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Baseline characteristics and clinical outcomes of prostate cancer patients on delayed palliative management: a PIONEER analysis based on big data

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Introduction Delayed palliative management (DPM) is an alternative for prostate cancer (PCa) patients with poor performance status, or those who received radical treatment but progressed and no longer meet the criteria for curative treatment. PIONEER is a large network of federated data analytic platforms in PCa that aims to improve its care through the application of big data analytics. The objective of this study was to describe clinical baseline characteristics and outcomes of PCa patients receiving DPM using big data.

Material and methods Descriptive study of patients on DPM from four databases in PIONEER (Pharmetrics Plus, Optum Clinformatics, Marketscan and Columbia University Irving Medical Center (CUIMC)). Baseline characteristics, including comorbidities (hypertension, type 2 diabetes (T2DM), asthma/chronic obstructive pulmonary disease (COPD) and obesity), were stratified by age. Outcomes of interest were annual emergency department (ED) visits, hospitalization and symptomatic progression. Additional outcomes were time to death, hospitalization and time to symptomatic progression for CUIMC.

Results We included 13246 men with a median age of 68–75 and Charlson Comorbidity index of 6–8. The three most common comorbidities were hypertension (80–93% [>80 years] vs 69–80% [55–80 years] vs 59–64% [<55 years]), T2DM (29–41% [>80 years] vs 26–38% [55–80 years] vs 23–26% [<55 years] and asthma/COPD (28–37% [>80 years] vs 19–30% [55–80 years] vs 16–19% [<55 years]). ED visits and hospitalizations were highest in the first year of follow-up (19–33% and 21–48% respectively). The median time to death was 548 days (IQR 1265 days) and to symptomatic progression was 408 days (IQR 1125 days) in CUIMC.

Conclusions Men on DPM were in their mid-seventies, with the three most common comorbidities being hypertension, T2DM and asthma/COPD, regardless of age groups. This study reflects the potential of PIONEER as a federated network of databases that may be used to harness big data in PCa research.

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Key Words: common data model ‹› data network ‹› observational research ‹› palliative management ‹› prostate cancer ‹› real world data

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in males and accounts for 15% of all cancers diagnosed worldwide [1, 2]. Although treatment is curative majority of cases, some patients are managed conservatively from the onset or after progression. The aim is to avoid unnecessary treatment and to maintain quality of life.

Watchful waiting (WW) refers to conservative management for patients considered unsuitable for curative treatment, and patients are clinically 'watched' for the development of local or systemic progression, at which stage they are then treated palliatively according to their symptoms [3]. However, patients undergoing conservative management have been poorly characterized in previous studies [4, 5]. This is highly important due to the under-representation of older patients with comorbidities in randomised controlled trials, of which clinical guidelines are based on [6].

The 'Prostate Cancer Diagnosis and Treatment Enhancement Through the Power of Big Data in Europe (PIONEER)' Big Data Platform, funded by the European Commission Innovative Medicines Initiative, offers a central and federated state-of-the-art analytic platform for PCa, aimed to better understand patient characteristics and clinical outcomes across various geographical regions [7]. This network of data is unified to an international Common Data Model (CDM), the Observational Medical Outcomes Partnership (OMOP), following appropriate legal and ethical considerations. The PIONEER consortium has identified an evidence gap in the management of PCa patients who receive palliative therapy and formulated a research question through a detailed prioritization exercise [7].

The aim of this study is to describe the baseline characteristics and clinical outcomes of patients undertaking delayed palliative management, using big data from an international network cohort of databases across the United States (US).

MATERIAL AND METHODS

Study design

As part of the PIONEER study-a-thon in March 2021, a multinational cohort study was conducted in collaboration with the European Health Data Evidence Network (EHDEN) and Observational Health Data Sciences and Informatics (OHDSI) [8]. Data across a network of hospital electronic health records (EHRs) were previously standardized to the OMOP CDM. Each institution retained their own data but made it available for querying and statistical evaluation by locally running standardized analysis programs in a federated manner [9]. The study protocol was recently published [10].

Data sources

Of the 13 databases evaluated by PIONEER, four databases had PCa patients on delayed palliative management: Pharmetrics Plus, Optum Clinformatics, MarketScan and Columbia University Irving Medical Center (CUIMC). A detailed description of the databases is available in Table 1. The results were collected from data partners up to 29th January 2022.

Study participants

We included all adult patients on delayed palliative management, defined as having a prostate biopsy within 30 days of the first visit with PCa diagnosis, and no history of PCa or prostate dysplasia within 365 days prior to first diagnosis. They were not exposed to any androgen deprivation therapy within 365 days prior to first diagnosis, received no curative or palliative treatment within the first six months after diagnosis, and only received palliative treatment after six months of initial PCa diagnosis. The palliative treatment options were systemic treatment (androgen deprivation therapy, chemotherapy, immunotherapy, PARP inhibitors), minor or major surgery (ureteric stent or nephrostomy insertion, suprapubic catheterization, orchiectomy, palliative transurethral resection or incision of prostate, colostomy, pelvic exenteration), palliative radiotherapy or any other palliative treatment options.

All patients were followed from the index date to the earliest of the following: 1) death, 2) diagnosis with another malignancy (except for non-melanoma skin cancer), or 3) end of the observation period [10].

Covariates and outcomes of interest

We collected patient demographics and disease characteristics at –1 to –365 days prior to the date

of PCa diagnosis. Baseline comorbidities were collected at 1 to 30 days after the date of diagnosis. Comparisons were made across 3 strata of age at diagnosis: <55 years, 55–80 years and ≥80 years. Outcomes of interest include 1) symptomatic progression (i.e., need for further treatment) rates, 2) hospitalization rates, and 3) emergency department (ED) visits within the first, second, and third year and beyond, after onset of symptoms. Additional outcomes were Kaplan-Meir curves of time to death, hospitalization and time to symptomatic progression for CUIMC.

Statistical analysis

Baseline patient demographics, comorbidities and disease characteristics were reported using medians for non-normally distributed continuous variables and proportions for categorical variables. Kaplan-Meier analyses were used to assess the outcomes of interest.

Data were analyzed using a common analysis code developed for the OHDSI methods library, and the codes were run locally in each database. De-identified data was used, and only the aggregated results from each database were publicly shared on an interactive website. This study is descriptive in nature, and no causal inference is intended. All data partners obtained institutional review board approval or equivalent governance approval prior to the start of this study.

RESULTS

Data from 13,246 men were included in this analysis. Except for Pharmetrics Plus (68 years), the median age at diagnosis for all the other three databases ranged from 74–75 years. Charlson Comorbidity Index average was 6–8. Additional demographic details for each database can be found in Table 1.

The prevalence of comorbidities was higher in older patients, except obesity. There were no distinguishable differences for anxiety and venous thromboembolism (VTE) across age groups and databases (Figure 1).

The most common comorbidities above 80 years old were hypertension (80–93%), type 2 diabetes (29–41%), asthma/chronic obstructive pulmonary disease (COPD) (28–37%) and cardiovascular disease (8–10%). Similar patterns were seen in the younger patient, with hypertension being the most prevalent (69–80% [55–80 years old] vs 59–64% [<55 years old]), followed by type 2 diabetes (26–38% [55–80 years old] vs 23–26% [<55 years old]), asthma/COPD (19–30% [55–80 years old] vs 16–19% [<55 years old]), and cardiovascular disease (3% [55–80 years old] vs 4–9% [<55 years old]). In contrast, obesity was more prevalent among younger patients (19–41% [<55 years old] vs 12–29% [55–80 years old] vs 4–17% [>80 years old]. The trend for anxiety was similar across the groups (6–12% [<55 years old] vs 3–9% [55–80 years old] vs 2–12% [>80 years old], so was stroke 1–3%

Table 1. *Baseline characteristics of prostate cancer patients on delayed palliative management*

	MarketScan (n = 5,293)	CUIMC (n = 352)	Optum (n = 4,525)	PPlus1124 (n = 3,076)
Age groups (%)				
30–44	<0.1	<1.4	0.2	<0.2
45–49	0.4	–	1.0	<0.2
50–54	2.6	2.3	3.0	4.0
55–59	7.3	5.1	7.0	11.0
60–64	16.2	8.8	14.0	24.0
65–69	8.0	17.6	25.0	18.0
70–74	14.8	18.5	24.0	16.0
75–79	19.2	19.6	17.0	16.0
80–84	18.4	15.6	9.0	11.0
85–89	10.3	8.2	–	0.0
90–94	2.4	3.4	–	–
95–99	0.3	<1.4		–
Physical therapy/exercise (%)	3.8	1.4	5.5	7.7
Family history of prostate cancer (%)	4.1	3.1	9.9	13.3
Transurethral prostatectomy (%)	4.7	18.5	1.9	0.3
Metastatic PCa (%)	–	1.4	0.1	1.4
Widespread metastatic malignant neoplastic disease (%)	0.5	1.4	0.4	0.2

PCa – prostate cancer; CUIMC – Columbia University Irving Medical Center

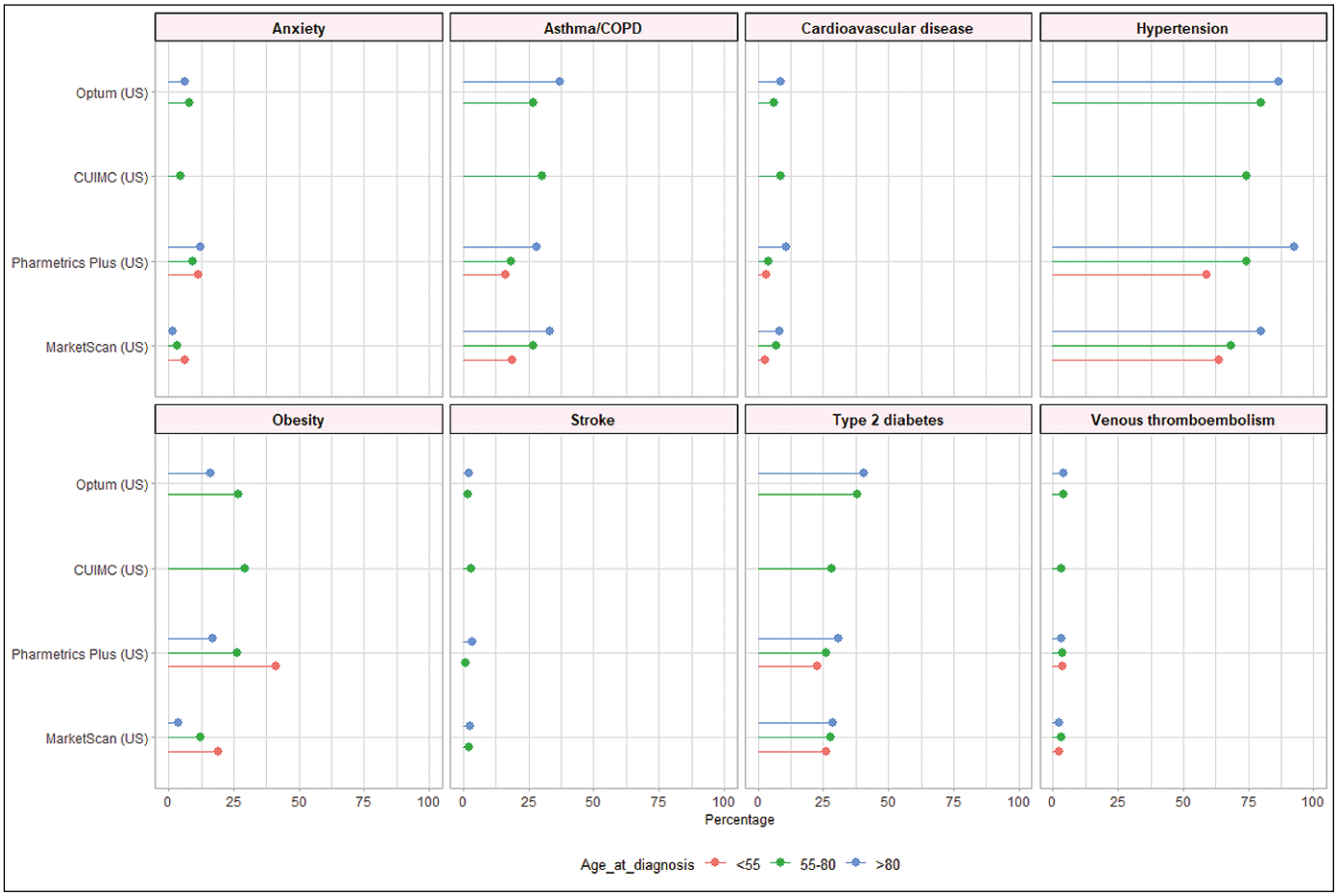

Figure 1. *Prevalence of baseline comorbidities among prostate cancer patients on delayed palliative management, stratified by age group at diagnosis and database.*

US – United States; CUIMC – Columbia University Irving Medical Center

[55–80 years old] vs 2–3% [>80 years old], and VTE (3–4% [<55 years old] vs 3–4% [55–80 years old] vs 2–3% [>80 years old].

Emergency department (ED) visits were more frequent in the first year of follow-up, with MarketScan having the highest number of visits (33%) vs the other three databases (19–23%). Hospitalization was also highest in the first year, with CUIMC having the highest percentage (48%) as compared to the other databases (21–29%; Figure 2). There were no distinguishable differences between trends for symptomatic progression and follow-up periods. While frequency was highest in year 1 across all outcomes (ED visits, hospitalizations, and symptomatic progression), year 3 and beyond had a higher frequency as compared to year 2. Only CUIMC provided insight on life expectancy, hospitalization and time to symptomatic progression (Figure 3A, 3B, and 3C). The median time to death was 548 days (IQR 1,265 days) and to symptomatic progression was 408 days (IQR 1,125 days).

DISCUSSION

Use of OMOP CDM within PIONEER has allowed us to explore the heterogeneity of baseline characteristics and clinical outcomes of PCa patients on delayed palliative management across various databases in the US. We observed that men on delayed palliation care were in their mid-seventies and had moderate to severe comorbidities. ED visits, hospitalization and symptomatic progression were similar across databases, (except for MarketScan for ED visits and CUIMC for hospitalization respectively). Frequency of all outcomes was highest within the first year of follow-up, followed by year 3 and beyond.

The prognosis of patients with PCa varies according to clinical factors such as tumour grade and stage, race, co-morbidities and age of diagnosis [11]. PCa patients in our study were in their mid-seventies at the point of diagnosis, which was higher than the median age of diagnosis (70 years) reported

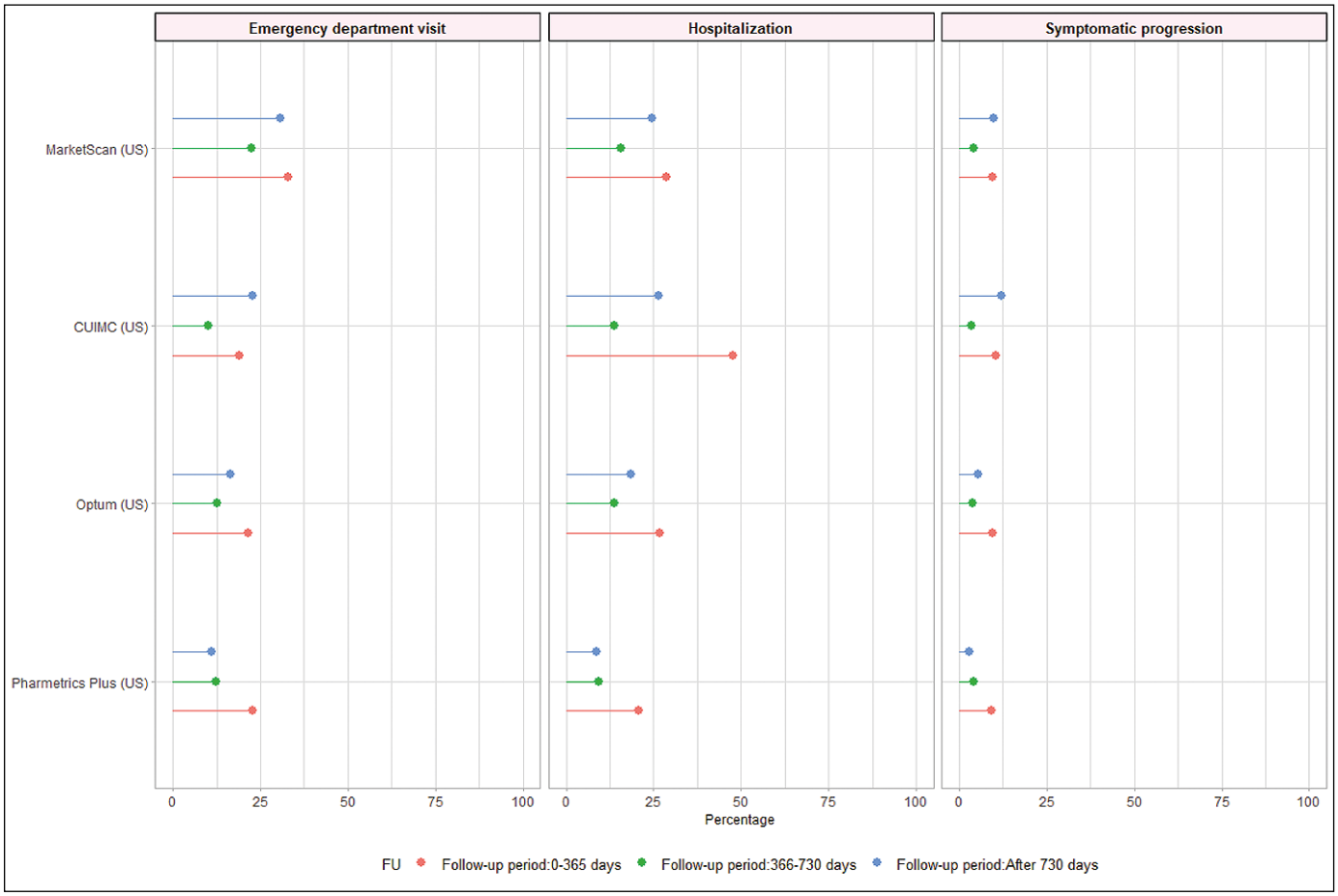

Figure 2. *Frequency of outcomes during year 1 (0–365 days post index), year 2 (366–730 days post index) and year 3+ (731+ days post index) among prostate cancer patients on delayed palliative management stratified by database.*

US – United States; CUIMC – Columbia University Irving Medical Center

in a large study of >100,000 PCa patients using the Surveillance, Epidemiology and End-Results (SEER) database [12]. Comorbidity is as important as age in predicting life expectancy in men with PCa [13]. However, tumor aggressiveness had little impact on overall survival (OS), suggesting that patients could have spared biopsy and diagnosis of cancer [3]. Most PCa patients in our study had at least one comorbidity such as obesity, hypertension, type 2 diabetes, asthma or COPD etc. These comorbidities are consistent with what has been reported as the more common comorbidities associated with western elderly men [14–17]. Considering that the median age at diagnosis was much older, with the presence of at least one comorbidity, it is therefore not surprising that PCa patients in our study were given delayed palliative management, in accordance to the most recent European Association of Urology and American Urological Association guidelines [3, 18], where conservative management with WW is recommended for men with PCa who have a life expectancy of shorter than 10 and 5 years, respectively.

Elevated PSA levels or progression to metastatic disease could serve as indicators for initiating a WW strategy [19]. In our study, only a few patients had PSA >20 ng/ml or metastatic disease, which could have led to delayed treatment intervention. The question of whether to defer the use of androgen deprivation therapy (ADT) as a sole treatment method was addressed in the EORTC 30891 trial [19], where the authors reported that patients with a baseline PSA <50 ng/ml and a slow PSA-DT <12 months were likely to die of causes unrelated to PCa, and thus could be spared from the burden of ADT. The median time to initiate deferred treatment was 7 years, and in the deferred treatment group, 25.6% of patients died without requiring treatment [20].

In the above-mentioned studies, patients were diagnosed before the PSA era and are less easily generalized to current urology practices, in which PSA

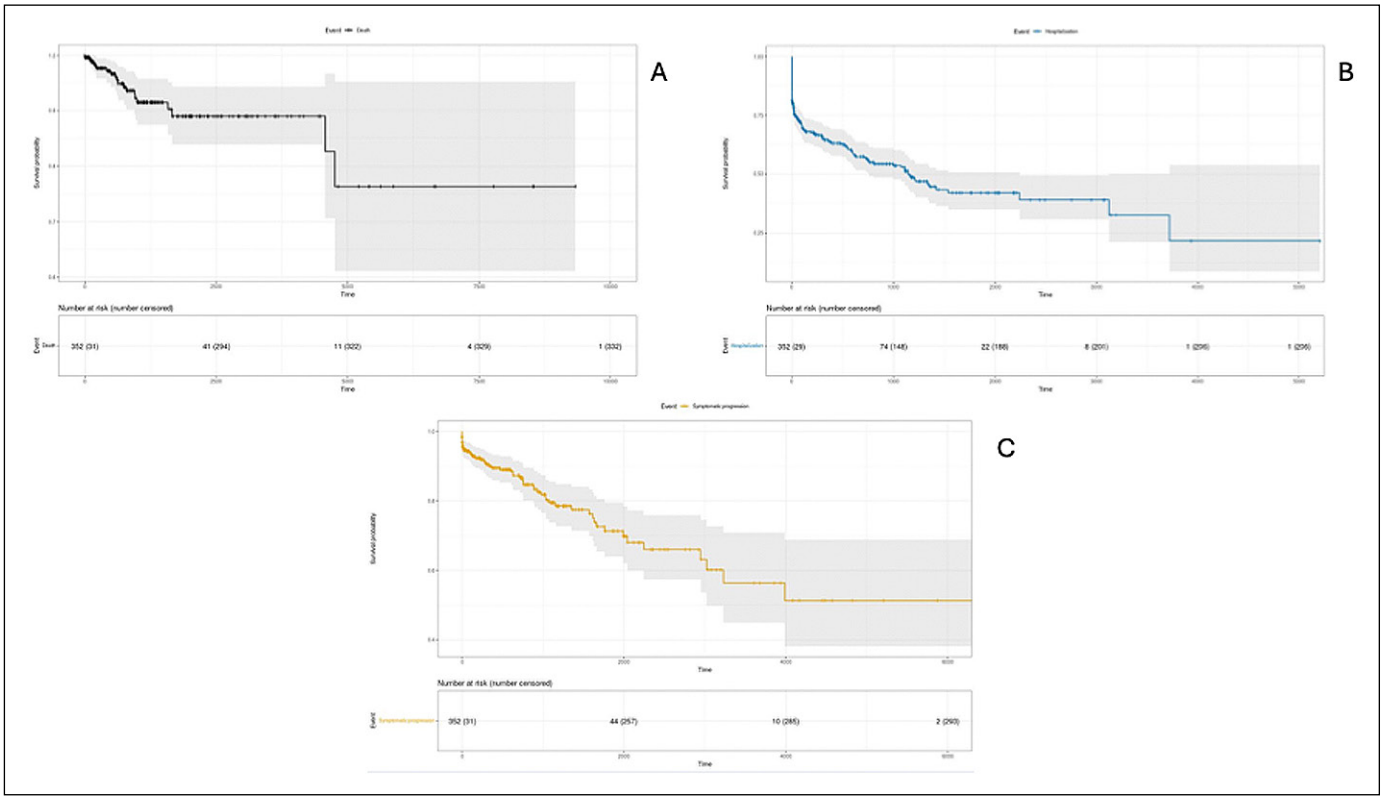

Figure 3. A) *Kaplan-Meir plot showing death among prostate cancer patients on delayed palliative management in Columbia University Irving Medical Center (CUIMC).* **B)** *Kaplan-Meir plot showing hospitalization among prostate cancer patients on delayed palliative management in CUIMC.* **C)** *Kaplan-Meir plot showing symptomatic progression among prostate cancer patients on delayed palliative management in CUIMC.*

testing plays an integral role in PCa management [21]. Zietman et al. [22] retrospectively reviewed 199 men managed by WW, showing 74% likelihood of progression to treatment or all-cause mortality within 7 years. Koppie TM et al. retrospectively compared patients choosing WW with other patients with PCa, all from The Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE), a national registry. They concluded that men who elect initial WW for prostate cancer tend to be older, have lower serum PSA and more favorable disease characteristics than those who seek treatment, being PSA at diagnosis the dominant factor for predicting secondary treatment [23].

Quality of Life (QoL) is the most important outcome for patients in palliative care along with symptom alleviation [24]. Palliative care focuses on three main realms to achieve these goals: morbidities associated with the disease, morbidities associated with the treatment, and the QoL of the patient [25]. The outcomes of interest in our study were symptomatic progression rates, hospitalization rates and ED visits, which would be important for clinicians to consider when counseling their patients on having conservative management as an alternative option. Our study showed that one-fourth of patients had an ED visit or were hospitalized within the first year of follow-up. This suggests that this period of WW does not constitute a 'treatment break' for a significant portion of patients; instead, this suggests that patient disease burden may be still high for many. Our study also showed that ED visits and hospitalization rates were higher in year 3 and beyond, as compared to year 2 of follow-up. We were not able to do a direct comparison of our findings with other studies as follow-up durations differed across studies. For example, one large study using the SEER database reported that 36.5% of patients with advanced stage PCa had between 1–3 ED visits, and 55.3% had 1–3 hospitalizations over a follow-up of at least 5 years.

There are some limitations in our study. A few important oncological characteristics such as Gleason score and clinical stage at time of PCa diagnosis were not captured, therefore we were unable to include them in the analyses. The lack of information on treatment intent and the difficulty in differentiating watchful waiting from active surveillance

were also major limitations of the study. Furthermore, only one database (CUIMC) had information for time-to-death and time-to-symptomatic progression. Finally, disparities in data sources due to different healthcare settings may result in differences in coding practice, making comparisons between databases challenging, with some disparities (although minor) in observed frequencies for comorbidities and clinical outcomes.

Our study represents one of the first attempts to characterize men with PCa undergoing palliative treatment management at a large-scale, which includes patients from international urology practices, therefore much more generalizable than single-institution studies. Other strengths of the study include the use of a common data model, centrally developed program (i.e. PIONEER) and a distributed network strategy that allowed us to harmonize and analyze the largest dataset on PCa on delayed palliative management. The use of routinely collected data allowed for a realistic characterization of actual practice in busy clinical settings through the minimization of selection bias. In addition, the use of existing data increases efficiency and maximizes the value of readily available information and enables inclusion of wider populations, including those on delayed palliative management who are often underrepresented in clinical trials.

CONCLUSIONS

To date, this is the largest study that uses real-world data from multiple databases to characterize PCa patients on delayed palliative management. Our patient population were mainly in their mid-seventies at the time of diagnosis and were likely to have multiple comorbidities. ED visits, hospitalization and symptomatic progression were consistent across databases, and with the highest frequency occurring within the first year of follow-up. This study also reflects the potential of PIONEER as a single innovative data platform, comprising private and public stakeholders, to improve patient care amongst patients with PCa.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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DATA ACCESS

In the interest of transparency and scientific reproducibility, all study materials including the computer-executable code (which is compatible with any data set in the OMOP common data model) have been made available.

Code: https://github.com/ohdsi-studies/PioneerWatchfulWaiting

Analysis apps: https://pioneer-shiny.hzdr.de/app/PioneerWatchfulWaiting_restricted/

The protocol is available on https://protocolexchange.researchsquare.com/article/pex-1468/v1

Further reading on study-a-thons and OHDSI is available on: https://ohdsi.github.io/TheBookOfOhdsi/.

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