Nonalcoholic fatty liver disease is a negative risk factor for prostate cancer recurrence

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is closely related to the metabolic syndrome, which is associated with an increased risk of various malignancies. In this study, we investigated the association between NAFLD and prostate cancer biochemical recurrence (BCR) after radical prostatectomy. Consecutive prostate cancer patients who underwent radical prostatectomy were enrolled from two hospitals in Korea and randomly assigned to the training ($n=147$) or validation set ($n=146$). The presence of NAFLD, BMI, preoperative prostate-specific antigen, and histological findings including Gleason score (GSc) were analyzed in regard to their association with BCR. NAFLD was diagnosed based on ultrasonography or unenhanced computed tomography images. BCR-free survival rates were calculated using the Kaplan–Meier method. In the training set, 32 (21.8%) patients developed BCR during a median follow-up period of 51 (inter-quartile range, 35–65) months. In the multivariate analysis, the presence of NAFLD (hazard ratio (HR), 0.36; 95% CI, 0.14–0.97; $P=0.04$) was an independent negative predictive factor of BCR after adjustment for pathological GSc. Applied to the validation set, the presence of NAFLD maintained its prognostic value for longer time-to-BCR (HR, 0.17; 95% CI, 0.06–0.49; $P=0.001$). In the subgroup analysis of patients with NAFLD, NAFLD fibrosis score was a single independent negative predictor for BCR (HR, 0.54; 95% CI, 0.30–0.98; $P=0.04$). Our study demonstrated that NAFLD may play a protective role against BCR after radical prostatectomy for prostate cancer. Further study is warranted to elucidate the mechanism of protective effect in patients with NAFLD.

Key Words
- nonalcoholic fatty liver disease
- prostate cancer
- radical prostatectomy
- biochemical recurrence

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is recognized as the most common cause of chronic liver disease: it has a reported prevalence of 30% in the Unites States adult population (Torres & Harrison 2008). In Korea as well, the

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prevalence of NAFLD has increased steadily and has been reported to be 16.1–27.2% due to the adoption of a Western lifestyle; thus, it has become an important healthcare issue (Kim *et al*. 2004, Park *et al*. 2006).

NAFLD is regarded as a hepatic manifestation of the metabolic syndrome because it is closely related to insulin resistance, obesity, type 2 diabetes mellitus (DM), and dyslipidemia (Angulo 2002). Obesity and metabolic syndrome are believed to increase the risk of various malignancies including endometrium, kidney, gallbladder, breast, and colon cancers (Van Gaal *et al*. 2006). However, the relationship of obesity or metabolic syndrome to prostate cancer risk has remained controversial. Although several studies investigating the association between obesity and prostate cancer showed conflicting results, a recent meta-analysis has concluded that obesity is associated with increased risk of prostate cancer-specific mortality and biochemical recurrence (BCR) after radical prostatectomy in prostate cancer patients (Cao & Ma 2011). As the 5-year risk of clinical progression in men with BCR ranged from 27 to 60% and BCR typically precedes metastatic progression and prostate cancer-specific mortality by a median of 8 and 13 years, respectively, following radical prostatectomy (Pound *et al*. 1999), it has a clinical significance and is widely used as a critical surrogate marker for disease recurrence. While a number of studies regarding the association between metabolic syndrome and prostate cancer showed inconsistent results (Håheim *et al*. 2006, Tande *et al*. 2006, Martin *et al*. 2009), type 2 DM was consistently associated with a reduced risk of prostate cancer (Kasper & Giovannucci 2006, Kasper *et al*. 2009, Lawrence *et al*. 2013).

Since NAFLD is strongly associated with metabolic syndrome, type 2 DM, and obesity and its association with prostate cancer is still unclear, we aimed to investigate the relationship between the presence of NAFLD and BCR of prostate cancer after radical prostatectomy.

Subjects and methods

Patients

We included 841 consecutive localized prostate cancer patients treated with radical prostatectomy from two different university-affiliated hospitals: Seoul National University Hospital (Seoul, Korea), between January 2005 and December 2008, and Seoul Metropolitan Government, Seoul National University Boramae Medical Center (Seoul, Korea), between February 2004 and November 2010. The inclusion criteria were as follows: i) follow-up for >24 months after radical prostatectomy; ii) pathological stage of pT2 or pT3; iii) absence of distant metastasis; iv) availability of complete data regarding pathological stage and margin status; and v) availability of clinical information and abdominal ultrasonography (US) or computed tomography (CT) images to diagnose NAFLD. We excluded patients with double-primary cancers, those with evidence of liver disease of other etiologies besides NAFLD (i.e., seropositivity for hepatitis B surface antigen or anti-hepatitis C virus antibody, excessive alcohol consumption >20 g/day, medications known to precipitate fatty liver during the previous 6 months, and other causes of liver disease, such as Wilson's disease or hemochromatosis), and patients who were treated with neoadjuvant hormone therapy, or who failed to achieve prostate-specific antigen (PSA) nadir <0.1 ng/ml after radical prostatectomy. A total of 293 patients remained for analysis and were randomly assigned, in a 1:1 ratio, to the training set ($n=147$) and the validation set ($n=146$).

Endpoints and assessments

The primary end-point was time-to-BCR. BCR was defined as two consecutive PSA levels ≥0.2 ng/ml. Time-to-BCR was measured from the date of radical prostatectomy until the date of BCR defined as the date of the first PSA level that was 0.2 ng/ml or greater. Patients without BCR were censored at the date of the last recorded PSA level. The follow-up after radical prostatectomy consisted of measurement of serum PSA levels: every 3 months during the first year, when negative; every 6 months during the second year; and then annually. Imaging studies were carried out when deemed necessary. In the subgroup analysis according to the risk group, patients were categorized as having low, intermediate, or high-risk disease using the D'Amico risk stratification system: low risk – clinical stage T1c or T2a, preoperative PSA ≤10 ng/ml, and biopsy Gleason score (GSc) ≤6; intermediate risk – clinical stage T2b or 10< preoperative PSA ≤20 ng/ml, or biopsy GSc 7; and high risk – clinical stage T2c or preoperative PSA ≥20 ng/ml, or biopsy GSc 8–10 (D'Amico *et al*. 1998). In another subgroup analysis with patients who were diagnosed as having NAFLD, NAFLD fibrosis score, the simple noninvasive scoring system composed of six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST:ALT ratio), was used to evaluate the effects of hepatic fibrosis on prostate cancer BCR (Angulo *et al*. 2007).

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NAFLD was diagnosed based on clinical information and US or unenhanced CT images of the liver. Hepatic ultrasonographies were performed by experienced radiologists unaware of clinical data. The severity of echogenicity was graded as follows: grade 0 – normal echogenicity; grade 1 – slight, diffuse increase in fine echoes in the liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders; grade 2 – moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; grade 3 – marked increase in fine echoes with poor or nonvisualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver (Saadeh *et al*. 2002). Unenhanced CT image acquisition through the liver was performed during a single breath hold and NAFLD was diagnosed according to the severity of hepatic fatty infiltration or the measurement of liver attenuation (in housefield unit (HU)) using a standard region of interest (ROI) technique as described below. First, the severity of hepatic fatty infiltration was graded as follows: grade 0 – normal; grade 1 – liver attenuation slightly less than spleen; grade 2 – more pronounced difference between liver and spleen and intrahepatic vessels not seen or slightly higher attenuation than liver; grade 3 – markedly reduced liver attenuation with sharp contrast between liver and intrahepatic vessels (grade 1–3 were diagnosed as NAFLD) (Saadeh *et al*. 2002). Second, mean unenhanced liver attenuation was obtained by averaging eight 1.5 cm^2 circular ROIs placed in Couinaud segments V–VIII, and the threshold of 48 HU was used to diagnose the presence of NAFLD (Pickhardt *et al*. 2012). All imaging studies were reviewed by an experienced radiologist (H-C K, with over 10 years of experience) who was unaware of the patient's clinical information.

Reviewed clinical and pathological data consisted of age, weight, BMI, the presence of DM, the presence of metabolic syndrome, the presence of NAFLD, preoperative PSA level, surgical technique (open retropubic vs laparoscopic), the presence and type of adjuvant treatment, pathological GSc (divided into score $\leq$6, score=7, and score=8–10), pathological T stage (pT2 vs pT3) composed with organ-confined status, presence of extraprostatic extension, or seminal vesicle invasion and lymph-node status. Metabolic syndrome was defined using the criteria established by National Cholesterol Education Program Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel (ATP) III) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). In order to accommodate the available study data, specific ATP III criteria were modified; BMI >25 kg/m^2 was used as the criterion for abdominal obesity as measures of waist circumference were unavailable. Pathological stages were classified according to the 2010 American Joint Committee on Cancer TNM staging system (Edge & Compton 2010).

The study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Boards of each center.

Statistical analysis

We compared the baseline clinical and pathological characteristics using the χ^2 test for categorical and the Student's *t*-test or the Mann–Whitney *U* test for continuous variables. Patients' age, weight, BMI, preoperative serum PSA level, and follow-up duration were evaluated as continuous variables, while others were considered to be categorical variables. The BCR-free survival rates were estimated by the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazard regression analysis was used to evaluate independent risk factors for BCR. Variables with $P<0.20$ in the univariate Cox regression analysis were preceded to multivariate analysis using forward stepwise selection. All analyses were conducted using PASW 18.0K (SPSS, Inc.), and *P* values of <0.05 were considered to be statistically significant.

Results

Baseline clinical and pathological characteristics

The baseline characteristics of the study population are shown in Table 1. Patients in both sets had similar baseline characteristics. The median follow-up duration was 51.0 months (inter-quartile range (IQR), 35.0–65.0 months) in the training set and 51.0 months (IQR, 33.8–62.0 months) in the validation set.

Among the 147 patients included in the training set, 51 patients were diagnosed as having NAFLD (the NAFLD group), while 96 patients were not (the non-NAFLD group). Patients in the NAFLD group were younger and exhibited significantly higher BMI and weight compared with the non-NAFLD group. Otherwise, no statistically significant differences for clinical or pathological findings were observed between the two groups. In the validation set, 51 patients were diagnosed as having NAFLD and 95 patients were not. Patient with NAFLD showed significantly higher BMI, weight, and presence of

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Table 1 Baseline characteristics of the study population

	Training set ($n=147$)	Validation set ($n=146$)	P
Age (years)	66 (61–70)	67 (62–72)	0.17
BMI (kg/m^2)	24.3 (22.3–26.1)	24.3 (22.0–26.3)	0.64
Weight (kg)	66.0 (60.6–73.0)	66.7 (59.1–73.8)	0.92
DM			0.44
Yes	26 (17.7%)	21 (14.4%)	
No	121 (82.3%)	125 (85.6%)	
Metabolic syndrome			0.23
Yes	25 (17.0%)	20 (13.7%)	
No	76 (51.7%)	90 (61.6%)	
Unknown	46 (31.3%)	36 (24.7%)	
Alcohol			0.97
Never	105 (71.4%)	104 (71.2%)	
Current/former	42 (28.6%)	42 (28.8%)	
NAFLD			0.97
Yes	51 (34.7%)	51 (34.9%)	
No	96 (65.3%)	95 (65.1%)	
Preoperative PSA (ng/ml)	6.8 (5.0–10.7)	7.3 (5.1–11.2)	0.62
Follow-up (months)	51.0 (35.0–65.0)	51.0 (33.8–62.0)	0.69
BCR			0.65
Yes	32 (21.8%)	35 (24.0%)	
No	115 (78.2%)	111 (76.0%)	
Surgery			0.28
Open	94 (63.9%)	102 (69.9%)	
Laparoscopic	53 (36.1%)	44 (30.1%)	
Adjuvant treatment			0.28
Active surveillance	113 (76.9%)	109 (74.7%)	
ADT	21 (14.3%)	29 (19.9%)	
ADT+RT	13 (8.8%)	8 (5.5%)	
Pathological Gleason score			0.19
<7	53 (36.1%)	41 (28.1%)	
7	80 (54.4%)	83 (56.8%)	
>7	14 (9.5%)	22 (15.1%)	
Pathological staging			0.59
pT2	99 (67.3%)	94 (64.4%)	
pT3	48 (32.7%)	52 (35.6%)	
Surgical margins			0.68
Positive	50 (34.0%)	53 (36.3%)	
Negative	97 (66.0%)	93 (63.7%)	
Extracapsular extension			0.97
Yes	47 (32.0%)	47 (32.2%)	
No	100 (68.0%)	99 (67.8%)	
Invasion seminal vesicles			0.98
Yes	15 (10.2%)	15 (10.3%)	
No	132 (89.8%)	131 (89.7%)	
Lymph node dissection	41 (27.9%)	52 (35.6%)	0.16
Positive lymph node	6 (4.1%)	5 (3.4%)	0.77

Data presented as median (IQR) or number (%). DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; PSA, prostate specific antigen; BCR, biochemical recurrence; ADT, androgen-deprivation therapy; RT, radiation therapy.

type 2 DM and metabolic syndrome, otherwise no significant differences between the two groups were observed (Table 2).

Time-to-BCR

In the training set, a total of 32 (21.8%) patients developed BCR after radical prostatectomy. Figure 1A presents Kaplan–Meier curves for the time-to-BCR with patients stratified by the presence of NAFLD. The BCR-free survival rates at 5 years were 88.5% in the NAFLD group and 69.9% in the non-NAFLD group. The NAFLD group showed significantly longer time-to-BCR compared with patients without NAFLD (hazard ratio (HR), 0.33; 95% CI, 0.16–0.69; $P=0.02$ by log-rank test; Fig. 1A). In the validation set, 35 (24.0%) patients developed BCR after radical prostatectomy. The BCR-free survival rates at 5 years were 92.1% in the NAFLD group and 66.1% in the non-NAFLD group. The NAFLD group exhibited significantly longer time-to-BCR compared with non-NAFLD group (HR, 0.22; 95% CI, 0.11–0.43; $P=0.001$; Fig. 1B).

In the multivariate Cox analysis of training set, the presence of NAFLD (HR, 0.36; 95% CI, 0.14–0.97; $P=0.04$) and pathological GSc (score 7 vs score ≤6: HR, 3.22; 95% CI, 1.21–8.59; $P=0.02$ and score 8–10 vs score ≤6: HR, 6.93; 95% CI, 2.16–22.16; $P=0.001$) was independent predictive factors for BCR after adjustment for pathological T stage (pT2 vs pT3), positive surgical margin, and positive lymph node. The presence of DM or metabolic syndrome or BMI was not a significant predictive factor for BCR after radical prostatectomy with univariate analysis. In the multivariate Cox analysis of validation set, the presence of NAFLD (HR, 0.17; 95% CI, 0.06–0.49; $P=0.001$), as well as pathological GSc (score 8–10 vs score ≤6: HR, 4.44; 95% CI, 1.39–14.21; $P=0.01$) and positive surgical margin (HR, 3.03; 95% CI, 1.52–6.01; $P=0.002$), was an independent predictive factor for BCR; however, the presence of DM or BMI failed to show any prognostic value with univariate analysis. In the validation set, the presence of metabolic syndrome was preceded to multivariate Cox analysis due to $P<0.20$ in the univariate analysis, which failed to show statistical significance after adjustment for other covariables other than the presence of NAFLD (Table 3).

Subgroup analyses according to the D'Amico risk group and NAFLD fibrosis score

In the subgroup analysis of the whole study population according to D'Amico risk stratification, 89 (30.4%) patients belonged to the low-risk group, 105 (35.8%) patients belonged to the intermediate-risk group, and 99 (33.8%) patients belonged to the high-risk group. The association between the presence of NAFLD and time-to-BCR remained significant in patients in the D'Amico high-risk group ($P=0.001$; Fig. 2C). Patients in the D'Amico low- or intermediate-risk group also showed similar trends; however, the difference was not statistically significant ($P=0.20$ and 0.07 respectively; Fig. 2A and B).

A total of 102 patients with NAFLD were divided into two groups according to NAFLD fibrosis score at the cutoff score of −1.455, which could exclude advanced fibrosis

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Table 2 Clinical and pathological characteristics of patients in training set and validation set

	Training set ($n=147$)			Validation set ($n=146$)		
	NAFLD (+) ($n=51$)	NAFLD (−) ($n=96$)	*P*	NAFLD (+) ($n=51$)	NAFLD (−) ($n=95$)	*P*
Age (years)	64 (59–68)	67 (62–71)	0.04	65 (61–69)	67 (63–72)	0.06
BMI (kg/m^2)	26.0 (24.6–27.1)	23.3 (21.6–25.2)	<0.001	25.6 (23.8–27.0)	24.0 (21.0–25.1)	<0.001
Weight (kg)	73.0 (66.4–77.0)	63.5 (58.6–68.8)	<0.001	71.9 (65.8–76.9)	64.2 (56.7–71.9)	<0.001
DM			0.37			0.01
Yes	11 (21.6%)	15 (15.6%)		13 (25.5%)	8 (8.4%)	
No	40 (78.4%)	81 (84.4%)		38 (74.5%)	87 (91.6%)	
Metabolic syndrome			0.53			0.02
Yes	11 (21.6%)	14 (14.6%)		12 (23.5%)	8 (8.4%)	
No	24 (47.1%)	52 (54.2%)		25 (49.0%)	65 (68.4%)	
Unknown	16 (31.4%)	30 (31.3%)		14 (27.5%)	22 (23.2%)	
Drugs[a]						
Statins	5 (13.2%)	8 (11.6%)	0.81	4 (10.5%)	5 (6.5%)	0.48
ACEI	2 (5.3%)	3 (4.3%)	1.00	–	–	
ARB	8 (21.1%)	15 (21.7%)	0.93	8 (21.1%)	15 (19.5%)	0.84
Alcohol			0.87			0.80
Never	36 (70.6%)	69 (71.9%)		37 (72.5%)	67 (70.5%)	
Current/former	15 (29.4%)	27 (28.1%)		14 (27.5%)	28 (29.5%)	
Preoperative PSA (ng/ml)	6.4 (5.1–10.9)	7.1 (4.9–10.7)	0.94	6.5 (4.8–9.6)	7.9 (5.3–12.1)	0.14
Surgery			0.83			0.81
Open	32 (62.7%)	62 (64.6%)		35 (68.6%)	67 (70.5%)	
Laparoscopic	19 (37.3%)	34 (35.4%)		16 (31.4%)	28 (29.5%)	
Adjuvant treatment			0.13			0.63
Active surveillance	44 (86.3%)	69 (71.9%)		37 (72.5%)	72 (75.8%)	
ADT	5 (9.8%)	16 (16.7%)		12 (23.5%)	17 (17.9%)	
ADT+RT	2 (3.9%)	11 (11.5%)		2 (3.9%)	6 (6.3%)	
Pathological Gleason score			0.06			0.31
<7	18 (35.3%)	35 (36.5%)		18 (35.3%)	23 (24.2%)	
7	32 (62.7%)	48 (50.0%)		25 (49.0%)	58 (61.1%)	
>7	1 (2.0%)	13 (13.5%)		8 (15.7%)	14 (14.7%)	
Pathological staging			0.22			0.67
pT2	31 (60.8%)	68 (70.8%)		34 (66.7%)	60 (63.2%)	
pT3	20 (39.2%)	28 (29.2%)		17 (33.3%)	35 (36.8%)	
Surgical margins			0.18			0.21
Positive	21 (41.2%)	29 (30.2%)		22 (43.1%)	31 (32.6%)	
Negative	30 (58.8%)	67 (69.8%)		29 (56.9%)	64 (67.4%)	
Extracapsular extension			0.32			0.20
Yes	19 (37.3%)	28 (29.2%)		13 (25.5%)	34 (35.8%)	
No	32 (62.7%)	68 (70.8%)		38 (74.5%)	61 (64.2%)	
Invasion seminal vesicles			0.09			0.66
Yes	2 (3.9%)	13 (13.5%)		6 (11.8%)	9 (9.5%)	
No	49 (96.1%)	83 (86.5%)		45 (88.2%)	86 (90.5%)	
Positive lymph node	1 (2.0%)	5 (5.2%)	0.67	3 (5.9%)	2 (2.1%)	0.34

Data presented as median (IQR) or number (%). NAFLD, nonalcoholic fatty liver disease; DM, diabetes mellitus; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PSA, prostate-specific antigen; ADT, androgen-deprivation therapy; RT, radiation therapy.
[a]Missing $n=40$ in the training set and 31 in the validation set because of unknown status of drug history.

with 90% sensitivity and 60% specificity. In total, 9 (8.8%) patients developed BCR after radical prostatectomy. The BCR-free survival rates at 5 years were 84.4% in the lower NAFLD fibrosis score group and 97.8% in the higher NAFLD fibrosis score group. The lower NAFLD fibrosis score group showed significantly longer time-to-BCR compared with the higher NAFLD fibrosis score group ($P=0.04$) (Fig. 3). In the multivariate Cox analysis, NAFLD fibrosis score, when treated as a continuous variable, was a single independent predictor for BCR (HR, 0.54; 95% CI, 0.30–0.98; $P=0.04$).

Discussion

The present study showed for the first time that the presence of NAFLD may be protective against BCR after radical prostatectomy for prostate cancer. Moreover, this is the first study showing that NAFLD may play a protective

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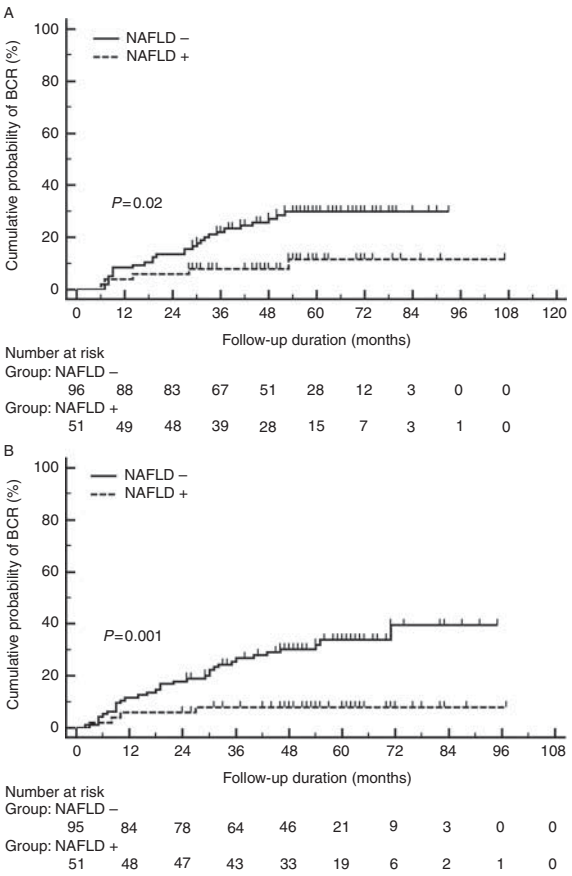

Figure 1
Time-to-BCR according to the presence of NAFLD. (A) Training set. (B) Validation set.

role against any other cancers to the best of our knowledge. Pathological GSc and/or positive surgical margin were also independent risk factors for BCR; however, the presence of DM and BMI failed to show any prognostic value in multivariate analyses of both training and validation sets. In the subgroup analyses according to D'Amico risk group, patients belonged to the high-risk group showed significant association between NAFLD and prostate cancer BCR, but patients belonged to the low or intermediate group showed similar trends without statistical significance. When NAFLD patients were stratified according to NAFLD fibrosis score, we found that the severity of fibrosis had significant correlation with BCR. In other words, it could be inferred that the risk of BCR decreased as NAFLD progressed to nonalcoholic steatohepatitis or cirrhosis with histological progression of fibrosis.

The possible mechanisms mediating the effects of NAFLD on prostate cancer BCR after radical prostatectomy are as follows. First, insulin, insulin resistance, and insulin-like growth factor 1 (IGF1) may play a critical role in the association of the NAFLD to prostate cancer BCR. Insulin is a potent mitogenic and anti-apoptotic factor, which induces potent growth effects on the prostate; furthermore, DNA polymorphisms in the insulin gene may be associated with increased prostate cancer risk (Hsing *et al.* 2007). A prospective case–cohort study in non-diabetic men showed that elevated fasting levels of serum insulin, but not glucose levels, appeared to be associated with a high risk of prostate cancer (Albanes *et al.* 2009). Insulin resistance is the most reproducible factor in the development of NAFLD (Marchesini *et al.* 1999); it may limit insulin actions and lead to protection against prostate cancer. An *in vitro* study showed that IGF1 promotes growth of primary prostate cell cultures and human prostate cancer cell lines (De Nunzio *et al.* 2012). In other studies, transgenic mice overexpressing human IGF1 in basal epithelial cells of the prostate were reported to develop prostate carcinoma at a high rate (DiGiovanni *et al.* 2000), and mice with global or liver-specific inactivation of IGF1 were associated with reduced prostate size and androgen-dependent prostate growth (Svensson *et al.* 2008). In addition, a meta-analysis of 42 observational studies demonstrated that elevated circulating IGF1 levels were significantly associated with prostate cancer risk (odds ratio, 1.21; 95% CI, 1.07–1.36) (Rowlands *et al.* 2009). The liver is the main site of circulating IGF1 in humans (Jones & Clemmons 1995), and an increasing body of evidence has suggested that NAFLD is associated with low circulating levels of IGF1 (Arturi *et al.* 2011, Fusco *et al.* 2012). Thus, low circulating levels of IGF1 in NAFLD could explain to some extent why NAFLD is negatively associated with prostate cancer BCR after radical prostatectomy. Second, it is well accepted that prostate cancer is a testosterone-dependent malignancy. Recent observational studies have showed that a low serum total testosterone level is independently associated with NAFLD regardless of visceral adipose tissue and insulin resistance (Völzke *et al.* 2010, Kim *et al.* 2012). In our study, consistent with previous findings, we could measure serum testosterone in 76 patients (28 patients with NAFLD and 48 patients without NAFLD) after excluding patients treated with androgen deprivation therapy (ADT). The NAFLD group showed significantly lower testosterone levels (4.0 vs 4.9 ng/ml; $P=0.01$) compared with the non-NAFLD group. Contrary to the expectation, serum testosterone level (HR, 1.04; 95% CI, 0.70–1.55; $P=0.85$), when treated as a continuous variable, was not an independent predictor of BCR. However, it is still unclear whether testosterone is

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Table 3 Univariate and multivariate analyses of factors associated with biochemical recurrence after radical prostatectomy

	Training set ($n=147$)						Validation set ($n=146$)					
	Univariate analysis			Multivariate analysis[a,b]			Univariate analysis			Multivariate analysis[a,b]		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
BMI	0.91	0.88–1.15	0.91				1.02	0.91–1.14	0.77			
BMI			–						–			
<23	1.00	–	–				1.00		–			
23–24.9	1.23	0.51–2.96	0.64				1.15	0.51–2.60	0.74			
>25	1.06	0.48–2.45	0.89				0.91	0.40–2.05	0.81			
Age	0.97	0.93–1.02	0.26				1.01	0.96–1.07	0.64			
DM	0.62	0.22–1.77	0.62				0.73	0.26–2.08	0.56			
Metabolic syndrome[c]	1.34	0.51–3.48	0.55				0.38	0.09–1.61	0.19			
Surgery			0.23						0.80			
Open	1.00	–	–				1.00	–	–			
Laparoscopic	0.61	0.28–1.37	–				0.91	0.42–1.95	–			
NAFLD	0.33	0.13–0.86	0.02	0.36	0.14–0.97	0.04	0.22	0.08–0.61	0.004	0.17	0.06–0.49	0.001
Preoperative PSA level	1.01	0.98–1.04	0.44				1.01	0.99–1.04	0.34			
Pathological GSc			–						–			
<7	1.00	–	–	1.00	–	–	1.00	–	–	1.00		
7	3.01	1.13–8.03	0.03	3.22	1.21–8.59	0.02	2.59	0.89–7.58	0.08	1.99	0.67–5.86	0.21
>7	8.39	2.64–26.68	<0.001	6.93	2.16–22.16	0.001	6.11	1.94–19.18	0.002	4.44	1.39–14.21	0.01
Pathological stage			0.09			0.62			0.01			0.63
pT2	1.00	–	–	1.00	–		1.00	–	–	1.00	–	
pT3	1.84	0.92–3.71	–	1.24	0.54–2.84		2.49	1.28–4.84	–	1.21	0.56–2.61	
Positive surgical margin	1.91	0.95–3.82	0.07	1.34	0.58–3.08	0.49	2.76	1.41–5.40	0.003	3.03	1.52–6.01	0.002
Extracapsular extension	1.92	0.95–3.87	0.07				2.63	1.35–5.10	0.004			
Invasion seminal vesicles	2.80	1.21–6.48	0.02				2.00	0.83–4.82	0.12			
Positive lymph nodes[d]	2.78	0.84–9.18	0.09	1.00	0.24–4.14	1.00	0.70	0.10–5.13	0.73			

DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; PSA, prostate-specific antigen; GSc, Gleason score.
[a]Variables in the multivariate model are adjusted for each other.
[b]Replacing pathological stage by extracapsular extension and seminal vesicle invasion in the multivariate model resulted in adjusted hazards ratio (95% CI) of 1.24 (0.50–3.06, $P=0.65$) for extracapsular extension and 1.11 (0.35–3.52, $P=0.87$) for seminal vesicle invasion in the training set and 1.21 (0.56–2.61, $P=0.63$) for extracapsular extension and 0.81 (0.30–2.20, $P=0.68$) for seminal vesicle invasion in the validation set, while the adjusted hazards ratios for the remaining variables hardly changed.
[c]Missing $n=46$ in the training set and 36 in the validation set because of unknown status of metabolic syndrome.
[d]The reference category is no lymph node dissection performed or no positive lymph nodes.

involved in the initiation of prostate cancer or testosterone therapy increases the risk of prostate cancer. A collaborative analysis of 18 prospective studies found that the risk of prostate cancer is irrelevant to serum concentrations of testosterone, calculated free testosterone, dihydrotestosterone, or any other sex steroid tested (Roddam *et al*. 2008). In addition, a meta-analysis of testosterone trials failed to show an increased risk of prostate cancer with testosterone therapy (Fernández-Balsells *et al*. 2010). This lack of correlation of testosterone with prostate cancer risk has led to the proposal of the so-called 'saturation model'. According to this model, a saturation point of circulating testosterone at the near-castrate range exists that saturates the target receptor. Above this point, the prostate cancer will no longer respond to further increases in circulating levels of testosterone, whereas below this point the androgenic response of prostate cancer will decrease as circulating levels of testosterone decreases (Morgentaler & Traish 2009). Although the saturation model is currently unproven and further research is needed, this model could explain the undefined detrimental effect of testosterone replacement therapy and the therapeutic effect of ADT on established prostate cancer. In the subgroup analysis according to D'Amico risk stratification, we found that patients belonged to the D'Amico high-risk group showed significant association between NAFLD and prostate cancer BCR; however, patients belonged to the low or intermediate group failed to show statistically significant results. The D'Amico high-risk group received adjuvant treatments with ADT (±radiation therapy) after radical prostatectomy more frequently (39.4 vs 16.5%; $P<0.001$) than the D'Amico low-to-intermediate risk group. Statistically different results with NAFLD and

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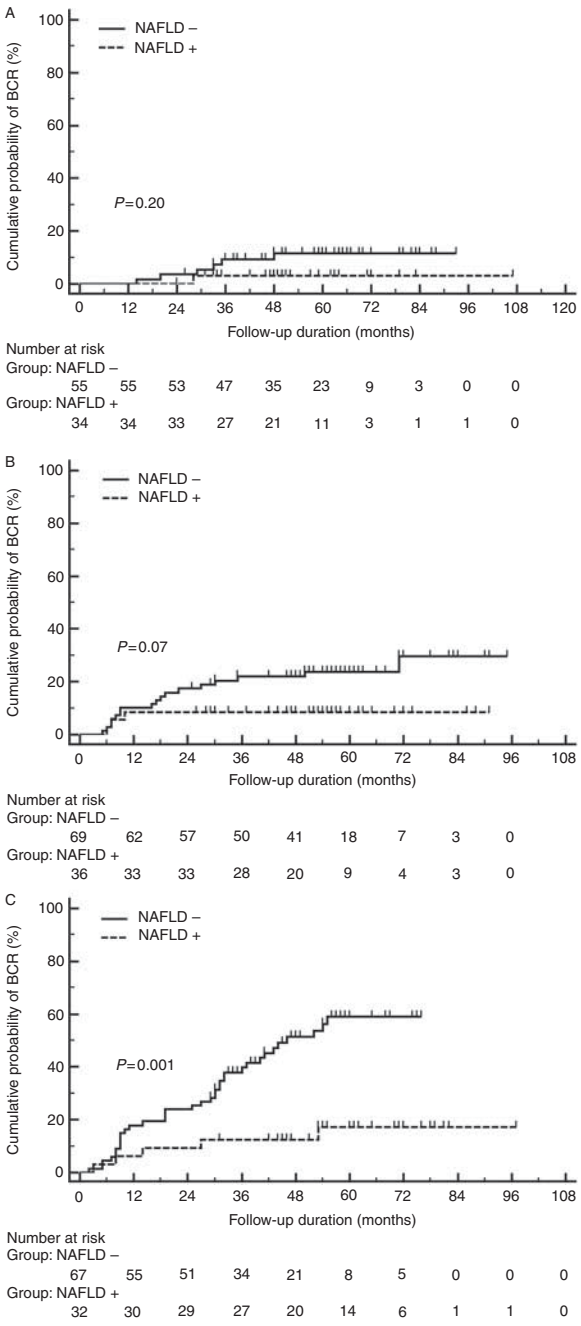

Figure 2
Time-to-BCR based on D'Amico risk group. (A) D'Amico low-risk group. (B) D'Amico intermediate risk group. (C) D'Amico high-risk group.

prostate cancer BCR according to D'Amico risk group could be explained by differences in the serum testosterone level depending on the presence of NAFLD and the frequency of ADT administration. Low serum testosterone levels in NAFLD and more frequent administration of ADT in the D'Amico high-risk group might intensify the therapeutic effect of ADT, which resulted in significantly longer time-to-BCR in the D'Amico high-risk patients with NAFLD compared with patients without NAFLD; however no statistically significant results were reported in the D'Amico low-or intermediate-risk patients. From these findings, it can be inferred that low serum testosterone levels in NAFLD could be another possible link between prostate cancer BCR and NAFLD.

Besides the relationship between NAFLD and prostate cancer BCR, which has not previously been evaluated, our findings are consistent with previous studies. Overall 5-year BCR-free survival rate was quite similar to previous studies which reported ranges from 70 to 87% (Han *et al.* 2001, Chun *et al.* 2006, Porter *et al.* 2006, Magheli *et al.* 2008). In regard to predictive factors of prostate cancer BCR, higher preoperative PSA level, higher GSc, advanced tumor stage, particularly with regard to seminal vesicle and/or lymph node invasion, and positive surgical margin have been generally reported to increase the risk of BCR (Han *et al.* 2001, Chun *et al.* 2006, Porter *et al.* 2006). Also in this study, pathological GSc and positive surgical margin were independent predictors for BCR. Although the relationship between obesity and prostate cancer, especially BCR after treatment for localized prostate cancer, has remained unclear, several prior studies failed to find a significant association between BMI and prostate cancer BCR after prostatectomy (Van Roermund *et al.* 2009, Lee *et al.* 2011, Tomaszewski *et al.* 2013). In contrast to the result from the previous studies indicating about the effect of DM on prostate cancer BCR, the present study failed to demonstrate the reduced risk of prostate cancer BCR in diabetic patients. As the duration of DM was not evaluated in the present study, this could be explained by

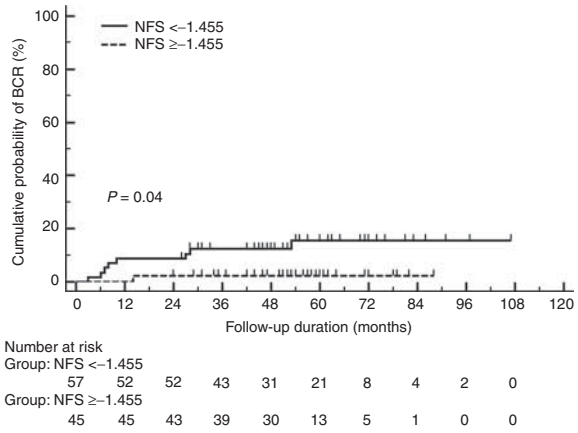

Figure 3
Time-to-BCR based on the NAFLD fibrosis score.

earlier studies which reported that prostate cancer risk is not reduced in the incipient time since DM diagnosis (Rodriguez *et al*. 2005, Kasper *et al*. 2009).

Our study has several limitations. First, we provided cross-validation results using data from two university affiliated hospitals of external validation results. At first, we were planning to externally validate the result of one hospital by that of the other hospital. However, the baseline characteristics (i.e., kind of surgical treatment) of the patients between two centers were quite different; thus, we used cross-validation after mixing and randomizing the data. Second, we used US or unenhanced CT as the mode of diagnosis for NAFLD, while liver biopsy is regarded as the gold standard. Furthermore, without liver biopsy, it is impossible to characterize liver histology such as degree of fibrosis and distinguish between nonalcoholic fatty liver and nonalcoholic steatohepatitis because nonalcoholic steatohepatitis can progress to cirrhosis, liver failure, and liver cancer and increase hepatic and extrahepatic morbidity and mortality (Chalasani *et al*. 2012). However, a meta-analysis from 46 articles comparing various imaging modalities to liver biopsy for diagnosis of NAFLD concluded that mean sensitivity estimates for US and CT were 73.3–90.5 and 46.1–72.0%, respectively, and mean specificity range were 69.6–85.2 and 88.1–94.6% respectively (Bohte *et al*. 2011). Specificity, sensitivity, positive predictive value, and negative predictive value of unenhanced CT liver attenuation alone with threshold of 48 HU for diagnosis of NAFLD used in this study were 100, 53.8, 100, and 93.9% respectively; these values are highly specific for diagnosing hepatic steatosis (Pickhardt *et al*. 2012). From these findings, US or unenhanced CT could be the diagnostic test of choice for NAFLD instead of liver biopsy, which has well-established drawbacks regarding its invasiveness and sampling error due to small sample size and inter-observer variability (Bravo *et al*. 2001). In terms of liver fibrosis, a meta-analysis from 13 studies consisting of 3064 patients documented that NAFLD fibrosis score has an AUROC of 0.85 for predicting advanced fibrosis and a score < -1.455 had 90% sensitivity and 60% specificity to exclude advanced fibrosis (Musso *et al*. 2011), which was used in this study instead of liver biopsy. In addition, the retrospective design and relatively small number of NAFLD patients may represent the limitations of our study. However, the clear inclusion and exclusion criteria might counteract this weak point. Another limitation is that many patients were excluded from the final analyses because of feasibility to diagnose NAFLD, with possible selection bias. In this study, actually, there were a number of patients diagnosed with NAFLD and prostate cancer through medical checkups. The mean age was lower in patients with NAFLD compared with patients without NAFLD. From this, it can be implied that it is more likely that an obese patient with a higher possibility of NAFLD is prone to receive early medical checkup, compared with the non-obese person. This phenomenon is likely to be related to concern for health and good compliance, thus affecting the good prognosis of prostate cancer.

In summary, the results of our study have shown that NAFLD may play a protective role against BCR after radical prostatectomy for prostate cancer. In addition, the protective role against BCR has strengthened as NAFLD progresses to advanced fibrosis. Further studies are warranted to elucidate the mechanism of the protective effect against prostate cancer presented above in patients with NAFLD.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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