

# The likelihood of having a serum PSA level of $\geq 2.5$ ng/mL according to the degree of fatty liver disease in a screened population

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## Abstract

**Introduction:** We sought to investigate the impact of fatty liver disease (FLD) on prostate cancer (PCa) screening by estimating the odds of having a prostate-specific antigen (PSA) value over the cutoff used to prompt for the recommendation of prostate biopsy.

**Methods:** Between 2007 and 2013, 18 533 native Korean men eligible to receive a serum PSA test, liver profiles, and abdominal ultrasonography were recruited. Logistic regression was used to estimate the odds of an abnormal PSA ( $\geq 2.5$  ng/mL) in these men (age 45–75 years, PSA  $\leq 10$  ng/mL) in relation to FLD. The FLD status was categorized as normal, mild, moderate, and severe grade by abdominal sonography.

**Results:** A total of 16 563 men (89.4%) were included in the study after applying the inclusion criteria. Liver profiles were negatively correlated with the serum PSA level. After controlling for age and obesity, there was a statistically significant trend towards a lower likelihood of having a serum PSA level of  $\geq 2.5$  ng/mL with severe FLD, having a 34.7% lower likelihood (odds ratio 0.653, 95% confidence interval 0.477–0.88;  $p < 0.01$ ) compared to men in the normal group.

**Conclusions:** Severe FLD is an independent predictor of a lower likelihood of having abnormal PSA level. Further studies are needed to better define these results in clinical biopsy practice.

## Introduction

Although the U.S. Preventive Service Task Force recently recommended against PSA-based screening of PCa,<sup>1</sup> the probability of finding cancer in a prostate biopsy is strongly related to the serum PSA level.<sup>2</sup> To improve the accuracy of serum PSA testing for PCa, a knowledge of PSA biochemistry and metabolism is required. The serum PSA concentration is directly correlated with age and prostate volume and is known to vary across ethnic groups.<sup>3</sup> Other notable conditions that can affect the PSA concentration included meta-

bolic syndrome (MS) or obesity, which has been associated with decreased serum PSA possibly due to hemodilution.<sup>4–7</sup>

MS or obesity are commonly associated with FLD.<sup>8</sup> FLD results from accumulation of fat exceeding the normal 5% of liver weight.<sup>9</sup> Fatty liver is caused by the increased accumulation of triglycerides within the hepatocytes and is a reversible cellular response to various disease states and alterations in metabolism.<sup>8</sup> Underlying liver disease may be a possible cause for alteration of serum PSA levels,<sup>10</sup> because the liver has a significant role in the elimination of serum PSA.<sup>11</sup> Free PSA is eliminated by the kidneys, but because of their size, PSA bound to alpha1-antichymotrypsin is cleared through the liver.<sup>11</sup> One might anticipate that chronic liver disease would prolong the half-life of serum PSA because of decreased clearance and would result in an increase in its serum concentration.<sup>12</sup> However, no consensus has been reached regarding the influence of liver disease on serum PSA levels.

FLD is prevalent in the general population, occurring in 45% of Hispanic-Americans, and is the most common cause of abnormal liver function tests in the U.S.<sup>8</sup> We investigated the relation of FLD with serum PSA and the impact of FLD on PCa screening, as well as its relationship with MS or obesity in a screened population.

## Materials and methods

### Data collection and study design

We used data gathered between 2007 and 2013 at the health promotion centre attached to Soonchunhyang University Seoul Hospital. All consecutive participants underwent detailed interviews, physical examinations, and laboratory examinations. This study was approved by our Institutional Review Board. A total of 18 533 native Korean men were eligible to receive a serum PSA test. For our analyses, only men aged 45–75 years were included, since this represents the

generally accepted age range for PCa screening. Individuals with a PSA level  $>10.0$  ng/ml were excluded, under the assumption they were likely to have PCa. Other exclusion criteria were as follows: a history of PCa, pyuria, hematuria, or bacteriuria on microscopic examination; taking medication such as a 5 $\alpha$ -reductase inhibitor; *Serenoa repens*, or testosterone before checking the PSA; men with clinically significant concomitant hepatobiliary disease, such as liver cirrhosis, hepatoma, cholecystitis, *Clonorchis sinensis* infection, etc; and cases with insufficient data.

All anthropometric measurements were made by trained observers using standardized techniques. Body mass index (BMI) was defined as the weight (kg) divided by the square of the height ( $m^2$ ).<sup>13</sup> The classification as non-obese or obese was based on the Asia-Pacific criteria for obesity,<sup>13</sup> and the definition of MS followed the recent consensus report of the National Cholesterol Education Program's Adult Treatment Panel III.<sup>14</sup> All subjects underwent abdominal ultrasonography by two experienced radiologists. The following grading of the degree of fatty infiltration was adopted: grade 1 (mild), echogenicity is slightly increased, with normal visualization of the diaphragm and the intrahepatic vessel borders; grade 2 (moderate), echogenicity is moderately increased, with slightly impaired visualization of the diaphragm or intrahepatic vessels; grade 3 (severe), echogenicity is markedly increased, with poor or no visualization of the diaphragm, the intrahepatic vessels, and posterior portion of the right lobe (Fig. 1).<sup>15</sup>

### Statistical analysis

The mean and standard deviation (SD) were used as appropriate to describe the statistical data. Univariate analysis with Pearson correlation test was used to check the linearity of the relationships among the variables. Multiple logistic regression analysis was used to test the linear effect of age, BMI, and various liver profiles in predicting serum PSA level. Those variables were adopted as a continuous variable. Only MS and FLD were adopted as categorical variables. A PSA threshold of 2.5 ng/ml was used to categorize PSA values as *normal* or *abnormal* for the analyses. To describe the association between FLD and the likelihood of a certain serum total PSA level, age-adjusted logistic regression analyses were used after grouping the men as having a PSA level  $\geq 2.5$  ng/ml, coupled with MS or obesity. The odds ratio of having an abnormal PSA level for threshold was then calculated, using men with normal values as the reference group. The SPSS (Statistical Package for the Social Science) 14.0 software (SPSS Inc., Chicago, IL, U.S.) was used for the statistical analyses and a  $p$  value of  $<0.05$  was considered statistically significant for all analyses.

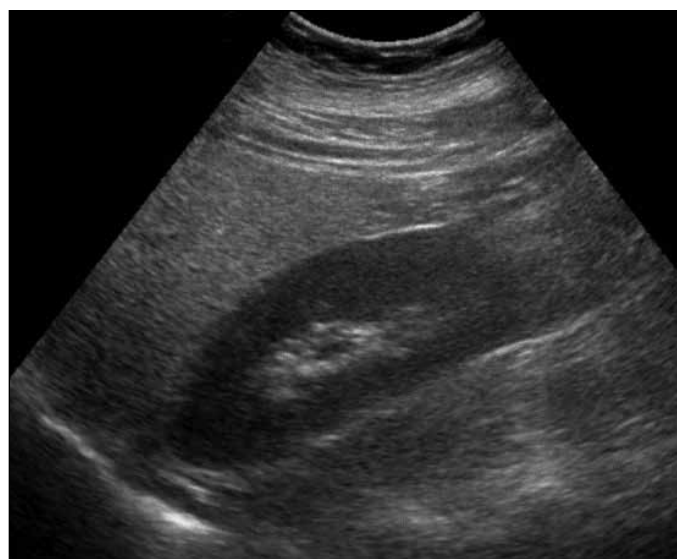
### Results

Of the 18 533 men considered, 16 563 (89.4%) remained after applying the inclusion criteria. One thousand sixty four (1064) were excluded for pyuria, hematuria, or bacteriuria on microscopic examination; 452 for taking medication that can influence the PSA level; 210 for clinically significant concomitant hepatobiliary disease; 52 having a PSA level  $>10$  ng/ml; 12 for known PCa; and 180 for insufficient data.

Table 1 provides the demographics of the study population. The median age was 49 years. Over half (51.9%) showed some degree of FLD and 6.8% of subjects had severe FLD according to the sonographic classification. The liver profiles, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and lactic dehydrogenase (LDH) significantly increased in men with severe FLD. The higher the grade of FLD, the higher the portion of subjects with MS or obesity, with 90.1% of men having severe FLD being obese, as represented by higher BMI ( $\geq 25$   $kg/m^2$ ). Mean PSA significantly decrease with higher-grade FLD (Table 1).

The univariate analysis with Pearson correlation test showed that the PSA was negatively correlated with all liver profiles (Table 2). Multiple linear regression analysis demonstrated that LDH was a significant factor in predicting PSA, as were age and BMI. We excluded ALT in the multivariate analysis due to their high variation inflation with AST.

In all, 1243 (7.5%) men had serum PSA levels of  $\geq 2.5$  ng/ml. The multiple logistic regression analyses after controlling for age, BMI, AST, ALT, GGT, and MS showed that BMI, AST, ALT, GGT, MS were not significant factors in predicting the PSA level. There was a statistically significant trend towards a lower likelihood (34.7% lower) of having a PSA



**Fig. 1.** Severe fatty liver disease. Liver echogenicity was markedly increased compared with renal parenchyma, with no visualization of intrahepatic vessel.

**Table 1. Demographics**

	Degree of fatty liver by sonography					<i>p</i> value
	Total n=16 563	Normal n=7965	Mild n=5867	Moderate n=1592	Severe n=1139	
Age	49 (45–55)	49 (44–54)	50 (45–55)	51 (45–56)	49 (45–55)	<0.001
PSA	0.95 (0.65–1.43)	0.98 (0.67–1.47)	0.93 (0.64–1.43)	0.91 (0.63–1.36)	0.85 (0.58–1.27)	<0.001
BMI	24.5 (22.9–26.2)	23.2 (21.8–24.6)	25.2 (23.9–26.7)	26.2 (24.8–27.7)	27.7 (26.2–29.4)	<0.001
SGOT	24 (20–29)	23 (19–27)	25 (21–30)	27 (22–34)	29 (23–38)	<0.001
SGPT	25 (19–36)	22 (17–28)	28 (21–38)	34 (25–49)	40 (28–58)	<0.001
GGT	33 (22–53)	27 (19–42)	37 (25–57)	44 (29–70)	46 (33–68)	<0.001
LDH	273 (189–335)	276 (187–332)	274 (189–339)	237 (188–332)	287 (198–355)	<0.001
MS	30.5	13.4	39.4	56.8	68.0	<0.001
Obesity	41.2	18.8	54.0	70.5	90.1	<0.001

Data presented as median (IQR) or %. BMI: body mass index; GGT: gamma-glutamyl transpeptidase; LDH: lactic dehydrogenase; MS: metabolic syndrome; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamate pyruvate transaminase.

level of  $\geq 2.5$  ng/ml with severe-grade FLD (odds ratio 0.653, 95% confidence interval 0.477–0.88;  $p < 0.01$ ) compared to men in the normal group (Table 3).

## Discussion

This study showed that there was a statistically significant trend towards a lower likelihood of having a total serum PSA level of  $\geq 2.5$  ng/ml with severe FLD, and that men with severe FLD had a 25.2% lower likelihood compared to men without FLD by sonography. When we considered this threshold, there was an observable trend of a decreasing PSA level with severe FLD, indicating significant differences in the point estimates of abnormal PSA risk between men with or without severe FLD. Liver profiles were negatively correlated with serum PSA level.

These findings were in contrast to the conventional understanding that since the liver is the most likely site of PSA metabolism,<sup>16</sup> it seems likely that a lowered liver function would result in delayed metabolism of PSA, and eventually, a higher serum PSA. However, only a few reports have supported this expectation.<sup>17,18</sup> Rather, results revealing no or negative relation between liver disease and serum PSA were predominant.<sup>19–24</sup>

Some investigators noted that serum PSA levels were not significantly different between healthy men and men with liver cirrhosis or chronic hepatitis.<sup>17,18</sup> Williams et al. found that serum bilirubin and aminotransferases declined significantly after liver transplantation, but the mean serum PSA levels before and after liver transplantation were not different.<sup>18</sup> Other investigators demonstrated that the mean serum PSA level was significantly lower in men with liver cirrhosis compared with healthy men.<sup>19,21–24</sup> Jin et al. found that before liver transplantation, the serum PSA concentrations in men with severe liver disease were significantly lower than those of healthy men and normalized after liver transplantation.<sup>22</sup>

Hepatic cirrhosis may influence estrogen and testosterone metabolism, with resultant increase in circulating estrogen level and decrease in testosterone concentrations.<sup>20</sup> These alterations may lower the serum PSA concentration in men with cirrhosis. Inci et al. suggested that the production of PSA in patients with severe liver disease might be affected by three mechanisms.<sup>21</sup> First, liver disease results in decreased

**Table 2. Univariate and multivariate correlation between PSA and various parameters, including liver profiles**

Variables	Univariate		Multivariate		VIF
	<i>r</i>	<i>p</i> value	Coefficient	<i>p</i> value	
Age	0.181	<0.001	0.180	<0.001	1.009
BMI	-0.045	<0.001	-0.039	<0.001	1.031
AST	-0.021	<0.01	-0.013	0.132	1.276
ALT	-0.016	<0.05	—	—	—
GGT	-0.019	<0.05	-0.012	0.143	1.243
LDH	-0.021	<0.01	-0.019	<0.05	1.032

ALT: alanine aminotransferase; AST: aminotransferase; BMI: body mass index; GGT: gamma-glutamyl transpeptidase; LDH: lactic dehydrogenase; VIF: variation inflation factor.

**Table 3. Age-adjusted odds of having a serum PSA level  $\geq 2.5$  ng/ml on MS and the degree of fatty liver**

PSA threshold 2.5 ng/ml	OR	95% CI	<i>p</i> value
Age	1.079	1.071–1.087	<0.01
BMI	0.982	0.955–1.01	0.216
AST	0.998	0.989–1.006	0.559
ALT	1.001	0.996–1.006	0.626
GGT	0.999	0.998–1.001	0.331
non-MS	reference		
MS	1.101	0.949–1.275	0.204
FLD: normal	reference		
Mild	0.944	0.818–1.09	0.433
Moderate	0.855	0.677–1.072	0.181
Severe	0.653	0.477–0.88	< 0.01

ALT: alanine aminotransferase; AST: aminotransferase; BMI: body mass index; CI: confidence interval; FLD: fatty liver disease; GGT: gamma-glutamyl transpeptidase; MS: metabolic syndrome; OR: odds ratio; PSA: prostate-specific antigen.

testosterone level because of the abnormal hypothalamic pituitary-testicular axis. Second, decreased testosterone causes shrunken prostatic volume. Third, the liver may diminish serum protein level in the composition of the PSA.<sup>21</sup>

It would be interesting to know the sex hormone level in patients with FLD compared to those with liver cirrhosis. Recently, observational studies have showed that a low serum total testosterone level is independently associated with nonalcoholic FLD, regardless of visceral adipose tissue and insulin resistance, similarly with liver cirrhosis.<sup>25,26</sup> Choi et al. reported that the nonalcoholic FLD group showed significantly lower testosterone levels compared with the non-FLD group.<sup>27</sup>

Besides testosterone, insulin, insulin resistance, and insulin-like growth factor 1 (IGF1) may play a critical role in the mechanism of prostate growth.<sup>28</sup> The liver is the main site of circulating IGF1 in humans and an increasing body of evidence has suggested that FLD is associated with low circulating levels of IGF1.<sup>29,30</sup> Thus, low circulating levels of IGF1 in FLD could explain, to some extent, why FLD is negatively associated with PSA.

FLD is not a single disease entity. It can be due to various causes, such as alcohol (most common), MS (diabetes, obesity), nutritional problems, various drugs, and hepatitis.<sup>8,9</sup> In the current study, men with severe FLD present with much higher liver profiles than those without FLD, therefore, it can be postulated that some phenomenon that occur in liver cirrhosis may also be present in severe FLD. Unfortunately, because we did not check the testosterone level or prostate volume in our recruited subjects, we cannot give the exact answers. Nevertheless, the strengths of our study includes the size of our cohort. The data generated from this large cohort with a significant proportion of men having obesity and FLD offers a fairly robust conclusion. Another limitation is that this association between PSA and FLD could not be reproduced in other races. Moreover, this study might have selection bias, including symptomatic benign prostatic hyperplasia or combined PCa patients, which could have an association with the state of FLD.

The PCa detection rate for non-palpable lesions among Korean men with a PSA level of 2.5–4.0 ng/ml was 21.8% and 20.2% in those with PSA level of 4.0–10.0 ng/ml, with no statistically significant difference between groups.<sup>31</sup> The pathologic characteristics of prostatectomy specimens were also similar between the two groups.<sup>26</sup> Many Korean institutions have adopted a PSA cutoff value of 2.5 ng/ml to prompt prostate biopsy. We set the PSA cutoff value for this study at 2.5 ng/ml.

Our results show that FLD might affect PCa screening using total serum PSA. This issue may be significant since FLD affects a substantial proportion of the male population.

## Conclusions

This study revealed that lower likelihood of having a PSA level of  $\geq 2.5$  ng/ml was associated with severe FLD. These results show that FLD might affect PCa screening efficiency using total serum PSA. Further studies that include biopsy may be needed to better define these results.

**Competing interests:** The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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