Non-alcoholic fatty liver disease increases the risk of biochemical recurrence in high-grade metastatic prostate cancer patients

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Research article

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Abstract

Background

Non-alcoholic fatty liver disease (NAFLD) has been reported to be helpful to identify high-risk individuals of developing prostate cancer. In the retrospective cohort study, our aim is to investigate the relationship between NAFLD and biochemical recurrence in metastatic prostate cancer patients.

Methods

We retrospectively investigated 602 patients with metastatic prostate cancer receiving androgen deprivation therapy. Liver fat was estimated with liver-to-spleen ratio by CT scans. The relationship between NAFLD and biochemical recurrence was investigated with Cox models. The model for biochemical recurrence was adjusted for multiple variables.

Results

NAFLD was significantly associated with biochemical recurrence in patients with Gleason score ≥ 4 + 3 when adjusting for each of body mass index (hazards ratio [HR] = 1.38; 95% confidence interval [CI] = 1.08–1.77; $p = 0.01$), visceral adipose tissue (HR = 1.36; 95% CI = 1.07–1.74; $p = 0.01$), hypertension (HR = 1.41; 95% CI = 1.10–1.80; $p = 0.01$) and diabetes mellitus (HR = 1.42; 95% CI = 1.11–1.82; $p = 0.01$), using age and prostate-specific antigen level as potential confounder. The 2-year biochemical recurrence rate in Gleason score ≥ 4 + 3 patients with and without NAFLD was 84.0% (100/119) and 72.2% (130/180), respectively ($p = 0.018$). The median biochemical recurrence free survival of Gleason score ≥ 4 + 3 patients with and without NAFLD were 17 and 21 months, respectively ($p = 0.005$).

Conclusions

NAFLD is an independent risk factor for biochemical recurrence in patients with high-grade metastatic prostate cancer. If validated in prospective studies, future research should test whether treatment of NAFLD can lead to better prognosis.

Background

The incidence rates of prostate cancer (PCa) have increased in most countries with increasing ageing populations. Although the five-year relative survival rates of local PCa are approximately 100%, metastatic PCa remains a fatal disease with poor prognosis [1]. Androgen deprivation therapy (ADT) is commonly applied in patients with metastatic PCa as primary treatment. Biochemical recurrence (BCR) constantly leads to treatment failure.

The previous studies on the relationship between obesity and PCa incidence have shown inconsistent results [2–5]. However, obesity has been verified to be associated with an increased risk for BCR and PCa-specific mortality [6]. Non-alcoholic fatty liver disease (NAFLD), the leading cause of chronic liver disease worldwide, is closely associated with obesity. The association of PCa with NAFLD has been paid more attention. NAFLD has been reported to be helpful in identifying high-risk PCa in the elderly and in the absence of obesity or metabolic syndrome [7]. However, to the best of our knowledge, the question of whether NAFLD is related to the risk of BCR has been less well studied. Only a study by Choi et al investigated the association of NAFLD and BCR and reported that the former was negatively related to the risk of BCR after radical prostatectomy. However, the sample size was small, only 32 patients developed BCR [8]. In the retropective study, we investigated the association between NAFLD and the risk of BCR in metastatic PCa patients.

Methods

Patients and diagnosis

The Ethics Committees of the Second Affiliated Hospital of Air Forth Medical University, the First Affiliated Hospital of Xi'an Medical University, and the Second Affiliated Hospital of Xi'an Jiaotong University approved all study procedures (Approval Number: TDLL-201811-28, 7 Nov 2018). The patients with metastatic PCa receiving ADT at these hospitals between January 2010 and December 2015 were included. Data were retrospectively collected from December 2018 to May 2019. Each patient provided informed-signed consent for data collection and analysis.

667 patients in three hospitals were diagnosed as metastatic PCa and received ADT between January 2010 and December 2015. We excluded 65 patients including (1) history of radical prostatectomy, orchiectomy, chemotherapy, radiation therapy (n = 21); (2) records with only two prostate-specific antigen (PSA) values and more than one year period between the first and second measures (n = 3); (3) increased PSA level after ADT initiation (n = 5); (4) Alcohol use being defined as > 20 g/day (n = 16); (5) other hepatic steatosis causes (n = 15); and (6) missing patient data (n = 5). Consequently, we included 602 patients in the study. All patients were treated with complete androgen blockade (50 mg bicalutamide daily plus a luteinising hormone-releasing-hormone agonist), and no Chinese medicine was used. All cases were confirmed through transrectal ultrasound (TRUS)-guided core needle biopsy or transurethral resection of the prostate and histopathological examination.

Patient follow-up and data collection

Subjects were followed up from the time of initial ADT until the date of BCR, loss to follow-up or study endpoint (31st December 2018). BCR was defined as first PSA increase that is ≥ 25% and ≥ 2 ng/ml above the nadir, which is confirmed by a second value obtained ≥ 3 week later [9]. BCR-free survival was defined as the time between the date of initial ADT and the date of BCR or last follow-up. Data were collected from the medical records including age, Gleason score, metastasis position, initial PSA level, baseline testosterone level, weight, height, body mass index (BMI), subcutaneous adipose tissue (SAT),

visceral adipose tissue (VAT), blood lipid parameters, liver-to-spleen (L/S) ratio, hypertension, fasting glucose and diabetes mellitus. The height and body weight of patients were measured, and BMI was calculated as the weight in kilograms divided by the height in square metre. Abdominal fat distribution was assessed through a non-contrast CT scan performed with GE (GE LightSpeed VCT 64, GE Healthcare, Waukesha, WI) multi-detector CT scanners. The VAT volume was defined as the sum of fat voxels in the area enclosed by the peritoneal membrane centred at the L4 and L5 disks with 10 mm slice thickness. VAT and SAT were assessed using commercially available software. NAFLD was defined as the L/S ratio < 1.0 after exclusion of other hepatic steatosis causes. The L/S ratio was graded as mild (0.7–1.0), moderate (0.5–0.7, including 0.7) and severe (≤ 0.5) [10]. Liver and spleen attenuations were measured using unenhanced abdominal CT scans [11]. The intraclass correlation coefficient between readers in randomly selected samples of 150 participants was 0.98 for liver attenuation, indicating high reproducibility of liver attenuation for assessment of NAFLD in this study.

Statistical analysis

The χ^2 test was used to assess the relation between clinical variables and NAFLD for categorical variables. The continuous variables were analysed using t-test or Wilcoxon rank-sum test. The Kaplan–Meier method and log-rank test were used to determine the differences in BCR-free survival. Cox proportional hazards regression models were used to test the association between NAFLD and BCR. The model for BCR was adjusted for BMI, VAT, hypertension and diabetes mellitus, respectively, using age, PSA level and Gleason score as potential confounder. Statistical tests were two-sided, and $p < 0.05$ was considered indicative of a statistically significant difference. All statistical analyses were performed using SPSS, version 19.0 (SPSS, Chicago, IL, USA).

Results

602 patients were included in the study. Table 1 shows the baseline patient characteristics. Amongst the 602 patients, 549 (91.2%) developed BCR, and 188 (31.2%) were diagnosed with NAFLD. A total of 3 (1.60%) patients showed moderate NAFLD, and 185 (98.4%) showed a mild diagnosis. The median BCR-free survival was 21 (7–86) months. Approximately 12.8% of patients were obese (BMI > 30 kg/m^2), and 50.8% were overweight (25–29.9 kg/m^2).

Table 1
Baseline characteristics

	Number (%)	Median	1/4–3/4 quantiles	Mean (standard deviation)
Age (years)		71	67–76	71 (6)
Gleason score				
≤ 3 + 4	303 (50.3)			
≥ 4 + 3	299 (49.7)			
Metastasis				
Visceral metastasis	59 (9.8)			
Bone and lymph node metastasis	543 (90.2)			
PSA (ng/ml)		66	45–80	64 (25)
Weight (kg)		76	72–79	76 (5)
BMI (kg/m^2)				
< 25	219 (36.4)			
25–29.9	306 (50.8)			
> 30	77 (12.8)			
SAT (cm^3)		356	272–381	331 (58)
VAT (cm^3)		328	246–353	303 (57)
Triglyceride (mmol/L)		1.4	1.2–1.8	1.6 (0.6)
Total cholesterol (mmol/L)		4.5	3.9-6.0	4.9 (1.4)
LDL cholesterol (mmol/L)		2.9	2.5–4.1	3.3 (1.1)
HDL cholesterol (mmol/L)		1.3	1.1–1.5	1.3 (0.3)
Baseline testosterone (ng/dL)		290	220–360	266 (62)
Fasting glucose (mmol/L)		6.5	6.1–8.4	6.4 (1.7)
Hyperlipidaemia				
Yes	263 (43.8)			

Abbreviations: PSA, prostate-specific antigen; BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NAFLD,non-alcoholic fatty liver disease.

	Number (%)	Median	1/4–3/4 quantiles	Mean (standard deviation)
No	338 (56.2)			
NAFLD				
Yes	188 (31.2)			
No	414 (68.8)			
Hypertension				
Yes	194(32.2)			
No	408(67.8)			
Diabetes mellitus				
Yes	117(19.4)			
No	485(80.6)			
Abbreviations: PSA, prostate-specific antigen; BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NAFLD,non-alcoholic fatty liver disease.				

We analysed the relationship between the clinical variables and the presence of NAFLD. The patients with NAFLD presented higher Gleason score, weight, BMI, serum triglyceride level, SAT and VAT volume and lower serum HDL cholesterol level compared with those without NAFLD. Hypertension, diabetes mellitus, fasting glucose and hyperlipidaemia were significantly related to NAFLD (all $p < 0.001$) (Table S1).

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Table 2 displays the results of univariate analyses of BCR. NAFLD ($p = 0.02$) and Gleason score ($p < 0.001$) was significantly associated with the risk of BCR. In the multivariate analysis, the presence of NAFLD remained a non-significant association with the risk of BCR when adjusted for each of BMI (HR = 1.21; 95% CI = 1.00-1.46; $p = 0.05$), VAT (HR = 1.19; 95% CI = 1.00-1.43; $p = 0.06$), hypertension (HR = 1.20; 95% CI = 1.00-1.43; $p = 0.05$) and diabetes mellitus (HR = 1.18; 95% CI = 0.99–1.41; $p = 0.07$), using age, PSA level and Gleason score as potential confounder (Table 3). We further assessed the association of NAFLD with the risk of BCR in patients with Gleason score $\geq 4 + 3$ and $\leq 3 + 4$, respectively. In patients with Gleason score $\geq 4 + 3$, the presence of NAFLD was significantly associated with BCR when adjusting for each of BMI (HR = 1.38; 95% CI = 1.08–1.77; $p = 0.01$), VAT (HR = 1.36; 95% CI = 1.07–1.74; $p = 0.01$), hypertension (HR = 1.41; 95% CI = 1.10–1.80; $p = 0.01$) and diabetes mellitus (HR = 1.42; 95% CI = 1.11–1.82; $p = 0.01$), using age and PSA level as potential confounder (Table 4). The 1-year BCR rate in Gleason score $\geq 4 + 3$ patients with and without NAFLD was 37.8% (45/119) and 41.1% (74/180), respectively (p = 0.569). The 2-year BCR rate in Gleason score $\geq 4 + 3$ patients with and without NAFLD was 84.0% (100/119) and 72.2% (130/180), respectively ($p = 0.018$). The median BCR-free survival of Gleason score

≥ 4 + 3 patients with and without NAFLD were 17 and 21 months, respectively ($p = 0.005$) (Fig. 1). No relationship was detected between NAFLD and BCR in patients with Gleason score ≤ 3 + 4 (Table S2).

Table 2
Univariate analyse for BCR-free survival

Characteristics	HR	95% CI	*p*
Age (years)	0.94	0.80–1.10	0.46
Gleason score	1.74	1.48–2.05	< 0.001
PSA (ng/ml)	0.88	0.75–1.04	0.13
BMI (kg/m^2)	1.02	0.91–1.16	0.71
Weight (kg)	1.04	0.88–1.23	0.65
SAT (cm^3)	1.08	0.92–1.27	0.35
VAT (cm^3)	1.01	0.86–1.19	0.87
NAFLD	1.22	1.03–1.46	0.02
Hyperlipidaemia	1.12	0.95–1.32	0.18
Triglyceride (mmol/L)	0.90	0.75–1.08	0.25
Total cholesterol (mmol/L)	0.97	0.83–1.14	0.71
LDL cholesterol (mmol/L)	0.96	0.81–1.12	0.59
HDL cholesterol (mmol/L)	0.99	0.84–1.17	0.92
Hypertension	1.03	0.87–1.23	0.72
Diabetes mellitus	0.87	0.71–1.06	0.17
Fasting glucose (mmol/L)	0.91	0.76–1.09	0.38
Baseline testosterone (ng/dL)	1.05	0.90–1.24	0.43

Abbreviations: BCR, biochemical recurrence; PSA, prostate-specific antigen; BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; NAFLD, non-alcoholic fatty liver disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HR, hazard ratio.

Table 3
Cox proportional hazard regression analysis for predicting the probability of BCR after ADT*

	HR	95% CI	*p*
Model 1			
BMI	1.00	0.77–1.29	0.99
NAFLD	1.21	1.00-1.46	0.05
Model 2			
VAT	1.03	0.87–1.22	0.72
NAFLD	1.19	1.00-1.43	0.06
Model 3			
hypertension	0.93	0.78–1.11	0.45
NAFLD	1.20	1.00-1.43	0.05
Model 4			
Diabetes mellitus	1.02	0.83–1.25	0.88
NAFLD	1.18	0.99–1.41	0.07
Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined as a fasting plasma glucose ≥ 7.0 mmol/L or 2-h glucose ≥ 11.1 mmol/L or a history of diabetes.			
*Adjusted for age, Gleason score and PSA level.			

Table 4
Cox proportional hazard regression analysis for predicting the probability of BCR in patients with Gleason score ≥ 4 + 3 after ADT[#]

	HR	95% CI	*p*
Model 1			
BMI	0.77	0.55–1.08	0.13
NAFLD	1.38	1.08–1.77	0.01
Model 2			
VAT	0.95	0.75–1.20	0.65
NAFLD	1.36	1.07–1.74	0.01
Model 3			
hypertension	0.90	0.70–1.15	0.40
NAFLD	1.41	1.10–1.80	0.01
Model 4			
Diabetes mellitus	0.83	0.63–1.11	0.21
NAFLD	1.42	1.11–1.82	0.01

[#]Adjusted for age and PSA level.

Discussion

In this study, metastatic PCa patients were treated with ADT only. No obesity measurement, such as BMI and VAT, as well as hypertension and diabetes mellitus were found to be associated with BCR. However, we did find that the presence of NAFLD was an independent risk factor for BCR in patients with high-grade PCa. Gleason score ≥ 4 + 3 was always regarded as high-grade prostate cancer, as previous reported [12].

Given the rapidly increasing incidence of NAFLD [13], it is important to identify and understand the association between NAFLD and PCa. To the best of our knowledge, only two studies have specifically investigated the relationship between NAFLD and PCa. One study investigated 10,516,985 subjects, amongst which NAFLD based on fatty liver and hepatic steatosis indexes was identified in 19% and 25% of patients, respectively. The results indicated that NAFLD might help in identifying elderly men at high risk of developing PCa, including in the absence of metabolic syndrome or obesity [7]. Another study showed NAFLD as an independent negative predictive factor of BCR after radical prostatectomy. However, the sample size was small, only 32 patients developed BCR [8]. The current study has the

advantage of a lager sample size of 602 metastatic PCa patients, amongst which 549 (91.2%) developed BCR, and 188 (31.2%) were diagnosed with NAFLD through multi-detector CT. In the univariate analysis, NAFLD and the high Gleason score were associated with BCR. By contrast, NAFLD showed no significant association with BCR in the multivariate analysis. The positive association in the univariate analysis may have been confounded by other predictors. Further analysis revealed that NAFLD was significantly associated with a high Gleason score. Thus, the positive association between NAFLD and BCR in the univariate analyses might have been confounded by Gleason score. NAFLD has been regarded as a common aspect of metabolic syndrome [14]. Several studies demonstrated that metabolic syndrome is associated with high-grade PCa [15, 16], which may explain the positive relation between NAFLD and high-grade PCa in our study.

We further assessed the association of NAFLD with the risk of BCR in patients with Gleason score $\geq 4+3$ and $\leq 3+4$, respectively. A total of 299 patients manifested Gleason score $\geq 4+3$ in the study, amongst which 119 were diagnosed with NAFLD, and 117 patients with NAFLD developed BCR. The high-grade PCa patients with NAFLD exhibited a significantly increased risk of BCR compared with those without NAFLD. The 2-year BCR rate in high-grade PCa patients with NAFLD significantly increased compared with that of patients without NAFLD. The median BCR-free survival of these patients with and without NAFLD was 17 and 21 months, respectively. However, no association between NAFLD and the risk of BCR was observed in patients with low-grade PCa (Gleason score $\leq 3+4$). Thus, NAFLD might help in identifying men at high risk of developing castration-resistant prostate cancer (CRPC) among patients with high-grade cancer. Over the past few decades, metabolic syndrome (MetS) has been thought to influence PCa etiology. Individual components of MetS, such as obesity, hypertension and diabetes mellitus have been reported to be associated with BCR after radical prostatectomy or radical radiotherapy [17–20]; however, our study failed to find such an association between obesity markers, including BMI, VAT or hypertension or diabetes mellitus and BCR. The associations between MetS and PCa risk are different between ethnic groups. It has been reported that MetS was associated with PCa risk in African-American men, but not in white men [21]. The study from Guiming et al found the presence of MetS was associated with an increased risk of high-grade PCa in a Chinese population [22]. Conversely, Jeon et al found that the presence of MetS was correlated with decreased risk of high-grade PCa in a Korean population [23]. In addition, most patients in our study exhibited overweightness or normal weight but not obesity. These may help to explain the negative relations observed. Thus, NAFLD may be a positive predictive factor for BCR in patients with high-grade PCa, especially in the absence of obesity. The causal mechanisms underlying these finding require further study. If there is indeed a causal association between NAFLD and BCR, then future research should investigate whether treatment of NAFLD can lead to better PCa prognosis, and the association between the presence of NAFLD and PCa prognosis in other ethnic populations warrant further study.

In subjects with NAFLD, liver fat is closely correlated with some measures of insulin resistance such as fasting serum insulin and glucose level [24]. It is interesting to note that there are increasing data that suggest that insulin may play a significant role in PCa. A study by Gucalp et al demonstrated that periprostatic white adipose tissue inflammation, which is related to high insulin level, is associated with

high-grade PCa [25]. Another study by Lehrer et al demonstrated that patients at the highest risk of PCa recurrence exhibited higher levels of serum insulin when comparing with those at medium and low risk [26]. These observations suggest that the higher levels of serum insulin required to counter insulin resistance in patients with NAFLD may promote the progression of CRPC. In the study, the 2-year BCR rate in Gleason score $\geq 4+3$ patients with NAFLD significantly increased compared with that of patients without NAFLD, but 1-year BCR rate had no significant difference between the two groups. A study from Sebastiano et al found prostate cancer patients receiving ADT had an increased risk of metabolic syndrome, which may be driven by increased serum insulin levels [27]. Thus, we suggest ADT may aggravate insulin resistance in patients with NAFLD. After a period of ADT, the aggravated insulin resistance may promote the progression of CRPC. In addition, In the Chinese and Japan population, the incidence of NAFLD is 15% and 14%, respectively, while NAFLD occur in 17%-33% of Western population due to metabolic syndrome prevalence which increases to 57.5–74% in obese people [28]. Many studies have reported that variants in or near TM6SF2, PNPLA3, NCAN, GCKR, LYPLAL1 are associated with the development of NAFLD in multiple ethnic groups. The study from Wang identified the variants of TM6SF2 and PNPLA3 were the most significant risk alleles of NAFLD in Chinese population [29]. Thus, the relationship between TM6SF2 and PNPLA3 variants and the risk of BCR after ADT will be investigated in the future.

This study featured several limitations. First, we investigated a limited number of patients treated in three hospitals. The way in which the patients were enrolled may have introduced selection bias. Second, Obesity is much less common in China than in the west. The study only included 12.8% of the patients with obesity and most of them showed mild NAFLD, which may limit the generalizability of our findings. Third, the results based on Chinese people, which cannot be generalized to other ethnic populations. Fourth, this work is a retrospective observational study, so additional prospective studies are necessary to elucidate the potential associations between NAFLD and the prognosis of PCa.

Conclusions

NAFLD is an independent risk factor for BCR in patients with high-grade metastatic PCa. Future studies are needed to understand whether NAFLD is of greater clinical significance. Prospective studies with longer follow-up are also needed to validate the finding of the current study.

Abbreviations

NAFLD Non-alcoholic fatty liver disease

BCR Biochemical recurrence

PCa Prostate cancer

ADT Androgen deprivation therapy

L/S Liver-to-spleen

HR Hazards ratio

PSA Prostate-specific antigen

BMI Body mass index

SAT Subcutaneous adipose tissue

VAT Visceral adipose tissue

LDL Low-density lipoprotein

HDL High-density lipoprotein

CRPC Castration-resistant prostate cancer

MetS Metabolic syndrome

Declarations

Ethics approval and consent to participate

The Ethics Committees of the Second Affiliated Hospital of Air Forth Medical University, the First Affiliated Hospital of Xi'an Medical University, and the Second Affiliated Hospital of Xi'an Jiaotong University approved all study procedures (Approval Number: TDLL-201811-28, 7 Nov 2018). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The informed consents were obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

Consent for publication

Not applicable

Availability of data and materials

The datasets used during the study could be provided by the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Data curation: HYZ, WZ; Project administration: JC; Formal analysis: HYZ, ZLW; Writing-original draft: HYZ, WZ; Writing-review & editing: JC, ZLW. All authors read and approved the final manuscript.

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References

[1] Attard G, Parker C, Eeles RA, Schröder F, Tomlins SA, Tannock I,et al. Prostate cancer. Lancet. 2016; 387:70-82.

[2] Discacciati A, Orsini N, Wolk A. Body mass index and incidence of localized and advanced prostate cancer–a dose-response meta-analysis of prospective studies. Ann Oncol. 2012; 23:1665-1671.

[3] Bhindi B, Locke J, Alibhai SMH, Kulkarni GS, Margel DS, Hamilton RJ, et al. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. Eur Urol. 2015; 67:64-70.

[4] Moller H, Roswall N, Van Hemelrijck M, Larsen SB, Cuzick J, Holmberg L, ,et al. Prostate cancer incidence, clinical stage and survival in relation to obesity: a prospective cohort study in Denmark. Int J Cancer. 2015;136:1940-1947.

[5] Lavalette C, Tretarre B, Rebillard X, Lamy PJ, Cenee S, Menegaux F. Abdominal obesity and prostate cancer risk: epidemiological evidence from the EPICAP study. Oncotarget. 2018; 9:34485-34494.

[6] Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila) 2011; 4:486-501.

[7] Choi YJ, Lee DH, Han KD, Yoon H, Shin CM, Park YS, et al. Is nonalcoholic fatty liver disease associated with the development of prostate cancer? A nationwide study with 10,516,985 Korean men. PLoS One. 2018;13:e0201308.

[8] Choi WM, Lee JH, Yoon JH, Kwak C, LeeYJ, Cho YY, et al. Nonalcoholic fatty liver disease is a negative risk factor for prostate cancer recurrence. Endocr Relat Cancer. 2014; 21(2):343-353.

[9] Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008; 26:1148-1159.

[10] Fan JG, Jia JD, Li YM, Wang BY, Lu LG, Shi JP, et al. Guidelines for the diagnosis and management of nonalcoholic fatty liver disease: update 2010. J Dig Dis. 2011;12:38-44.

[11] VanWagner LB, Wilcox JE, Colangelo LA, Lloyd-Jones DM, Carr JJ, Lima JA, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology. 2015; 62:773-783.

[12] Fanning DM , Kay E , Fan Y , Fitzpatrick JM, Watson RW. Prostate cancer grading: The effect of stratification of needle biopsy Gleason Score 4 + 3 as high or intermediate grade. BJU International. 2010; 105:631-635.

[13] Younossi ZM. Non-alcoholic fatty liver disease-A global public health perspective. J Hepatol. 2019;70:531-544.

[14] Ma J, Hwang SJ, Pedley A, Massaro JM, Hoffmann U, Chung RT, et al. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. J Hepatol. 2017; 66:390-397.

[15] De Nunzio C, Truscelli G, Trucchi A, Petta S, Tubaro M, Gacci M, et al. Metabolic abnormalities linked to an increased cardiovascular risk are associated with high-grade prostate cancer: a single biopsy cohort analysis. Prostate Cancer Prostatic Dis. 2016; 19:35-39.

[16] Bhindi B, Xie WY, Kulkarni GS, Hamilton RJ, Nesbitt M, Finelli A, et al. Influence of Metabolic Syndrome on Prostate Cancer Stage, Grade, and Overall Recurrence Risk in Men Undergoing Radical Prostatectomy. Urology. 2016; 93:77-85.

[17] Wang LS, Murphy CT, Ruth K, Zaorsky NG, Smaldone MC, Sobczak ML, et al. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. Cancer. 2015; 121:3010-3017.

[18] McDonald AM, Fiveash JB, Kirkland RS, Cardan RA, Jacob R, Kim RY, et al. Subcutaneous adipose tissue characteristics and the risk of biochemical recurrence in men with high-risk prostate cancer. Urol Oncol. 2017; 35:663.e15-663.e21.

[19] Ohwaki K, Endo F, Hattori K. Abdominal obesity, hypertension, antihypertensive medication use and biochemical recurrence of prostate cancer after radical prostatectomy. Eur J Cancer. 2015; 51:604-609.

[20] Nik-Ahd F, Howard LE, Eisenberg AT, Aronson WJ, Terris MK, Cooperberg MR, et al. Poorly controlled diabetes increases the risk of metastases and castration-resistant prostate cancer in men undergoing radical prostatectomy: Results from the SEARCH database. Cancer. 2019; 125:2861-2867.

[21] Beebe-Dimmer JL, Nock NL, Neslund-Dudas C, Rundle A, Bock CH, Tang D, et al. Racial differences in risk of prostate cancer associated with metabolic syndrome. Urology. 2009; 74:185-190.

[22] Zhang GM, Zhu Y, Dong DH, Han CT, Gu CY, Gu WJ, et al. The association between metabolic syndrome and advanced prostate cancer in Chinese patients receiving radical prostatectomy. Asian J Androl. 2015;17:839-844.

[23] Jeon KP, Jeong TY, Lee SY, Hwang SW, Shin JH, Kim DS. Prostate cancer in patients with metabolic syndrome is associated with low grade Gleason score when diagnosed on biopsy. Korean J Urol. 2012; 53:593-597.

[24] Petäjä EM, Yki-Järvinen H. Definitions of Normal Liver Fat and the Association of Insulin Sensitivity with Acquired and Genetic NAFLD-A Systematic Review. Int J Mol Sci. 2016;17: pii: E633.

[25] Gucalp A, Iyengar NM, Zhou XK, Giri DD, Falcone DJ, Wang H, et al. Periprostatic adipose inflammation is associated with high-grade prostate cancer. Prostate Cancer Prostatic Dis. 2017; 20:418-423.

[26] Lehrer S, Diamond EJ, Stagger S, Stone NN, Stock RG. Increased serum insulin associated with increased risk of prostate cancer recurrence. Prostate. 2002; 50:1-3.

[27] Di Sebastiano KM, Pinthus JH, Duivenvoorden WCM, Mourtzakis M. Glucose impairments and insulin resistance in prostate cancer: the role of obesity, nutrition and exercise. Obes Rev. 2018; 19:1008-1016.

[28] Fan JG , Peng YD. Metabolic syndrome and non-alcoholic fatty liver disease: Asian definitions and Asian studies. Hepatobiliary Pancreat Dis Int. 2007; 6:572-578.

[29] Wang X, Liu Z, Wang K, Wang Z, Sun X, Zhong L, et al. Additive Effects of the Risk Alleles of PNPLA3 and TM6SF2 on Non-alcoholic Fatty Liver Disease (NAFLD) in a Chinese Population. Frontiers in Genetics. 2016; 7:140.

Figures

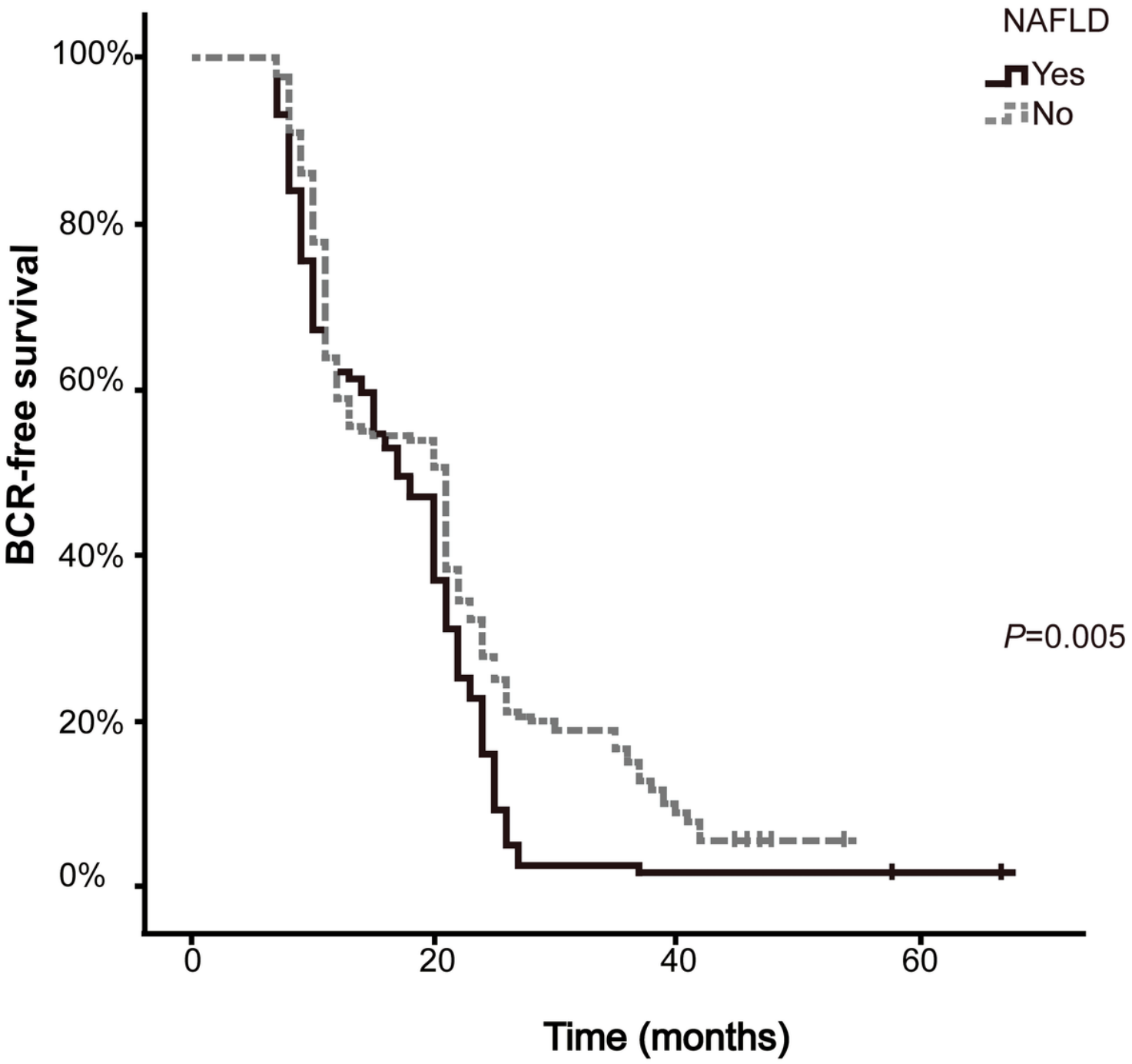

Figure 1

Kaplan–Meier estimates of BCR-free survival. The groups were stratified based on presence of NAFLD in metastatic PCa patients with Gleason score ≥4+3. BCR, biochemical recurrence; NAFLD, non-alcoholic fatty liver disease; PCa, prostate cancer

Supplementary Files

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