.1093/annonc/mdu525
33 34	19	13	Shariat SF, Kattan MW, Vickers AJ, et al. Critical review of prostate cancer predictive tools.
35 36	20		<i>Futur Oncol</i> 2009; <b>5</b> :1555–84.http://www.futuremedicine.com/doi/10.2217/fon.09.121
37	21	14	Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: A
39	22		framework for researching clinical outcomes. BMJ 2013; <b>346</b> :e5595–
40 41	23		e5595.http://www.bmj.com/cgi/doi/10.1136/bmj.e5595
42 43	24	15	Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2:
44 45	25		Prognostic Factor Research. PLoS Med 2013;10:e1001380-
46 47	26		9.http://dx.plos.org/10.1371/journal.pmed.1001380
48	27	16	Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis Research Strategy
50	28		(PROGRESS) 3: Prognostic Model Research. PLoS Med 2013;10:e1001381-
51 52	29		9.http://dx.plos.org/10.1371/journal.pmed.1001381
53 54	30	17	Hingorani AD, Windt DA v d, Riley RD, et al. Prognosis research strategy (PROGRESS) 4:
55 56			
57 58			
59 60			

Page 17 of 29

1	1		Stratified medicine research. BMJ 2013;346:e5793-
2	2		e5793.http://www.bmj.com/cgi/doi/10.1136/bmj.e5793
4	3	18	Merriel SWD, May MT, Martin RM. Predicting prostate cancer progression: protocol for a
5 6	4		retrospective cohort study to identify prognostic factors for prostate cancer outcomes using
7 8	5		routine primary care data. BMJ Open 2018;8:e019409. doi:10.1136/ bmjopen-2017-019409
9 10	6	19	CPRD. Welcome to the Clinical Practice Research Datalink. https://www.cprd.com/home/
11 12	7	20	NCRAS. National Cancer Research and Analysis Service.
13	8		papers3://publication/uuid/CBEF1C52-AEBE-4B92-A099-2BC799944207
14	9	21	ONS. Deaths Registered in England and Wales (Series DR), 2016. London: 2017.
16 17	10		http://www.ons.gov.uk/ons/rel/vsob1/mortality-statisticsdeaths-registered-in-england-
18 19	11		and-walesseries-dr-/2014/stb-mortality-stats-2014.html
20 21	12	22	Henson KE, Elliss-Brookes L, Coupland VH, et al. Data Resource Profile: National Cancer
22 23	13		Registration Dataset in England. Int J Epidemiol 2020;49:16-16h. doi:10.1093/ije/dyz076
24 25	14	23	Merriel SWD, Turner EL, Walsh E, et al. Cross-sectional study evaluating data quality of the
25 26	15		National Cancer Registration and Analysis Service (NCRAS) prostate cancer registry data
27 28	16		using the Cluster randomised trial of PSA testing for Prostate cancer (CAP). BMJ Open
29 30	17		2017; <b>7</b> :e015994. doi:10.1136/bmjopen-2017-015994
31 32	18	24	Rohrmann S, Genkinger JM, Burke A, et al. Smoking and Risk of Fatal Prostate Cancer in a
33 34	19		Prospective U.S. Study. Urology 2007;69:721–
35	20		5.http://linkinghub.elsevier.com/retrieve/pii/S0090429506026446
37	21	25	Arthur R, Williams R, Garmo H, et al. Serum inflammatory markers in relation to prostate
38 39	22		cancer severity and death in the Swedish AMORIS study. Int J Cancer 2018;142:2254–62.
40 41	23		doi:10.1002/ijc.31256
42 43	24	26	Van Belle SJP. What is the value of hemoglobin as a prognostic and predictive factor in
44 45	25		cancer? <i>Eur J Cancer, Suppl</i> 2004; <b>2</b> :11–9. doi:10.1016/S1359-6349(03)00103-4
46 47	26	27	Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: A systematic
48	27		review of the epidemiological literature. <i>Nutr J</i> 2010; <b>9</b> :1–16. doi:10.1186/1475-2891-9-69
49 50	28	28	Assayag J, Pollak MN, Azoulay L. Post-diagnostic use of beta-blockers and the risk of death
51 52	29		in patients with prostate cancer. Eur J Cancer 2014;50:2838-
53 54	30		45.http://dx.doi.org/10.1016/j.ejca.2014.08.006
55 56			
57 58			
59 60			
00			

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1	1	29	Cantarutti A, Bonn SE, Adami H-O, et al. Body mass index and mortality in men with
2	2		prostate cancer. Prostate 2015;75:1129–36. doi:10.1002/pros.23001
4 5	3	30	Haque R, Van Den Eeden SK, Wallner LP, et al. Association of body mass index and prostate
5 6	4		cancer mortality. Obes Res Clin Pract 2014;8:e374-81. doi:10.1016/j.orcp.2013.06.002
7 8	5	31	Greenlee H, Unger JM, LeBlanc M, et al. Association between body mass index and cancer
9 10	6		survival in a pooled analysis of 22 clinical trials. Cancer Epidemiol Biomarkers Prev
11 12	7		2017; <b>26</b> :21–9. doi:10.1158/1055-9965.EPI-15-1336
13 14	8	32	Gnanapragasam VJ, Lophatananon A, Wright KA, et al. Improving Clinical Risk Stratification
15	9		at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study. PLoS Med
17	10		2016; <b>13</b> :1–18. doi:10.1371/journal.pmed.1002063
18 19	11	33	Kyzas PA, Denaxa-Kyza D, Ioannidis JPA. Almost all articles on cancer prognostic markers
20 21	12		report statistically significant results. <i>Eur J Cancer</i> 2007; <b>43</b> :2559–79.
22 23	13		doi:10.1016/j.ejca.2007.08.030
24 25	14	34	Kyzas PA, Loizou KT, Ioannidis JPA. Selective reporting biases in cancer prognostic factor
26 27	15		studies. <i>J Natl Cancer Inst</i> 2005; <b>97</b> :1043–55. doi:10.1093/jnci/dji184
27	16	35	Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. BMJ
29 30	17		2010; <b>340</b> :410–4. doi:10.1136/bmj.b4184
31 32	18	36	McShane LM, Altman DG, Sauerbrei W, et al. Reporting Recommendations for Tumor
33 34	19		Marker Prognostic Studies (REMARK). JNCI J Natl Cancer Inst 2005;97:1180–
35 36	20		4.https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/dji237
37 38	21	37	Moghanaki D, Howard LE, De Hoedt A, et al. Validity of the National Death Index to
39	22		ascertain the date and cause of death in men having undergone prostatectomy for prostate
40 41	23		cancer. Prostate Cancer Prostatic Dis 2019;22:633–5. doi:10.1038/s41391-019-0146-1
42 43	24	38	Löffeler S, Halland A, Weedon-Fekjær H, et al. High Norwegian prostate cancer mortality:
44 45	25		evidence of over-reporting. <i>Scand J Urol</i> 2018; <b>52</b> :122–8.
46 47	26		doi:10.1080/21681805.2017.1421260
48 49	27	39	Turner EL, Metcalfe C, Donovan JL, et al. Contemporary accuracy of death certificates for
50	28		coding prostate cancer as a cause of death: Is reliance on death certification good enough?
51	29		A comparison with blinded review by an independent cause of death evaluation committee.
53 54	30		Br J Cancer 2016; <b>115</b> :90–4.http://dx.doi.org/10.1038/bjc.2016.162
55 56			
57 58			
59 60			
00			

1 2 3	1 2	40	Reeves D, Springate DA, Ashcroft DM, et al. Can analyses of electronic patient records be independently and externally validated? The effect of statins on the mortality of patients
4 5	3		with ischaemic heart disease: a cohort study with nest case-control analysis. BMJ Open
6 7	4		2014; <b>4</b> :1–11.http://dx.doi.org/10.1136/bmjopen-2014-004952
8 0	5		
10 11	6		
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	Localised	Missing data
	n = 10,901	
Vlean (SD)		I
Age (yrs)	74.38 (+/- 9.03)	0%
3MI (kg/m²)	27.43 (+/- 4.48)	5.64%
ollow-up (yrs)	14.12 (+/- 6.36)	0%
Vedian (IQR)		<u> </u>
PSA (ng/mL)	8.4 (5.55, 14.6)	30.66%
า (%)		
Gleason score		
6	3,655 (33.53%)	22 220/
7+	4,420 (40.55%)	. 55.2570
amily history of	70 (0 64%)	EE 110/
prostate cancer	70 (0.04%)	55.11%
Ethnicity		
White	7,361 (67.53%)	
Mixed	21 (0.19%)	
Asian	75 (0.69%)	29.79%
Black	156 (1.43%)	
Othor	41 (0.38%)	
Other		

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		Prostate cancer	All-cause	Systemic	Upstaging <sup>a</sup>
		mortality	mortality	therapy	
Included	Localised (T1/2 N0 M0) n = 10,901	1,250 (11.47%)	3,450 (31.65%)	2,331 (21.38%)	45 (0.41%)
uded	Invasive (T3+ / N1 / M1) n = 12,318	3,894 (31.61%)	6,916 (56.15%)	10,881 (88.33%)	28 (0.23%)
Excl	Unknown n = 31,281	1,540 (4.92%)	5,420 (17.33%)	31,954 (58.63%)	19 (0.06%)

Table 2 - Primary and Secondary outcomes for included and excluded participants <sup>10</sup>α., g for 50,119 (91.96%).

<sup>a</sup> Repeat staging data missing for 50,119 (91.96%) of sample

n = 10,901			Prost	ate cancer mor	tality	AI	l-cause mortali	ty	j∓ ⊒ Sy	Atemic therapy	/
Factor	Mean (SD)	Missing [n (%)]	HR per SD <sup>a</sup>	95% CI	р	HR per SD <sup>a</sup>	95% CI	p	cler HR per SD <sup>a</sup> g	0 4495% CI	р
Age	74.39 (9.03)	0	1.70	1.40, 2.06	<0.01	1.92	1.74, 2.12	<0.01		<b>0.95</b> , 1.06	0.98
BMI	27.43 (4.48)	394 (3.61%)	1.05	0.90, 1.08	0.52	0.97	0.90, 1.05	0.51	1.04	<b>B</b> 0.99, 1.09	0.10
Triglycerides	1.45 (0.80)	3,856 (35.37%)	0.83	0.64, 1.08	0.16	1.00 <sup>b</sup>	0.90, 1.13	0.93	1.088	0.97, 1.09	0.37
HDL cholesterol	1.35 (0.43)	3,954 (36.27%)	1.05	0.89, 1.23	0.56	1.01 <sup>b</sup>	0.91, 1.12	0.86		<b>8</b> 0.95, 1.07	0.75
LDL cholesterol	2.95 (0.99)	4,698 (43.10%)	0.86	0.69, 1.07	0.18	0.92 <sup>b</sup>	0.82, 1.02	0.12	0.9	0.94, 1.05	0.86
Hb	144.28 (14.35)	2,696 (24.73%)	0.72	0.59, 0.88	<0.01	0.74	0.67, 0.82	<0.01	0.9 <b>2</b>	0.86, 0.98	0.01
Albumin	41.83 (3.94)	2,954 (27.10%)	0.81	0.67, 0.97	0.02	0.83	0.76, 0.91	<0.01	0.940	0.89, 0.99	0.04
Random glucose	5.70 (2.11)	4,525 (41.51%)	1.27	1.06, 1.54	0.01	1.12	0.99, 1.25	0.06	1.0 <b>2</b> b	0.95, 1.09	0.66
	Median (IQR)	Missing [n (%)]							ing,		
PSA	8.4 (5.55, 14.60)	2,352 (21.58%)	1.71	1.32, 2.23	<0.01	1.46	1.19, 1.78	<0.01	1.34	1.06, 1.68	0.01
CRP	3.9 (2, 8)	8,061 (73.95%)	1.35 <sup>b</sup>	1.02, 1.77	0.03	1.23 <sup>b</sup>	1.05, 1.45	0.01	1.07	0.95, 1.20	0.24
Ferritin	108.6 (47, 196)	9,495 (87.10%)	2.03	1.21, 3.39	<0.01	0.98 b	0.60, 1.59	0.93	1.05	0.85, 1.31	0.64
Adjusted for age,	PSA, Gleason score, ards assumption tes	, TNM stage .t not met iation: BMI – Body I	Mass Index	; PSA – Prostate	e Specific	Antigen; H	IDL – High Dens	ity Lipopi	imilar techno otein;joL	Son	
Proportional Haza IR – Hazard Ratio;	SD – Standard Devi	bouy i							2		

3 of 29					BMJ (	Open			by copyri	/bmjopen	
n = 10,901			Prosta	te cancer mo	rtality	A	ll-cause mortal	ity	ight, in	<u>&gt;</u> Systemic thera	ру
Factor	n (%)	Missing [n(%)]	HR <sup>a</sup>	95% CI	р	HR <sup>a</sup>	95% CI	р	HRE	2 495% CI	р
Smoker (current/ ex-)	5,112 (46.89%)	777 (7.13%)	1.47	1.05, 2.05	0.02	1.66	1.39, 1.98	<0.01	1. <b>@</b> 1	<b>0</b> 1.09, 1.33	<0.0
Excess alcohol	1,829 (16.78%)	4,370 (40.09%)	0.61	0.36, 1.04	0.07	0.91 <sup>b</sup>	0.71, 1.18	0.47	0.99	<b>D</b> 0.87, 1.13	0.88
ВРН	1,169 (10.72%)	3,526 (32.35%)	0.64	0.36, 1.11	0.11	0.81	0.62, 1.05	0.11	0.%	<b>6</b> 0.65, 0.90	<0.0
COPD	862 (7.91%)	3,583 (32.87%)	0.86	0.47, 1.57	0.63	1.64	1.29, 2.09	<0.01	1.18	0.99, 1.41	0.06
CVA	553 (5.07%)	3,584 (32.88%)	0.90	0.42, 1,94	0.79	1.19	0.85, 1.68	0.30	0. <u>55</u> 20	<b>8</b> 0.72, 1.17	0.49
IHD	1,548 (14.20%)	3,405 (31.24%)	1.79	1.20, 2.66	<0.01	1.25	1.02, 1.55	0.04		0.87, 1.18	0.86
PVD	202 (1.85%)	3,582 (32.86%)	2.24	0.98, 5.12	0.06	1.91	1.24, 2.95	<0.01		<b>b</b> 0.71, 1.51	0.85
T2DM	1,508 (13.83%)	3,448 (31.63%)	0.97	0.62, 1.51	0.89	0.95	0.76, 1.19	0.68	0. 👷 O	0.86, 1.14	0.91
Aspirin	426 (3.91%)		1.88	0.96, 3.70	0.06	1.58	1.09, 2.29	0.02	1.24	<b>6</b> <b>6</b> 0.95, 1.60	0.11
Metformin	33 (0.30%)	-			6	2.74	0.88, 8.49	0.08	1. <b>2</b> 3	<b>0.77, 3.85</b>	0.18
Alpha blockers	305 (2.80%)		1.55	0.72, 3.35	0.26	1.15	0.76, 1.73	0.52	0.54	0.39, 0.82	<0.0
Beta blockers	265 (2.43%)	_ 16 (0.15%)	2.03	0.89, 4.60	0.09	1.79	1.18, 2.72	<0.01	1.428	<u>.</u> 1.09, 1.99	0.01
Statins	339 (3.11%)	-	1.65	0.87, 3.15	0.13	1.01	0.66, 1.53	0.97	1.006	0.84, 1.34	0.61
Vitamin D	465 (4.27%)	-	1.33	0.65, 2.71	0.44	1.13	0.78, 1.65	0.51	1.35	1.09, 1.68	<0.02
able 4 – Prognostic fact Adjusted for age, PSA, C Proportional Hazards a R – Hazard Ratio; BPH -	ors for men with loc Gleason score, TNM ssumption test not r - Benign Prostatic Hy	alised disease asso stage net ypertrophy; COPD	– Chronic	th outcomes Obstructive F	Pulmonar	y Disease	; CVA – Cerebro	ovascular	illar technologies	on May tHD – Ischaen	nic Hear
Jisease; PVD – Periphera	ai Vascular Disease;	i 2DM – Type 2 Dia	idetes Me	llitus						)25 at Department GEZ-LT	
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Mean (SD)	Missing [n (%)]	HR per	95% CI	р	HR per	95% CI	p ding	∯R per	95% CI	р
		SD			SD		for u	SD ND		
74.39 (9.03)	0	1.66	1.56, 1.76	<0.01	1.82	1.76, 1.89	<0.0	<b>6</b> 0.81	0.77, 0.84	<0.01
27.43 (4.48)	394 (3.61%)	0.96	0.91, 1.02	0.19	0.97	0.94, 1.01	0.1	<b>n</b> a 1.07	1.03, 1.12	<0.01
1.45 (0.80)	3,856 (35.37%)	0.93	0.84, 1.02	0.12	0.97	0.92, 1.02	0.28		0.95, 1.04	0.82
1.35 (0.43)	3,954 (36.27%)	0.98	0.88, 1.09	0.66	0.98	0.92, 1.04	0.455		0.98, 1.08	0.23
2.95 (0.99)	4,698 (43.10%)	0.90	0.81, 0.99	0.03	0.87	0.82, 0.92	<0.0	<b>G o o o o o o o o o o</b>	0.91, 0.99	0.03
144.28 (14.35)	2,696 (24.73%)	0.55	0.51, 0.58	<0.01	0.62	0.59, 0.64	<0.0		0.89, 0.99	0.03
41.83 (3.94)	2,954 (27.10%)	0.71	0.67, 0.74	<0.01	0.74	0.71, 0.77	<0.0	• <b>å</b> 0.96	0.91, 1.00	0.06
5.70 (2.11)	4,525 (41.51%)	1.18	1.10, 1.27	<0.01	1.14	1.09, 1.20	<0.0	<b>B</b> 1.02	0.97, 1.07	0.48
Median (IQR)	Missing [n (%)]			9,			Alt	http:/		
8.4 (5.55, 14.60)	2,352 (21.58%)	1.45	1.39, 1.51	<0.01	1.36	1.31, 1.41	<0.0	1.01	0.86, 1.18	0.90
3.9 (2, 8)	8,061 (73.95%)	1.27	1.19, 1.36	<0.01	1.22	1.16, 1.28	<0.69	<b>8</b> 1.01	0.92, 1.10	0.90
108.6 (47, 196)	9,495 (87.10%)	1.48	1.25, 1.75	<0.01	1.13	0.97, 1.31	0.1	<b>1</b> .02	0.89, 1.16	0.79
ted HRs for progno	stic factors for men iation; BMI – Body I	with local Mass Index	ised disease asso ; PSA – Prostate	ociated v Specific	vith outcor Antigen; H	nes IDL – High Dens	ity Lipop	protein; LDL	– Low Density I	ipoproteir
;; CRP – C-Reactive	Protein; Hb – Haem	ioglobin					nologi	May 15,		
							S.	2025		
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	74.39 (9.03) 27.43 (4.48) 1.45 (0.80) 1.35 (0.43) 2.95 (0.99) 144.28 (14.35) 41.83 (3.94) 5.70 (2.11) Median (IQR) 8.4 (5.55, 14.60) 3.9 (2, 8) 108.6 (47, 196) ced HRs for progno SD – Standard Dev ; CRP – C-Reactive	74.39 (9.03)       0         27.43 (4.48)       394 (3.61%)         1.45 (0.80)       3,856 (35.37%)         1.35 (0.43)       3,954 (36.27%)         2.95 (0.99)       4,698 (43.10%)         144.28 (14.35)       2,696 (24.73%)         41.83 (3.94)       2,954 (27.10%)         5.70 (2.11)       4,525 (41.51%)         Median (IQR)       Missing [n (%)]         8.4 (5.55, 14.60)       2,352 (21.58%)         3.9 (2, 8)       8,061 (73.95%)         108.6 (47, 196)       9,495 (87.10%)         :ed HRs for prognostic factors for men         SD – Standard Deviation; BMI – Body I         ; CRP – C-Reactive Protein; Hb – Haem	Integer       Integer         74.39 (9.03)       0       1.66         27.43 (4.48)       394 (3.61%)       0.96         1.45 (0.80)       3,856 (35.37%)       0.93         1.35 (0.43)       3,954 (36.27%)       0.98         2.95 (0.99)       4,698 (43.10%)       0.90         144.28 (14.35)       2,696 (24.73%)       0.55         41.83 (3.94)       2,954 (27.10%)       0.71         5.70 (2.11)       4,525 (41.51%)       1.18         Median (IQR)       Missing [n (%)]       1.45         3.9 (2, 8)       8,061 (73.95%)       1.27         108.6 (47, 196)       9,495 (87.10%)       1.48         SD       2.95 (2.12.58%)       1.48         SD       8,061 (73.95%)       1.27         108.6 (47, 196)       9,495 (87.10%)       1.48         SD       SD       Standard Deviation; BMI – Body Mass Index         ; CRP – C-Reactive Protein; Hb – Haemoglobin       ; CRP – C-Reactive Protein; Hb – Haemoglobin	Millioning [H (N)]       Milliper       Joint Jec.       Joint Jec.         74.39 (9.03)       0       1.66       1.56, 1.76         27.43 (4.48)       394 (3.61%)       0.96       0.91, 1.02         1.45 (0.80)       3,856 (35.37%)       0.93       0.84, 1.02         1.35 (0.43)       3,954 (36.27%)       0.98       0.88, 1.09         2.95 (0.99)       4,698 (43.10%)       0.90       0.81, 0.99         144.28 (14.35)       2,696 (24.73%)       0.55       0.51, 0.58         41.83 (3.94)       2,954 (27.10%)       0.71       0.67, 0.74         5.70 (2.11)       4,525 (41.51%)       1.18       1.10, 1.27         Median (IQR)       Missing [n (%)]       1.45       1.39, 1.51         3.9 (2, 8)       8,061 (73.95%)       1.27       1.19, 1.36         108.6 (47, 196)       9,495 (87.10%)       1.48       1.25, 1.75         red HRs for prognostic factors for men with localised disease asses       SD – Standard Deviation; BMI – Body Mass Index; PSA – Prostate         ; CRP – C-Reactive Protein; Hb – Haemoglobin       CRP – C-Reactive Protein; Hb – Haemoglobin	Initial (1, (x))       Init periods       355 Cell       p         74.39 (9.03)       0       1.66       1.56, 1.76       <0.01	International (ICR)       International (ICR)       International (ICR)       International (ICR)         144.83       3.94 (3.61%)       0.96       0.91, 1.02       0.19       0.97         1.45 (0.80)       3.856 (35.37%)       0.93       0.84, 1.02       0.12       0.97         1.35 (0.43)       3.954 (36.27%)       0.98       0.88, 1.09       0.66       0.98         2.95 (0.99)       4,698 (43.10%)       0.90       0.81, 0.99       0.03       0.87         144.28 (14.35)       2,696 (24.73%)       0.55       0.51, 0.58       <0.01	Intern (EP)       Integer       Solution       p       Integer       Solution         74.39 (9.03)       0       1.66       1.56, 1.76       <0.01	Intern (b)       Intern (b)       SD       SD       Intern (b)       SD       SD       Intern (b)       SD       SD       SD       Intern (b)       SD       SD <th< td=""><td>Internet (b)       Internet (b)       SD       Internet (b)       Internet (b</td><td>Intern (pb)       Intern (pb)       <thintern (pb)<="" th=""> <thintern (pb)<="" th=""></thintern></thintern></td></th<>	Internet (b)       Internet (b)       SD       Internet (b)       Internet (b	Intern (pb)       Intern (pb) <thintern (pb)<="" th=""> <thintern (pb)<="" th=""></thintern></thintern>

n = 10.901			Prosta	te cancer mo	rtality	Α	ll-cause mortal	ity C		Systemic therai	ov
Factor	n (%)	Missing [n(%)]	HR	95% CI	p	HR	95% CI	p uding	HR C	95% Cl	р р
Smoker (current/ ex-)	5,112 (46.89%)	777 (7.13%)	1.24	1.09, 1.40	<0.01	1.36	1.26, 1.46	<0.01	<b>9</b> 1.20	1.10, 1.30	<0.01
Excess alcohol	1,829 (16.78%)	4,370 (40.09%)	0.75	0.62, 0.91	<0.01	0.67	0.60, 0.74	<0 <b>9</b> 1	<b>0</b> .92	0.80, 1.06	0.26
BPH	1,169 (10.72%)	3,526 (32.35%)	0.61	0.49, 0.76	<0.01	0.79	0.70, 0.88	<0 <b>⊉1</b>	0.70	0.61, 0.80	<0.01
COPD	862 (7.91%)	3,583 (32.87%)	0.95	0.77, 1.18	0.67	1.41	1.26, 1.58	<0.015	< 8 1.08	0.94, 1.25	0.26
CVA	553 (5.07%)	3,584 (32.88%)	1.48	1.18, 1.85	<0.01	1.89	1.67, 2.13	<0.60	<u>9</u> 0.78	0.64, 0.96	0.02
HD	1,548 (14.20%)	3,405 (31.24%)	1.62	1.39, 1.88	<0.01	1.79	1.64, 1.95	<0.916	<b>6</b> 0.89	0.79, 1.00	0.05
PVD	202 (1.85%)	3,582 (32.86%)	1.80	1.31, 2.49	<0.01	1.87	1.55, 2.25	<0.210	0.84	0.62, 1.14	0.26
r2dm	1,508 (13.83%)	3,448 (31.63%)	1.13	0.96, 1.33	0.16	1.03	0.94, 1.14	0.459'	0.93	0.83, 1.04	0.20
Aspirin	426 (3.91%)		2.33	1.88, 2.90	<0.01	2.18	1.90, 2.49	<0 <b>,9</b> 1	1.24	0.99, 1.54	0.06
Metformin	33 (0.30%)		1.99	0.90, 4.46	0.09	2.63	1.71, 4.04	<0.≹1	2.59	1.47, 4.57	<0.01
Alpha blockers	305 (2.80%)	16 (0 15%)	1.24	0.92, 1.67	0.16	1.17	0.97, 1.41	0.000	0.51	0.37, 0.71	<0.01
Beta blockers	265 (2.43%)	10 (0.1570)	2.15	1.65, 2.81	<0.01	1.76	1.48, 2.10	<0 <del>,0</del> 1 ລ	1.11	0.85, 1.46	0.43
Statins	339 (3.11%)		1.34	1.01, 1.77	0.04	0.93	0.76, 1.13	0.455 S	1.42	1.16, 1.73	<0.01
Vitamin D	465 (4.27%)		1.63	1.29, 2.05	<0.01	1.24	1.06, 1.46	<0.101	<b>1.52</b>	1.27, 1.82	<0.01
R – Hazard Ratio; BPH – VD – Peripheral Vascula	- Benign Prostatic Hy ır Disease; T2DM – T	/pertrophy; COPD	– Chronic ellitus	Obstructive P	ulmonar	y Disease	; CVA – Cerebro	ovascoogies.	on May 15. 2025 at Department GEZ-L	; IHD – Ischaem	ic Heart

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n = 42, 182			Prost	ate cancer mor	tality	Al	l-cause mortali	ty Clu	044 S	ystemic therap	ру
Factor	Mean (SD)	Missing [n (%)]	HR per	95% CI	р	HR per	95% CI	p p	HR per	95% CI	р
			SD			SD		for u	on A		
Age	76.70 (9.42)	0	1.55	1.49, 1.62	<0.01	1.78	1.74, 1.82	<0.0	<b>6</b> 0.67	0.65, 0.70	<0.01
BMI	27.37 (4.49)	394 (3.61%)	0.96	0.92, 0.99	0.05	0.96	0.94, 0.98	<0.0	ມີ ສູ່ 1.06	1.02, 1.10	<0.01
Triglycerides	1.48 (0.82)	3,856 (35.37%)	0.92	0.87, 0.99	0.02	0.95	0.91, 0.98	<0.0	8 <sup>0.96</sup>	0.91, 1.00	0.06
HDL cholesterol	1.34 (0.53)	3,954 (36.27%)	1	0.94, 1.07	0.60	1	0.97, 1.04	0.86	<u>1.03</u>	0.99, 1.06	0.12
LDL cholesterol	2.84 (0.99)	4,698 (43.10%)	0.93	0.86, 0.99	0.03	0.89	0.86, 0.93	<0.0	<b>§</b> 1.05	1, 1.10	0.03
Hb	141.81 (16.58)	2,696 (24.73%)	0.61	0.58, 0.63	<0.01	0.66	0.64, 0.67	<0.0	a 1.07	1.02, 1.13	<0.01
Albumin	41.41 (4.31)	2,954 (27.10%)	1.71	0.99, 2.96	0.06	1.33	0.91, 1.94	0.15	<b>ã</b> 0.75 <b>1</b>	0.46, 1.21	0.24
Random glucose	5.92 (2.11)	4,525 (41.51%)	1.06	1.01, 1.10	0.01	1.07	1.04, 1.09	<0.0	<b>8</b> 0.92	0.87, 0.98	0.01
	Median (IQR)	Missing [n (%)]			0,			Alt	http:/		
PSA	10.4 (6.11, 24.6)	2,352 (21.58%)	1.28	0.96, 1.71	0.10	0.84	0.73, 0.98	0.0	2.37	1.88, 2.99	<0.01
CRP	5 (2, 10)	8,061 (73.95%)	2.50	1.03, 6.08	0.04	2.55	1.47, 4.42	<0.69	<b>1</b> .03	0.51, 2.06	0.94
Ferritin	101.5 (45, 197)	9,495 (87.10%)	1.10	1.06, 1.15	<0.01	1.04	0.99, 1.09	0.1	<b>9</b> 0.99	0.90, 1.09	.089
IR – Hazard Ratio; Haemoglobin A1	SD – Standard Devi c; CRP – C-Reactive	ation; BMI – Body I Protein; Hb – Haem	Vass Index	; PSA – Prostate	e Specific	Antigen; H	IDL – High Dens	ity Lipæchnologies.	omæin; in; omæin May 15, 2025 at Department GEZ-	. – Low Density	/ Lipoprote

n = 42, 182			Prosta	te cancer mo	rtality	A	ll-cause mortali	ty מַ	<u>с</u> , 0 ог	Systemic thera	у
Factor	n (%)	Missing [n(%)]	HR	95% CI	р	HR	95% CI	p us	ਹ ਹੋ <sup>HR</sup>	95% CI	р
Smoker (current/ ex-)	19,215 (45.56%)	777 (7.13%)	1.24	1.09, 1.40	<0.01	1.36	1.26, 1.46	<0.001	<b>e</b> 1.20	1.10, 1.30	<0.01
Excess alcohol	5,926 (14.05%)	4,370 (40.09%)	0.75	0.62, 0.90	<0.01	0.79 <sup>b</sup>	0.71, 0.88	<0.001	1.01	0.90, 1.13	0.86
ВРН	4,318 (10.24%)	3,526 (32.35%)	0.61	0.49, 0.76	<0.01	0.79	0.70, 0.89	<0.012	<b>8</b> 0.70	0.61, 0.80	<0.01
COPD	3,866 (9.17%)	3,583 (32.87%)	0.95	0.77, 1.19	0.66	1.41	1.26, 1.58	<0.50 100 100 100 100 100 100 100 100 100 1	1.08	0.94, 1.25	0.26
CVA	2,973 (7.05%)	3,584 (32.88%)	1.48	1.19, 1.85	<0.01	1.89	1.67, 2.12	<0.315	0.78	0.64, 0.96	0.02
IHD	7,512 (17.81%)	3,405 (31.24%)	1.62	1.39, 1.88	<0.01	1.79	1.64, 1.95	<0 ឆ្នាំ <u>6</u>	0.89	0.79, 1.00	0.05
PVD	1,138 (2.70%)	3,582 (32.86%)	1.8	1.31, 2.49	<0.01	1.89	1.55, 2.25	<0₽1	<b>e</b> fr 0.84	0.62, 1.14	0.26
T2DM	6,233 (14.78%)	3,448 (31.63%)	1.13	0.96, 1.33	0.16	1.04	0.94, 1.14	0.	0.93	0.83, 1.04	0.20
Aspirin	2,022 (4.79%)		2.33	1.88, 2.90	<0.01	2.18	1.90, 2.49	<0.41	1.24	0.99, 1.54	0.06
Metformin	220 (0.52%)		1.99	0.90, 4.46	0.09	2.63	1.71, 4.04	<0.91	2.59	1.47, 4.57	<0.01
Alpha blockers	1,025 (2.43%)	16 (0 15%)	1.24	0.92, 1.67	0.16	1.17	0.98, 1.41	0.09	<b>0</b> .51	0.37, 0.71	<0.01
Beta blockers	1,127 (2.67%)	10 (0.1570)	2.15	1.65, 2.81	<0.01	1.76	1.48, 2.10	<0.01	1.11	0.85, 1.46	0.43
Statins	1,299 (3.08%)		1.34	1.01, 1.77	0.04	0.93	0.78, 1.13	0. <b>4</b>	<b>6</b> 1.42	1.16, 1.73	<0.01
Vitamin D	2,093 (4.96%)		1.63	1.29, 2.05	<0.01	1.24	1.06, 1.46	0.6	<b>g</b> 1.52	1.27, 1.88	<0.01
R – Hazard Ratio; BPH – VD – Peripheral Vascula	- Benign Prostatic Hy nr Disease; T2DM – T	vpertrophy; COPD	– Chronic	Obstructive P	ulmonar	y Disease	; CVA – Cerebro	ovascælar s	ay 14, 2025 at Department GEZ-L	t; IHD – Ischaen	nic Heart C

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n = 42, 182			Prosta	2, 182 Prostate cancer mortality All-cause mortality								
Factor	Mean (SD)	Missing [n (%)]	HR per 95% Cl p			HR per 95% Cl p			₩ A Per	95% CI	p	
			SD <sup>a</sup>			SD <sup>a</sup>		for	ong			
Age	76.70 (9.42)	0	1.82	1.54, 2.16	<0.01	2.00	1.84, 2.19	<0.0	<b>E</b> 0.96	0.90, 1.01	0.01	
BMI	27.37 (4.49)	394 (3.61%)	1.07	0.93, 1.23	0.36	0.96	0.89, 1.03	0.2	ច្រុំ រុំឆ្នាំ 1.04	0.99, 1.09	0.10	
Triglycerides	1.48 (0.82)	3,856 (35.37%)	0.89	0.70, 1.12	0.31	1.02 <sup>b</sup>	0.92, 1.13	0.72	≥ ≥1.03	0.97, 1.09	0.38	
HDL cholesterol	1.34 (0.53)	3,954 (36.27%)	1.04	0.88, 1.23	0.67	0.97 <sup>b</sup>	0.86, 1.09	0.585	<u>1.01</u>	0.95, 1.07	0.79	
LDL cholesterol	2.84 (0.99)	4,698 (43.10%)	0.84	0.68, 1.03	0.09	0.90 <sup>b</sup>	0.82, 1.01	0.0	<b>9</b> 0.99	0.94, 1.05	0.81	
Hb	141.81 (16.58)	2,696 (24.73%)	0.71	0.59, 0.85	<0.01	0.74	0.67, 0.80	<0.0	<b>a</b> 0.90	0.85, 0.96	<0.01	
Albumin	41.41 (4.31)	2,954 (27.10%)	0.76	0.65, 0.89	<0.01	0.81	0.75, 0.88	<0.0	<b>å</b> 0.92	0.87, 0.97	<0.01	
Random glucose	5.92 (2.11)	4,525 (41.51%)	1.28	1.08, 1.53	<0.01	1.11	0.99, 1.24	0.0	<b>3</b> 1.02 <sup>b</sup>	0.95, 1.09	0.58	
	Median (IQR)	Missing [n (%)]			0.			, ∧It	http:/			
PSA	10.4 (6.11, 24.6)	2,352 (21.58%)	1.19	1.04, 1.35	0.01	1.14	1.02, 1.28	0.0	<b>1</b> .09	0.92, 1.30	0.33	
CRP	5 (2, 10)	8,061 (73.95%)	1.41 <sup>b</sup>	1.12, 1.77	<0.01	1.28 <sup>b</sup>	1.11, 1.47	<0.691	<b>1</b> .07	0.95, 1.20	0.25	
Ferritin	101.5 (45, 197)	9,495 (87.10%)	1.80	1.08, 3.00	0.02	1.02 <sup>b</sup>	0.67, 1.56	0.9	<b>9</b> 1.06	0.85, 1.32	0.62	
Adjusted for age, F Proportional Haza IR – Hazard Ratio; S - Haemoglobin A1c	PSA, Gleason score, rds assumption tes SD – Standard Devi ;; CRP – C-Reactive	. TNM stage t not met ation; BMI – Body I Protein; Hb – Haem	Mass Index	; PSA – Prostate	e Specific	Antigen; H	DL – High Dens	ilar technologies.	om/ on May #5, 202	.– Low Density	/ Lipopro	

n = 42, 182				Prostate cancer mortality			All-cause mortality			Systemic therapy		
Factor	n (%)	Missing [n(%)]	HRª	95% CI	р	HR <sup>a</sup>	95% CI	p		95% CI	р	
Smoker (current/ ex-)	19,215 (45.56%)	777 (7.13%)	1.41	1.04, 1.90	0.03	1.67	1.43, 1.96	<0.01	1.22	1.10, 1.34	<0.01	
Excess alcohol	5,926 (14.05%)	4,370 (40.09%)	0.65	0.40, 1.05	0.08	0.89 <sup>b</sup>	0.71, 1.13	0.\$	<b>e</b> 0.99	0.86, 1.13	0.85	
врн	4,318 (10.24%)	3,526 (32.35%)	0.63	0.38, 1.05	0.08	0.82	0.65, 1.03	0.	uar 0.73	0.62, 0.86	<0.01	
COPD	3,866 (9.17%)	3,583 (32.87%)	0.99	0.58, 1.66	0.96	1.68	1.35, 2.09		× 201.18	0.99, 1.40	0.06	
CVA	2,973 (7.05%)	3,584 (32.88%)	0.64	0.30, 1.38	0.26	1.47	1.12, 1.93		0.90	0.71, 1.15	0.41	
IHD	7,512 (17.81%)	3,405 (31.24%)	1.70	1.19, 2.44	<0.01	1.31	1.08, 1.58	<0.30	<b>§</b> 1.01	0.87, 1.00	0.9	
PVD	1,138 (2.70%)	3,582 (32.86%)	2.52	1.23, 5.16	0.01	1.91	1.27, 2.85	<0.210	<b>0</b> 1.09	0.75, 1.59	0.64	
T2DM	6,233 (14.78%)	3,448 (31.63%)	1.06	0.72, 1.58	0.76	0.97	0.79, 1.19	0.25	<b>6</b> 1.02	0.88, 1.17	0.83	
Aspirin	2,022 (4.79%)		1.55	0.79, 3.02	0.20	1.41	0.99, 2.00	0.@6	<b>8</b> 1.23	0.95, 1.60	0.12	
Metformin	220 (0.52%)	- 16 (0.15%)			) <b>.</b>	2.76	1.03, 7.38	0.24	1.43	0.64, 3.20	0.38	
Alpha blockers	1,025 (2.43%)		1.28	0.59, 2.75	0.53	1.19	0.85, 1.67	0.52	0.55	0.38, 0.79	<0.01	
Beta blockers	1,127 (2.67%)		1.76	0.82, 3.75	0.15	1.82	1.27, 2.62	<0,01	1.43	1.06, 1.93	0.02	
Statins	1,299 (3.08%)		1.42	0.75, 2.69	0.28	0.87	0.57, 1.32	0.94 s	1.09	0.86, 1.37	0.48	
Vitamin D	2,093 (4.96%)		1.13	0.55, 2.30	0.74	1.13	0.78, 1.65	0.5	<mark>8</mark> 1.38	1.12, 1.72	<0.01	
able S6 – Prognostic fac Adjusted for age, PSA, G Proportional Hazards as R – Hazard Ratio; BPH – VD – Peripheral Vascula	tors for men with Io Gleason score, TNM s ssumption test not n - Benign Prostatic Hy n Disease; T2DM – T	calised disease an stage net pertrophy; COPD ype 2 Diabetes Me	d unknow – Chronic ellitus	n location ass Obstructive P	ociated v ulmonar	vith outco	omes ;; CVA – Cerebro	bvasc@lar	on May 15, 2025 at Department GEZ-L	; IHD – Ischaem	iic Heart Di	

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## **BMJ** Open

# TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page			
Title and abstract							
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.				
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.				
Introduction	ı.	1	, , , , , , , , , , , , , , , , , , ,				
Background	За	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4-5			
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3, 5			
Methods	I						
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6			
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6			
Participants Outcome	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.				
	5b	D;V	Describe eligibility criteria for participants.	6			
	50	D;V	Give details of treatments received, if relevant. Clearly define the outcome that is predicted by the prediction model, including how and	6			
	6a 6b	D;V	when assessed. Report any actions to blind assessment of the outcome to be predicted	0 n/a			
Predictors	7a		Clearly define all predictors used in developing the multivariable prediction model,	6.8			
	74		including how and when they were measured. Report any actions to blind assessment of predictors for the outcome and other	0,0			
Comple size	/D	D;V	predictors.	n/a			
Sample size	8	D;v	Explain now the study size was arrived at. Describe how missing data were handled (e.g. complete-case analysis, single	/			
Missing data Statistical analysis methods	9	D;V	imputation, multiple imputation) with details of any imputation method.	6-7			
	10a		Specify type of model, all model-building procedures (including any predictor selection).	6-7			
	10b	D	and method for internal validation.	6-7			
	10c	V	For validation, describe how the predictions were calculated.	n/a			
	10d	D;V	multiple models.	n/a			
10e         V         Describe any model u           Pisk groups         11         D:V         Provide details on bo			Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a			
Development	12	V	For validation, identify any differences from the development data in setting, eligibility	n/a			
vs. validation	<u> </u>		criteria, outcome, and predictors.				
Results	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8			
Participants	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8, Table 1			
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a			
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	8			
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	S1-2			
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	n/a			
	15b	D	Explain how to use the prediction model.	n/a			
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	n/a			
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).				
Discussion	r T						
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11			
Interprotation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	n/a			
Interpretation	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-12			
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	12			
Other information			Provide information about the availability of supplementary resources, such as study				
information	21	D;V	protocol, Web calculator, and data sets.	6			
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2			

\*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.