Research Article

Tissue Biomarkers for Prognosis of Prostate Cancer: A Systematic Review and Meta-analysis

Liuyang Zhao1, Na Yu1, Tianfang Guo1, Yixuan Hou1,2, Zongyue Zeng1, Xiaorong Yang1, Ping Hu1, Xi Tang1, Jian Wang1, and Manran Liu1

Abstract

Background: Although numerous investigators have made efforts to assess prognostic biomarkers of prostate cancer, no biomarker has been recommended for clinical practice.

Methods: According to REMARK (Reporting recommendations for tumor marker prognostic studies) and MISFISHIE (Minimum information specification for in situ hybridization and immunohistochemistry experiments) guidelines, the published articles of immunohistochemistry-based prognostic biomarkers on prostate cancer were extracted and pooled.

Results: Ninety-three prognostic biomarkers from 92 high-quality cohort studies were included in this meta-analysis. Our analysis reveals some promising independent prognostic biomarkers, including Ki-67 [all-cause mortality (ACM) HR, 1.85; 95% confidence interval (CI), 1.06–3.25; PSM HR, 1.82; 95% CI, 1.42–2.34; DFS HR, 1.51; 95% CI, 1.31–1.75]; Bcl-2 (ACM HR, 2.14; 95% CI, 1.27–3.58; PSM HR, 1.61; 95% CI, 1.01–2.57; DFS HR, 3.86; 95% CI, 2.14–6.96); CD147 (ACM HR, 2.63; 95% CI, 1.19–5.81; DFS HR, 5.84; 95% CI, 3.41–9.99); COX-2 (PSM HR, 7.6; 95% CI, 0.7–80.1; DFS HR, 7.9; 95% CI, 2.62–23.83); ALDH1A1 (ACM HR, 1.73; 95% CI, 1.163–2.527; PSM HR, 1.05; 95% CI, 1.028–1.107), and FVIII (ACM HR, 1.76; 95% CI, 1.19–2.60; PSM HR, 1.01; 95% CI, 1.01–1.02).

Conclusions: Our analysis identified a subset of biomarkers (Ki-67, Bcl-2, CD147, COX-2, ALDH1A1, and FVIII) that may have prognostic value for predicting the outcome of patients with prostate cancer.

Impact: These reliable prognostic biomarkers will improve the clinical management of patients with prostate cancer. Cancer Epidemiol Biomarkers Prev; 23(6); 1–8. ©2014 AACR.

Introduction

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of death among patients suffering from cancer in the world (1). Surgery and adjuvant therapies are some effective treatments. However, a substantial number of patients will have a relapse after treatment (2). Therefore, there is a big challenge in predicting the outcome of patient and in their efficient clinical management. Certain biomarkers as well as clinical index, such as prostate-specific antigen and Gleason score, are widely used in clinics. Yet, more strict biomarkers are urgently required to predict the clinical course and its outcomes in a better way (3). We believe that a systemic review of the biomarkers associated with the outcome of prostate cancer is the first step to select the useful predictive biomarkers in patients having prostate cancer.

Immunohistochemistry (IHC) is a widely applied and well-documented method to characterize protein expression (4). In solid tumor pathology, most of the established diagnostic and prognostic markers are commonly assessed by IHC (5). Thus, some of the IHC-evaluated biomarkers are recognized to have a potent value in the clinical diagnosis and prediction of the prognostic outcome of patients having prostate cancer.

In addition, the tissue microarray (TMA), a high-throughput analysis using tissue blocks from several hundred individuals on a single slide, has extended the utility of the IHC-based screening of the candidate biomarkers and reduced pseudo-positive or negative candidate protein by standardizing the staining conditions and reagents (6, 7).

Recently, several reviews have been published on the prognostic utility of IHC markers in prostate cancer (8–10). However, none of these reviews evaluated the available data according to the REMARK (Reporting recommendations for tumor marker prognostic studies; ref. 11) and MISFISHIE (Minimum information specification for in situ hybridization and immunohistochemistry experiments; ref. 12) study design or methodologic
assessments and quality metrics. In addition, owing to the heterogeneity in experimental procedures, tremendous variations still exist among different reports including the high-quality studies. For example, antigen retrieval, antibody dilution, antibody validation through the positive and negative controls, interobserver variability in evaluating the staining patterns, threshold selection, and assignment of specimens to different categories are very likely to affect the statistical significance of the proposed association.

To determine which protein markers are effective candidates in predicting the outcome of prostate cancer, we did a systematic review and meta-analysis by using a pool of published articles during inception on October 10, 2012. To further investigate the considerable biomarkers that have been evaluated over and beyond clinical features, only the HRs from multivariate analysis were pooled. We identified the subset of interesting candidate IHC-based biomarkers, including Ki-67, p53, Bcl-2, CD147, COX-2, ALDH1A1, coagulation factor VIII (FVIII), p16, and MMP9 in prostate cancer. Our data highlight the potential predictive value of Ki-67, Bcl-2, CD147, COX-2, ALDH1A1, and FVIII as an independent prognostic biomarker of prostate cancer.

Materials and Methods

Data sources and research strategy

To identify all the original research articles that evaluated expression levels of candidate proteins measured by IHC in the resected prostate cancer, we searched all available data from PubMed database and Embase database up to October 10, 2012 (last updated), limited in title and abstract, using the following search queries: (prostate or prostatic) and (cancer or carcinoma or tumor or neoplasm or cancers or tumors or neoplasms) and (immunohistochemical) and (prognos* or surviv* or mortality) and (marker or markers or mark or marks or biomarker or biomarkers).

Selection criteria

First, two investigators independently identified the articles, which are likely to report the candidate proteins of prostate cancer using immunohistochemical staining, by screening the title and abstract of each article. Subsequently, the eligibility of articles was carefully decided by the two investigators according to the criteria listed in Table 1, which were derived from the published guidelines (REMARK and MISFISHIE) for reporting IHC-based tumor marker studies. Their disagreements were resolved by discussing with a third senior investigator.

Data extraction

Each eligible article was reviewed and data on the characteristics of the study were independently extracted by the two investigators, using a predefined form. The data recorded about each study for metrics in this form included the first author’s surname and country of origin, year of publication, sample size, tissue preservation and section (whole slides vs. TMA), numbers of positive and negative patients, protein assay method, the set of candidate proteins evaluated, IHC cutoff value, mention of blinding of those who assessed immunohistochemical staining to outcome, clinical covariates incorporated in multivariable statistical analysis, and outcomes assessed. Special attention was given to survival analysis thresholds, the computed multivariable HR, and its 95% confidence interval (95% CI) with corresponding P value, and immunohistochemical methods within each study including primary antibody and dilution used, secondary signal amplification, and immunohistochemical stain scoring scheme. The disagreements were resolved by discussing with the third senior investigator.

Functional analysis and statistical analysis

All eligible candidate proteins were first sorted according to their associated value with the patients outcome and then according to their major biologic functions determined by comprehensive review of the current scientific articles. The candidate proteins were then classified into 10 acquired hallmarks of cancer as defined by Hanahan and Weinberg (13): activating invasion and metastasis, avoiding immune destruction, deregulating cellular energetics, enabling replicative immortality, evading growth suppressors, genome instability and mutation, inducing angiogenesis, resisting cell death, sustaining proliferative signaling, and tumor promotion inflammation.

If a direct report of HR and 95% CI was available, pooled estimates of the HRs and 95% CI were obtained using inverse variance fixed effects model and Der Simonian–Laird random effects model. Otherwise, the estimated

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**Table 1. Inclusion criteria of prognostic IHC-based studies**

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<tr>
<th>Item</th>
<th>Criteria description</th>
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<tbody>
<tr>
<td>1</td>
<td>Assay of resected primary prostatic tumor materials, not cell lines and metastatic carcinoma</td>
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<tr>
<td>2</td>
<td>Prospective or retrospective cohort design with a well-defined study population with justification for excluded cases</td>
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<td>3</td>
<td>Clear description of IHC cutoff point determination</td>
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<td>4</td>
<td>Statistical analysis using multivariate proportional hazards modeling that adjusted for clinical prognostic factors</td>
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<td>5</td>
<td>ACM or cancer-specific mortality or DFS was used as clinical endpoints</td>
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<td>6</td>
<td>Reporting of the resulting HR and corresponding 95% CI (or enough data to calculate them)</td>
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value was derived indirectly from other presented data using the methods described by Tierney and colleagues (14). If an observed HR was more than 1 and the 95% CI did not overlap 1 (P < 0.05), it implied a worse outcome for the test group relative to the reference group. The heterogeneity between studies was quantified using the I² test, and it was considered as a severe heterogeneity with a value more than 50%. All analyses were performed using Review Manager 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; http://ims.cochrane.org/revman).

Results

Excluded studies

The research strategy of the IHC-based prognostic literature on the prostate cancer identified 545 articles for consideration in this systematic review and meta-analysis (Fig. 1). On reviewing the title and abstract of these

Figure 1. Flow diagram of the eligible literature search and selection protocol. Flowchart showing the results at each stage of the process used to identify the final set of relevant papers in the ESFT review. A paper was classified as ‘relevant’ if it provided a quantitative result or gave tabulated IPD about a human tumor marker in ESFT associated with the prostate cancer prognosis.
articles, 272 articles, in which the immunohistochemical staining was used on the prostate cancer samples, were identified, and full text of these was retrieved. Of these 272 studies, seven were first excluded from further analysis (one study used the mouse prostate tissues; ref. 15; and the other six studies assessed combined markers). After careful review of study methods, 34 articles were excluded for their non-IHC–based methods (three studies) or the samples used being less than 50 cases (31 studies). Thus, 231 studies, which described immunohistochemical results, were triaged according to the study design. Although 152 studies met the criteria for cohort studies with univariate log-rank or multivariable analysis, 79 articles were excluded for inappropriate study design (eight case series studies, 65 cross-sectional analysis, and six case–control studies). Among the remaining 152 cohort studies, an additional 60 studies were excluded according to statistical criteria. Forty studies limited their analysis to the univariate log-rank or proportional hazards computations (Supplementary Table S1). Twenty studies conducted multivariable analyses on methodologically robust data, but failed to report an HR (95% CI; Supplementary Table S2).

**Included studies**

Ninety-two high-quality cohort studies met all the eligibility criteria by presenting multivariable survival estimates for differential levels of candidate biomarker expression as measured by IHC on prostate cancer samples derived from biopsies and/or prostatectomy tissues, and were included in this systematic review and meta-analysis (Supplementary Table S3). These studies were used to extract data for multivariable-adjusted survival estimates analysis, to evaluate the relationship between candidate protein expression levels and survival time, and their associations with the outcomes of patients with prostate cancer. We sent 26 E-mails to the authors to request for more details about materials, methods, and the data of HR (95% CI) following the REMARK standards. Six authors claimed that all data were present in the paper and there was no additional information for us. The other 20 authors did not reply to our E-mails.

Among the 92 included studies, 60 reported that IHC was evaluated on individual whole-slide tissue sections, 32 studies performed TMAs of 2.0, 1.0, or 0.6 mm diameter cores from representative tissue samples for IHC. Of these, 75 studies (81.5%) obtained samples from prostatectomy tissue, five studies (5.4%) used both biopsies and prostatectomy tissue, and 12 studies (13.04%) used biopsies tissue only. Immunohistochemical staining was blindly assessed to the outcome status in 38 studies, but blinding status was unknown for the remaining 54 studies. The sample sizes of qualified studies ranged from 53 to 3,261 cases of patients with prostate cancer. In summary, 29 studies examined 53 to 100 cases, 45 studies included 101 to 300 cases, and 16 studies examined more than 300 cases. In addition, two studies (16, 17) included two experimental groups, the test set and validation set, respectively.

**The candidate proteins included**

Collectively, a total of 93 candidate proteins were presented in these 92 studies. Sixty-five eligible reports restricted their analysis to a single candidate protein as the prognosis biomarker of prostate cancer. Fortunately, 27 additional studies considered between two and six candidate proteins. Five candidate biomarkers (Ki-67; refs. 18–29; p53; refs. 19, 25, 30–35; Bcl-2; refs. 26, 31, 36, 37; p16; refs. 38, 39, and MMP9; ref. 40) were evaluated across all three outcomes [all-cause mortality (ACM), prostate cancer-specific mortality (PSM), and disease-free survival (DFS)]. Eleven of the candidate proteins (ALDH1A1; ref. 41; CD147; ref. 42; Chromogranin A; refs. 28, 43, 44; COX-2; refs. 20, 45, 46; MUC1; refs. 40, 48, 49; coagulation factor VIII, FVIII; refs. 36, 50; p27; refs. 24, 51; PTEN; refs. 25, 52; TGF-β; refs. 20, 53) were assessed for two outcomes. Stratified by the patients’ outcome, data were available on 17 proteins for ACM (Supplementary Table S4), 25 proteins for PSM (Supplementary Table S5), and 71 proteins for DFS (Supplementary table S6). Of 79 of 93 unique biomarker-outcome combinations, a multivariable HR and associated 95% CI were available only from a single study. For the other 14 biomarker-outcome combinations, data were available from more than two studies and were comprehensively combined using both fixed effects general inverse variance and Der Simonian–Laird random effects model to produce a combined HR with 95% CI to estimate the prognosis outcome (Supplementary Fig. S1).

**All-cause mortality**

The 17 biomarkers evaluated for ACM were sorted into eight functional groups according to the 10 modified Hanahan and Weinberg hallmark functional capabilities of cancer (13) and other four functional groups associated with prostate cancer (e.g., transcription factor, cytokine, anioncogene, and prostate-specific biomarker; Supplementary Table S4). No eligible candidates were available for the hallmarks of "avoiding immune destruction," "deregulating cellular energetics," and other four functional groups associated with prostate cancer. Of the eight functional groups, no available candidates in the hallmark "of evading growth suppressors group" showed statistically significant association with ACM. Fortunately, 11 prognosis proteins (ALDH1A1; ref. 41; ER; ref. 18; Bcl-2; ref. 36; Ki-67; refs. 18, 19; ref. MDM2; ref. 19; FVIII; ref. ANXA2; ref. 54; cortactin; ref. 55; UTR; ref. 56; CD147; ref. 42; and BRCA1; ref. 57) had a statistically significant association with ACM at P < 0.05. Among these potential prognosis biomarkers, ANXA2 (P < 0.001; ref. 54), cortactin (P = 0.001; ref. 55), and Urotensin II receptor (UTR; P = 0.003; ref. 56) are available in the "activating invasion and metastasis" group; MDM2 (P = 0.003; ref. 19) and Ki-67 (P = 0.03; refs. 18, 19) proteins are the members in the "enabling replicative immortality" group; and ALDH1A1
(P = 0.0066; ref. 41) and ER (P = 0.03; ref. 18) belong to the "sustaining proliferative signaling" group.

Prostate cancer-specific mortality

Twelve of the 25 qualified candidates with eligible data for PSM demonstrated a statistically significant association with this outcome (Supplementary Table S5). These proteins were represented in 10 of the 14 functional groups. Intriguingly, candidate biomarkers from three functional groups (sustaining proliferative signaling, resisting cell death, and inducing angiogenesis) possessed statistical significance associated with PSM. Three PSM biomarkers (ALDH1A1, FVIII, and MDM2) were also assessed for ACM. ALDH1A1 (41) and FVIII (36, 50) showed concordant associations between the two outcomes, ACM and PSM. High level of these two biomarkers is associated with increased risk of both ACM and PSM. Discordant results were observed for MDM2 with the outcome of ACM and PSM (ACM, P = 0.003; PSM, P = 0.08; ref. 19).

Disease-free survival

Seventy-one available biomarkers representing 13 functional groups were analyzed for DFS, and 49 candidates (69.01%) were found to be statistically significant in association with DFS (Supplementary Table S6). Thirteen of these potential DFS biomarkers (Ki-67, p53, Bcl-2, p16, MMP9, COX-2, p27/kip1, TGF-β, CD147, Mcm2, MUC1, Chromogranin A, and PTEN) were also evaluated for either or both of the survival outcomes (ACM and PSM). Furthermore, elevated expression of each of the four biomarkers (Bcl-2; refs. 26, 31, 36, 37; CD147; ref. 42; COX-2; refs. 20, 45, 46; and Ki-67; refs. 18–23) yielded concordant results for outcomes of DFS, ACM, and/or PSM. However, certain biomarkers (such as p53, p16, p27/kip1, TGF-β, Mcm2, MUC1, and PTEN) yielded discordant results in the assessed outcomes (DFS, ACM, and PSM) by a multivariate analysis. For example, Mcm2 (P = 0.01), PTEN (P = 0.035), p16 (P = 0.03), MUC1 (P < 0.0001), and TGF-β (P = 0.03) were statistically significant for DFS, but not for ACM and/or PSM.

In summary, Ki-67, p53, Bcl-2, p16, and MMP9 were evaluated for patients’ outcomes of ACM, PSM, and DFS, and Ki-67, Bcl-2, and MMP9 were found to be potentially useful candidates in the assessment for all three outcomes.

Discussion

This systematic review and meta-analysis were performed to identify the prognostic biomarkers for predicting outcomes of patients having prostate cancer. All the independent prognostic biomarkers can be routinely assessed by IHC in clinical prostate cancer specimens, such as biopsies and prostatectomy samples. Using stringent inclusion and exclusion criteria that examined patient selection, as well as laboratory and statistical methods, we identified 93 proteins associated with prostate cancer outcome from 92 high-quality cohort studies, which reported multivariable survival analysis data on prostate cancer (11). These qualified biomarkers within each outcome (ACM, PSM, and DFS) were separately classified into 8, 10, and 13 functional groups that reflected the acquired capabilities of cancer as defined by Hanahan and Weinberg (13) and four additional functional groups associated with prostate cancer. In terms of functional capabilities, a set of hallmarks in "activating invasion and metastasis," "sustaining proliferative signaling," and "enabling replicative immortality" groups displayed statistically significant results with one or more outcomes.

More importantly, it was found that the proteins that facilitate tissue invasion and metastasis were most closely associated with prostate cancer prognosis. In total, 18 biomarkers (Supplementary Tables S4–S6) showed statistically significant associations with the outcomes of prostate cancer. Increased expressions of such biomarkers (ANXA2, integrin a3, and a3B1) were associated with worse DFS for patients with prostate cancer (58).

Eight of the regulators (ALDH1A1, ER, CD24, ErbB3, KLK14, KLK15, SOX7, and SOX9) representing one of the functional capabilities, the sustaining proliferative signaling, showed statistically significant associations with the worse outcomes. The elevated levels of ALDH1A1 showed the concordant statistical significance in both ACM (P = 0.0066) and PSM (P = 0.0062; ref. 41). KLK14 and KLK15, belonging to a subgroup of serine proteases, were implicated in carcinogenesis and might act as the novel prostate cancer biomarkers to predict the outcomes (59, 60). Our data indicate that these regulator proteins may be suitable candidates in predicting the outcome of ACM in prostate cancer.

Among the 12 biomarkers that are associated with enabling replicative immortality (Supplementary Tables S4–S6), Ki-67 and p53 seemed to be the most valuable biomarkers for ACM, PSM, and DFS. The integrated data derived from 12 high-quality cohort studies revealed that the biomarker Ki-67 had the concordant statistically significant results with worse outcomes of ACM (P = 0.03), PSM (P < 0.0001), and DFS (P = 0.0001). Although p53 had been robustly investigated among 32 studies for prognostic effect, only eight studies met all the inclusion criteria in this work. The integrated data that assessed for ACM (P = 0.82) and DFS (P = 0.14) failed to highlight the prognostic value of p53. However, the prognostic value of increased p53 was statistically associated with a worse outcome of PSM (P = 0.01). Other investigated proteins, such as Her-2, S100A2, S100A4, S100A8, and S100A9, met all criteria, yet none of them yielded statistically significant relations to DFS by a multivariate analysis.

The biomarkers (FVIII, COX-2, VEGF, and CD31), associated with inducing angiogenesis, had statistically significant associations with the patients outcome. The available data in this work revealed the consistent result that the elevated levels of FVIII were associated with both ACM (P = 0.005) and PSM (P = 0.0004). High level of COX-2, VEGF, and CD31 showed statistically significant relations with the worse outcome of PSM and/or DFS. Thus,
the increased expression level of angiogenesis-associated biomarkers indicated a poor prognosis of the prostate cancer.

To highlight our merit in this study, it is necessary to stress the appreciated methods being used; that is, (i) the eligible prostate cancer studies were extracted by using unbiased search strategy; (ii) the standardized systematic review was used; and (iii) the articles with sufficient data for summarization and conclusion were objectively included in this meta-analysis. For example, to avoid repeating the study data, we attempted to find duplicates from different publications. To increase reliability and comprehensiveness of this systematic review and meta-analysis, we retrieved the articles from two databases, PubMed and Embase.

However, there were still some shortages and imminent limitations in this work. First, we did not expand our retrieval range to unpublished data that would most likely increase the proportions of negative results. Although we ruled out the systematic constraints to reduce the risks of publication bias referring to the guidelines (REMARK and MISFISHIE) for studies with statistically significant results, some of the eligible articles might not yet meet all the inclusion criteria due to nonsufficient methodologic descriptions in these articles. Thus, it may reduce the consistency of the data about one biomarker taken from various articles. Second, for the purpose of forecasting the different parameters and the underlying sources of outcome measurement errors, we divided the standardized oncological endpoint overall survival into ACM and PSM. However, we could not integrate the data from these two mortality outcomes. It may mitigate our ability to estimate the statistical significance of the identical biomarker through this systematic review and meta-analysis. Third, the interstudy variance might enhance the heterogeneity across the studies. Because 15 biomarkers were assessed in more than one study, the methodologic differences across the studies in the performance of IHC, the categorization, and adjustment for the clinicopathological parameters could result in measurement error of biomarkers to the statistically significant associations with outcomes. Generally, three main factors may cause interstudy variance: independent evaluation of immunostaining by different pathologists, the method used to assess immunostains, and the interpathologist variance in interpreting immunostains. Finally, although a huge body of initial literature was retrieved, only a few of high-quality articles could be used in this study.

Other limitations of this study may have resulted from potential source of publication bias because of the expression assessment and cutoff value selection of candidate proteins across different studies. The protein expression levels evaluated by different investigators might result in incorrect classification. Especially, more than half of the studies (54 studies, 58.7%) did not report the blinding status by the investigators for the clinicopathological parameter details. The cutoff value for most of the biomarkers might be another source of heterogeneities among the different studies. The immunostaining intensity determination for the candidate proteins was subjective and varied among studies even for the identical biomarker. For example, the cutoff value in assessing p53 was set at more than 10% tumor cells to be considered as positive staining in two studies. However, in the other six studies, the cutoff value was set at >50%, ≥2%, ≥1%, respectively. Therefore, validation and adoption of identical cutoff value across the studies could improve the reliability and replication of the results. To independently replicate and verify the immunohistochemical experiments, it is necessary to encourage the investigators to provide the information following the MISFISHIE guidelines (12), which can facilitate researchers to report their results in sufficient detail, and is expected to benefit the wider research community.

In consideration of a prognostic biomarker to be of clinical usefulness, the results from biopsies should be better than that from prostatectomy tissues in assessing the patients’ outcome. Prostatectomy changes the clinical outcome of the disease, and the results obtained from prostatectomy might not fully predict the clinical course and its outcomes. However, among the included eligible studies, only 12 studies (13.04%) used biopsy tissue. The representation of prognostic markers obtained from a small amount of biopsies will be limited in predicting the clinical outcomes. Thus, more evaluation on applying these prognostic biomarkers should be addressed.

Taken together, this systematic review and meta-analysis using the IHC-based prognostic protein data supported that the regulators are associated with tissue invasion and metastasis, effectors of cell proliferation, and limitless replication, and the regulators of angiogenesis are related to prostate cancer development. To apply these biomarkers in clinical management, appropriate validations across executing vast majority of authoritative prospective cohort studies are necessary.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: L. Zhao, N. Yu, J. Wang, M. Liu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Yu, T. Guo, Y. Hou, X. Yang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Zhao, N. Yu, T. Guo, Y. Hou, Z. Zeng, X. Yang, M. Liu
Writing, review, and/or revision of the manuscript: L. Zhao, N. Yu, J. Wang, M. Liu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Zhao, N. Yu, P. Hu, X. Tang, M. Liu
Study supervision: L. Zhao, N. Yu, J. Wang, M. Liu

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