

Quality of venous thromboembolism diagnoses among prostate cancer patients in the Danish National Registry of Patients

Aska Drljevic¹
Michael Borre²
Morten Høyer³
Vera Ehrenstein⁴
Mary Nguyen-Nielsen⁴

¹Department of Pharmacology,
²Department of Urology, ³Department
of Oncology, ⁴Department of Clinical
Epidemiology, Aarhus University
Hospital, Aarhus, Denmark

Background and aim: It is well established that cancer patients have an increased risk of venous thromboembolism (VTE). However, no previous study has examined the quality of VTE diagnoses related to cancer patients in the Danish National Registry of Patients (DNRP). To support future studies on cancer and risk of VTE, this study aimed to estimate the positive predictive value (PPV) of VTE diagnoses among prostate cancer (PC) patients registered in the DNRP.

Materials and methods: We conducted a validation study using data from hospitals within the Central Denmark Region, which covers a population of 1.3 million people. Using the DNRP, we identified a total of 120 PC patients registered with VTE within the period 1995–2012. We also identified a random sample of 120 PC patients with no VTE registration within the same period. Therefore, a total of 240 patients were selected for medical chart review. We compared data from the DNRP to data collected from medical record review (ie, reference standard). We then computed PPV, sensitivity, and specificity with corresponding 95% confidence intervals (CIs) using the Jeffreys method.

Results: The final study sample included 232 PC patients, of which 115 were registered with VTE and 117 had no registration of VTE in the DNRP. We found the overall PPV of VTE diagnoses in the DNRP to be 86.1% (95% CI 78.9%–91.5%). Sensitivity was 98.0% (95% CI 93.8%–99.6%), and specificity was 87.8% (95% CI 81.4%–92.6%). We also found the PPV of incident PC diagnoses in the DNRP to be 98.3% (95% CI 96.1%–99.4%).

Conclusion: For PC patients, the registration of VTE diagnoses in the DNRP is associated with a high PPV. We provide evidence that data from the DNRP are valid for studies on risk of VTE among cancer patients.

Keywords: positive predictive value, prostatic neoplasms, validation study, venous thromboembolism

Introduction

Prostate cancer (PC) is the most common cancer among men in Denmark.^{1,2} The average annual number of Danish men newly diagnosed with PC in the period 2007–2011 was 4,362.² In the 10-year period from 2002 to 2011, PC incidence increased by 86%, while PC mortality remained stable.^{3,4} A large part of the increase in PC incidence is screening-induced, and PC incidence and prevalence rates are projected to increase further with the growing elderly population.⁵

The risk of venous thromboembolism (VTE) is increased among cancer patients, and is highest among patients with metastatic disease.⁶ In 2010, Severinsen et al used data from a cancer-free population and estimated that the positive predictive value (PPV) of in-hospital VTE diagnoses in Denmark was 75%.⁷ Severinsen et al also

Correspondence: Aska Drljevic
Department of Pharmacology, Aarhus
University Hospital, 44 Nørrebrogade,
Aarhus 8000, Denmark
Tel +45 2849 0381
Email askadrjlj@rm.dk

showed that the PPV varied by type of VTE (deep venous thrombosis [DVT] or pulmonary embolism [PE]), type of diagnosis (primary or secondary), and sex. Since the PPV is directly proportional to the prevalence of disease,⁸ that study provides a conservative PPV estimate for cancer-specific populations. The PPV of VTE in cancer patients is expected to be higher than in the general population.

The Danish National Registry of Patients (DNRP) is a registry of all admittances to national hospitals since 1977, as well as contacts with emergency rooms and outpatient clinics since 1995.⁹ The registration of incident PC in the DNRP has previously been shown to be reliable, with a PPV of 87% when compared to the registration of incident PC in the Danish Cancer Registry (DCR) as the reference standard.¹⁰ However, no previous study has examined the quality of VTE diagnoses among Danish cancer patients. Therefore, to support future studies on cancer and risk of VTE, this data-validation study aimed to estimate the PPV of VTE diagnoses related to PC patients in the DNRP.

Materials and methods

Study design and setting

We conducted a validation study set in the Central Denmark Region, restricted to admittances and contacts to Aarhus hospitals. The Central Denmark Region covers approximately 1.3 million residents (23% of the total Danish population).¹¹ The public health care system provides the entire Danish population (5.6 million residents) with free and equal access to hospital services and treatments.^{12,13}

Study population

Using the DNRP, we identified a total of 6,584 incident PC patients who were diagnosed at Aarhus hospitals within the period 1995–2012. Among these, 120 patients with PC were registered with VTE. VTE was strictly defined as either PE or DVT. All inpatient and outpatient admissions and discharges (both primary and secondary diagnoses) registered with VTE were included. However, registrations to emergency rooms were excluded since, these have previously been shown to be unreliable.⁷ We also queried a random sample of 120 PC patients not registered with VTE. Therefore, a total of 240 patients with PC were identified for detailed medical chart review, and these were spread among 20 different medical and surgical departments (see Figure 1). After review of the medical records, three patients from the VTE group and one patient from the non-VTE group were identified as not having PC and were therefore excluded. Two patients from the non-VTE group had a registered

VTE – 2 and 15 years – prior to the PC diagnosis dates, and two patients from the VTE group were registered with VTE – 3 and 10 years – prior to their PC diagnosis dates. These four patients were also excluded (see Figure 1).

The Danish National Registry of Patients

The DNRP is a registry of all admittances to national hospitals since 1977, including contacts with emergency rooms and outpatient clinics since 1995.⁹ The registry contains data on dates of admission and discharge, diagnoses, procedures, some hospital-administered medications, and a unique ten-digit civil registration (CPR) number that all Danish residents are assigned upon birth or immigration.⁹ The CPR number allows for unambiguous data linkage across multiple registries.¹³ Diagnoses are coded by the treating physicians at the time of discharge using the International Classification of Diseases (ICD)-8 (1977–1993) and the ICD-10 (1994–present). Since 1996, surgical procedures have been coded by the Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures.

Medical record review

We retrieved patients' medical records for review (n=240). The same physician reviewed all of the medical records. In the data abstraction, we confirmed/invalidated VTE diagnoses and collected supplemental data on metastases, history of recent surgery, related VTE diagnostics (eg, scans, D-dimer, etc.), and administered VTE treatments. Double data entry and proofreading of data were performed by two independent persons in order to minimize and control for eventual data-entry errors and typos. Patients who, according to the medical record, did not have a biopsy-verified PC or who were registered with VTE ≥ 2 years prior to the PC diagnosis date were then excluded from the analyses (see Figure 1).

Statistical analyses

We estimated the PPV, sensitivity, and specificity with corresponding 95% confidence intervals (CIs) to find the concordance between VTE diagnoses in the DNRP and the medical records.¹⁴ We estimated the corresponding 95% CIs using Jeffreys method.¹⁵ We computed descriptive statistics to describe and compare PC patients in the VTE group and PC patients in the non-VTE group. We also estimated the PPV of incident PC diagnoses in the DNRP and the sensitivity of VTE diagnostics among PC patients with VTE. Sampling from the DNRP was performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA). All other data management and analyses were performed using

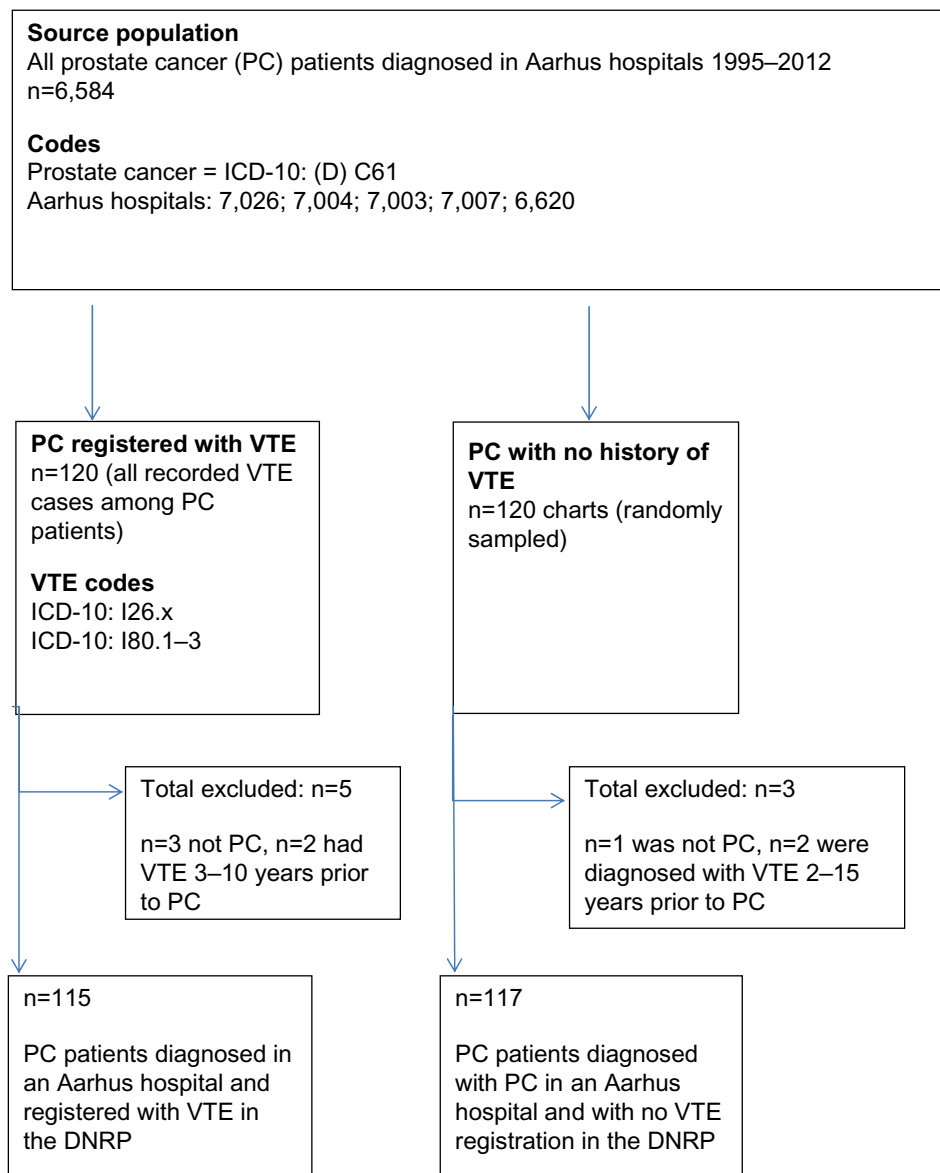


Figure 1 Flow chart of PC patients selected for study sample.

Abbreviations: DNRP, Danish National Registry of Patients; ICD, International Classification of Diseases; VTE, venous thromboembolism.

STATA statistical software, version 12 (StataCorp, College Station, TX, USA).

Results

Characteristics

Table 1 summarizes the descriptive statistics for the study sample, including information extracted from medical record review on age, metastases, history of surgery, VTE-related diagnostics, and VTE-related treatments. Patients registered with VTE were slightly older (median age 73.2 years, interquartile range 59.6–86.8 years) than the patients registered without VTE (median age 72.0 years, interquartile range 60.4–83.6 years).

Among the PC patients registered with VTE, 40.0% (n=46) had evidence of metastases at the time of PC diagnosis, 30.4% (n=35) had evidence of metastases before VTE diagnosis, and 21.7% (n=25) had evidence of metastases occurring after the VTE diagnosis. In contrast, within the non-VTE group, 30.0% (n=35) had evidence of metastases at the time of PC diagnosis, no patients had evidence of metastases before the VTE diagnosis, and 0.9% (n=1) had evidence of metastases after the VTE diagnosis. Also, 9.6% (n=11) of patients in the VTE group had a history of PC-related surgery within 3 months of the VTE diagnosis, whereas no patients in the non-VTE group had a history of recent PC-related surgery.

Table 1 Characteristics of 232 PC patients included in study sample

Characteristics	PC registered with VTE, n=115, n (%)	PC registered without VTE, n=117, n (%)
Age at PC dx, years		
Mean	72.5	71.9
Median	73.2	72.0
Interquartile range	59.6–86.8	60.4–83.6
Metastasis status		
Metastases at time of PC dx	46 (40.0)	35 (30.0)
Regional metastases	16 (13.9)	11 (9.4)
Distant metastases	40 (34.8)	28 (24.0)
Metastases before VTE dx	35 (30.4)	0 (0)
Regional metastases	14 (12.2)	0 (0)
Distant metastases	32 (27.8)	0 (0)
Metastases after VTE dx	25 (21.7)	1 (0.9)
Regional metastases	7 (6.1)	0 (0)
Distant metastases	23 (20.0)	1 (0.9)
History of PC metastases	65 (56.5)	55 (47.0)
Surgery status		
History of PC-related surgery within 3 months of VTE dx	11 (9.6)	0 (0)
VTE diagnostics and treatments		
VTE-related diagnostics		
Ultrasound	75 (65.2)	3 (2.6)
CT	35 (30.4)	1 (0.9)
PVPS	26 (22.6)	0 (0)
D-dimer	18 (15.7)	0 (0)
ECG	11 (9.6)	1 (0.9)
ECHO	25 (21.7)	0 (0)
Others/unknown	5 (4.3)	5 (4.3)
VTE-related treatment		
Thrombectomy	0 (0.0)	0 (0.0)
Antithrombotic	90 (76.3)	1 (0.9)
Thrombolysis	5 (4.3)	0 (0.0)
Others/unknown	5 (4.3)	2 (1.7)

Abbreviations: CT, computed tomography; dx, diagnosis; ECG, electrocardiogram; ECHO, echocardiogram; PVPS, pulmonary ventilation and perfusion scan, PC, prostate cancer; VTE, venous thromboembolism.

Among patients registered with VTE, 65.2% (n=75) underwent an ultrasound examination, 30.4% (n=35) underwent a computed tomography examination, and 22.6% (n=26) underwent a pulmonary ventilation and perfusion scan (PVPS). As would be expected for those without a VTE diagnosis, only 2.6% (n=3) underwent an ultrasound, 0.9% (n=1) had a computed tomography scan, and no patients had a PVPS within the non-VTE group. With respect to treatment with antithrombotic drugs, again, consistent with expectations, 76.3% (n=90) were treated within the VTE group and only 0.9% (n=1) in the non-VTE group.

PPV, sensitivity, and specificity of VTE diagnosis among PC patients

The final study sample comprised 232 PC patients, of which 115 were registered with VTE and 117 without VTE in

the DNRP. Based on our review of medical records, of the 115 patients registered with VTE, we confirmed 99 patients with VTE (ie, true positives) and found 16 to be erroneously coded with VTE (ie, false positives). Of the 117 patients registered without VTE, we confirmed 115 patients without VTE (ie, true negatives) and found two patients with VTE (ie, false negatives). Using the medical record review as the reference standard, we then computed the overall PPV of VTE diagnoses in the DNRP related to PC patients to be 86.1% (95% CI 78.9%–91.5%). The corresponding sensitivity was 98.0% (95% CI 93.8%–99.6%), and specificity was 87.8% (95% CI 81.4%–92.6%) (see Table 2). Finally, we also computed the PPV of the registration of incident PC in the DNRP to be 98.3% (95% CI 96.1%–99.4%), again using the medical record review as the reference standard (see Table 3).

Sensitivity of VTE diagnostics among PC patients

Table 4 summarizes our findings on the sensitivity of VTE diagnostic tests. Ultrasound and elevated D-dimer were the most sensitive VTE diagnostics among Danish PC patients, with a sensitivity of 94.1% (95% CI 86.6%–98.0%) and 54.8% (95% CI 39.8%–69.1%), respectively. Electrocardiography and echocardiography had the lowest sensitivity in VTE diagnostics, with sensitivity of 6.7% (95% CI 0.7%–27.2%) and 15.2% (95% CI 6.1%–30.1%), respectively.

Discussion

To summarize the key findings of this study, we found a high PPV (86%), sensitivity (98%), and specificity (88%) of the

Table 2 Measures of agreement and validity comparing reporting of VTE diagnoses among prostate cancer patients in the DNRP with patient medical records

DNRP (test standard)	Medical record review by physician (reference standard)		
	VTE	No VTE	Total
VTE registration	TP =99	FP =16	115
No VTE registration	FN =2	TN =115	117
Total	101	131	232
Measures	Proportions (95% CI using Jeffreys method)		
PPV = TP/(TP + FP)	99/(99 + 16) = 0.861 (CI 78.9% – 91.5%)		
Sensitivity = TP/(TP + FN)	99/(99 + 2) = 0.980 (CI 93.8% – 99.6%)		
Specificity = TN/(TN + FP)	115/(115 + 16) = 0.878 (CI 81.4% – 92.6%)		

Abbreviations: CI, confidence interval; DNRP, Danish National Registry of Patients; FP, false positive; FN, false negative; PPV, positive predictive value; TP, true positive; TN, true negative; VTE, venous thromboembolism.

Table 3 PPV of PC diagnosis in the DNRP and proportions of metastases and PC-related surgery

	Number of confirmed records/ number of relevant records reviewed	PPV% (95% CI) TP/(TP + FP)
Correct coding of PC dx (histologically/biopsy-verified) in the DNRP	236/240 = 98.3%	236/ (236 + 4) = 98.3% (CI 96.1%–99.4%)
Metastases at time of PC dx	81/236 = 34.3%	–
Metastases prior to/at time of VTE dx	35/115 = 30.4%	–
Metastases after VTE dx	25/115 = 21.7%	–
PC-related surgery \leq 3 months of VTE dx	11/115 = 9.6%	–

Abbreviations: CI, confidence interval; DNRP, Danish National Registry of Patients; dx, diagnosis; FP, false positive; PC, prostate cancer; PPV, positive predictive value; TP, true positive; VTE, venous thromboembolism.

registration of VTE diagnoses in the DNRP related to PC patients. We also found a very high PPV (98%) of incident PC diagnoses in the DNRP. To our knowledge, this is the first study to investigate the quality of VTE diagnosis in the DNRP in a cancer-specific population.

We identified 16 PC patients who were registered with false-positive VTE. Interestingly, our detailed medical chart review showed that indeed eight of these patients were hospitalized/admitted with suspected VTE, but subsequent in-hospital confirmatory diagnostics ruled out the presence of VTE. Therefore, at least half of the false-positive findings

Table 4 Sensitivity of VTE diagnostics among Danish PC patients

	Number of positive tests/number of relevant VTE cases tested	Sensitivity % (95% CI) TP/(TP + FN)
US-confirmed VTE	64/68 ^a	64/(64 + 4) = 94.1% (CI 86.6%–98.0%)
CT-confirmed VTE	39/85 ^b	39/(39 + 46) = 45.9% (CI 35.6%–6.5%)
PVPS-confirmed VTE	21/62 ^c	21/(21 + 41) = 33.9% (CI 23.0%–46.2%)
Elevated D-dimer above cutoff point (0.5 mg/L)	23/42	23/(23 + 19) = 54.8% (CI 39.8%–69.1%)
ECG with findings consistent with VTE	1/15	1/(1 + 14) = 6.7% (CI 0.7%–27.2%)
ECHO with findings consistent with VTE	5/33	5/(5 + 28) = 15.2% (CI 6.0%–30.1%)

Notes: ^aTrue VTE cases that were confirmed by US divided by the number of true VTE cases examined by US; ^btrue VTE cases that were confirmed by CT divided by the number of true VTE cases examined by CT; ^ctrue VTE cases that were confirmed by PVPS divided by the number of true VTE cases examined by PVPS.

Abbreviations: CI, confidence interval; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; FN, false negative; PVPS, pulmonary ventilation and perfusion scan; PC, prostate cancer; TP, true positive; US, ultrasound; VTE, venous thromboembolism.

could be attributed to systematic coding error by physicians. A previous study showed that asymptomatic superficial venous thrombosis and asymptomatic DVT occurs more frequently among cancer patients than noncancer patients, further illustrating that timely and valid VTE diagnosis is a particular challenge for cancer-specific populations.¹⁶ In 2010, Severinsen et al investigated a cancer-free population and showed that the PPV of in-hospital VTE diagnoses in Denmark was 75%.⁷ We showed that the PPV of VTE coding related to a cancer-specific population in the DNRP is higher, at 86.1%. We also found that the registration of incident PC in the DNRP is highly reliable, with a PPV of 98.3%. In a previous study, Gammelager et al found that the registration of incident PC in the DNRP had a PPV of 87%; however, that study compared registered DNRP cancer diagnoses to registered DCR diagnoses (where the DCR was the reference standard).¹⁰ In contrast, we used data extracted from medical records and case-by-case physician evaluation as the reference standard. Also, our findings showing relatively high sensitivity for D-dimer as a diagnostic measure support previous research.^{17,18} Finally, our estimates of sensitivity for PVPS, electrocardiography, and echocardiography diagnostic examinations are most likely underestimated, since these analyses were not restricted to PE patients.

Our study has several notable strengths and features. Most importantly, we linked national registry data to collect information on all PC and VTE diagnoses and related therapies provided in the country. We were thus able to identify all PC patients registered with and without VTE in the central region of Denmark. The sample size was sufficient to provide good precision of the PPV, specificity, and sensitivity estimates. Detailed medical chart review was performed by one physician, and all diagnoses were validated/invalidated based on the reviewing physician's global assessment of the information available in the medical charts. Finally, double data entry was performed by two independent persons in order to minimize and control for eventual data-entry errors and typos.

Nevertheless, this study also has some limitations. Firstly, we included data from only one region in Denmark, which could limit the generalizability of our findings to other regions or countries. However, data were included from five different hospitals in the region, all of which are representative of other hospitals in Denmark. Furthermore, the homogeneous and standardized health care system in Denmark makes it possible to generalize our findings to other regions.^{13,19} Secondly, the medical record reviewer was not blinded to the VTE-registration status, which potentially could have biased the evaluation process when confirming/invalidating

VTE status. Thirdly, the quality and amount of data recorded in the medical records varied, which meant that we had more details and data on some patients than on others. Lastly, we excluded two patients with no VTE registration, which according to the medical records did have VTE years before their PC diagnoses. Similarly, we excluded two patients registered with VTE, but where the VTE date was several years before the PC diagnosis. These patients were excluded on the premise that their VTE diagnoses were not likely to be related to their PC diagnoses, but these patients might nevertheless have had occult PC at the time of the VTE. However, the inclusion of these four excluded patients would have only marginally affected the PPV estimate that is reported here.

Conclusion

In conclusion, we found high PPV of VTE diagnoses (86%) among PC patients, as well as high PPV of incident PC diagnoses (98%) in the DNRP. Data on PC and VTE diagnoses in the DNRP have high validity. This study further substantiates that the DNRP is a valuable and valid data source for epidemiological studies on cancer and risk of VTE.

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Disclosure

The authors report no conflicts of interest in this work.

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