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Review

Prostate Cancer Outcomes in Immunocompromised Patients: A Systematic Review and Meta-analysis

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Abstract

Background and objective: The role of immunosuppression in prostate cancer (PCa) mortality is a debated topic, with a low level of evidence. This review aims to evaluate the cancer-specific mortality (CSM) and overall mortality (OM) of PCa in immunocompromised patients compared with immunocompetent individuals.

Methods: A literature search was conducted in the PubMed/Medline, Embase, and Web of Science databases (up to the March 31, 2024). The analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (CRD42022361504). Data were pooled using a fixed-effect model and adjusted hazard ratios (HRs).

Key findings and limitations: A total of 13 studies ($n \approx 3.4$ million PCa patients) were included in the qualitative analysis; 11 studies were included in the quantitative analysis. The forest plot for CSM in immunocompromised patients failed to reach statistical significance (HR 1.04 [95% confidence interval {CI}, 0.91–1.18], $p = 0.57$). OM was higher in the immunocompromised cohort (HR 2.04 [95% CI, 1.94–2.15], $p < 0.001$). CSM for transplanted patients was comparable with that for the controls (HR 1.01 [95% CI, 0.86–1.18], $p = 0.94$). Patients with human immunodeficiency virus (HIV) had higher CSM rates (HR 1.83 [95% CI, 1.21–2.75], $p = 0.004$). Limitations included retrospective cohort studies and heterogeneity in reporting PCa stages.

Conclusions and clinical implications: Transplanted patients present a CSM rate comparable with the controls, despite a higher OM rate. Other immunocompromised patients present an overall worse prognosis. The treatment algorithm should be applied by

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international guidelines for transplanted patients, delivering more aggressive treatments and screening strategies.

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ADVANCING PRACTICE

What does this study add?

This study investigated the cancer-specific mortality as well as overall mortality of immunocompromised patients with prostate cancer (PCa). It relied on a huge sample size, furnishing a robust evaluation of both the CSM and the OM outcomes. Specifically, the manuscript shed light on indications available for PCa management both in transplanted and human immunodeficiency virus-affected patients.

Clinical Relevance

This study highlights the importance of differentiating therapeutic approaches for immunocompromised patients with prostate cancer, showing that transplanted patients have cancer-specific mortality comparable to immunocompetent patients, despite higher overall mortality. For HIV patients, more aggressive treatment strategies and increased screening may be recommended due to a generally poorer prognosis. These findings also underscore the need to tailor treatment protocols based on patients' immune status to optimize clinical outcomes. Associate Editor: Guillaume Ploussard, MD.

Patient Summary

Patients with immunocompromised status have worse prognosis, which should be considered when planning the treatment strategy.

1. Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with age-standardized rates per 100 000 persons of 97.2, 94.9, and 85 in Northern America, Western Europe, and Northern Europe, respectively [1]. Although various risk factors have been related to PCa incidence and progression [1], the role of immunosuppression condition is still a debated topic [2]. PCa is considered a “cold” tumor [2], as few immune cells infiltrate malignant prostate lesions; these findings have been the main reason to explain the poor response to immune checkpoint inhibitors in PCa. Nevertheless, two recent systematic reviews and meta-analyses have highlighted an association between chronic inflammatory condition and development of PCa [3,4]. The complexity of the immune-related events and their potential role in the generation and proliferation of neoplastic clones in the prostate have also raised concerns on how the natural history of PCa in immunosuppressed patients would be different—either drug-induced (eg, transplanted recipients) or disease-induced (eg, autoimmune diseases, AIDS, etc.) immunosuppression.

There is evidence in literature suggesting a higher risk of solid cancers in transplant recipients [5,6], with some medications potentially able to promote carcinogenic effects or tumor growth [7,8]. Accordingly, if immunosuppression drugs might adversely affect PCa outcomes, a higher risk

of advanced PCa and worse oncological outcomes should be observed in transplanted patients [9,10].

In human immunodeficiency virus (HIV)-affected patients, the introduction of antiretroviral therapy has led to improvements in immune function, with overall better life expectancy. Unfortunately, this condition has also led to a higher incidence of non-AIDS defining cancers (NADCs), contributing to a rise in mortality rates in these patients and highlighting the biological effects of HIV-related immunosuppression [11–13,45].

The objective of this study was to conduct a systematic review and meta-analysis to evaluate the oncological outcomes of PCa in immunocompromised patients, compared with the immunocompetent controls, according to the type of immunosuppression.

2. Methods

2.1. Eligibility criteria

We developed the study protocol in accordance with the patients, intervention, comparison, and outcomes (PICO) framework. The studies were deemed eligible if they respected the following inclusion criteria: (1) immunocompromised patients diagnosed with PCa at any stage; (2) any kind of PCa treatment modality except watchful waiting; (3) a comparison with immunocompetent patients with PCa; and (4) cancer-specific mortality (CSM) and overall mortal-

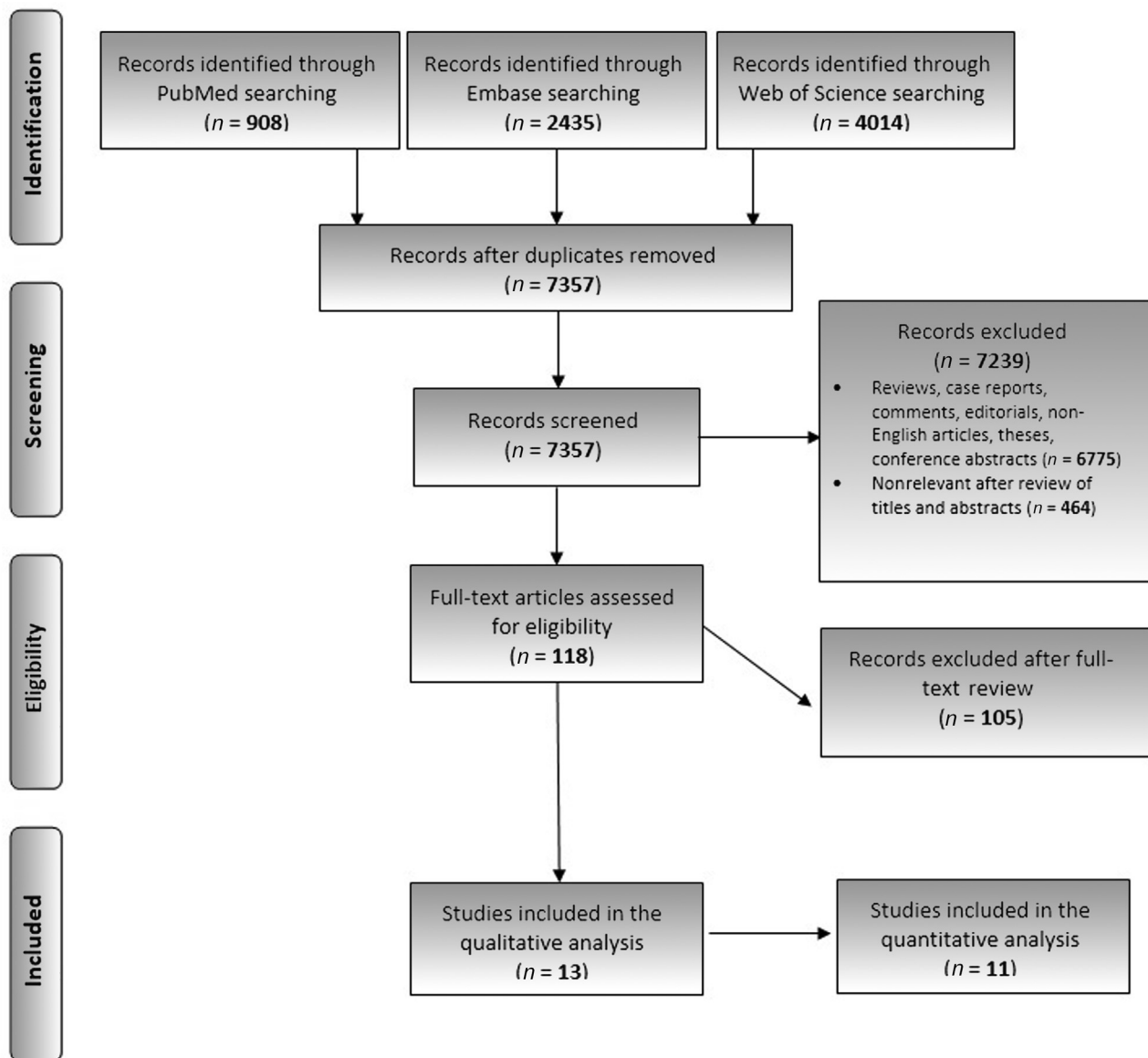


Fig. 1 – PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

ity (OM) as the primary and secondary outcomes of interest, respectively. After consultation with an internal medicine physician with relevant expertise in the field of immunodeficiency, the immunosuppression definition involved the following conditions: leukemia, solid organ or stem cell transplantation, dialysis, HIV infection, autoimmune diseases, and congenital or acquired immunodeficiency. In case of duplicate publications, either the higher-quality or the most recent publication was selected. Reviews, meta-analyses, editorials, commentaries, authors' replies, abstracts of unpublished studies, and case reports were excluded. No restriction on language, publication date, or study design (prospective or retrospective) was applied for study eligibility.

Studies with <50 immunocompromised patients were excluded as these were not a representative of the condition.

2.2. Data sources and extraction

We conducted this study in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [14]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42022361504).

We conducted a literature search in the PubMed/Medline, Embase, and Web of Science databases from inception to March 31, 2024, in order to identify studies that addressed the inclusion criteria. The full search strategy is provided in the Supplementary material. Two independent investigators (A.T. and A.U.) performed an initial screening based on a review of the titles and abstracts. Reasons for exclusions were noted. Potentially relevant studies were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process.

Disagreements were resolved by consultation with two senior coauthors (M.B. and F.S.).

Data extraction was conducted independently on selected studies in a double-blind manner by two authors (A.T. and A.U.). For the included studies, the following variables were noted: first author's name and publication year, journal, study design, country of research, registry of research, study duration, type of immunosuppression, number of patients included, patients age, tumor stage (localized, regional, or advanced), type of treatment, duration of follow-up, outcomes (CSM or OM), and adjustment criteria.

2.3. Risk of bias assessment

Two authors (A.T. and A.U.) independently assessed the studies' quality and the risk of bias (RoB) for nonrandomized studies using the Newcastle-Ottawa Scale, thus evaluating the following: (1) study group selection, (2) group comparability, and (3) exposure and outcome assessment [15]. We a priori set CSM as the main factor and OM as an additional factor. The follow-up was judged adequate if it was >5 yr.

Studies with a score of >7 were considered to be of high quality, 4–6 moderate quality, and <4 poor quality.

Eventual disagreements were resolved by consultation with a third coauthor (M.B.).

2.4. Statistical analysis

For the quantitative analysis, the adjusted hazard ratios (aHRs) were extracted from individual studies, and the results were then summarized and pooled. A meta-analysis was performed when two or more studies reported the same outcome under the same definition. The inverse variance method with HR and 95% confidence interval (CI) derived from the Cox proportional hazard model was used to report the outcomes of interest. We used either a fixed-effect or a random-effect model according to the heterogeneity of the pooled studies [16]. We assessed heterogeneity using the Cochrane Q test and quantified it using I^2 values. In the case of heterogeneity (Cochrane Q test $p < 0.05$ and $I^2 > 50\%$), we used a random-effect model and attempted to investigate and further explain the heterogeneity; otherwise, the fixed-effect model was used for the forest plots. To investigate the observed heterogeneity, sensitivity and subgroup analyses were performed. The Cochrane Collaboration Review Manager software (RevMan v.5.4; Cochrane Collaboration, Oxford, UK) was used for all the calculations. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Study selection

The study selection process is outlined in the PRISMA flow diagram (Fig. 1). A total of 118 studies were selected for a full-text review. At the end of the review process, 13 registry-based studies met the inclusion criteria and were thus included in the qualitative analysis. A total of 11 studies reported aHRs for the outcomes of interest and were included in the quantitative analysis. A full description of

the reasons for exclusion is provided in the Supplementary material.

3.2. Characteristics of included studies

The characteristics of the included studies are summarized in Tables 1 and 2.

Overall, >3.4 million patients were included from North America and Europe, and the following topics were noted: solid organ transplantation (five studies) [17–21], HIV infection (five studies) [22–26], hematopoietic stem cell transplantation (one study) [27], and rheumatoid arthritis (RA; two studies) [28,29]. All studies were registry-based cohort studies, with a publication period ranging from 2010 to 2023. When data on age were available, immunocompromised patients with PCa were generally younger than the controls, ranging in age from 50 to 70 yr [24,26]. PCa stage was reported in all the included studies, except in one [27]. High heterogeneity was noted in PCa stage definition, and proper consensual staging of PCa was lacking, as some studies reported the tumor-node-metastasis classification and others the American Joint Committee on Cancer stage from I to IV, or simply a PCa description as “nonadvanced” or “distant” disease. We summarized and pooled the PCa stage for all the included studies as follows: “localized,” “regional,” or “advanced” PCa. Specifically, localized PCa patients were defined as those with no evidence of N+ or M+, regional PCa patients as those with only N+, and advanced PCa patients as those with only M+ disease. When available, the median follow-up time ranged from 1 to 10 yr. The adjustment criteria for aHRs were noted and reported for all the studies except two [26,27]. The most common criteria were demographic and medical factors, such as patients' age, cancer stage, treatment modalities, and patients' comorbidities.

3.3. Risk of bias

Study quality and RoB assessment are summarized in Supplementary Fig. 1. Overall, a low RoB was reported.

3.4. Narrative synthesis

3.4.1. Cancer-specific mortality

Overall, eight [17–23,27] studies reported data for CSM. Transplanted patients were not significantly associated with a higher CSM rate in most of the included studies, with only one exception [27]. Overall, transplanted patients present a PCa-related mortality rate comparable with that of the controls (Table 2). More specifically, Liauw et al [17] reported comparable CSM rates for any PCa stage. In line, Bratt et al [20] reported a comparable CSM rate after an adequate follow-up of 9 yr. Although D'Arcy et al [19] observed a higher CSM rate only for localized PCa patients who underwent curative treatment, the outcome was always comparable with those of the controls in the overall and advanced disease cohorts. Furthermore, secondary PCa presented favorable oncological outcomes in transplanted patients, when compared with other cancer types [27]. Two studies [22,23] reported a higher CSM rate in HIV patients than in the controls, after adjusting for age, PCa stage, treatment, and other risk factors.

Table 1 – Baseline characteristics of 13 papers analyzed in the study

Author	Country	Topic	Journal	Study design	Search Registry	Study period	Inclusion
Liauw (2020) [17]	USA	Solid organ transplantation	<i>Journal of the National Cancer Institute</i>	Registry based	National Cancer Institute, SEER-Medicare	1991–2003, 2004–2011	SR + MA
D'Arcy (2019) [19]	USA	Solid organ transplantation	<i>Cancer</i>	Registry based	National Cancer Institute's Transplant Cancer Match (TCM) Study	1987–2014	SR + MA
Benoni (2020) [18]	EUR (Sweden)	Solid organ transplantation	<i>International Journal of Cancer</i>	Registry based	Swedish Cancer Registry	1992–2013	SR + MA
Bratt (2020) [20]	EUR (Sweden)	Solid organ transplantation	<i>BJU International</i>	Registry based	Swedish Renal Register, National Prostate Cancer Register of Sweden, PCBaSe	1998 – 2016	SR + MA
Coghill (2019) [22]	USA	HIV/AIDS	<i>JAMA Oncology</i>	Registry based	SEER-Medicare	1996–2014	SR + MA
Coghill (2019) [25]	USA	HIV/AIDS	<i>Cancer</i>	Registry based	National Cancer Data Base	2004–2014	SR + MA
Marcus (2015) [23]	USA	HIV/AIDS	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	Registry based	Kaiser Permanente Northern and Southern California, SEER-Medicare	1996–2011	SR + MA
Shiels (2010) [24]	USA	HIV/AIDS	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	Registry based	HIV/AIDS Cancer Match Study	1992–2007	SR + MA
Coghill (2017) [26]	USA	HIV/AIDS	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	Registry based	HIV/AIDS Cancer Match Study, National Center for Health Statistics	1996–2010	SR
Tichelli (2019) [27]	EUR (multiple countries)	Hematopoietic stem cell transplantation	<i>JAMA Oncology</i>	Registry based	EBMT Registry	2000–2014	SR
Nayak (2017) [28]	USA	Rheumatoid arthritis	<i>Arthritis Care & Research</i>	Registry based	Texas Cancer Registry, Medicare	2001–2010	SR + MA
Wheeler (2023) [29]	USA	Rheumatoid arthritis	<i>Arthritis Care & Research</i>	Registry based	Corporat Data Warehouse	2000–2018	SR + MA
Sarabu (2023) [21]	USA	Solid organ transplantation	<i>Cancer Medicine</i>	Registry based	SEER-Medicare	2004–2015	SR + MA

EUR = Europe; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; MA = meta-analysis; SR = systematic review.

3.4.2. Overall mortality

In all the included studies, immunocompromised patients had a higher OM rate in than the controls, and this observation was found for all the immunosuppression conditions included.

More specifically, for transplanted patients, the risk of all-cause mortality was at least 65% higher than that for the controls [17–19,21], with a reduction in life expectancy up to 3 yr [20]. For patients who underwent stem cell transplantation, the standardized mortality ratio (SMR) was higher than primitive PCa patients in the general population, but the median overall survival was 10 yr, without any differences between allogenic and autologous transplantation [27].

In HIV patients, most of the series ($n = 3$ out of 5) [22,24,25] reported a higher risk of all-cause mortality than in the controls, ranging from 34% to 58%. Only one study reported no differences in terms of OM [26].

For RA-affected patients, a higher mortality rate was observed than in the controls [28,29].

3.5. Meta-analysis

The quantitative analysis was conducted for both CSM and OM. The results for CSM are reported in Fig. 2. Overall, the

immunocompromised cohort included 59 344 patients compared with 2 121 927 controls. The forest plot showed the suggestion of a higher risk of mortality in immunocompromised patients, but it did not reach the predefined threshold for statistical significance (HR 1.04 [95% CI, 0.91–1.18], $p = 0.57$). To further investigate the oncological outcomes separately for the different immunosuppression conditions, a subgroup analysis was then conducted for organ recipients and HIV patients. The transplantation cohort included 2510 patients compared with 1 636 387 controls, and the forest plot showed no significant differences in CSM for transplanted patients (HR 1.01 [95% CI, 0.86–1.18], $p = 0.94$, $Z = 0.08$; $\chi^2 = 1.25$, $I^2 = 0\%$, $p = 0.74$).

The HIV cohort consisted of 320 patients compared with 135 066 controls. The forest plot showed a significant association between HIV and a higher risk of mortality (HR 1.83 [95% CI, 1.21–2.75], $p = 0.004$).

The results for OM are reported in Fig. 3. The forest plot showed an association between immunosuppression and a higher all-cause mortality rate (HR 2.04 [95% CI, 1.94–2.15], $p < 0.001$). Since significant heterogeneity was found ($I^2 = 92\%$, $p < 0.001$), a sensitivity analysis was performed (Supplementary Fig. 2). After the adjustments, the immunocompromised cohort still had a higher mortality risk than the controls (HR 1.61 [95% CI, 1.50–1.72], $p < 0.001$).

Table 2 – Outcomes of interest within the 13 papers analyzed in the study

Author	Total no. of patients	IC patients	Age	Stage	Treatment	FU time	CSM	OM	HR adjustment criteria
Liauw (2020) [17]	3720	620	73.3 vs 74.1	Loc. + Reg. + Adv.	RP, RT, BT, HT, AS	5.5 yr	0.88 (0.61–1.27)	1.65 (1.47–2.14)	Time of transplantation, age, grade, stage, CCI, diagnosis time
D'Arcy (2019) [19]	1 457 319	1607	NA ^a	Loc. + Reg. + Adv.	RP, RT, HT	34.6 × 10 ⁶ persons/yr	1.07 (0.88–1.30)	2.68 (2.49–2.89)	Sex, age, race, surveillance, epidemiology, stage, diagnosis time, treatment
Benoni (2020) [18]	177 060	150	NA ^a	Loc. + Reg. + Adv.	NA	2.9 yr	0.84 (0.35–2.02)	1.79 (1.39–2.29)	Type of transplant, age, sex, stage, diagnosis time
Bratt (2020) [20]	798	133	65 vs 66	Loc. + Reg. + Adv.	RP, RT, HT, AS	9 yr	0.87 (0.47–1.62)	8.7 vs 12.5 yr ^b	Age, stage, treatment
Coghill (2019) [22]	133 186	170	NA ^a	Loc. + Reg. + Adv.	RP, RT, HT	>1 yr	1.65 (0.98–2.79)	1.58 (1.23–2.03)	Age, race, income, stage, treatment, diagnosis time
Coghill (2019) [25]	1 136 297	1513	NA ^a	Loc. + Reg. + Adv.	RP, RT, HT	NA ^c	NA	1.56 (1.37–1.77)	Age, race, sex, income, stage, treatment, diagnosis time
Marcus (2015) [23]	2200	150	59 vs 60	Loc. + Reg. + Adv.	RP, RT, HT	5 yr	2.14 (1.11–4.11)	85.5% vs 91.6% ^b	Age, race, sex, stage, treatment, smoking
Shiels (2010) [24]	NA	230	NA ^d	Loc. + Reg. + Adv.	NA	5 yr	NA	1.34 (1.05–1.71)	Age, race, HIV risk group, HAART period, stage
Coghill (2017) [26]	NA	NA	NA ^d	Loc. + Reg. + Adv.	NA	14 903 persons/yr	NA	60.3 × 1000 vs 38.5 × 1000	NA
Tichelli (2019) [27]	NA	410	NA ^a	NA	NA	10 yr	NA ^e	69% (64–75) ^e	NA
Nayak (2017) [28]	NA	43 181	75.1 vs 75.6	Loc. + Reg. + Adv.	NA	>7 yr	NA	1.53 (1.26–1.85)	Demographic factors, medical factors, CCI
Wheeler (2023) [29]	406 988	56 514	64.3 vs 63.7	Loc. + Reg. + Adv.	NA	6.6 yr	0.92 (0.73–1.16)	NA	Race, smoking status, Agent Orange exposure, number of outpatient visits, PSA testing, body mass index, and Rheumatic Disease Comorbidity Index score
Sarabu (2023) [21]	85 942	124	70.5 vs 72.1	Loc.	RP, RT	4.1 and 7.1 yr for KT and controls patients in low-risk group 4.3 and 6.0 yr for KT and controls patients in intermediate-risk group	NA	Low risk: 2.69 (1.40–5.18) Intermediate risk: 2.15 (1.50–3.10)	ESKD status, age, race, socioeconomic status, comorbidity, definitive treatment

Adv. = advanced; AS = active surveillance; BT = brachytherapy; CCI = Charlson Comorbidity Index; CSM = cancer-specific mortality; ESKD = end-stage kidney disease; FU = follow-up; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; HT = hormonal therapy; HR = hazard ratio; IC = immunocompromised; KT = kidney transplantation; Loc. = local; NA = not available; OM = overall mortality; PSA = prostate-specific antigen; Reg. = regional; RP = radical prostatectomy; RT = radiotherapy.

^a No specified age data for patients with prostate cancer (multicancer studies); overall, transplanted patients were younger than controls.

^b Overall survival of immunocompromised cohort versus controls.

^c From cancer diagnosis to death or end of follow-up in 2014.

^d No specified age data as mean or median, but most of the patients were in the following age groups: 60–69 and 70–79 yr [24]; 50–69 and >70 yr [26].

^e Higher standardized mortality ratio (SMR) in comparison with the general population (SMR 1.75 [1.28, 2.28], but 5-yr overall survival was 69% [64–75], with a median follow-up of 10 yr from stem cell transplantation).

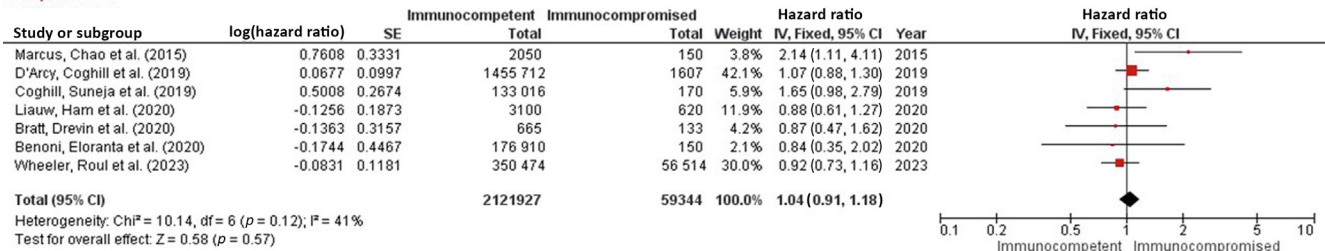
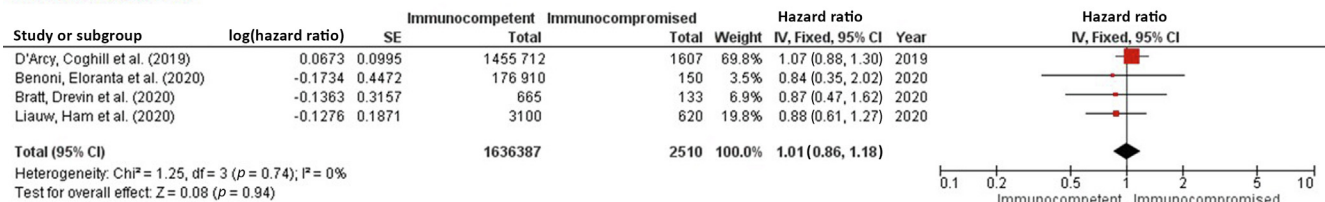
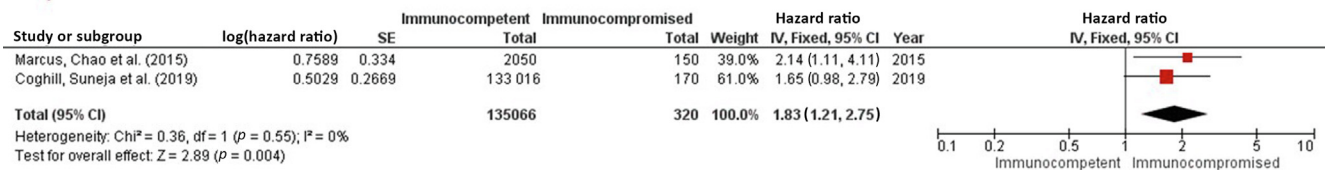
All patients**Transplanted patients****HIV patients**

Fig. 2 – Cancer-specific mortality. CI = confidence interval; IV = inverse variance; SE = standard error.

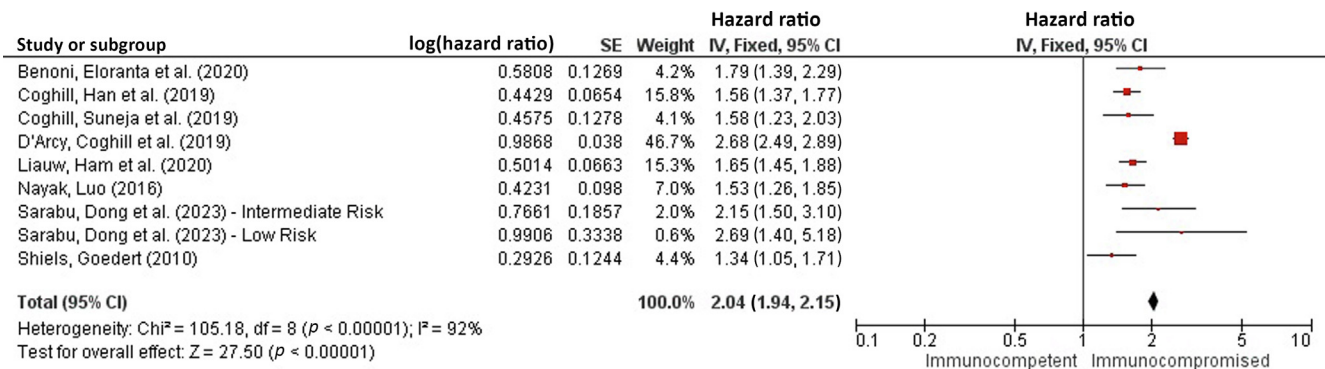


Fig. 3 – Overall mortality. CI = confidence interval; IV = inverse variance; SE = standard error.

4. Discussion

PCa management in immunocompromised patients is a fairly heterogeneous task, as the diverse immunological conditions might variably affect the oncological outcomes. Immunocompromised patients are generally believed to be at a higher risk of developing more aggressive diseases, including PCa, so that PCa patients are often offered more aggressive treatment options, even in case of nonadvanced disease [30,31,46]. However, despite the lack of properly designed prospective trials for cancer treatment in immunocompromised patients, the evidence suggests different scenarios for PCa, depending on the underlying immunosuppression. Furthermore, when considering treatment options, it should be recognized that PCa is a “cold

tumor” and is scarcely responding to either nonsteroidal anti-inflammatory drugs or immunotherapy as well as checkpoint inhibitors. Indeed, Flamiatos et al [32] reported the data of a phase 2 study on neoadjuvant celecoxib, a selective COX-2 inhibitor, in radical prostatectomy candidates. The authors demonstrated that celecoxib did not guarantee the biological basis for chemoprevention in these patients' setting [32]. Moreover, the role of checkpoint inhibitors, historically underscrutinized, was not associated with major survival benefits in localized as well as more advanced PCa stages [33]. This aspect is particularly relevant in populations burdened by immune dysregulation, such as transplanted or HIV+ patients, who may deserve a tailored treatment. Specifically, transplanted patients, when compared with the controls, present a higher incidence and

a higher CSM rate for some specific types of cancers, such as adenocarcinoma of the colon, melanoma, lymphoma, etc. This circumstance might be related to the potential effects of the immunosuppression medications directly contributing to cancer development among transplanted patients affected by different types of cancers [6,18–20,34]. Moreover, if these drugs affect cancer outcomes, all transplanted patients should present a worse prognosis. However, PCa mortality after a solid organ transplantation is comparable with that in the controls, and this evidence is furthermore confirmed by the results of this study. Some controversial results report a higher CSM rate for PCa in patients with previous transplantation; however, these results came from a non-population-based study, with few reported cases and many patients excluded from the final evaluation for a lack of clinical data [35]. As confirmed by other authors [10], the SMR of PCa is not increased in transplant recipients. Moreover, since CSM is a function of both cancer incidence and survival, an elevated SMR does not necessarily translate into a worse cancer prognosis among transplanted patients. Tichelli et al [27] evaluated the oncological outcomes associated with a second solid cancer (SSC) diagnosed in patients with previous stem cell transplantation for hematopoietic tumors; however, despite a higher PCa SMR than in the general population (1.75 [95% CI, 1.28, 2.28]), the 5-yr survival rate was 69% (95% CI: 64–75), with a follow-up time of 10 yr after PCa diagnosis. In this specific case, it is plausible to imagine that the biological behavior of the SSC and its responsiveness to treatment might differ from *de novo* PCa. Moreover, many transplant-associated factors could interfere with the cancer progression and outcomes in recipients, leading to differences in the type of cancer and transplantation [18,27]. Our study highlights comparable stage/treatment-adjusted CSM for transplanted patients, strengthening the available evidence on the topic. Furthermore, Liauw et al [17] observed that the primary hormonal therapy was not associated with a reduction in CSM compared with no therapy or active surveillance, suggesting that it may not be the preferred option for transplanted patients with localized disease. These results further confirm the evidence on treatment modality for nonadvanced PCa after solid organ transplantation [30], suggesting that local treatment or active surveillance may be justifiable options in this population, despite being a contraindication in the past [36,37].

On the contrary, the higher mortality rate of HIV-infected patients diagnosed with PCa does not seem to be completely explained by tumor stage, smoking, or other risk factors. It is plausible that various mechanisms could explain the higher mortality rate of NADC patients, such as chronic inflammation, activation of proto-oncogenes, inhibition of tumor-suppressor genes, and endothelial abnormalities that favor tumor development and progression [23,38–41]. However, another possible option could be the biological explanation, namely, the independent effect of HIV infection and the virus-related immunosuppression, which may play a direct role in affecting tumor behavior and patients' outcomes [23,24]. Nonetheless, the lack or underused screening for early PCa due to the patients' characteristics (poor prognosis or very young

age) may also play a crucial role in predicting CSM [42]. All these reasons may be helpful for better understanding the worse prognosis of HIV patients diagnosed with a wide variety of cancers, independently from etiology, health care facility, or medical insurance, since the stage-adjusted mortality rate is higher even if these patients are more likely to be diagnosed with a lower-stage tumor [43].

Our study also shows a higher OM rate for the overall immunocompromised patients' cohort, independently from the underlying condition. Transplanted patients generally present a higher risk of dying from transplant-related conditions, with overall lower life expectancy than the immunocompetent patients (3 yr shorter than the controls in some series [20]). This trend is further confirmed for different immunosuppression conditions also. People living with HIV infection are expected to die at higher rates due to late disease/AIDS-related complications and comorbidities. Furthermore, not only elderly patients, but also younger (≥ 65 yr old) patients may experience a higher mortality rate, which persists even after adjusting for health insurance and type of cancer care [13,25]. In contrast, Shiels et al [24] found that localized or regional PCa was not associated with a higher mortality rate in men with AIDS, with a relative survival rate no worse than in the controls. The results of their study suggest that mortality following a PCa diagnosis is not harming AIDS patients who underwent relatively reduced screening.

Lastly, Nayak et al [28] showed that patients with RA claims diagnosed with PCa have more or less a 50% higher risk of mortality when compared with the controls, even after adjusting for demographic and medical factors. These results are even more emphasized for patients with at least two claims of RA in a year, further confirming previous data on the topic, with a higher OM rate for patients with RA and PCa than for the controls (HR 1.18) [44].

This work presents some limitations. All the included papers were originally designed as retrospective cohort studies, mostly coming from the USA and Scandinavian area. Outcome data are sometimes lacking for CSM, since many studies were designed with the purpose to evaluate the outcomes of many cancers in the overall cohort, so that PCa-specific data are lacking. For this reason, even if the aHRs consider the minimum adjustment criteria such as PCa stage and treatment, a separate evaluation of the oncological outcomes for different tumor stages or treatments is not available, thus forcing to pool out an evaluation of all the cancer stages and therapies summed up. For the same reason, a complete demographic evaluation of the immunocompromised cohort was not possible. Last but not least, among HIV+ patients, granular information regarding treatment for HIV as well as disease status was not distinguishable. This study also presents some strengths. The combined studies accounted for a quite large number of patients, allowing for a robust evaluation of both the CSM and the OM outcomes. The results confirm the literature evidence on specific topics, further suggesting an improvement in treatment choice for different categories of immunocompromised patients, trying to add something to the very few indications available for PCa management in both transplanted and HIV patients.

5. Conclusions

Transplanted patients present a CSM rate comparable with the immunocompetent controls, despite a higher OM rate probably related to the immune system status and transplant-specific complications. On the contrary, some immunocompromised categories present an overall worse prognosis, in particular, the patients affected by HIV. For this reason, it is advisable that the treatment algorithm for PCa should be applied according to the international guidelines, with no difference between normal population and transplanted recipients, while more aggressive treatments and more intense screening strategies should be recommended for other immunocompromised categories.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2025.05.021>.

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