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Using microRNAs as Novel Predictors of Urologic Cancer Survival: An Integrated Analysis

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ABSTRACT

Background: MicroRNAs(miRNAs) are involved in the formation, maintenance, and metastasis of urologic cancer. Here, we aim to gather and evaluate all of the evidence regarding the potential role of miRNAs as novel predictors of urologic cancer survival.
Methods: A systematic review was performed to identify and score all of the published studies that evaluated the prognostic effects of miRNAs in kidney (KCa), bladder (BCa) or prostate cancer (PCa). Where appropriate, the summary effects of miRNAs on urologic cancer were meta-analysed. The reliability of those results was then further validated by an integrated analysis of the TCGA cohort and miRNA panel.
Results: Of 151 datasets, 80 miRNAs were enrolled in this systematic review. A meta-analysis of the prognostic qualities of each miRNA identified an objective association between miRNA and prognosis. miR-21 was identified as an unfavourable miRNA with the overall survival (HR:2.699, 1.76–4.14, $P < 0.001$) across various prognostic events. Our further meta-analyses, integrating a parallel TCGA analysis, confirmed these partial previous results and further revealed different summary effects, such as the moderate effect of miR-21 in BCa. The refined miRNA panel (KCa-6: miR-27b, −942, −497, −144, −141 and -27a) was more capable of predicting the overall survival than was any single miRNAs included in it (HR: 3.214, 1.971–5.240, $P < 0.01$).
Conclusions: A miRNA panel may be able to determine the prognosis of urologic tumour more effectively and compensate for the unreliability of individual miRNA in estimating prognosis. More large-scale studies are therefore required to evaluate the unbiased prognostic value of miRNAs in urologic cancer effectively.

1. Introduction

The evaluation of cancer prognosis is necessary for treatment selection, patient counselling, the design and analysis of clinical trials, and understanding the disease process and outcome [1]. Cancer prognosis is interrelated with diverse factors including the physical status of the patient, pathological stage or clinical stage of tumour, disease development, and clinical interventions [2–4]. It is yet far from satisfied that accessing the prognosis by the current prediction tools. For prostate cancer (PCa), there is no consensus about whether prostate specific

Abbreviations: RNA, ribonucleic acid; miRNA, microRNA; KCa, kidney cancer; BCa, bladder cancer; PCa, prostate cancer; TCGA, The Cancer Genome Atlas; OS, overall survival; PSA, prostate specific antigen; WHO, World Health Organization; NMIBC, non-muscle-invasive bladder cancer; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; DFS, disease free survival; PFS, progression free survival; RFS, relapse free survival; CSS, cancer/disease specific survival; BCR-FS, biochemical recurrence free survival; HR, Hazard Ratio; 95%CI, 95% Confidence interval; T, size or direct extent of the primary tumour; LNM, lymph nodes metastasis; DM, distant metastasis; G, histology grade; Gleason, gleason score; Stage, TNM stage; GEO, Gene Expression Omnibus; NOS, Newcastle-Ottawa quality assessment scale; FFPE, formalin fixed paraffin-embedded; qRT-PCR, quantitative real-time polymerase chain reaction; qPCR, quantitative polymerase chain reaction; ISH, in-situ hybridization; AT, advanced T-stage; HG, higher histologic grade; AS, advanced TNM stage; OR, odds ratios; SE, standard error; TCGA-BLCA, bladder cancer in TCGA chort; TCGA-KIRC, kidney clear cell carcinoma in TCGA chort; TCGA-KIRP, kidney papillary cell carcinoma in TCGA chort; TCGA-KICH, kidney chromophobe carcinoma in TCGA chort; TCGA-PRAD, prostate adenocarcinoma in TCGA chort; IQR, interquartile range; CHN, Chinese; non-CHN, Non-Chinese; AUC, the area under the curve; ROC curve, receiver operating characteristic curve; BRISQ, Biospecimen Reporting for Improved Study Quality; REMARK, Reporting Recommendations for Tumour Marker Prognostic Studies; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.

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Research in Context

Evidence Before this Study

In this study, the PubMed, Cochrane Library and Web of Science electronic databases were systematically searched for studies by using "microRNA with prostate carcinoma or bladder carcinoma or kidney carcinoma" as keywords to combine screening. The literature search was last updated on November 21, 2017.

After removing duplicate records, we screened titles and abstracts to identify relevant articles. Relevant studies must meet the following criteria before being included: [1] the published miRNA studies focused on kidney carcinoma or bladder carcinoma or prostate carcinoma; [2] the studies must have explored the association between the expression level of any single or combination of miRNAs and any of the following types of survival analysis: overall survival; disease-free survival; progression-free survival; relapse-free survival; cancer−/disease-specific survival and biochemical recurrence-free survival. The studies had to provide an explicit HR (Hazard Ratio), 95%CI (Confidence interval) and *P* value or a survival curve from which we could extract the HR, CI and P value; [3] eligible studies without any survival analyses had to contain the following clinicopathologic characteristics: T stage (the size or direct extent of the primary tumour), lymph node metastasis, distant metastasis, histology grade, prostate specific antigen, Gleason score and TNM stage. Clinicopathologic characteristics had to be grouped by miRNA expression level; [4] the full text was available. Correspondingly, the study was excluded based on the following criteria: [1] duplicate publications; [2] an animal or non-clinical study; [3] reviews, case reports, letters, editorials, or expert opinions; [4] studies not grouped according to miRNA expression level; [5] studies on the genetic alteration of miRNAs, including polymorphisms and methylation patterns; and [6] clinical and survival analysis data obtained from The Cancer Genome Atlas (TCGA), the Gene Expression Omnibus (GEO) or other tumour databases.

Newcastle-Ottawa quality assessment scale (NOS) was using to access the quality of the included studies. In order to further quantify its prognostic ability, we scored the miRNA by its prognostic event, including clinical and survival events. Publication bias in this meta-analysis was evaluated with either Egger's test or Begg's test.Added Value of this Study

Of 151 datasets, 80 miRNAs were enrolled in this systematic review. A meta-analysis of the prognostic qualities of each miRNA identified an objective association between miRNA and prognosis. miR-21, which was the most frequently studied miRNA and had high consistency among these studies, was identified as an unfavourable miRNA with the overall survival (HR:2.699, 1.76–4.14, $P < .001$) across various prognostic events. Our further meta-analyses, integrating a parallel TCGA analysis, confirmed these partial previous results and further revealed different summary effects, such as the moderate effect of miR-21 in bladder carcinoma. The refined miRNA panel (KCa-6: miR-27b, −942, −497, −144, −141 and -27a) was more capable of predicting the overall survival than was any single miRNAs included in it (AUC:0.755, HR: 3.214, 1.971–5.240, $P < .01$) and nearly the same as that of pathologic stage (AUC:0.763, HR: 4.502, 2.719–7.454, $P < .01$). Patients who were separated by integrating KCa-6 and staging had significantly different prognoses ($P < .0001$).Implications of all the Available Evidence

In this study, we have gathered almost all of the prognostic data regarding the association between miRNA and urologic cancers. A miRNA panel may be able to determine the prognosis of urologic tumour more effectively and compensate for the unreliability of individual miRNA in estimating prognosis. Researchers can draw attention to large-scale studies with a standardized methodology that assess both single and multiple miRNAs and, it is hoped, evaluate the unbiased prognostic value of miRNAs in urologic cancer effectively.

antigen (PSA) tracking can effectively evaluate the risk of death [5, 6]. For bladder cancer (BCa), the prognostic performance and reproducibility of the 1973 and 2004/2016 WHO grading classification systems in non-muscle-invasive BCa (NMIBC) is still debated [7, 8]. Therefore, it is necessary to improve the accuracy and timeliness of disease management by refining the current prognostic judging systems and strategies.

An unparalleled achievement in cancer genomics has been achieved due to the rapid evolution and development of gene sequencing. All kinds of cancer-associated molecular biomarkers, ranging from coding genes [9–11] to non-coding genes [12, 13], have been identified in various biologic and clinical aspects. microRNA(miRNA) is one kind of non-coding RNAs (19–25 nucleotides) which can silence RNA and post-transcriptionally regulate gene expression, playing an essential role in different cancers [14, 15]. Some miRNAs abnormally and dysfunctionally expressed in cancer, and they serve as tumour suppressors that target oncogenes or oncomiRNAs that target suppressor genes [16]. Benefitting from recent technical advances in the methods used to examine miRNA expression and function, miRNAs have been widely studied and applied in cancer diagnosis, classification, and prognostic indication [17–19]. Further, several miRNA-targeted therapeutics have already entered clinical trial phase and are being tested at different centres [20–22]. It is reasonable to believe that miRNAs will be fully transformed from bench to bedside in the near future.

Remarkably, it is now clear that miRNAs are vital regulators in urologic cancers [13, 23–26]. Approximately 18 meta-analyses concerning the roles of miRNAs in urologic cancers have been published over the past five years. All of these studies focused on a survival analysis of a single cancer without a reasonable subgroup, while Only 40% of them considered the prognosis of urologic cancer [27–30]. Here we carried out a comprehensive integrated analysis to systematically identify and investigate the potential roles of all miRNAs that were ever included in prognostic studies on human urologic cancer to better understand the relationship between miRNAs and urologic cancer prognosis.

2. Materials and Methods

2.1. Search Strategy

This report has been structured based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [31]. The PubMed, Cochrane Library and Web of Science electronic databases were systematically searched for studies in English that analysed the associations between miRNA and the prognoses of three main human urologic cancers: KCa, BCa and PCa. The literature search was last updated on November 21, 2017.

The following search algorithms were used:"((microRNA OR micro RNA OR micro ribonucleic acid OR miRNA) AND ((prostate carcinoma OR prostate carcinomas OR prostate cancer OR prostate cancers OR prostate tumour OR prostate tumours) OR (bladder carcinoma OR bladder carcinomas OR bladder cancer OR bladder cancers OR bladder tumour OR bladder tumours)) OR (kidney carcinoma OR renal carcinoma OR kidney carcinomas OR renal carcinomas OR kidney cancer OR renal cancer OR kidney cancers OR renal cancers OR kidney tumour OR renal tumour OR kidney tumours OR renal tumours)) AND (Humans [Mesh] AND English[lang]))".

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