Serum lipid profiles: novel biomarkers predicting advanced prostate cancer in patients receiving radical prostatectomy

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This study aimed to evaluate the role of serum lipid profiles as novel biomarkers in predicting pathological characteristics of prostate cancer (PCa). We retrospectively analyzed 322 consecutive patients with clinically localized PCa receiving radical prostatectomy (RP) and extended pelvic lymphadenectomy. Unconditional logistic regression was used to estimate the prostatectomy Gleason score (pGS), pathological stage and lymph node involvement (LNI) in RP specimens. Preoperative prostate-specific antigen (PSA) levels, biopsy GS (bGS), and preoperative tumor, node, metastasis staging were used as basic variables to predict postoperative pathological characteristics. Preoperative serum lipid profiles were introduced as potential predictors. A receiver operating characteristic (ROC) curve was used to determine predictive efficacy. Significant differences in pathological characteristics were observed among patients with normal and abnormal total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) levels, with the exception of pGS in the TG group. Multivariable regression analysis revealed that the odds ratio for high levels of TC for LNI compared with normal TC was 6.386 (95% confidence interval [CI] 1.510–27.010), 3.270 (95% CI: 1.470–7.278) for high levels of TG for pT3–4 disease, and 2.670 (95% CI: 1.134–6.287) for high levels of LDL for pGS. The area under the ROC curve of the models with dyslipidemia was larger than that in models without dyslipidemia, in predicting pathological characteristics. Abnormal TC, TG, and LDL levels are significantly associated with postoperative pathological status in PCa patients. Together with preoperative PSA levels, bGS, and clinical stage, dyslipidemia is more accurate in predicting pathological characteristics.

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INTRODUCTION
In developed countries, prostate cancer (PCa) is the most common malignancy in men and the second leading cause of cancer-related mortality.¹ In China, the incidence of PCa has gradually increased over recent decades. According to the latest Chinese Cancer Registry Annual Report (2012), PCa has become the 6th most prevalent cancer and the 9th leading cause of cancer-related mortality in men, especially in urban areas.²³ Although the exact mechanisms that underlie PCa carcinogenesis are not well understood, growing evidence suggests that it is partly due to Western lifestyle factors, for example, a high-fat diet.³⁵

Many studies have demonstrated that, as a predominant component of metabolic syndrome, dyslipidemia plays an important role in the carcinogenesis of various cancers. An increased risk of colon cancer has been observed in people with high triglyceride (TG) levels,⁴ and hypercholesterolemia is considered as a risk factor for rectal cancer development.⁷ A positive association between elevated low-density lipoprotein (LDL) levels and kidney cancer has been observed,⁸ and low high-density lipoprotein (HDL) levels are associated with breast cancer and non-Hodgkin lymphoma.⁹¹⁰ To date, a large number of epidemiological studies have revealed an association between dyslipidemia and development of PCa.¹¹⁻¹⁴ In addition, patients with low total cholesterol (TC) levels are less likely to present with high-grade PCa (Gleason score [GS] ≥8),¹⁵ and inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, also called statins and used for dyslipidemia treatment, reduce the risk of advanced PCa.¹⁵¹⁷ However, only a few studies have targeted the relationship between abnormal serum lipid levels and postoperative pathological status of PCa.

Together with preoperative prostate-specific antigen (PSA) levels, GS and pathological stage are critical risk factors determining the subsequent interventions after radical prostatectomy (RP); the most effective treatment for PCa patients with organ-confined disease (OCD). However, preoperative imaging currently has limitations with an accurate diagnosis of OCD and micrometastasis to pelvic lymph nodes. Given the intimate relationship between dyslipidemia and PCa, we hypothesized that abnormal levels of serum lipid profiles might be associated with postoperative pathological status.
and stage. The present investigation was designed to evaluate serum lipid profiles as novel biomarkers to predict pathological characteristics in PCa patients undergoing RP.

**PATIENTS AND METHODS**

**Study subjects**

This was a retrospective analysis of 322 consecutive patients with clinically localized PCa who underwent RP and extended pelvic lymphadenectomy in Fudan University, Shanghai Cancer Center (FUSCC) from August 2012 to June 2013. None of the patients enrolled received neoadjuvant therapy. Data on age, history of hypertension or diabetes mellitus, BMI, smoking status, lipid profiles, statin usage, preoperative PSA levels, biopsy GS (bGS), histopathology, and stage at diagnosis (tumor, node, metastasis [TNM] classification) were obtained from electronic records and medical charts. Enzymatic methods were used to detect fasting serum lipid profiles by a Hitachi 7600 automatic clinical chemistry analyzer (Boehringer Mannheim, Mannheim, Germany) with reagent kits supplied by the manufacturer. Protocols were approved by the Institutional Research Review Boards of FUSCC, and written informed consent was obtained from all subjects.

Body mass index was defined as weight/height$^2$ (kg $m^{-2}$), and stratified according to guidelines for prevention and control of overweight and obesity in Chinese adults (<24: normal; ≥24: overweight). Serum lipid profiles were stratified in accordance with the Chinese Guidelines on Adult Dyslipidemias (2007 version); preoperative PSA levels, bGS, and clinical stage were divided into high-, medium-, and low-risk groups, respectively.

To establish a relationship between preoperative predictive factors and postoperative pathological characteristics, preoperative PSA levels, bGS, and clinical stage were used as basic variables, and preoperative lipid profiles were introduced as potential predictive variables. Age, BMI, hypertension, diabetes, family history of PCa, smoking status, and statin usage were included in the analyses as potential confounders.

**Statistical analysis**

Differences in categorical variables were compared using $\chi^2$ tests. Unconditional multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of the probability of lymph node involvement (LNI), pT3–4 disease, and prostatectomy GS (pGS) in RP specimens. A receiver operating characteristic (ROC) curve was used to determine the efficacy of the predictive variables. The values of $P$ were two sided, and $P < 0.05$ was considered statistically significant. SPSS version 20.0 (IBM Corporation, Somers, NY, USA) was used for statistical analyses.

**RESULTS**

The study included 322 cases of newly diagnosed PCa (age range: 47–79 years, median age: 68 years), whose preoperative PSA levels were in the range of 3.7–143.0 ng ml$^{-1}$ (median: 14.34 ng ml$^{-1}$). There were 172, 90, and 60 patients with ≤cT2a, cT2b, and cT2c disease, respectively, according to the American Joint Committee on Cancer TNM staging system (2002). Distribution of PCa cases according to demographic and clinical characteristics is indicated in Table 1.

No significant differences in age, hypertension, and statin usage were observed between patients with normal and abnormal levels in TC, TG, LDL, and HDL groups. Differences in preoperative PSA levels, bGS, clinical stage, smoking status, BMI, diabetes, pGS, pathological stage, and LNI varied in different groups. As far as postoperative pathological characteristics were concerned, notable differences existed among the TC, TG, and LDL groups, with the exception of pGS in the TG group. Interestingly, there were no differences observed between patients with normal and abnormal HDL levels (Table 1).

We investigated the association of postoperative pathological characteristics with preoperative PSA levels, bGS, a clinical stage, and TC, TG, and LDL levels, using univariate and multivariable logistic regression models, respectively. As shown in Table 2, after adjusting for potential confounders, high levels of TC were associated with increased risk of LNI (OR: 6.386, 95% CI: 1.510–27.010), and elevated TG levels were associated with a more than two-fold increased risk of pT3–4 disease (OR: 3.270, 95% CI: 1.470–7.278). In addition, high levels of LDL were an independent predictor of pGS ≥8 (OR: 2.670, 95% CI: 1.134–6.287). Further, we examined the OR (95% CI) of postoperative pathological characteristics when a patient harbored one, two or all three of the lipid-related risk factors. With the increase of the number of abnormal lipid components, a higher probability of pT3–4 disease and LNI was observed, yet no significant association was found with respect to pGS, whether in univariate or multivariable logistic regression models (Table 2).

We used ROC curves to detect the efficacy of predictive variables for postoperative pathological characteristics of PCa. The models were constructed using preoperative PSA levels, bGS, and clinical stage, with or without lipid profiles. As shown in Figure 1, area under the ROC curve of the models with dyslipidemia was larger than that without dyslipidemia, with regard to all the pathological status, including pGS, pT3–4 disease, and LNI.

**DISCUSSION**

There was a significant association between dyslipidemia and postoperative pathological characteristics, including pGS, pT3–4 disease, and LNI, and the association persisted after adjusting for multiple risk factors for PCa and other lipid parameters. Furthermore, ROC curve analysis suggested that abnormal lipid levels might be efficient predictors of pathological status of PCa.

In recent years, much attention has been focused on the association of lipid profiles with PCa, with conflicting conclusions. As far as TC is concerned, although controversy remains, many researchers have found a positive association between TC levels and total PCa incidence. Some prospective studies did not show increased total PCa risks in populations with high TC levels, whereas increased risk of high-grade or advanced PCa was seen. Apart from this epidemiological evidence, statins are also protective against the development of advanced PCa. Our study adds to the literature supporting the relationship between dyslipidemia and PCa development. Mondul et al conducted a large cohort study and found that men with normal TC levels were less likely to develop high-grade PCa. Similarly, another study conducted by Platz et al reported that men with < 200 mg dl$^{-1}$ TC had a lower risk of PCa with GS ≥7. Our study focused on the relationship between dyslipidemia and postoperative pathological characteristics of PCa. Although the association of different serum lipid components with pathological status and stage varied, we did observe that dyslipidemia contributed to PCa progression. Several vital prognostic factors, such as pGS, pT3–4 disease, and LNI, were closely related to elevated LDL, TG, and TC levels, respectively. Abnormal HDL levels seemed not to be associated with PCa prognosis in our study, although a close relationship was reported between low HDL levels and PCa risk. However, a large-scale external validation of these results is warranted.

At present, the exact molecular mechanisms associated with the role of dyslipidemia in PCa carcinogenesis remain unclear, although several explanations have been proposed. Abnormal regulation of
Table 1: Demographic and clinical characteristics stratified by serum lipid profiles in PCa patients receiving RP

| Variables | TC (n (%) | P | TG (n (%)) | P | LDL (n (%)) | P | HDL (n (%)) | P |
|-----------|----------|---|------------|---|-------------|---|-------------|---|
| Age (year) | | | | | | | | |
| <68 | 102 (47.2) | 50 (47.2) | 0.993 | 106 (44.2) | 46 (56.1) | 0.062 | 96 (46.6) | 56 (48.3) | 0.773 |
| ≥68 | 114 (52.8) | 56 (52.8) | | 134 (55.8) | 36 (43.9) | | 110 (53.4) | 60 (51.7) | 0.773 |
| Preoperative PSA | | | | | | | | |
| <10 | 76 (35.2) | 18 (17.0) | 0.003 | 74 (30.8) | 20 (24.4) | 0.374 | 68 (33.0) | 26 (22.4) | 0.133 |
| ≥10 | 74 (34.3) | 48 (45.3) | | 86 (35.9) | 36 (43.9) | | 74 (35.9) | 48 (41.4) | 0.133 |
| Smoking status | | | | | | | | |
| Low (≤5) | 78 (36.1) | 22 (20.8) | 0.003 | 74 (30.8) | 26 (31.7) | 0.842 | 76 (36.9) | 24 (20.7) | 0.010 |
| Middle (≥6) | 90 (41.7) | 44 (41.5) | | 102 (42.5) | 32 (39.0) | | 78 (37.9) | 56 (48.3) | 0.654 |
| High (≥8) | 48 (22.2) | 40 (37.7) | | 64 (26.7) | 24 (29.3) | | 52 (25.2) | 36 (31.0) | 0.004 |
| Clinical stage | | | | | | | | |
| cT1c2a | 112 (51.9) | 60 (56.6) | 0.116 | 128 (53.3) | 44 (53.7) | 0.085 | 102 (49.5) | 70 (60.3) | 0.006 |
| cT2b | 57 (26.4) | 33 (31.1) | | 73 (30.4) | 17 (20.7) | | 55 (26.7) | 35 (30.2) | 0.553 |
| cT2c | 47 (21.7) | 13 (12.3) | | 39 (16.3) | 21 (25.6) | | 49 (23.8) | 11 (9.5) | 0.553 |
| Hypertension | | | | | | | | |
| Yes | 36 (16.7) | 16 (15.1) | 0.719 | 40 (16.7) | 12 (14.6) | 0.666 | 34 (16.5) | 18 (15.5) | 0.817 |
| No | 180 (83.3) | 90 (84.9) | | 200 (83.3) | 70 (85.4) | | 172 (83.5) | 98 (84.5) | 0.483 |
| Diabetes | | | | | | | | |
| Yes | 26 (12.0) | 16 (15.1) | 0.444 | 24 (10.0) | 18 (22.0) | 0.006 | 26 (12.6) | 16 (13.8) | 0.764 |
| No | 190 (88.0) | 90 (84.9) | | 216 (90.0) | 64 (78.0) | | 180 (87.4) | 100 (86.2) | 0.544 |
| Statin usage | | | | | | | | |
| Yes | 12 (5.6) | 2 (1.9) | 0.129 | 10 (4.2) | 4 (4.9) | 0.785 | 10 (4.9) | 4 (3.4) | 0.553 |
| No | 204 (94.4) | 104 (98.1) | | 230 (95.8) | 78 (95.1) | | 196 (95.1) | 112 (96.6) | 0.643 |
| prostatectomy GS | | | | | | | | |
| Non-high risk (≤7) | 166 (76.9) | 70 (66.0) | 0.039 | 178 (74.2) | 58 (70.7) | 0.544 | 162 (78.7) | 74 (63.8) | 0.004 |
| High risk (≥8) | 50 (23.1) | 36 (34.0) | | 62 (25.8) | 24 (29.3) | | 44 (21.3) | 42 (36.2) | 0.764 |
| Pathological stage | | | | | | | | |
| pT2 | 158 (73.1) | 44 (41.5) | <0.001 | 164 (68.3) | 38 (46.3) | <0.001 | 148 (71.8) | 54 (46.6) | <0.001 |
| pT3a | 58 (26.9) | 62 (58.5) | | 76 (31.7) | 44 (53.7) | | 58 (28.2) | 62 (53.4) | 0.106 |
| LNI | 10 (4.6) | 20 (18.9) | <0.001 | 17 (7.1) | 13 (15.8) | 0.018 | 12 (5.8) | 18 (15.5) | 0.004 |

PCa: prostate cancer; RP: radical prostatectomy; PSA: prostate-specific antigen; bGS: biopsy Gleason score; BMI: body mass index; GS: Gleason score; LNI: lymph node involvement; TC: total cholesterol; TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

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Cholesterol metabolism may result in elevated cholesterol levels in PCa cells. Meanwhile, aberrant lipid metabolism can influence signal transduction in PCa, for example, through promoting cancer cell growth and inhibiting apoptosis.\(^a\) Androgen receptors located in PCa cells can recruit several transcription factors involved in lipid metabolism,\(^b\) of which sterol regulatory element binding protein 2 is notably upregulated in PCa cell xenograft tumors.\(^c\) In addition, several important signaling pathways involved in carcinogenesis, such as Akt and sonic hedgehog pathways, are the cholesterol sensitive.\(^d\) Hence, abnormal serum lipid levels may promote these pro-carcinogenic process in PCa.

Given the important role of dyslipidemia in PCa development and progression, we hypothesized that lipid profiles might be potential biomarkers to predict advanced disease. The present study verified our speculation. Besides preoperative PSA, bGS, and clinical stage, we introduced preoperative TC, TG, and LDL levels into the predictive model, and higher efficiency was observed. Therefore, our results suggest that information about preoperative serum lipid profiles may improve the accuracy of pathological prediction and enable the choice of more appropriate medical intervention.

Furthermore, our results provided another clinical implication. It is well known that dyslipidemia functions as a critical risk factor in the development of coronary artery disease (CAD), which remains a leading cause of health impairment worldwide.\(^e\) Intriguingly, some recent studies have found a significant association of CAD with increased PCa diagnosis, and speculated that CAD share etiology with...
Table 2: Logistic regression analysis of the association between serum lipid profiles and pathological characteristics in PCa patients

| Variables | Prostatectomy GS | Pathological stage | Lymph node involvement |
|-----------|------------------|--------------------|------------------------|
|           | Preoperative PSA |                    |                        |
| (<10)     | 84 10 Reference  | <0.001             | Reference              |
|           | (1.641-7.537)   | 0.026              | (95% CI)               |
|           | 90 4 Reference   | <0.001             | Reference              |
|           | (1.052-6.340)   | 0.007              | (95% CI)               |
| (<20)     | 104 30 Reference | <0.001             | Reference              |
|           | (1.448-7.599)   | 0.018              | (95% CI)               |
|           | 86 14 Reference  | <0.001             | Reference              |
|           | (1.205-7.155)   | 0.004              | (95% CI)               |
| (≥20)     | 166 50 Reference | 0.004              | Reference              |
|           | (0.990-3.037)   | 0.001              | (95% CI)               |
|           | 116 56 Reference | 0.001              | Reference              |
|           | (0.776-2.240)   | 0.030              | (95% CI)               |
|           | 55 35 Reference  | 0.001              | Reference              |
|           | (1.065-3.525)   | 0.079              | (95% CI)               |
|           | 31 29 Reference  | 0.001              | Reference              |
|           | (0.915-5.022)   | 0.112              | (95% CI)               |
| Normal    | 178 62 Reference | 0.004              | Reference              |
| (<200 mg dl⁻¹) | 0.001            | Reference          | (95% CI)               |
|           | 164 76 Reference | 0.001              | Reference              |
|           | (1.262-3.460)   | 0.001              | (95% CI)               |
|           | 44 42 Reference  | 0.001              | Reference              |
|           | (1.134-6.287)   | 0.001              | (95% CI)               |
| Abnormal  | 74 42 Reference  | 0.004              | Reference              |
| (≥100 mg dl⁻¹) | 0.006            | Reference          | (95% CI)               |
|           | 118 42 Reference | 0.001              | Reference              |
|           | (1.823-7.409)   | 0.001              | (95% CI)               |
|           | 54 62 Reference  | 0.001              | Reference              |
|           | (0.862-1.960)   | 0.001              | (95% CI)               |
| 0         | 124 36 Reference | 0.006              | Reference              |
|           | (0.479-1.941)   | 0.019              | (95% CI)               |
| 1         | 50 14 Reference  | 0.019              | Reference              |
|           | (0.337-1.691)   | 0.019              | (95% CI)               |
| 2         | 34 20 Reference  | 0.019              | Reference              |
|           | (1.042-3.491)   | 0.019              | (95% CI)               |
| 3         | 28 16 Reference  | 0.019              | Reference              |
|           | (0.960-4.034)   | 0.019              | (95% CI)               |

*Adjusted for age, BMI, hypertension, diabetes, smoking status, statin usage, preoperative PSA, bGS, clinical stage, TC, TG and LDL; §Adjusted for age, BMI, hypertension, diabetes, smoking status, statin usage, preoperative PSA, bGS, clinical stage. PCa: prostate cancer; PSA: prostate-specific antigen; bGS: biopsy Gleason score; GS: Gleason score; TC: total cholesterol; TG: triglyceride; LDL: low-density lipoprotein; OR: odds ratio; CI: confidence interval; BMI: body mass index
Papas. Now that dyslipidemia plays an important role in both CAD and PCa development, we believe that better control of dyslipidemia may obtain more benefits than we have expected.

Our study had certain limitations and constraints. First, it was conducted in a single medical center with a small sample, and the results were subject to inherent biases of a retrospective nature. Second, unlike the Partin table, we stratified preoperative PSA levels, bGS, and clinical stage in a simple manner. It is uncertain whether more precise stratification might have influenced the predictive efficacy. Finally, although dyslipidemia was suggested as a prognostic factor, different serum lipid components had various relationships with pathological status. A consistent association was not observed between a certain lipid component and pathological characteristics. Clearly, additional prospective studies are necessary to validate our observations in a large population.

CONCLUSIONS
The present study found a significant association between elevated serum TC, TG, and LDL levels and pathological characteristics in PCa patients. Together with preoperative PSA levels, bGS, and clinical stage, dyslipidemia is a novel and useful predictive biomarker for advanced PCa patients. Dyslipidemia is common and preventable; therefore, large prospective, population-based studies are warranted.

AUTHOR CONTRIBUTIONS
GMZ and XJQ designed the study, collected, analyzed and interpreted the clinical data, and wrote the manuscript. HLZ, WJX, YZ and CYG contributed in part the patients' clinical data. BD and GHS analyzed part the clinical data, and wrote the manuscript. GMZ and XJQ designed the study, collected, analyzed and interpreted

COMPETING INTERESTS
The authors declare that they have no competing interest.

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