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Stabellini, N., Cullen, J., Bittencourt, M. S., Moore, J. X., Cao, L., Weintraub, N. L., Harris, R. A., Wang, X., Datta, B., Coughlin, S. S., Garcia, J., Shanahan, J., Hamerschlag, N., Waite, K., Fillmore, N. R., Terris, M., Montero, A. J., Barnholtz-Sloan, J. S., & Guha, A. (2023). Allostatic load and cardiovascular outcomes in males with prostate cancer. *JNCI cancer spectrum*, 7(2), Article pkad005. Advance online publication. <https://doi.org/10.1093/jncics/pkad005>

[Link to publication record in Ulster University Research Portal](#)

Published in:

JNCI cancer spectrum

Publication Status:

Published online: 08/02/2023

DOI:

[10.1093/jncics/pkad005](https://doi.org/10.1093/jncics/pkad005)

Document Version

Author Accepted version

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Allostatic load and cardiovascular outcomes in males with prostate cancer

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in men with PC. Accumulated stress plays an important role in CVD development. The cumulative burden of chronic stress and life events can be measured using allostatic load (AL).

Methods: The initial cohort included males ≥ 18 years diagnosed with PC (2005-2019). AL was modeled as an ordinal variable (0 to 11). Fine-Gray competing risk regressions measured the impact of pre-cancer diagnosis AL and post-diagnosis AL in 2-year major cardiac events (MACE). The effect of AL changes over time on MACE development was calculated via piecewise Cox Regression (before, and 2 months, 6 months and 1-year after PC diagnosis).

Results: We included 5,261 PC patients, of which 6.6% had a 2-year MACE. For every 1-point increase in AL before and within 60 days after PC diagnosis, the risk of MACE increased 25% (adjusted Hazards Ratio [aHR] =1.25, 95% Confidence Interval [CI] = 1.18-1.33), and 27% (aHR=1.27; 95% CI = 1.20-1.35), respectively. Using AL as a time varying exposure, the risk of MACE increased 19% (aHR=1.19, 95% CI 1.11-1.27), 22% (aHR=1.22, 95% CI 1.14-1.33), 28% (aHR=1.28, 95% CI 1.23-1.33), and 31% (aHR=1.31, 95% CI 1.27-1.35) for every 1-point increase in AL before, 2 months after, 6 months after and 1-year after PC diagnosis, respectively.

Conclusion: AL and its changes over time are associated with MACE in PC patients, suggesting a role of a biological measure of stress as a marker of CVD risk among men with PC.

Prostate cancer (PC) is the second most common type of cancer in males (1). In the United States (US), it represents 13.1% of all new cancer cases (2,3). Despite a high 5-year relative survival, it is one of the leading causes of death in men, having caused approximately 375,304 deaths worldwide in 2020 (1,3). Cardiovascular disease (CVD) is the leading cause of death in men with PC, excluding those that are cancer-related (4–10).

There is association between cancer and CVDs, through shared risk factors and biological factors (11–17). In patients with PC, androgen deprivation therapy (ADT) is associated with the development of CVDs (18–21). In addition, accumulated stress also plays an important role in CVD (22,23). The cumulative burden of chronic stress and life events can be measured by allostatic load (AL), a score that computes multiple markers representing the impact of stress on cardiovascular (CV), metabolic, and immune systems and whose high values (overload) are related to poorer health outcomes and increased risk of CVD (23–26).

The role of AL and its influence on the development of CV events in patients with PC is unknown. We hypothesize that pre-cancer diagnosis AL and its variation over time may be associated with and predict CVD events in these patients. Therefore, the primary objective of this study is to analyze the impact of AL on the development of major cardiac events (MACE) after the diagnosis of PC.

Methods

Data Source

The study setting was the University Hospitals (UH) Seidman Cancer Center (Cleveland, Ohio). Data were obtained from the UH repository, which consists of an open-source, web-based cancer data management system that integrates disparate sources of data (27). All records were deidentified, and the study was approved by the UH of Cleveland Institutional Review Board. All the information obtained was complemented with electronic

health record (EHR) information captured via EMERSE (Electronic Medical Record Search Engine) in order to obtain the most accurate and complete information per patient (28).

The cohort (**Figure 1**) included males ≥ 18 years diagnosed with PC between 01/01/2005 and 12/31/2019, providing a minimum follow-up of 2 years. Patients were excluded from the analysis if they had an unknown diagnosis date, and histology different than adenocarcinoma.

Exposure

AL was utilized as an ordinal measure from 0 to 11 (**Supplementary Figure 1**) using the methodology described by Rodriguez et al. (29). We assigned 1 point for the presence of each of the following: systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, heart rate (HR) > 100 bpm, total cholesterol ≥ 240 mg/dl, high-density lipoprotein cholesterol (HDL) ≤ 50 mg/dl, triglycerides ≥ 150 mg/dl, glycated hemoglobin (HbA1c) ≥ 6.5 , body mass index (BMI) ≥ 30 kg/m², glucose ≥ 110 mg/dl, C-reactive protein (CRP) > 3 mg/L and interleukin-6 (IL-6) > 1.8 pg/ml (26,30–34). Higher scores indicate greater physiological dysregulation.

AL was calculated as that prior to a day before cancer diagnosis, post-diagnosis (captured up to 60 days after the cancer diagnosis), 2-6 months after, 6-12 months after, and 1-year after the cancer diagnosis. There was no need for the presence of all biomarkers at all the time points for all patients. In cases with multiple measures within the time period, only those that crossed the established thresholds added 1 point to AL.

Outcomes

The co-primary endpoints were the diagnosis and time-to-event of 2-year MACE following the cancer diagnosis. The MACE included in this study were heart failure (HF), acute coronary syndrome (ACS), atrial fibrillation (A-fib), and ischemic stroke (IS), defined using ICD 9/10 codes (**Supplementary Table 1**) (35).

Covariates

Demographic characteristics included age at diagnosis, self-reported race (Black, Other – any other reported race than Black or White, and White), and self-reported ethnicity (Hispanic, non-Hispanic). Risk factors were extracted based on ICD-9/10 codes (Supplementary Table 1) that were presented in the patient's EHR and included smoking status (yes, no, former, unknown), Elixhauser's comorbidity index, and CVD history/risk factor (yes, no). The Elixhauser's comorbidity index is similar to the Charlson Comorbidity Index, but while the later includes only 17 features, the first includes up to 30 (36,37). The Elixhauser's score has showed to be superior over the Charlson Comorbidity Score (38,39). CVD history/risk factor included hyperlipidemia, cardiomyopathy, known coronary artery disease, prior myocardial infarction (MI), carotid disease, prior transient ischemic attack (TIA)/stroke, and/or chronic kidney disease (CKD).

Tumor characteristics included cancer diagnosis date, biopsy Gleason score (categorized as high risk for scores \geq 8), and TNM staging group (with stage IV considered advanced stage) (40–42). Encounters included related information about hospitalizations related to MACEs ICD9/10s (length of stay in days and number of hospitalizations). Treatment characteristics included compliance to treatment (number of appointments and % of appointments attended) and the use of a single or combination of treatments during a lifetime: radiotherapy, chemotherapy, androgen deprivation therapies (ADTs, Supplementary Table 1), and/or surgery.

Statistical Analysis

The data was presented as absolute values and percentages for categorical variables and as median and quartiles for continuous variables, and stratified according to the occurrence of MACE. The Pearson Chi-Square test was used to compare categorical variables. Data

distribution assumptions for continuous variables were confirmed using histograms and the Kolmogorov-Smirnov test, followed by Student's T-tests for normally distributed factors and non-parametric Kruskal-Wallis tests for non-normal distributed factors. AL measures were represented via histograms (**Supplementary Figure 1**).

Fine-Gray competing risk regressions were used to calculate the impact of AL pre- and post-diagnosis of cancer on 2-year MACE after confirming the model's proportional hazards assumptions, accounting for competing risk of all-cause mortality (43). Subsequently, the effect of AL changes over time on MACE development was calculated via a piecewise Cox proportional hazards model with 4 follow-up time segments, accounting only for MACEs diagnosed after AL measures (**Figure 2**) (44). Subgroup analysis was performed stratifying the population by race and ethnicity (Non-Hispanic Blacks, Non-Hispanic Whites,). Sensitivity analysis was performed stratifying the population by ADT (yes, no) due to the association of ADT with a higher risk of CVDs and by year of PC diagnosis (after 2012) to account for time-related changes in treatment and practices (18–21). Finally, the methods were replicated using AL calculated via Chen et al. and Parente et al. methodologies to account for variations in the calculation of AL score (26,31,45). All the results were presented as Hazard Ratios (HR), associated with 95% confidence intervals (CI).

The variables selected for multivariable analysis were those that achieved a $p < 0.10$ in univariable analyses for the primary outcome and those deemed to have clinical importance by study investigators. Correlated variables were not included simultaneously in the final models. A p -value < 0.05 was considered significant, and missing values were not included in the final analysis, with a maximum reported missing rate of 4.1% in the covariates, excluding the AL biomarkers. The missing rates for each of the AL biomarkers are shown in **Supplementary Table 2**. All analysis were performed using RStudio software (46). The STROBE cohort checklist was used (47).

Results

Population

We included 5,261 (19,840 person-years) PC patients (**Table 1**). The cohort's median age was 68 (interquartile range [IQR] 61-75) years, with a predominance of White patients (69.2%) and non-Hispanic patients (94.8%). Most of the patients had an Elixhauser's Score between 1-4 (60.3%) and had no CVD history/risk factors prior to the cancer diagnosis (89.9%). Eight percent of the cases were advanced stage (IV), and 9.1% were high risk (Gleason \geq 8). Surgery was performed in 28.9% of the cohort, while 35.7% received radiotherapy, 5.5% received chemotherapy, 1.3% received immunotherapy and 22.4% received ADT.

Comparing MACE with no MACE, there was a higher median age in the MACE group (74, IQR 68-82 vs 67, IQR 61-74, $p<0.001$), higher rates of ADT (28.5% vs 22%, $p=0.005$), lower rates of surgery (14.1% vs 29.9%, $p<0.001$) and radiotherapy (28.8% vs 36.2%, $p<0.001$), and lower proportions of appointments attended (63.4%, IQR 33.3-80% vs 68.5%, IQR 50-84.6%, $p=0.007$).

Outcomes

Among 5,261 patients, 6.6% had a 2-year MACE, with a median time-to-event of 226 days (IQR 52-453) after PC diagnosis. HF was diagnosed in 2.6% (median time-to-event of 256 days, IQR 91-482), IS in 1.3% (median time-to-event of 249 days, IQR 97-512), ACS in 2.1% (median time-to-event of 309 days, IQR 71-489) and A-fib in 2.2% (median time-to-event of 222 days, IQR 52-403). Each patient had a median of 1 admission due to MACE (IQR 1-1), with a median length of stay (LOS) of 2 (IQR 1-4) days. MACEs are summarized in **Supplementary Table 3**.

The median AL before and post the diagnosis was 2 (IQR 0-4), and the number rose to 3 (IQR 1-4) after the first year. Patients diagnosed with 2-year MACE compared to those without MACE had higher median AL before PC diagnosis (4, IQR 3-5 vs 1, IQR 0-3, $p<0.001$), and higher median AL after the first year (4, IQR 3-5 vs 3, IQR 0-4, $p<0.001$). AL variation over time is represented in **Supplementary Figure 1**.

Impact of AL in the development of MACE

For every 1-point increase in AL prior to PC diagnosis we observed a 25% increased risk of MACE (adjusted HR [aHR]=1.25, 95% CI 1.18-1.33, **Table 2**). One point increase in AL post-PC diagnosis was associated with 27% increased risk of MACE (aHR=1.27; 95% CI 1.20-1.35). Pre and post-diagnosis AL significantly increased the risk of HF, IS, ACS, and A-fib (Table 2).

Among non-Hispanic Black patients (n=1,278), 1-point increase in AL before the diagnosis increased the risk of MACE by 25% (aHR=1.25, 95% CI 1.13-1.38), HF by 35%, and ACS by 33% (**Supplementary Table 4**). Among non-Hispanic White patients (n=3,478), 1-point increase in AL before the diagnosis increased the risk of MACE by 25% (aHR=1.25; 95% CI 1.16-1.35), HF by 17%, IS by 29%, ACS by 38%, and A-fib by 20% (Supplementary Table 4). Similar associations were noted with post-diagnosis AL among non-Hispanic Black patients and non-Hispanic White patients (Supplementary Table 4).

In patients on ADT, every 1-point increase in AL increased the risk of MACE by 26% (aHR=1.26, 95% CI 1.16-1.38), HF by 28%, IS by 20%, and ACS by 29% (**Supplementary Table 5**). Similar associations were noted with post-diagnosis AL for patients on ADT (Supplementary Table 5). For those diagnosed with PC after 2012, every 1-point increase in AL increased the risk of MACE by 10% (aHR=1.10, 95% CI 1.02-1.19; Supplementary Table

5). Results from the analysis using AL calculated via Chen et al. and Parente et al. methodology were similar.

Effect of AL changes in the diagnosis of MACE

Using AL as a time varying exposure, the risk of MACE increased 19% (aHR=1.19, 95% CI 1.11-1.27), 22% (aHR=1.22, 95% CI 1.14-1.33), 28% (aHR=1.28, 95% CI 1.23-1.33), and 31% (aHR=1.31, 95% CI 1.27-1.35) for every 1-point increase in AL before PC diagnosis, 2 months after, 6 months after and 1-year after PC diagnosis, respectively (**Table 3**). This association persisted for HF, IS, ACS and A-fib (Table 3).

In non-Hispanic Black patients, the risk of MACE increased 22% (aHR=1.22, 95% CI 1.06-1.40), 26% (aHR=1.26, 95% CI 1.10-1.45), 33% (aHR=1.33, 95% CI 1.22-1.41), and 34% (aHR=1.34, 95% CI 1.26-1.42) for every 1-point increase in AL before PC diagnosis, 2 months after, 6 months after and 1-year after PC diagnosis, respectively, with similar associations for HF, IS, ACS and A-fib (**Supplementary Table 6**). In non-Hispanic White patients, the risk of MACE increased 16% (aHR=1.16, 95% CI 1.06-1.27), 20% (aHR=1.20, 95% CI 1.10-1.31), 27% (aHR=1.27, 95% CI 1.21-1.33), and 31% (aHR=1.31, 95% CI 1.26-1.36) for every 1-point increase in AL before PC diagnosis, 2 months after, 6 months after and 1-year after PC diagnosis, respectively, with similar associations for HF, IS, ACS and A-fib (Supplementary Table 6).

Sensitivity analysis by ADT and year of diagnosis, and analysis using an alternative method for AL calculation showed the similar results (Supplementary Table 6).

Discussion

This is the first study to demonstrate that a higher level of AL, irrespective of time before or after PC diagnosis, is associated with a 25-30% higher risk of 2-year MACEs. In addition to our main findings, the most common MACE across all subgroups was HF, with the

second most common being ischemic stroke/ACS, and the median time-to-event was 226 days after the cancer diagnosis.

The concept of AL originated in 1993, defined as the cumulative effect of experiences in daily life that involve subtle and long-standing life situations, significant challenges (life events), and the physiological consequences of the resulting health-damaging behaviors (e.g.: poor sleep, lack of exercise, smoking, alcohol consumption, and unhealthy diet) (48,49). Chemical messengers are released in response to stressors and exert cellular effects, causing systemic dysregulation of metabolic, inflammatory, and CV biomarkers, culminating in a range of health effects (48,50–54). Higher AL scores in the general population are associated with a higher risk of mortality, cognitive decline, physical function decline, and CVDs, particularly coronary heart disease, ischemic heart disease, and peripheral arterial disease (22,49,55–58). Our findings demonstrate the same patterns for PC patients, in which higher AL scores (pre and post-PC-diagnosis) were associated with MACE, especially HF. In addition, patients with higher AL had multiple CV risk factors such as age, higher rates of smoking, and higher Elixhauser's scores, showing that AL seems to capture CV risk factors and to perform well as a marker of CVD in cancer patients, much like the general population.

One of the potential differentiators of AL over current used scores (such as the Framingham risk score, Reynolds risk score, etc.) is, as it is an objective measure of chronic stress, it may have the ability to capture social determinants of health (SDOH), which the individual risk factors (e.g., hypertension) are unable to capture (29,49,59). People living in adverse social economic conditions tend to experience a higher stress exposure and accumulation (60–63). In line with these descriptions, we showed lower appointment attendance rates in those with MACE, which may primarily an effect of transportation, social support, and health care access system for the cancer patient rather than the effect of a CV risk factor.

Racial and ethnic disparities are crucial when dealing with a measure affected by living conditions. Non-Hispanic Black men have a higher incidence of CVD and tend to live in worse living conditions, experience inequalities in access to health, and accumulate a higher rate of stress, with AL already having been shown to be partially related to higher mortality in Black patients (64–67). We demonstrated, upon facing disparity in the form of higher AL, non-Hispanic Black patients and non-Hispanic White patients with PC both have a higher risk of MACE. Thus, biological measurement of disparities in the form of AL may help to understand the role of adverse SDOHs and race-related disparities differently (68).

Another sensitivity analysis considered ADT, which is the mainstay of treatment for advanced prostate tumors and is implicated in CVDs (69,70). The use of ADT has been associated with increased CV risk and mortality, leading to a joint scientific statement in 2010 (20,71,72,72,73). We showed that, considering AL measures, the risk of MACE, except IS, is higher irrespective of ADT use, probably reflecting the burden caused by a cancer diagnosis and treatment. Thus, a paradigm shift in risk measurement may be warranted, where, in addition to measuring a standard set of risk measures per the 2010 statement, measures of adverse SDOHs and/or AL may help in risk stratifying all patients with PC and not just ones starting ADT.

On a clinical perspective, our results encourage the use of AL scores by practitioners as a marker of MACE risk in patients diagnosed with PC. Patients can have their score measured soon after diagnosis and those characterized as high risk have a closer follow-up, with multidisciplinary participation of cardio-oncology teams, aiming risk mitigation. Moreover, this measure as a routine in clinical practice, such as in primary care, can be a driver for the formulation of personalized support plans that reduce the impact of stressful events and, consequently, the development of risk factors and CVD. However, we emphasize that future

studies should objectively analyze the superiority of the incorporation of AL over the methods/scores already used.

This study has several limitations. Our institutional database is EMR-based, and some of the information may be incomplete or unavailable (i.e. cause of death). As a single institution, some patients may have been to lost follow-up or sought emergency care at other institutions. The timeframe employed can encompass generational changes in treatment, which we hopefully mitigated with analysis of patients diagnosed after 2012. Some of the biomarkers are not routinely measured (i.e. IL-6) and were not available at all time points for all patients. Moreover, some of these biomarkers are requested and/or measured more frequently in patients with clinical indications (eg diabetic patients and HbA1c), which may lead to an over-representation of these patients in the results and may have generated lower AL levels in patients without these clinical indications. In contrast, in our analysis we considered large time periods (before PC diagnosis, 0-2 months after PC diagnosis, 2-6 months after PC diagnosis and 6-12 months after PC diagnosis) where only 1 read of each component was needed to account it in AL and the adequate availability of these markets was shown by our group (68). In the competing-risks analysis, a little number of the all-cause mortality may be comprised by deaths from cardiac events that were not diagnosed before and should be accounted as MACE. However, our database integrates disparate sources, including individual detailed and longitudinal information rarely seen in other databases. In addition, the large number of patients and different statistical models with multivariable and sensitivity analysis mitigated the systematic errors pointed above. Finally, as an oncology center, we maintain a close follow-up with patients who usually come to our emergency (ED). Future studies should focus on multicentric designs, comparison of AL over currently used scores for CVD risk, aiming to understand the applicability of these results to other cancer types and the role of SDOH in the relationship between AL and CVD.

In conclusion, AL and its variation over time are associated with MACE, suggesting that the physiological changes and cumulative stress leading up to cancer diagnosis could serve as a marker of risk for MACE in patients with PC. Identifying reasons for higher AL, such as adverse SDOH when evaluating a patient with PC, will help identify those at the highest risk of MACE.

Data Availability statement: University Hospitals (UH) Seidman Cancer Center database is available at University Hospitals Cleveland Medical Center and has access restricted to researchers with IRB approval.

Ethical approval information: Patient records were deidentified, and the study was approved by the University Hospitals of Cleveland Institutional Review Board (IRB).

Sources of Funding: AG is supported by American Heart Association-Strategically Focused Research Network Grant in Disparities in Cardio-Oncology (#847740, #863620); NS is supported through funding from the Sociedade Beneficente Israelita Brasileira Albert Einstein on the program "Marcos Lottenberg & Marcos Wolosker International Fellowship for Physicians Scientist - Case Western". NLW is supported by the American Heart Association-Strategically Focused Research Network Grant in Disparities in Cardio-Oncology (#847740, #863622) and NIH grants R01AG076235, R01HL142097, and R01AR070029.

Role of the funder: The author`s funders did not play a role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Prior presentation: This work was presented as a poster at the 2022 American Heart Association Scientific Sessions.

Disclosures: JBS is a full-time, paid employee of the NCI/NIH. KW is a full-time, paid contractor of the NCI/NIH.

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Tables

Table 1. Prostate cancer adenocarcinoma University Hospitals (UH) population (2005-2019) description and comparison stratified by major cardiac event (MACE). A total of 5,261 patients were analyzed, with 347 (6.6%) in the 2-year MACE group. IQR = interquartile range.

Patient's characteristics	Prostate Cancer UH population (n=5,261)		
	MACE	no MACE	<i>P</i>
Total, n (%)	347 (6.6)	4,914 (93.4)	
Age at diagnosis, median (IQR)	74 (68, 82)	67 (61, 74)	<0.001
Race, n (%)			
Black	83 (23.9)	1,229 (25)	0.50
Other	16 (4.6)	290 (5.9)	
White	248 (71.5)	3,395 (69.1)	
Ethnicity, n (%)			
Hispanic	11 (3.2)	262 (5.3)	
Non-Hispanic	336 (96.8)	4,652 (94.6)	0.40
Smoking status, n (%)			
Smoker	19 (5.5)	341 (6.9)	
Never smoker	103 (29.7)	1,299 (26.4)	
Former	138 (39.8)	1,204 (24.5)	<0.001
Unknown	87 (25.1)	2,070 (42.1)	
Elixhauser's Score, n (%)			
0	3 (0.9)	173 (3.5)	
1 to 4	57 (16.4)	3,114 (63.4)	<0.001

≥ 5	287 (82.7)	1,627 (33.1)	
CVD history/risk factors pre-diagnosis, n (%)			
No	252 (72.6)	4,479 (91.1)	
Yes	95 (27.4)	435 (8.9)	<0.001
Cardiomyopathy	9 (2.6)	21 (0.4)	<0.001
Coronary artery disease (CAD)	37 (10.7)	114 (2.3)	<0.001
Myocardial infarction (MI)	1 (0.3)	2	0.48
Carotid disease	7 (2.0)	12 (0.2)	<0.001
Transient ischemic attack (TIA)/Stroke	0	4 (0.1)	1
Chronic kidney disease (CKD)	19 (5.5)	56 (1.1)	<0.001
Hyperlipidemia	35 (10.1)	150 (3.1)	<0.001
No. of CVD history/risk factors pre-diagnosis per patient, median (IQR)	2 (1, 3)	1 (1, 2)	0.14
Advanced cancer stage (IV), n (%)	21 (6.1)	401 (8.2)	0.19
High risk (Gleason 8-10), n (%)	34 (9.8)	445 (9.1)	0.71
Prostate surgery, n (%)	49 (14.1)	1,471 (29.9)	<0.001
Radiotherapy, n (%)	100 (28.8)	1,779 (36.2)	<0.001
Chemotherapy, n (%)	27 (7.8)	262 (5.3)	0.06
ADT, n (%)	99 (28.5)	1,079 (22)	0.005
No. of appointments, median (IQR)	9 (3, 21)	7 (2, 21)	0.02
% appointments attended, median (IQR)	63.4 (33.3, 80)	68.5 (50, 84.6)	0.007

Other race was defined as any other self-reported race than Black or White.

Table 2. Fine and Gray competing risk regressions analyzing the impact of each one point increase in allostatic load prior and post to the cancer diagnosis in the risk of developing a 2-year major cardiac event (MACE) and its subtypes (heart failure, ischemic stroke, acute coronary syndrome, and atrial fibrillation).^a

Outcome	Prostate Cancer population (n=5,261)			
	Pre-cancer diagnostic allostatic load		Post-diagnosis allostatic load	
	Univariable HR (95% CI)	Multivariable HR (95% CI)	Univariable HR (95% CI)	Multivariable HR (95% CI)
MACE	1.44 (1.39-1.50)	1.25 (1.18-1.33)	1.46 (1.40-1.51)	1.27 (1.20-1.35)
Heart Failure	1.46 (1.39-1.54)	1.22 (1.11-1.34)	1.46 (1.39-1.54)	1.24 (1.13-1.36)
Ischemic Stroke	1.39 (1.29-1.50)	1.19 (1.06-1.33)	1.42 (1.33-1.54)	1.24 (1.11-11.38)
Acute Coronary Syndrome	1.53 (1.43-1.63)	1.38 (1.22-1.55)	1.55 (1.45-1.65)	1.39 (1.23-1.57)
Atrial Fibrillation	1.36 (1.27-1.44)	1.18 (1.07-1.30)	1.37 (1.29-1.46)	1.18 (1.08-1.30)

^aMultivariable models were adjusted for age at diagnosis, race, smoking status, surgery, radiotherapy, androgen deprivation therapy (ADT), Elixhauser's score, % of appointments attended and cardiovascular risk factors. All tests achieved $p < 0.05$. CI = confidence interval. HR = hazard ratio.

Table 3. Multivariable piecewise Cox model with 4 follow-up time segments related to cancer diagnosis date (before, 0-2 months after, 2-6 months after and 6-months to 1-year after) accounting for the effect of allostatic load variation in 2-year major cardiac event (MACE).^a

Prostate Cancer UH population (n=5,261)					
AL and follow-up time	2-year MACE aHR (95% CI)	2-year HF aHR (95% CI)	2-year IS aHR (95% CI)	2-year ACS aHR (95% CI)	2-year A-fib aHR (95% CI)
AL Before diagnosis	1.19 (1.11-1.27)	1.28 (1.24-1.33)	1.31 (1.26-1.37)	1.42 (1.37-1.47)	1.24 (1.20-1.29)
AL 2 months after diagnosis	1.22 (1.14-1.31)	1.29 (1.24-1.34)	1.32 (1.26-1.38)	1.42 (1.37-1.48)	1.25 (1.20-1.29)
AL 2-6 months after diagnosis	1.28 (1.23-1.33)	1.29 (1.24-1.34)	1.32 (1.26-1.39)	1.42 (1.37-1.49)	1.25 (1.20-1.30)
AL 6-12 months after diagnosis	1.31 (1.27-1.35)	1.29 (1.23-1.36)	1.33 (1.25-1.42)	1.42 (1.35-1.50)	1.26 (1.20-1.32)

^aMultivariable models were adjusted for age at diagnosis, race, smoking status, surgery, radiotherapy, androgen deprivation therapy (ADT), Elixhauser's score, % of appointments attended and cardiovascular risk factors. All tests achieved $p < 0.05$. aHR = adjusted hazard ratio; CI = confidence interval; HF=heart failure; IS=ischemic stroke; ACS=acute coronary syndrome; A-fib=atrial fibrillation.

Figure Legends

Figure 1. Study consort diagram detailing inclusion and exclusion criteria for prostate cancer adenocarcinoma University Hospitals (UH) population (2005-2019). The final cohort included 5,261 patients, of which 347 had a 2-year major cardiac event (MACE).

Figure 2. Overview of piecewise Cox model. 4 follow-up time segments related to cancer diagnosis date (before, 2 months after, 6 months after and 1-year after) were established to account the effect of allostatic load variation in in 2-year major cardiac event (MACE).



