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Androgen Deprivation Therapy and Iron-Deficiency Anemia among Patients with Prostate Cancer

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* Li-Ting Kao and Yih-Dih Cheng have equal contributions to this study

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Abstract

Objectives: Administration of androgen deprivation therapy (ADT) for metastatic prostate cancer might be associated with some adverse effects, such as anemia, but very few studies have been performed in East Asian populations. This study aimed to investigate the association between ADT and iron-deficiency anemia (IDA) among prostate cancer patients in a population-based nationwide cohort.

Design: Cohort study.

Setting: Taiwan.

Participants: Data for the cohort study was retrieved from the Taiwan National Health Insurance Research Dataset. Propensity score matching was used to select 8,474 prostate cancer patients who received ADT as study group and 4,237 prostate cancer patients who did not receive ADT as control group.

Primary and secondary outcome measures: This study individually tracked each patient for a 3-year study period and identify those who were subsequently diagnosed with IDA following the index date.

Results: This study revealed a 3.68 (95% CI 3.29-4.13) and 2.26 (95% CI 1.85-2.77) incidence rate of IDA per 100,000 person-years for prostate cancer patients receiving and not receiving ADT, respectively. Furthermore, proportional Cox regression showed

an hazard ratio (HR) for IDA in prostate cancer patients receiving ADT of 1.61 (95% CI 1.28–2.03) after adjusting for patients' age, monthly income, geographic location, residential urbanization level, hyperlipidemia, diabetes, hypertension, coronary heart disease, and inflammatory bowel disease.

Conclusion: ADT use was found to be associated with a higher risk of IDA compared with androgen deprivation therapy non-use among patients with prostate cancer.

Key words: androgen deprivation therapy, iron-deficiency anemia, prostate cancer, anemia, drug safety.

Strengths and limitations of this study

1. Data for this cohort study was retrieved from a large, Asian population-based dataset in Taiwan.
2. This study used the propensity score-matched strategy to eliminate the potential bias such as patients' demographic characteristics and comorbidities between the study cohort and the comparison cohort.
3. The sample size and statistical power were sufficient in this study.
4. Selection bias could be eliminated due to the use of population-based dataset.
5. Information on personal history and lifestyle was unavailable when data was retrieved.

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Competing interests: None declared.

INTRODUCTION

Prostate cancer (PC) is the leading cause of male cancer and accounts for 293,000 deaths globally.[1 2] In 2018, an estimated 164,690 new male diagnoses and 29,430 deaths from the disease were reported in the United States [3]. Androgen deprivation therapy (ADT), also known as hormone therapy, has been a fundamental component of metastatic PC management for more than half a century.[4] Although androgen deprivation treatment may improve long-term survival for many patients,[5 6] however, decreased serum levels of endogenous androgen in men with PC which have been linked to potential adverse effects, including decreased muscle mass, increased insulin resistance and fall risk.[7-10]

Iron-deficiency anemia (IDA) is a common type of anemia and approximately 5% females and 2% males would experience this clinical symptoms in the United States [11]. More and more studies have recognized as that anemia may have a potential detrimental impact on quality of life and survival among PC patients.[12-15] Previous study (InCHIANTI study) further suggested that androgen deficiency may be a factor that contribute to the development of anemia in men with PC [16]. Some studies had proposed that androgens may stimulate erythropoiesis through directly effect on erythroid progenitor cells and indirectly inhibit on hepcidin.[17-19] Therefore, it is plausible that ADT use may be associated with the incidence of IDA.

Accordingly, the association between ADT and anemia has been reported in several Western studies with Caucasian population.[20-22] To date, very few studies have been conducted in East Asian populations, even though the hereditary of prostate cancer was substantially vary by ethnicity and geography.[23] To fill the gap, this study proposed to examine whether ADT is associated with a subsequent risk of anemia in PC patients by employing the propensity score-matched strategy with an Asian population-based dataset in Taiwan.

METHODS

Database

Data for the retrospective cohort study was retrieved from the Taiwan National Health Insurance Research Dataset (NHIRD). The NHIRD is derived from the Taiwan Bureau of National Health Insurance. It consists of inpatient and ambulatory medical benefit claims from approximately 22 million enrollees, representing over 99% of Taiwan's population. Therefore, this database provides scientists in Taiwan with an exclusive opportunity to analyze and keep track of medical service use by enrollees since the beginning of the Taiwan National Health Insurance program in 1995. This study was exempt from full revision by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No. 2-105-05-082), since the dataset used was blinded to the public for research purposes.

Study Sample

This cohort study included a study and a comparison group. For the study group, 28,367 patients who received a first-time diagnosis of PC (ICD-9-CM code 185) between January 1, 2001 to December 31, 2010, were selected from the Registry of Catastrophic Illness Patient Database in NHIRD. A total of 454 patients aged less than 40 years were excluded. The date of ADT administration (including gonadotropin-releasing hormone (GnRH) agonists, antiandrogens, and estrogens) was assigned as the

index date for PC patients who subsequently received ADT treatment. Furthermore, the date of the first outpatient visit in which patients received the diagnosis of PC was set as the index date for PC patients who did not receive ADT. A total of 681 patients who had never received a diagnosis of IDA (ICD-9-CM codes 280, 280.0, 280.1, 280.8, and 280.9) prior to their index date were further excluded, as well as 2,730 patients who had received an orchiectomy. As a result, 24,502 PC patients remained in the study, 20,265 of which received ADT and 4,237 did not receive ADT during the 3-year study period.

Propensity score matching was used to identify 8,474 PC patients who received ADT (two for every PC patient who did not receive ADT) from the remaining ADT group. Matching variables included age, monthly income, geographic location, urbanization level of patients' residence (that were divided into 5 levels, with 1 being the most urbanized and 5 being the least urbanized),[24] hyperlipidemia, diabetes, hypertension, coronary heart disease, and inflammatory bowel disease. Ultimately, 12,711 patients were enrolled in this study, including 8,474 who received ADT and 4,237 who did not receive ADT. Each patient was subsequently followed individually for a 3-year study period to identify those who received an IDA diagnosis following index date.

Statistical Analysis

All statistical analyses were performed with the SAS system (SAS System for Windows, vers. 9.4 SAS Institute). Chi-squared tests were used to investigate differences in sociodemographic characteristics and medical comorbidities between PC patients receiving and not receiving ADT. Additionally, Cox proportional hazard regressions were conducted to examine the relationship between ADT and IDA risk during the 3-year study period. A total of 2,716 patients who died during the 3-year study period (2,020 ADT use and 796 non - ADT users) were censored. The two-sided *p* value=0.05 was used to determine statistical significance.

Patient and Public Involvement

Patients or public were not involved in the development of the research question, outcome measures, study design, and recruitment/ conducting of the present study.

RESULTS

This study included 8,474 PC patients receiving ADT and 4,237 propensity score matching PC patients who did not receive ADT. Patients' sociodemographic characteristics and medical comorbidities were shown in Table 1. No statistically significant differences were found in age, monthly income, geographic location, urbanization level of patients' residence, hyperlipidemia, diabetes, hypertension, coronary heart disease, and inflammatory bowel disease between PC patients receiving and not receiving ADT.

IDA incidence during the 3-year study period is presented in Table 2. IDA incidence rate per 100,000 person-years for the 12,711 PC patients was 3.20 (95% CI 2.89-3.53). IDA incidence rate per 100,000 person-years for PC patients receiving and not receiving ADT was 3.68 (95% CI 3.29-4.13) and 2.26 (95% CI 1.85-2.77), respectively. Log-rank test revealed that PC patients receiving ADT had a significantly lower 3-year IDA-free survival rate than patients not receiving ADT ($p < 0.001$). Figure 1 shows the 3-year IDA-free survival curves for the study and comparison groups.

Table 2 further shows that hazard ratio (HR) for IDA in PC patients receiving ADT compared with those not receiving ADT was 1.62 (95% CI 1.29-2.05). After

adjusting for patients' age, monthly income, geographic location, residential urbanization level, hyperlipidemia, diabetes, hypertension, coronary heart disease, and inflammatory bowel disease, HR for PC patients receiving ADT compared with nonusers was 1.61 (95% CI 1.28-2.03).

DISCUSSION

As far as the authors are aware, this is the first study that proposed to investigate the relationship between men receiving ADT for PC and 3-year IDA risk in East Asian populations. This study only included PC patients for relevant analyses in order to avoid the potential effects due to cancer. To mitigate selection bias, propensity score-matched strategy (by age, monthly income, geographical location, residential urbanization level, and medical comorbidities) was used to selected comparisons with PC patients not receiving ADT. In this population-based retrospective cohort study of PC patients, a significant increase in IDA risk was seen with men receiving ADT. The study reported an adjusted HR for IDA among PC patients receiving ADT of 1.61 (95% CI 1.28-2.03).

The findings in our study were consistent with some prior western studies. For instance, among 110 PC patients receiving ADT, one cohort study reported an average hemoglobin drop from 14.8 g/dL at baseline to 12.9 g/dL at evaluation [20]. One Canadian clinical study including 250 PC patients found that the average decline in hemoglobin level of ADT users was a mean of 8.9 g/L [21]. In the United States, Strum et al. demonstrated the low hemoglobin levels in 90% of PC patients receiving ADT [25]. Another study have reported PC patients receiving adjuvant radiotherapy plus ADT, with a decrease in hemoglobin level of 14.8 g/dL from the baseline to a minimum of 10.5 g/dL [26]. In addition, one cohort study using the United Kingdom Clinical Practice

Research Database linked to the Hospital Episode Statistics repository found that prostate patients with ADT had almost three-fold greater risk of anemia than nonusers (HR 2.90, 95% CI: 2.67-3.16) [22]. Meanwhile, the clinical studies were designed with small sample sizes and short duration which were mostly performed with Western population [22].

Our study indicated the association between ADT and 3-year IDA risk among PC patients; however, anemia that caused by ADT has remained elusive. To date, increasing biological evidences suggested a potential connection between men receiving ADT and subsequent IDA risk.[27] A possible explanation for the underlying mechanism may be that androgen significantly increases the bone marrow erythroid precursors and enhances the differentiation of bone marrow erythroid stem cells to erythrocytes.[19 28] Furthermore, testosterone may have an influence on the erythropoietin secretion via peritubular fibroblast-like cells level in kidney.[29] In animal experiments, testosterone was able to induce erythropoiesis-stimulating factor by a bioassay using a polycythemic mouse model.[30] Guo et al. found that the sensitivity of erythropoietin was stimulated and the stress erythropoiesis could be increased, as result of testosterone upregulated the expression of GATA binding protein 1 and GATA-dependent genes in the study of aging male mice [31]. In addition, Bachman et al. indicated that men treated with testosterone was related to serum hepcidin suppression in a randomized double-blind clinical study.[17]

Testosterone directly interact with bone morphogenetic protein-Smad signaling pathway in hepatocytes and lead to the downregulation of hepcidin transcription.[32] Furthermore, this effects of androgen on hepatic hepcidin and renal erythropoietin gene expression could increase systemic iron transport and erythropoietin levels.[32]

The strength of our study was the identification of the association between ADT in PC patients and subsequent IDA risk using a large population-based database. The Taiwan NHIRD provides high accessibility for medical services and an adequate statistical power to detect IDA risk between study and comparison groups. Moreover, PC patients' sociodemographic characteristics and medical comorbidities acknowledged as risk factors were also included. Furthermore, we also conducted a propensity score-matched strategy to eliminate what potential bias such as patients' demographic characteristics and comorbidities between the study cohort and the comparison cohort.

Several limitations of our retrospective study should be addressed. The study lacked information on potentially important patient characteristics, such as body mass index, smoking, nutrition, or nonprescription medication use. Secondly, it is plausible that the database did not include all PC patients with IDA in Taiwan, since some of these patients may seek alternative medicines not recorded by the NHI program. Thirdly, information on personal history, including family history of anemia was unavailable when data was retrieved.

CONCLUSIONS

In conclusion, after adjusting for patient sociodemographic characteristics and comorbid medical disorders, the present study detected an increased IDA risk among PC patients who received ADT during the considered 3-year follow-up. Medical professionals were suggested to be aware of the adverse effect of anemia by using ADT. Clinicians and pharmacists need to consider their PC patients with ADT for the possible IDA risk and determine the efficacy of prevention and treatment modalities for anemia.

Contributors

Conceptualization: Fang-Jen Wu & Yih-Dih Cheng & Li-Ting Kao; Methodology: Yih-Dih Cheng & Li-Ting Kao & Wu-Chien Chien; Formal analysis and investigation: Fang-Jen Wu & Jui-Hu Shih & Li-Ting Kao; Writing - original draft preparation: Fang-Jen Wu & & I-Hsun Li & Chin-Min Chuang & Li-Ting Kao

Ethics approval

This study was exempt from full revision by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No. 2-105-05-082), since the dataset used was blinded to the public for research purposes.

Data sharing statement

No additional data available.

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Figure Legends

Figure 1 Kaplan–Meier curve for iron-deficiency anemia (IDA) among prostate cancer patients during a 3-year follow-up period, stratified by previous administration or non-administration of androgen deprivation therapy (ADT)

Table 1 Demographic characteristics of prostate cancer patients, stratified by previous administration or non-administration of androgen deprivation therapy (ADT) (n = 12,711)

Characteristic	Patients not receiving ADT (n = 4,237)		Patients receiving ADT (n = 8,474)		p value
	Total no.	Column %	Total no.	Column %	
Age (years), mean (SD)	70.99 (8.65)		71.03 (8.59)		0.7971
Urbanization level					0.9921
1 (most urbanized)	1,168	27.57	2,326	27.45	
2	990	23.37	1,985	23.42	
3	584	13.78	1,163	13.72	
4	537	12.67	1,056	12.46	
5 (least urbanized)	958	22.61	1,944	22.94	
Geographic region					0.9757
Northern	2,255	53.22	4,500	53.10	
Central	994	23.46	1,969	23.24	
Southern	948	22.37	1,923	22.69	
Eastern	40	0.94	82	0.97	
Monthly income					0.5705
NT$0–15,840	2,840	67.03	5,741	67.75	
NT$15,841–25,000	1,036	24.45	2,053	24.23	
≥NT$25,001	361	8.52	680	8.02	
Hypertension	2,338	55.18	4,820	56.88	0.0686
Hyperlipidemia	894	21.10	1,705	20.12	0.1968
Diabetes	911	21.50	1,790	21.1	0.6237
Coronary heart disease	952	22.47	1,802	21.27	0.1205
Inflammatory bowel disease	37	0.87	70	0.83	0.7836

Notes: The average exchange rate in 2015 was US$1.00≈New Taiwan (NT)$30.

Table 2 Crude and adjusted hazard ratios (HRs) for anemia among prostate cancer patients during a 3-year follow-up period, stratified by previous administration or non-administration of androgen deprivation therapy (ADT)

Presence of iron-deficiency anemia	Total sample (n = 12,711)	Patients receiving ADT (n = 8,474)	Patients not receiving ADT (n = 4,237)
Three-year follow-up period			
Incidence rate per 100,000 person-years (95% CI)	3.20 (2.89–3.53)	3.68 (3.29–4.11)	2.26 (1.85–2.77)
Crude HR (95% CI)	--	1.62*** (1.29–2.03)	1.00
Adjusted [a] HR (95% CI)	--	1.61*** (1.28–2.03)	1.00

Notes: [a] Using a Cox proportional regression with cases censored if individuals died during the 3-year follow-up period; [a] Adjustments were made for patients' geographic location, monthly income, urbanization level, age, hyperlipidemia, diabetes, hypertension, coronary heart disease, and inflammatory bowel disease.

* $p < 0.05$. ** $p < 0.01$. *** $p \leq 0.001$

CI, confidence interval

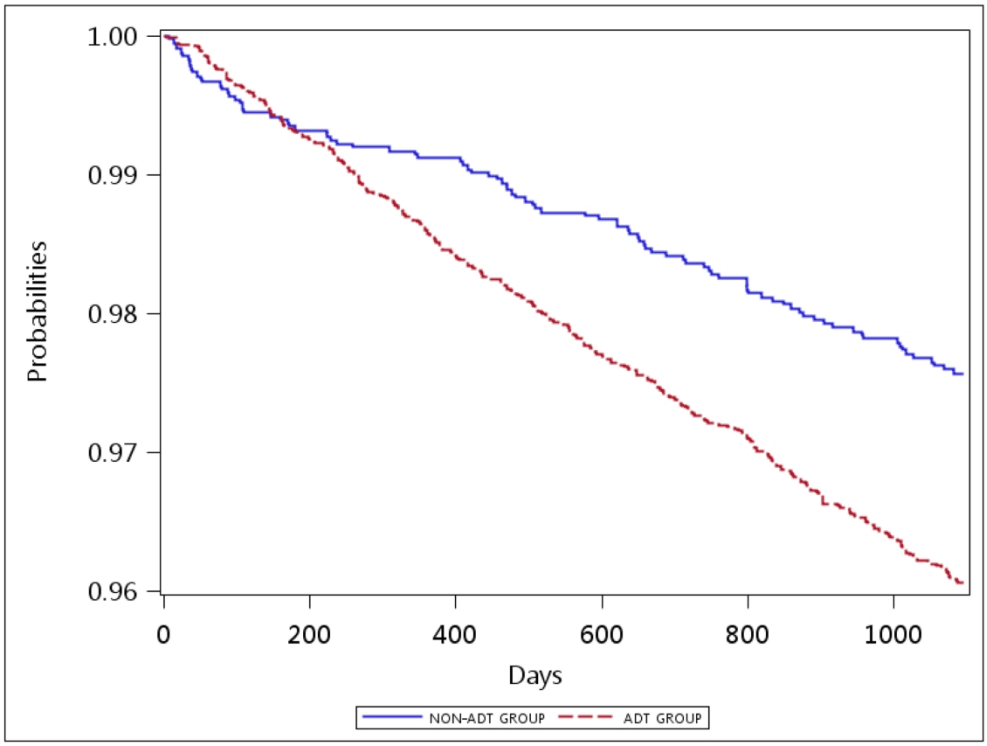

Figure 1 Kaplan–Meier curve for iron-deficiency anemia (IDA) among prostate cancer patients during a 3-year follow-up period, stratified by previous administration or non-administration of androgen deprivation therapy (ADT)

199x149mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	10-11
		(c) Consider use of a flow diagram	10-11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	10-11
		(c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Androgen Deprivation Therapy and the Risk of Iron-Deficiency Anaemia among Patients with Prostate Cancer: A Population-based Cohort Study

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Abstract

Objectives: The administration of androgen deprivation therapy (ADT) to patients with metastatic prostate cancer might be associated with some adverse effects such as anaemia; however, few studies have been performed in East Asian populations. This study aimed to investigate the association between ADT and iron-deficiency anaemia (IDA) among patients with prostate cancer in a population-based nationwide cohort.

Design: Cohort study.

Setting: Taiwan.

Participants: Data for the cohort study were retrieved from the Taiwan National Health Insurance Research Database. Propensity score matching was used to select 8474 patients with prostate cancer who received ADT as the study group and 4237 patients with 4237 who did not receive ADT as the control group.

Primary and secondary outcome measures: This study individually tracked patients over a 3-year study period and identified those who were subsequently diagnosed with IDA following the index date.

Results: The incidence rates of IDA in the study and control groups were 1.35 (95% confidence interval [CI] = 1.20–1.51) and 0.83 per 100 person-years (95% CI = 0.67–1.01), respectively. Furthermore, proportional Cox regression revealed a hazard ratio

(HR) of 1.61 (95% CI = 1.28–2.03) for IDA in the study group after adjusting for patients' age, monthly income, geographic location, residential urbanisation level and incidence of hyperlipidemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding.

Conclusion: Compared with its non-use among patients with prostate cancer, ADT use was associated with a higher risk of IDA.

Key words: androgen deprivation therapy, iron-deficiency anaemia, prostate cancer, anaemia, drug safety

Strengths and limitations of this study

1. Data for this cohort study were retrieved from a large Asian population-based dataset in Taiwan.
2. This study used a propensity score matching strategy to eliminate potential biases such as patients' demographics and comorbidities between the study and control cohorts.
3. The sample size and statistical power were sufficient in this study.
4. Selection bias may have been eliminated by the use of a population-based dataset.
5. Information on personal history and lifestyle was unavailable when data were retrieved.

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INTRODUCTION

Prostate cancer (PCa) is the leading cause of cancer in males, and it accounted for 293,000 deaths globally in 2013.[1 2] In 2018, an estimated 164,690 new diagnoses in males and 29,430 deaths from the disease were reported in the United States.[3] Androgen deprivation therapy (ADT), also known as hormone therapy, has been a fundamental component of metastatic PCa management for more than half a century.[4] This therapy can improve long-term survival for many patients.[5 6] However, the decreased serum levels of endogenous androgen associated with ADT might result in some adverse effects, including decreased muscle mass, increased insulin resistance and fall risk, among patients with PCa.[7-12]

Iron-deficiency anaemia (IDA) is a common disease that affects approximately 5% of females and 2% of males in the United States.[13] Increasing numbers of studies have recognised that anaemia may have a potentially detrimental impact on the quality of life and survival of patients with PCa.[14-17] A previous study (InCHIANTI study) further suggested that androgen deficiency contributes to the development of anaemia in men with PCa.[18] Some studies proposed that androgens may stimulate erythropoiesis through direct effects on erythroid progenitor cells and indirect inhibitory effects on hepcidin.[19-21] Therefore, it is plausible that ADT may be associated with the incidence of IDA.

Accordingly, the association between ADT and anaemia has been reported in several Western studies using Caucasian populations.[22-24] However, to date, few studies have been conducted in East Asian populations even though the hereditary risk of PCa substantially varies by ethnicity and geography.[25 26] In addition, the haemoglobin concentration, which is a critical indicator of anaemia, is recognised to vary by race/ethnicity, lifestyle, demographics and other variables.[27] Furthermore, a recent study of 32 patients receiving ADT demonstrated that haematologic toxicities such as anaemia were more frequent in Chinese patients with PCa than in their Western counterparts.[28] Consequently, this study examined whether ADT is associated with a subsequent risk of anaemia in patients with PCa by employing a propensity score matching strategy using an Asian population-based dataset in Taiwan.

METHODS

Database

Data for the retrospective cohort study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD, which derived from the Taiwan Bureau of National Health Insurance, consists of inpatient and ambulatory medical benefit claims from approximately 22 million enrolees, representing more than 99% of Taiwan's population. Therefore, this database provides scientists in Taiwan with an exclusive opportunity to analyse and track medical service use by enrolees since the beginning of the Taiwan National Health Insurance programme in 1995. This study was exempt from full revision by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No. 2-105-05-082) because the dataset used was blinded to the public for research purposes.

Study Sample

This cohort study included study and control groups. For the study group, 28,367 patients who received a first-time diagnosis of PCa (ICD-9-CM code 185) between January 1, 2001 and December 31, 2010 were selected from the Registry of Catastrophic Illness Patient Database in NHIRD. In total, 454 patients younger than 40 years were excluded because the prevalence of PCa is extremely low in this age strata. The date of ADT administration (including gonadotropin-releasing hormone agonists, anti-

androgens, ketoconazole and estrogens; ATC codes L02AE03, L02AE02, L02AE04, L02BB03, G03HA01, L02BB01, J02AB02 and L02AA) was assigned as the index date for patients with PCa who subsequently received ADT treatment. Furthermore, the date of a randomly selected outpatient visit was assigned as the index date for the diagnosis of PCa for patients who did not receive ADT. Meanwhile, 681 patients who had received a diagnosis of IDA (ICD-9-CM codes 280, 280.0, 280.1, 280.8 and 280.9) and 2730 patients who had undergone orchiectomy prior to their index date were excluded. As a result, 24,502 patients with PCa remained in the study, including 20,265 and 4237 patients with ADT use and non-use, respectively, during the 3-year study period. Specifically, 49.50, 17.98, 15.74, and 16.78% of the ADT prescriptions were for cyproterone, bicalutamide, flutamide and other types of medications, respectively. The average time from PCa diagnosis was approximately 111.17 days in our study.

Propensity score matching was used to identify 8474 patients with PCa who received ADT. This methodology could eliminate the differences attributable to differences in patient demographics and medical history between the groups. We used propensity score matching using the Mahalanobis metric (caliper of 0.25 standard deviations of the propensity score). The matching variables included age, monthly income, geographic location, residential urbanisation level (divided into five levels, with 1 being the most urbanised and 5 being the least urbanised),[29] hyperlipidaemia, diabetes,

hypertension, coronary heart disease and inflammatory bowel disease. We performed a 2:1 matching study, because increasing sample size of cases or controls could increase the statistic power of the findings. Ultimately, 12,711 patients were enrolled in this study, including 8474 who received ADT and 4237 who did not receive ADT. We categorised the patients receiving ADT into two levels according to the median duration of ADT use (median = 353 days). The power for this study was adequate (power = 0.987). Each patient was subsequently followed individually for a 3-year period to identify those who received an IDA diagnosis following the index date.

Statistical Analysis

All statistical analyses were performed using the SAS System for Windows (ver. 9.4, SAS Institute). Chi-squared tests were used to investigate differences in sociodemographic characteristics and medical comorbidities between the study and control groups. Additionally, Cox proportional hazard regression analysis was conducted to examine the relationship between ADT use and IDA risk during the 3-year study period. Data for patients who died or who were lost to follow-up during the study period were censored in the Cox regression. In total, 2716 patients died during the 3-year study period (2020 ADT users and 796 non-users). A two-sided p value < 0.05 denoted statistical significance.

Patient and Public Involvement

Patients and the public were not involved in the development of the research question, outcome measures, study design and recruitment/conduct of the present study.

RESULTS

Data for patients' sociodemographic characteristics and medical comorbidities are shown in Table 1. No statistically significant differences were found regarding age, monthly income, geographic location, residential urbanisation level and the incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease between the study and control groups.

The incidence of IDA during the 3-year study period is presented in Table 2. The IDA incidence rate per 100 person-years for the entire 12,711-patient cohort was 1.17 (95% confidence interval [CI] = 1.05–1.29). The incidence rates per 100 person-years for the study and control groups were 1.35 (95% CI = 1.20–1.51) and 0.83 (95% CI = 0.67–1.01), respectively. The log-rank test revealed that the study group had a significantly lower 3-year IDA-free survival rate than the control group ($p < 0.001$, Figure 1).

Table 2 further illustrates that the hazard ratio (HR) for IDA in the study group relative to the findings in the control group was 1.62 (95% CI = 1.29–2.05; $p \leq 0.001$). After adjusting for patients' age, monthly income, geographic location, residential urbanisation level and the incidence of hyperlipidemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal

bleeding, the HR for the study group compared with the control group was 1.61 (95% CI = 1.28–2.03; $p \leq 0.001$). This study further classified patients in the study group as short-term and long-term ADT users based on the median duration of use. Data presented in Table 3 reveal that both short-term and long-term and ADT use can increase the risk of anaemia. Compared with the findings in the control group, the adjusted HRs for long-term and short-term ADT use in the study group were 1.65 (95% CI = 1.28–2.13) and 1.56 (95% CI = 1.19–2.04), respectively.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the relationship between ADT use in men with PCa and the 3-year IDA risk in an East Asian population. This study only included patients with PCa in the relevant analyses to avoid the potential effects attributable to cancer. To mitigate selection bias, a propensity score matching strategy (by age, monthly income, geographical location, residential urbanisation level and medical comorbidities) was used to facilitate comparisons with patients with PCa who did not receive ADT. In this population-based retrospective cohort study of patients with PCa, a significant increase in IDA risk was observed with men treated with ADT.

The findings were consistent with those of prior Western studies. For instance, in the United States, Strum et al. demonstrated that the haemoglobin levels of patients who received ADT for PCa declined from a mean of 149 g/L at baseline to 139, 132 and 131 g/L after 1, 2 and 3 months, respectively.[30] In Canada, Timilshina et al. performed an observational study of 250 patients with non-metastatic PCa and found that ADT was independently associated with a reduction of haemoglobin levels over 12 months.[23] Among 110 patients with PCa who received ADT, one cohort study reported a decline in haemoglobin levels from 14.8 g/dL at baseline to 12.9 g/dL at evaluation.[22] Another study of 72 patients with non-metastatic PCa who received adjuvant radiotherapy plus ADT reported that the haemoglobin level had significant declined after 2 years of

androgen suppression.[31] All of these studies investigated the association of ADT with haemoglobin levels, which is vital given that haemoglobin levels are important for identifying anaemia. However, these clinical studies included small sample sizes and featured a short duration.[22 23 30 31] Separately, Hicks et al. performed a cohort study using the United Kingdom Clinical Practice Research Database linked to the Hospital Episode Statistics repository. Their findings revealed that patients with non-metastatic PCa who received ADT had a nearly 3-fold greater risk of anaemia than non-users (HR = 2.90, 95% CI = 2.67–3.16).[24] However, this study was performed in a Western population, and generalisation of its findings to other ethnic groups is not possible.

Our study examined the association between ADT and the 3-year IDA risk among patients with PCa; however, the risk of anaemia caused by ADT use has remained unclear. To date, increasing biological evidence has suggested a potential connection between the receipt of ADT and subsequent IDA risk.[32] A possible explanation for the underlying mechanism may be that androgen significantly increases the levels of bone marrow erythroid precursors and enhances the differentiation of bone marrow erythroid stem cells to erythrocytes.[21 33] Furthermore, testosterone might influence erythropoietin secretion via peritubular fibroblast-like cells in the kidneys.[34] In animal experiments, testosterone induced erythropoiesis-stimulating factor production in a bioassay using a mouse model of polycythaemia vera.[35] Guo et al. found that sensitivity to erythropoietin

was induced and stress erythropoiesis was increased by testosterone, which upregulated the expression of GATA binding protein 1 and GATA-dependent genes, in a study of ageing male mice.[36] In addition, Bachman et al. observed that treatment with testosterone in men was related to serum hepcidin suppression in a randomised double-blind clinical study.[19] Testosterone directly interacts with the bone morphogenetic protein-Smad signalling pathway in hepatocytes and induces the downregulation of hepcidin transcription.[37] Furthermore, these effects of androgen on hepatic hepcidin and renal erythropoietin gene expression could increase systemic iron transport and erythropoietin levels.[37]

The strengths of our study included the identification of the association between ADT use in patients with PCa and subsequent IDA risk using a large population-based database. The Taiwan NHIRD provides high accessibility to medical service data and adequate to detect IDA risk between the study and control groups. Moreover, the sociodemographic characteristics and medical comorbidities of patients with PCa were acknowledged as risk factors. Furthermore, we also used a propensity score matching strategy to eliminate potential biases such as patients' demographics and comorbidities between the study and control cohorts.

Several limitations of our retrospective study should be addressed. The study lacked information on potentially important patient characteristics, such as body mass

index, smoking, nutrition and non-prescription medication use. Second, it is plausible that the database did not include all patients with PCa and IDA in Taiwan because some patients might have sought alternative medicines not recorded by the NHI programme and some patients with mild or normocytic anaemia may not have immediately sought medical treatment. Therefore, these patients might not have been captured via diagnosis codes. Third, information on the family history of anaemia, cancer stage and grade for the presence of metastases, chemotherapy, radiotherapy and surgery was unavailable this study. Finally, this study lacked information regarding blood variables. Nevertheless, this study identified patients with PCa who used ADT as cases and patients with PCa patients who did not use ADT as controls. In general, physicians in Taiwan perform complete blood counts for patients with PCa to identify suitable treatments. Consequently, we considered that these factors may not have affected the findings in this study.

CONCLUSIONS

In conclusion, the present study detected an increased IDA risk during a 3-year follow-up period among patients with PCa who received ADT. Medical professionals are recommended to be aware of the risk of anaemia following ADT. Clinicians and pharmacists need to consider the possible risk of IDA among patients with PCa who received ADT and assess the efficacy of preventative and treatment modalities for

anaemia.

Contributors

Conceptualisation: Fang-Jen Wu, Yih-Dih Cheng and Li-Ting Kao; Methodology: Yih-Dih Cheng, Yi-Chun Lin, Li-Ting Kao and Wu-Chien Chien; Formal analysis and investigation: Fang-Jen Wu, Jui-Hu Shih and Li-Ting Kao; Writing - original draft preparation: Fang-Jen Wu, I-Hsun Li, Chin-Min Chuang and Li-Ting Kao

Ethics approval

This study was exempt from full revision by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No. 2-105-05-082) because the dataset used was blinded to the public for research purposes.

Data sharing statement

No additional data available.

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Figure Legend

Figure 1 Kaplan–Meier curve of the risk of iron-deficiency anaemia (IDA) among patients with prostate cancer during a 3-year follow-up period as stratified by the previous use or non-use of androgen deprivation therapy (ADT).

Table 1 Demographic characteristics of patients with prostate cancer stratified by the previous use or non-use of androgen deprivation therapy (ADT) (n = 12,711)

Characteristic	Patients not receiving ADT (n = 4237)		Patients receiving ADT (n = 8474)		p value
	Total no.	Column %	Total no.	Column %	
Age (years), mean (SD)	70.99 (8.65)		71.03 (8.59)		0.7971
Urbanisation level					0.9921
1 (most urbanised)	1168	27.57	2326	27.45	
2	990	23.37	1985	23.42	
3	584	13.78	1163	13.72	
4	537	12.67	1056	12.46	
5 (least urbanised)	958	22.61	1944	22.94	
Geographic region					0.9757
Northern	2255	53.22	4500	53.10	
Central	994	23.46	1969	23.24	
Southern	948	22.37	1923	22.69	
Eastern	40	0.94	82	0.97	
Monthly income					0.5705
NT$0–15,840	2840	67.03	5741	67.75	
NT$15,841–25,000	1036	24.45	2053	24.23	
≥NT$25,001	361	8.52	680	8.02	
Hypertension	2338	55.18	4820	56.88	0.0686
Hyperlipidemia	894	21.10	1705	20.12	0.1968
Diabetes	911	21.50	1790	21.1	0.6237
Coronary heart disease	952	22.47	1802	21.27	0.1205
Inflammatory bowel disease	37	0.87	70	0.83	0.7836
Gastrointestinal bleeding	116	2.74	216	2.55	0.5292
Previous cancers	258	6.09	490	5.78	0.4884

Notes: The average exchange rate in 2015 was US$1.00 ≈ New Taiwan (NT)$30.

Table 2 Crude and adjusted hazard ratios (HRs) for anaemia among patients with prostate cancer during a 3-year follow-up period stratified by the previous use or non-use of androgen deprivation therapy (ADT)

Presence of iron-deficiency anaemia	Total sample (n = 12,711)	Patients receiving ADT (n = 8474)	Patients not receiving ADT (n = 4237)
Three-year follow-up period			
Incidence rate per 100 person-years (95% CI)	1.17 (1.05–1.29)	1.35 (1.20–1.5	0.83 (0.67–1.01)
Crude HR (95% CI)	--	1.62 (1.29–2.05	1.00
Adjusted HR (95% CI) [a,b]	--	1.61 (1.28–2.03	1.00
Adjusted HR (95% CI) [a,c]	--	1.61 (1.28–2.03	1.00

Notes: [a] Using a Cox proportional regression with data censored if individuals died during the 3-year follow-up period; [b] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. [c] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding.

CI, confidence interval

Table 3 Crude and adjusted hazard ratios (HRs) for anaemia among patients with prostate cancer during a 3-year follow-up period stratified by the duration of androgen deprivation therapy (ADT)

Presence of iron-deficiency anaemia	Patients receiving long-term ADT (*n* =4239) [d]	Patients receiving short-term ADT (*n* =4235)	Patients not receiving ADT (*n* = 4237)
Three-year follow-up period			
Incidence rate per 100 person-years (95% CI)	1.41 (1.20–1.64)	1.27 (1.06–1.51)	0.83 (0.67–1.01)
Crude HR (95% CI)	1.70 (1.32–2.19)	1.53 (1.17–2.00)	1.00
Adjusted HR (95% CI) [a,b]	1.65 (1.28–2.13)	1.56 (1.20–2.04)	1.00
Adjusted HR (95% CI) [a,c]	1.65 (1.28–2.13)	1.56 (1.19–2.04)	1.00

Notes: [a] Using a Cox proportional regression with data censored if individuals died during the 3-year follow-up period; [b] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. [c] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding. [d] We categorised the patients receiving ADT into two levels according to the median duration of ADT use (353 days). CI, confidence interval

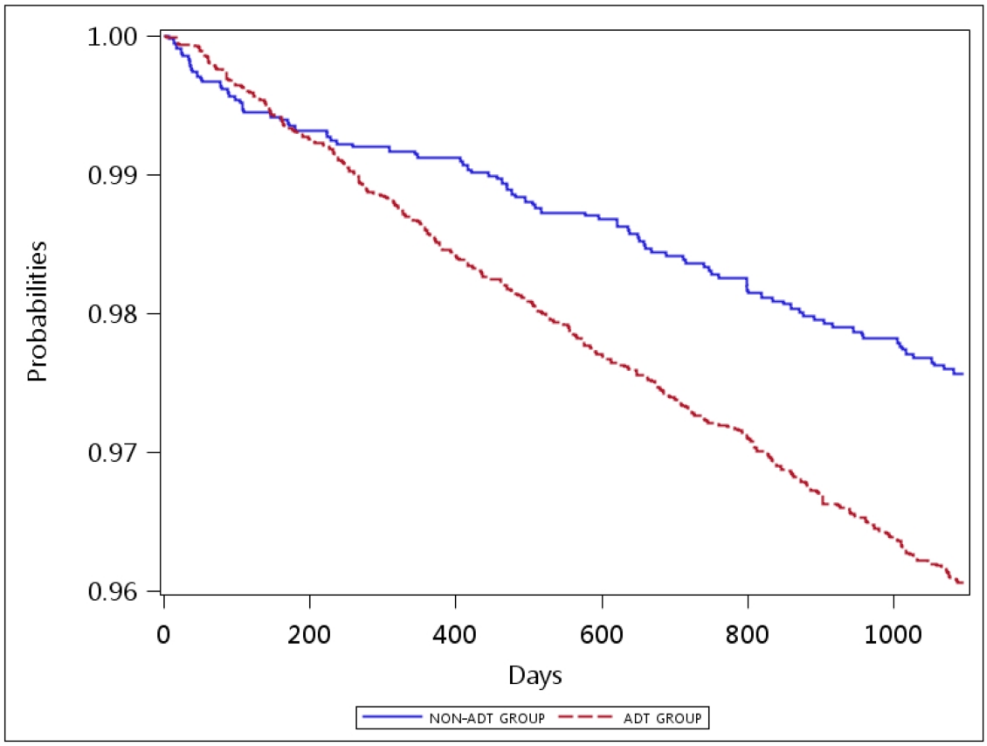

Figure 1 Kaplan–Meier curve of the risk of iron-deficiency anaemia (IDA) among patients with prostate cancer during a 3-year follow-up period as stratified by the previous use or non-use of androgen deprivation therapy (ADT).

199x150mm (500 x 500 DPI)

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Androgen Deprivation Therapy and the Risk of Iron-Deficiency Anaemia among Patients with Prostate Cancer: A Population-based Cohort Study

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Abstract

Objectives: The administration of androgen deprivation therapy (ADT) to patients with metastatic prostate cancer might be associated with some adverse effects such as anaemia; however, few studies have been performed in East Asian populations. This study aimed to investigate the association between ADT and iron-deficiency anaemia (IDA) among patients with prostate cancer in a population-based nationwide cohort.

Design: Cohort study.

Setting: Taiwan.

Participants: Data for the cohort study were retrieved from the Taiwan National Health Insurance Research Database. Propensity score matching was used to select 7,262 patients with prostate cancer who received ADT as the study group and 3,631 patients who did not receive ADT as the control group.

Primary and secondary outcome measures: This study individually tracked patients over a 3-year study period and identified those who were subsequently diagnosed with IDA following the index date.

Results: The incidence rates of IDA in the study and control groups were 1.66 (95% confidence interval [CI] = 1.45–1.86) and 1.01 per 100 person-years (95% CI = 0.78–1.25), respectively. Furthermore, proportional Cox regression revealed a hazard ratio

(HR) of 1.62 (95% CI = 1.24–2.12) for IDA in the study group after adjusting for patients' age, monthly income, geographic location, residential urbanisation level and incidence of hyperlipidemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding.

Conclusion: Compared with its non-use among patients with prostate cancer, ADT use was associated with a higher risk of IDA.

Key words: androgen deprivation therapy, iron-deficiency anaemia, prostate cancer, anaemia, drug safety

Strengths and limitations of this study

1. Data for this cohort study were retrieved from a large Asian population-based dataset in Taiwan.
2. This study used a propensity score matching strategy to eliminate potential biases such as patients' demographics and comorbidities between the study and control cohorts.
3. The sample size and statistical power were sufficient in this study.
4. Selection bias may have been eliminated by the use of a population-based dataset.
5. Information on personal history and lifestyle was unavailable when data were retrieved.

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INTRODUCTION

Prostate cancer (PCa) is the leading cause of cancer in males, and it accounted for 293,000 deaths globally in 2013.[1 2] In 2018, an estimated 164,690 new diagnoses in males and 29,430 deaths from the disease were reported in the United States.[3] Androgen deprivation therapy (ADT), also known as hormone therapy, has been a fundamental component of metastatic PCa management for more than half a century.[4] This therapy can improve long-term survival for many patients.[5 6] However, the decreased serum levels of endogenous androgen associated with ADT might result in some adverse effects, including decreased muscle mass, increased insulin resistance and fall risk, among patients with PCa.[7-12]

Iron-deficiency anaemia (IDA) is a common disease that affects approximately 5% of females and 2% of males in the United States.[13] Increasing numbers of studies have recognised that anaemia may have a potentially detrimental impact on the quality of life and survival of patients with PCa.[14-17] A previous study (InCHIANTI study) further suggested that androgen deficiency contributes to the development of anaemia in men with PCa.[18] Some studies proposed that androgens may stimulate erythropoiesis through direct effects on erythroid progenitor cells and indirect inhibitory effects on hepcidin.[19-21] Therefore, it is plausible that ADT may be associated with the incidence of IDA.

Accordingly, the association between ADT and anaemia has been reported in several Western studies using Caucasian populations.[22-24] However, to date, few studies have been conducted in East Asian populations even though the hereditary risk of PCa substantially varies by ethnicity and geography.[25 26] In addition, the haemoglobin concentration, which is a critical indicator of anaemia, is recognised to vary by race/ethnicity, lifestyle, demographics and other variables.[27] Furthermore, a recent study of 32 patients receiving ADT demonstrated that haematologic toxicities such as anaemia were more frequent in Chinese patients with PCa than in their Western counterparts.[28] Consequently, this study examined whether ADT is associated with a subsequent risk of anaemia in patients with PCa by employing a propensity score matching strategy using an Asian population-based dataset in Taiwan.

METHODS

Database

Data for the retrospective cohort study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD, which derived from the Taiwan Bureau of National Health Insurance, consists of inpatient and ambulatory medical benefit claims from approximately 22 million enrolees, representing more than 99% of Taiwan's population. Therefore, this database provides scientists in Taiwan with an exclusive opportunity to analyse and track medical service use by enrolees since the beginning of the Taiwan National Health Insurance programme in 1995. This study was exempt from full revision by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No. 2-105-05-082) because the dataset used was blinded to the public for research purposes.

Study Sample

This cohort study included study and control groups. For the study group, 28,367 patients who received a first-time diagnosis of PCa (ICD-9-CM code 185) between January 1, 2001 and December 31, 2010 were selected from the Registry of Catastrophic Illness Patient Database in NHIRD. In total, 454 patients younger than 40 years were excluded because the prevalence of PCa is extremely low in this age strata. The date of ADT administration (including gonadotropin-releasing hormone agonists, anti-

androgens, ketoconazole and estrogens; ATC codes L02AE03, L02AE02, L02AE04, L02BB03, G03HA01, L02BB01, J02AB02 and L02AA) was assigned as the index date for patients with PCa who subsequently received ADT treatment. Furthermore, the date of a randomly selected outpatient visit was assigned as the index date for the diagnosis of PCa for patients who did not receive ADT. Meanwhile, 1,605 patients who had received a diagnosis of IDA (ICD-9-CM codes 280, 280.0, 280.1, 280.8 and 280.9) and 1,533 patients who had undergone orchiectomy prior to their index date were excluded. As a result, 24,775 patients with PCa remained in the study, including 20,272 and 4,503 patients with ADT use and non-use, respectively, during the 3-year study period. Specifically, 44.06, 26.06, 14.65, and 15.23% of the ADT prescriptions were for cyproterone, bicalutamide, flutamide and other types of medications, respectively. The average time from PCa diagnosis date to patient entry date for both non-users and users were 758.4 days and 796.9 days, respectively.

Propensity score matching was used to identify 7,262 patients with PCa who received ADT. This methodology could eliminate the differences attributable to differences in patient demographics and medical history between the groups. We used propensity score matching using the Mahalanobis metric (caliper of 0.25 standard deviations of the propensity score). The matching variables included year of the entry date, age, monthly income, geographic location, residential urbanisation level (divided

into five levels, with 1 being the most urbanised and 5 being the least urbanised),[29] hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. We performed a 2:1 matching study, because increasing sample size of cases or controls could increase the statistic power of the findings. Ultimately, 10,893 patients were enrolled in this study, including 7,262 who received ADT and 3,631 who did not receive ADT. We categorised the patients receiving ADT into two levels according to the median duration of ADT use (median = 144 days). Those patients who received ADT <144 days were identified as short-term ADT users. Moreover, patients receiving ADT ≥ 144 days were defined as long-term ADT users. The power for this study was adequate (power > 0.9). Each patient was subsequently followed individually for a 3-year period to identify those who received an IDA diagnosis following the index date.

Statistical Analysis

All statistical analyses were performed using the SAS System for Windows (ver. 9.4, SAS Institute). Chi-squared tests were used to investigate differences in sociodemographic characteristics and medical comorbidities between the study and control groups. Additionally, Cox proportional hazard regression analysis was conducted to examine the relationship between ADT use and IDA risk during the 3-year study period. Data for patients who died or who were lost to follow-up during the study

period were censored in the Cox regression. In total, 3,152 patients died during the 3-year study period (2,153 ADT users and 999 non-users). A two-sided p value < 0.05 denoted statistical significance.

Patient and Public Involvement

Patients and the public were not involved in the development of the research question, outcome measures, study design and recruitment/conduct of the present study.

RESULTS

Data for patients' sociodemographic characteristics and medical comorbidities are shown in Table 1. No statistically significant differences were found regarding age, monthly income, geographic location, residential urbanisation level and the incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease between the study and control groups.

The incidence of IDA during the 3-year study period is presented in Table 2. The IDA incidence rate per 100 person-years for the entire 10,893-patient cohort was 1.45 (95% confidence interval [CI] = 1.29–1.61). The incidence rates per 100 person-years for the study and control groups were 1.66 (95% CI = 1.45–1.86) and 1.01 (95% CI = 0.78–1.25), respectively. The log-rank test revealed that the study group had a significantly lower 3-year IDA-free survival rate than the control group ($p < 0.001$, Figure 1).

Table 2 further illustrates that the hazard ratio (HR) for IDA in the study group relative to the findings in the control group was 1.64 (95% CI = 1.25–2.14; $p \leq 0.001$). After adjusting for patients' age, monthly income, geographic location, residential urbanisation level and the incidence of hyperlipidemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal

bleeding, the HR for the study group compared with the control group was 1.62 (95% CI = 1.24–2.12; $p \leq 0.001$). This study further classified patients in the study group as short-term and long-term ADT users based on the median duration of use. Compared with the findings in the control group, the adjusted HRs for short-term ADT use in the study group were 2.06 (95% CI = 1.53–2.76) (Table 3). Furthermore, sensitivity analyses were displayed in Supplementary Table 1 and Supplementary Table 2.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the relationship between ADT use in men with PCa and the 3-year IDA risk in an East Asian population. This study only included patients with PCa in the relevant analyses to avoid the potential effects attributable to cancer. To mitigate selection bias, a propensity score matching strategy (by year of the entry date, age, monthly income, geographical location, residential urbanisation level and medical comorbidities) was used to facilitate comparisons with patients with PCa who did not receive ADT. In this population-based retrospective cohort study of patients with PCa, a significant increase in IDA risk was observed with men treated with ADT.

The findings were consistent with those of prior Western studies. For instance, in the United States, Strum et al. demonstrated that the haemoglobin levels of patients who received ADT for PCa declined from a mean of 149 g/L at baseline to 139, 132 and 131 g/L after 1, 2 and 3 months, respectively.[30] In Canada, Timilshina et al. performed an observational study of 250 patients with non-metastatic PCa and found that ADT was independently associated with a reduction of haemoglobin levels over 12 months.[23] Among 110 patients with PCa who received ADT, one cohort study reported a decline in haemoglobin levels from 14.8 g/dL at baseline to 12.9 g/dL at evaluation.[22] Another study of 72 patients with non-metastatic PCa who received adjuvant radiotherapy plus

ADT reported that the haemoglobin level had significant declined after 2 years of androgen suppression.[31] All of these studies investigated the association of ADT with haemoglobin levels, which is vital given that haemoglobin levels are important for identifying anaemia. However, these clinical studies included small sample sizes and featured a short duration.[22 23 30 31] Separately, Hicks et al. performed a cohort study using the United Kingdom Clinical Practice Research Database linked to the Hospital Episode Statistics repository. Their findings revealed that patients with non-metastatic PCa who received ADT had a nearly 3-fold greater risk of anaemia than non-users (HR = 2.90, 95% CI = 2.67–3.16).[24] However, this study was performed in a Western population, and generalisation of its findings to other ethnic groups is not possible.

Our study examined the association between ADT and the 3-year IDA risk among patients with PCa; however, the risk of anaemia caused by ADT use has remained unclear. To date, increasing biological evidence has suggested a potential connection between the receipt of ADT and subsequent IDA risk.[32] A possible explanation for the underlying mechanism may be that androgen significantly increases the levels of bone marrow erythroid precursors and enhances the differentiation of bone marrow erythroid stem cells to erythrocytes.[21 33] Furthermore, testosterone might influence erythropoietin secretion via peritubular fibroblast-like cells in the kidneys.[34] In animal experiments, testosterone induced erythropoiesis-stimulating factor production in a bioassay using a

mouse model of polycythaemia vera.[35] Guo et al. found that sensitivity to erythropoietin was induced and stress erythropoiesis was increased by testosterone, which upregulated the expression of GATA binding protein 1 and GATA-dependent genes, in a study of ageing male mice.[36] In addition, Bachman et al. observed that treatment with testosterone in men was related to serum hepcidin suppression in a randomised double-blind clinical study.[19] Testosterone directly interacts with the bone morphogenetic protein-Smad signalling pathway in hepatocytes and induces the downregulation of hepcidin transcription.[37] Furthermore, these effects of androgen on hepatic hepcidin and renal erythropoietin gene expression could increase systemic iron transport and erythropoietin levels.[37]

The strengths of our study included the identification of the association between ADT use in patients with PCa and subsequent IDA risk using a large population-based database. The Taiwan NHIRD provides high accessibility to medical service data and adequate to detect IDA risk between the study and control groups. Moreover, the sociodemographic characteristics and medical comorbidities of patients with PCa were acknowledged as risk factors. Furthermore, we also used a propensity score matching strategy to eliminate potential biases such as patients' demographics and comorbidities between the study and control cohorts.

Several limitations of our retrospective study should be addressed. The study

lacked information on potentially important patient characteristics, such as body mass index, smoking, nutrition and non-prescription medication use. Second, it is plausible that the database did not include all patients with PCa and IDA in Taiwan because some patients might have sought alternative medicines not recorded by the NHI programme and some patients with mild or normocytic anaemia may not have immediately sought medical treatment. Therefore, these patients might not have been captured via diagnosis codes. Third, information on the family history of anaemia, cancer stage and grade for the presence of metastases, chemotherapy, radiotherapy and surgery was unavailable this study. Finally, this study lacked information regarding blood variables. Nevertheless, this study identified patients with PCa who used ADT as cases and patients with PCa patients who did not use ADT as controls. In general, physicians in Taiwan perform complete blood counts for patients with PCa to identify suitable treatments. Consequently, we considered that these factors may not have affected the findings in this study.

CONCLUSIONS

In conclusion, the present study detected an increased IDA risk during a 3-year follow-up period among patients with PCa who received ADT. Medical professionals are recommended to be aware of the risk of anaemia following ADT. Clinicians and pharmacists need to consider the possible risk of IDA among patients with PCa who

received ADT and assess the efficacy of preventative and treatment modalities for anaemia.

Contributors

Conceptualisation: Fang-Jen Wu, Yih-Dih Cheng, I-Hsun Li and Li-Ting Kao; Methodology: Fang-Jen Wu, Yih-Dih Cheng, Yi-Chun Lin, and Li-Ting Kao; Formal analysis and investigation: Fang-Jen Wu and Wu-Chien Chien; Writing - original draft preparation: Fang-Jen Wu, Jui-Hu Shih, Chin-Min Chuang and Yih-Dih Cheng

Ethics approval

This study was exempt from full revision by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No. 2-105-05-082) because the dataset used was blinded to the public for research purposes.

Data sharing statement

No additional data available.

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Figure Legend

Figure 1 Kaplan–Meier curve of the risk of iron-deficiency anaemia (IDA) among patients with prostate cancer during a 3-year follow-up period as stratified by the previous use or non-use of androgen deprivation therapy (ADT).

Table 1 Demographic characteristics of patients with prostate cancer stratified by the previous use or non-use of androgen deprivation therapy (ADT) (*n* =10,893)

Characteristic	Patients not receiving ADT (*n* =3,631)		Patients receiving ADT (*n* =7,262)		*p* value
	Total no.	Column %	Total no.	Column %	
Age (years), mean (SD)	74.26 (8.81)		74.46 (8.81)		0.284
Urbanisation level					0.792
1 (most urbanised)	943	25.97	1,816	25.01	
2	871	23.99	1,734	23.88	
3	492	13.55	1,024	14.10	
4	492	13.55	1,011	13.92	
5 (least urbanised)	833	22.94	1,677	23.09	
Geographic region					0.454
Northern	1,876	51.67	3,676	50.62	
Central	850	23.41	1,688	23.24	
Southern	860	23.68	1,789	24.64	
Eastern	45	1.24	109	1.50	
Monthly income					0.385
NT$0–15,840	2,426	66.81	4,826	66.46	
NT$15,841–25,000	932	25.67	1,931	26.59	
≥NT$25,001	273	7.52	505	6.95	
Hypertension	2,047	56.38	4,099	56.44	0.946
Hyperlipidemia	718	19.77	1,308	18.01	0.026
Diabetes	792	21.81	1,511	20.81	0.226
Coronary heart disease	838	23.08	1,679	23.12	0.962
Inflammatory bowel disease	29	0.80	65	0.90	0.608
Gastrointestinal bleeding	122	3.36	265	3.65	0.442
Previous cancers	348	9.58	533	7.34	<0.001

Notes: The average exchange rate in 2015 was US$1.00 ≈ New Taiwan (NT)$30.

Table 2 Crude and adjusted hazard ratios (HRs) for anaemia among patients with prostate cancer during a 3-year follow-up period stratified by the previous use or non-use of androgen deprivation therapy (ADT)

Presence of iron-deficiency anaemia	Total sample (n = 10,893)	Patients receiving ADT (n = 7,262)	Patients not receiving ADT (n = 3,631)
Three-year follow-up period			
Incidence rate per 100 person-years (95% CI)	1.45 (1.29-1.61)	1.66 (1.45-1.86)	1.01 (0.78-1.25)
Crude HR (95% CI)	--	1.64 (1.25-2.14)	1.00
Adjusted HR (95% CI) [a,b]	--	1.58 (1.21-2.07)	1.00
Adjusted HR (95% CI) [a,c]	--	1.62 (1.24-2.12)	1.00

Notes: [a] Using a Cox proportional regression with data censored if individuals died during the 3-year follow-up period; [b] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. [c] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding.

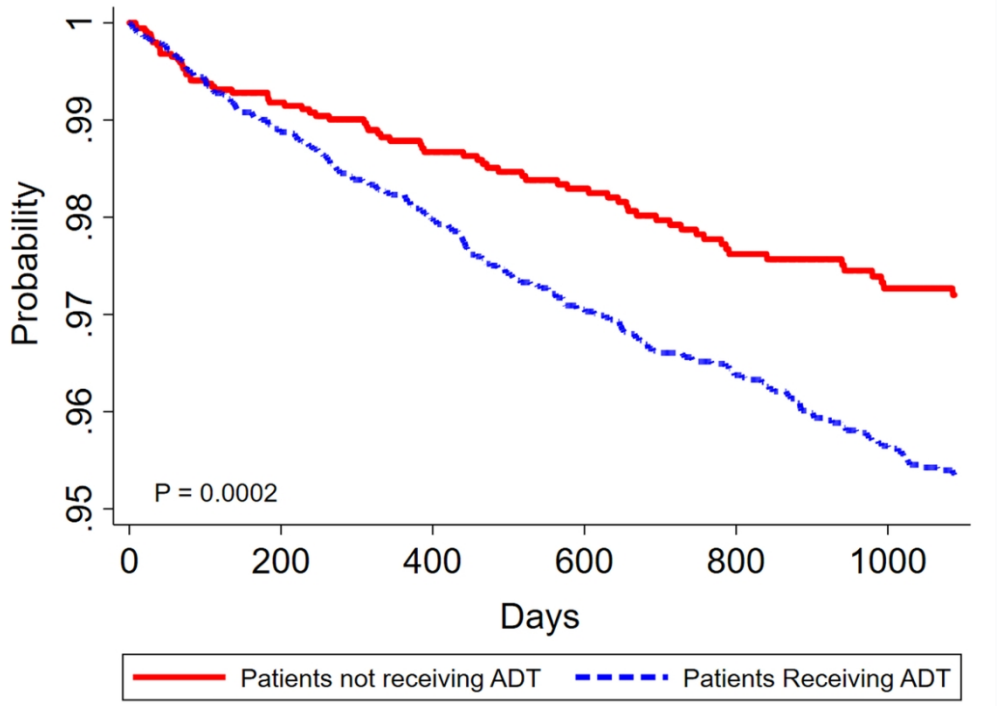
CI, confidence interval

Table 3 Crude and adjusted hazard ratios (HRs) for anaemia among patients with prostate cancer during a 3-year follow-up period stratified by the duration of androgen deprivation therapy (ADT)

Presence of iron-deficiency anaemia	Patients receiving short-term ADT (*n* =3,631) [d]	Patients receiving long-term ADT (*n* =3,631)	Patients not receiving ADT (*n* = 3,631)
Three-year follow-up period			
Incidence rate per 100 person-years (95% CI)	2.24 (1.87-2.62)	1.25 (1.02-1.48)	1.01 (0.78-1.25)
Crude HR (95% CI)	2.19 (1.64-2.92)	1.25 (0.93-1.69)	1.00
Adjusted HR (95% CI) [a,b]	2.20 (1.64-2.94)	1.22 (0.90-1.65)	1.00
Adjusted HR (95% CI) [a,c]	2.06 (1.53-2.76)	1.23 (0.91-1.66)	1.00

Notes: [a] Using a Cox proportional regression with data censored if individuals died during the 3-year follow-up period; [b] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. [c] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding. [d] We categorised the patients receiving ADT into two levels according to the median duration of ADT use (144 days).

CI, confidence interval



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Supplementary Material

Supplementary Table 1 Crude and adjusted hazard ratios (HRs) for anaemia among patients with prostate cancer during a 3-year follow-up period stratified by the different androgen deprivation therapy (ADT) exposure definition

Presence of iron-deficiency anaemia	Current ADT users (n =109) [d]	Past ADT users (n =7,1[illegible])	Patients not receiving ADT (n = 3,631)
Three-year follow-up period			
Incidence rate per 100 person-years (95% CI)	93.65 (76.07-111.24)	0.94 (0.78-1.09)	1.01 (0.78-1.25)
Crude HR (95% CI)	90.74 (68.88-119.55)	0.93 (0.69-1.24)	1.00
Adjusted HR (95% CI) [a,b]	89.64 (67.19-119.58)	0.91 (0.68-1.22)	1.00
Adjusted HR (95% CI) [a,c]	81.52 (60.58-109.69)	0.90 (0.67-1.20)	1.00

Notes: [a] Using a Cox proportional regression with data censored if individuals died during the 3-year follow-up period; [b] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. [c] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding. [d] We categorised the patients receiving ADT into current users (patients who had received ADT prior to the outcome date within 1 month) and past users (other remaining users).

CI, confidence interval

Supplementary Table 2 Sensitivity analysis

Outcome variable	Outcome definition: cases with anaemia diagnosis		Outcome definition: cases with anaemia diagnosis and receiving iron supplementation	
	Patients receiving ADT (n = 7,262)	Patients not receiving ADT (n = 3,631)	Patients receiving ADT (n = 7,262)	Patients not receiving ADT (n = 3,631)
Presence of iron-deficiency anaemia				
Three-year follow-up period				
Incidence rate per 100 person-years (95% CI)	1.66 (1.45-1.86)	1.01 (0.78-1.25)	1.66 (1.45-1.86)	0.08 (0.02-0.15)
Crude HR (95% CI)	1.64 (1.25-2.14)	1.00	19.56 (8.69-44.02)	1.00
Adjusted HR (95% CI) [a,b]	1.58 (1.21-2.07)	1.00	19.43 (8.63-43.76)	1.00
Adjusted HR (95% CI) [a,c]	1.62 (1.24-2.12)	1.00	19.14 (8.50-43.10)	1.00

Notes: [a] Using a Cox proportional regression with data censored if individuals died during the 3-year follow-up period; [b] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease and inflammatory bowel disease. [c] Adjustments were made for patients' geographic location, monthly income, urbanisation level, age and incidence of hyperlipidaemia, diabetes, hypertension, coronary heart disease, inflammatory bowel disease, other cancers and gastrointestinal bleeding.
CI, confidence interval