Research Article

Period Family of Clock Genes as Novel Predictors of Survival in Human Cancer: A Systematic Review and Meta-Analysis

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Background. Period genes are important core clock genes, including PER1, PER2, and PER3. A number of studies have demonstrated that the abnormal expression of the PER gene family of clock genes is associated with the survival and prognosis of patients with cancer; however, the sample sizes included in the majority of these studies were small, and the reported results were inconsistent. This study was the first to collect the relevant publications to systematically evaluate the value of the expression of the PER gene family in the prediction of survival and prognosis of human tumors.

Methods. The PubMed, Cochrane Library, Embase, and Web of Science databases were searched systematically, and a meta-analysis was performed.

Results. A total of 12 eligible publications met the inclusion criteria for the meta-analysis, including 1,369 patients and 9 different types of cancer. The pooled hazard ratio for overall survival indicated that the overall survival of patients in the high PER1, PER2, and PER3 protein expression group was significantly higher than that in the low-expression group, respectively. The sensitivity analysis revealed that the result was stable and reliable. The association between PER1 and PER3 mRNA expression levels and cancer prognosis was not meta-analyzed as the number of experimental studies was <3. There was no significant association between the expression of PER2 mRNA and the overall survival of patients with cancer.

Conclusion. PER1, PER2, and PER3 protein expression levels can be used as novel potential biomarkers for predicting cancer prognosis.

1. Introduction

The circadian clock is an endogenous adaptive regulatory system formed by the long-term evolution of organisms to adapt to the living environment of the earth’s rotation [1]. The circadian clock is primarily composed and regulated by the circadian clock genes, which exist in almost all cells of the human body [2]. Current research has reported that the clock genes regulate ~43% of protein-coding genes in the genomes of mammals [3], thus regulating numerous complex life activities in the body. The period (PER)1/2/3 genes are core clock genes and form part of the PER gene family [4, 5]. Previous studies have suggested that the PER gene family plays a role in the regulation of cell physiological processes, such as the cell cycle [6], DNA damage response [6, 7], cell proliferation, and apoptosis [8]. Abnormal expression of the PER genes has been demonstrated to be associated with the occurrence and development of cancer [9–12].

Previous studies have revealed that PER1-3 expression levels are significantly changed in gastric cancer, colorectal cancer, head and neck squamous cell carcinoma, non-small cell lung cancer, pancreatic cancer, prostate cancer, chronic lymphocytic leukemia, melanoma, hepatocellular carcinoma, breast cancer, and so on [13–22]. The abnormal expression of the PER genes is associated with the survival time of patients with cancer [23]. However, the sample size of the majority of the published studies is small, and the reported results are discrete and inconsistent [13–15, 24, 25]. To the best of our knowledge, the present study is the first to collect the relevant literature currently published and to construct a meta-
analysis model that was aimed at systematically evaluating the value of the expression of the PER gene family in predicting the clinical prognosis of patients with cancer.

2. Materials and Methods

2.1. Search Strategy. This report has been structured on the basis of PRISMA [26]. The PubMed, Cochrane Library, Embase, and Web of Science databases were independently searched, and all literature published before April 2, 2019, was searched. The following keywords were used in the search process: ("PER1" or "PER2" or "PER3" or "period1" or "period2" or "period3") and ("cancer" or "carcinoma" or "tumor" or "neoplasm" or "tumour") and ("survival" or "prognosis" or "outcome" or "predict"). See Table S1 in the Supplementary Material for the literature search strategy. The reference lists of the retrieved articles were also screened manually to obtain any missing literature that met the requirements.

2.2. Inclusion and Exclusion Criteria. The study eligibility criteria were established by two authors (Yang and Deng). Any discrepancies were resolved by consensus or determined by a third party (Zheng). The present study focused on the association between the expression of mRNA and protein in the PER gene family and overall survival (OS; OS was defined as the time from diagnosis to mortality from any cause). All studies met the following inclusion criteria: (1) cohort or case-control studies, (2) evaluated the association between the expression of the PER gene family and cancer prognosis, (3) provided a diagnosis of cancer via pathological methods, (4) provided sufficient information for calculating the hazard ratio (HR) with 95% confidence interval (CI) for OS, (5) the patients were divided into a PER-positive group and PER-negative group or a high-expression group and low-expression group for the survival analysis, (6) the sample size of the patients was not <20, and (7) published in the English language, and the exclusion criteria are the following: (1) reviews, comments, letters, or case reports; (2) in vitro and animal experimental studies; (3) the same patient samples in different literature; (4) genetic variation of PER gene (polymorphism or methylation pattern); and (5) public database analysis. A flow diagram of the article selection process is presented in Figure 1.

2.3. Data Extraction and Quality Assessment. The literature was independently screened and extracted according to the aforementioned inclusion and exclusion criteria. The primary prognostic outcome index was OS, and the following data were extracted: the first author, year of publication, geographical area, cancer type, preoperative and postoperative treatment information, PER gene expression level, detection method, follow-up time, cut-off value, multivariate or univariate analysis model, age of patients, number of patients, HR value, and 95% CI. HRs and 95% CIs of OS were directly...
Table 1: Main characteristics of the studies included in the meta-analysis.

| Study (publish year) | Country     | Cancer type | Gene type | Sample size | Detection method | Follow-up (months) | Expression (+) (%) | Cut-off | Age          | Stage | NOS scores |
|----------------------|-------------|-------------|-----------|-------------|------------------|--------------------|--------------------|---------|--------------|-------|------------|
| Zhao (2014) [13]     | China       | GC          | PER1      | 246         | IHC              | 25 (1-161)         | (103/143) 41.87%   | SP > 4  | 57.1 (23–79) | I-IV  | 8          |
| Zhao (2014) [13]     | China       | GC          | PER2      | 246         | IHC              | 25 (1-161)         | (86/160) 34.96%    | SP > 4  | 57.1 (23–79) | I-IV  | 8          |
| Xiong (2017) [29]    | China       | OSCC        | PER2      | 40          | IHC              | >60                | (16/24) 40%        | SP ≥ 2  | N/A          | I-IV  | 8          |
| Liu (2014) [16]      | China       | NSCLC       | PER1      | 130         | IHC              | >60                | (86/44) 66.15%     | SP > 4  | 61 (38–79)  | I-III | 8          |
| Liu (2014) [16]      | China       | NSCLC       | PER2      | 130         | IHC              | >60                | (77/53) 59.23%     | SP > 4  | 61 (38–79)  | I-III | 8          |
| Liu (2014) [16]      | China       | NSCLC       | PER3      | 130         | IHC              | >60                | (82/48) 63.08%     | SP > 4  | 61 (38–79)  | I-III | 8          |
| Wang (2015) [30]     | China       | CC          | PER1      | 203         | IHC              | 61 (9-89)          | (182/21) 89.66%    | SP ≥ 2  | 68 (22–95)  | I-IV  | 8          |
| Wang (2012) [31]     | China       | CC          | PER3      | 203         | IHC              | 61 (9-89)          | (167/36) 82.57%    | SP ≥ 2  | 65 (22–95)  | I-IV  | 8          |
| Tavano (2015) [17]   | Italy       | PDA         | PER2      | 34          | qRT-PCR          | 25.2               | N/A                | N/A     | 68.5 (51–74) | IA-III| 8          |
| Oshima 2011 [37]     | Japan       | CRC         | PER2      | 202         | qRT-PCR          | >60                | (101/101) 50%      | Median value | 66     | N/A         | 8     |
| Hwang-Verslues (2013) [32] | Taiwan   | BC          | PER2      | 101         | qRT-PCR          | 0-120              | (50/51) 49.50%     | N/A     | 53.8 ± 12.6 | N/A   | 6          |
| Pluquet (2013) [33]  | France      | GBM         | PER1      | 60          | qRT-PCR          | >80                | (31/29) 51.67%     | Average value | N/A     | N/A         | 7     |
| Hu (2014) [34]       | Taiwan      | GC          | PER1      | 29          | qRT-PCR          | 60                 | N/A                | N/A     | 69.76 (51–81) | I-IV  | 7          |
| Hu (2014) [34]       | Taiwan      | GC          | PER2      | 29          | qRT-PCR          | 60                 | N/A                | N/A     | 69.76 (51–81) | I-IV  | 7          |
| Hu (2014) [34]       | Taiwan      | GC          | PER3      | 29          | qRT-PCR          | 60                 | N/A                | N/A     | 69.76 (51–81) | I-IV  | 7          |
| Wang (2017) [36]     | China       | HNSCC       | PER1      | 60          | IHC              | 0-60               | (29/31) 48.33%     | SP ≥ 2  | 59 (41–84)  | I-IV  | 9          |
| Wang (2017) [36]     | China       | HNSCC       | PER2      | 60          | IHC              | 0-60               | (27/33) 45%        | SP ≥ 2  | 59 (41–84)  | I-IV  | 9          |
| Wang (2017) [36]     | China       | HNSCC       | PER3      | 60          | IHC              | 0-60               | (29/31) 48.33%     | SP ≥ 2  | 59 (41–84)  | I-IV  | 9          |
| Hasakova (2018) [35] | Slovak Republic | CRC     | PER2      | 38          | qRT-PCR          | 0-60               | (19/19) 50%        | Median value | 69 ± 12 | I-IV  | 6          |
| Hasakova (2018) [35] | Slovak Republic | CRC     | PER2      | 38          | qRT-PCR          | 0-60               | (11/12) 47.83%     | Median value | 69 ± 12 | I-IV  | 6          |

GC: gastric cancer; CRC: colorectal cancer; CC: colon cancer; PDA: pancreatic ductal adenocarcinoma; BC: breast cancer; GBM: glioblastoma; NSCLC: non-small cell lung cancer; OSCC: oral squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; IHC: immunohistochemistry; qRT-PCR: real-time quantitative reverse transcriptase-polymerase chain reaction; SP: staining intensity score and percentage of positive cells; NA: not available.
Iff results, and a random e
end indicated that there was heterogeneity among the research
p
ies were used to identify statistical heterogeneity. If
p
Overall (I² = 47.9%) (p = 0.124)

Study ID Cancer HR (95% CI) % weight
Zhao (2014) Gastric 0.80 (0.57, 1.13) 60.90
Liu (2014) Lung 0.39 (0.20, 0.76) 15.71
Wang (2015) Colon 0.90 (0.42, 1.93) 12.04
Wang (2017) Head and neck 0.41 (0.19, 0.89) 11.35
Overall (I² = 47.9%) 0.67 (0.52, 0.88) 100.00

(b)

Study ID Cancer HR (95% CI) % weight
Zhao (2014) Gastric 0.68 (0.49, 0.95) 61.58
Xiong (2017) Oral 0.42 (0.18, 0.98) 9.28
Liu (2014) Lung 0.34 (0.19, 0.62) 19.06
Wang (2017) Head and neck 0.45 (0.20, 1.01) 10.08
Overall (I² = 38.2%) 0.55 (0.42, 0.71) 100.00 (p = 0.183)

(d)

Study ID Cancer HR (95% CI) % weight
Wang (2012) Colon 0.54 (0.32, 0.92) 42.35
Wang (2017) Head and neck 0.41 (0.19, 0.90) 19.48
Liu (2014) Lung 0.42 (0.24, 0.73) 38.17
Overall (I² = 0%) 0.47 (0.33, 0.66) 100.00 (p = 0.767)

Figure 2: Forest plot of the HR for the relationship between PER family expression and OS. (a) Pooled HR for PER1 protein expression and OS. The detection method of PER1 protein level was IHC. (b) Pooled HR for PER2 protein expression and OS. The detection method of PER2 protein level was IHC. (c) Pooled HR for PER2 mRNA expression and OS. The detection method of PER2 mRNA expression was qRT-PCR. (d) Pooled HR for PER3 protein expression and OS. The detection method of PER3 protein level was IHC.

extracted if they were provided in the articles. Or HRs and 95% CIs of OS were estimated via Kaplan-Meier survival curves using the software Engauge Digitizer (version 4.1; http://markummitchell.github.io/engauge-digitizer) according to the method reported by Tierney et al. [27]. The quality of included studies was independently evaluated according to the Newcastle-Ottawa scale (NOS) criteria [28]. The quality scores ranged from 0 (lowest) to 9 (highest); studies with a score > 6 were considered high quality, and low-quality studies were excluded. Any disagreements were resolved by consensus or determined by a third party.

2.4. Statistical Analysis. In the present meta-analysis, the association between PER expression and cancer prognosis was assessed using pooled HRs and 95% CIs of OS. A HR > 1 indicated poor prognosis in patients with high PER expression. In contrast, a HR < 1 indicated improved prognosis in patients with high PER expression. The χ² test and I² test were used to identify statistical heterogeneity. If p > 0.1 and I² < 50%, the results indicated that there was homogeneity among the research results, and the fixed-effect model was used for the meta-analysis. If p < 0.1 and I² ≥ 50%, the results indicated that there was heterogeneity among the research results, and a random effects model was used. The effectiveness and reliability of the meta-analysis were assessed using a sensitivity analysis, which evaluated the impact of a single study on the results of the overall analysis. The publication bias was evaluated using a funnel diagram or Begg’s test. All statistical analyses were performed using Stata software (version 14.0; Stata Corporation). In addition to the heterogeneity test, p < 0.05 was considered to indicate a statistically significant result.

3. Results

3.1. Literature Search Results. A total of 394 articles were searched from the database according to the search strategy. Of these, 12 articles were considered eligible according to the inclusion and exclusion criteria after screening [13, 16, 17, 29–37], which included a total of 1,369 cases and 9 types of cancer. Two articles evaluated gastric cancer (GC) [13, 34], one article evaluated oral squamous cell carcinoma (OSCC) [29], one article evaluated non-small cell lung cancer (NSCLC) [16], two articles evaluated colon cancer (CC) [30, 31], one article evaluated pancreatic ductal adenocarcinoma (PDAC) [17], two articles evaluated colorectal cancer (CRC) [35, 37], one article evaluated breast cancer (BC) [32], one article evaluated glioblastoma (GBM) [33], and one article evaluated head and neck squamous cell carcinoma (HNSCC) [36]. The characteristics of the eligible studies are presented in Table 1. No new research was identified in the references lists. The study on the association between only one gene (PER1, PER2, or PER3) mRNA
expression level or protein expression level and OS in one literature was regarded as an independent study. However, certain publications reported the associations between two or three PER family genes and OS [13, 16, 34, 36]. Therefore, a total of 12 articles with 20 independent studies were included in the present meta-analysis. A total of 70% (14/20) of the studies demonstrated that the expression level of PERs was significantly associated with the survival and prognosis of patients with cancer. The remaining 30% (6/20) of the studies suggested that there was no significant association between PER expression and the survival and prognosis of patients with cancer. The PER1, PER2, and PER3 mRNA expression and protein expression level were determined in cancerous tissues. Cut-off values were used to divide the expression of PER1-3 into high and low levels (or positive and negative groups). Regarding detection method, the protein expression level of PER1-3 was evaluated by immunohistochemistry (IHC). The cut-off value for the PER1-3 protein expression was based on the staining intensity score and percentage of positive cells (SP). The mRNA expression level of PER1-3 was evaluated by real-time quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR). The cut-off value for the PER1-3 mRNA expression was based on the median or mean value. Expression (+) is defined as the positive expression rate of the PER family, indicating the proportion of high-expression specimens in the total specimens according to the cut-off point. Of the 12 publications included, 6 (with a total of 11 studies) assessed the PER protein expression level. Among them, there were 4 studies with a total of 476 cases that assessed PER1 protein expression in the prognosis of cancer. There were 4 studies with a total of 639 cases that assessed PER2 protein expression in the prognosis of cancer and 3 studies with a total of 393 cases that assessed PER3 protein expression in the prognosis of cancer. There were 6 publications (with a total of 9 studies) that assessed the PER mRNA expression level. Among them, there were 2 studies with a total of 89 cases that assessed PER1 mRNA expression in the prognosis of cancer. There were 6 studies with a total of 427 cases that assessed PER2 mRNA expression in the prognosis of cancer and only 1 study with a total of 29 cases that assessed PER3 mRNA expression in the prognosis of cancer. The year of publication of the 12 articles included was centralized between 2011 and 2018, and the sample sizes were between 23 and 246. There were 3 studies performed in Europe, 1 in Japan, 2 in Taiwan, and 6 in China. NOS scores were ≥6 in all of the included studies. See Table S2 in the Supplementary Material for the Newcastle-Ottawa scale to assess the quality of the included studies.

3.2. Prognostic Value of PER1 for OS. A total of 4 studies reported the association between the protein expression level of PER1 and cancer prognosis. The fixed-effect model was used due to the heterogeneity ($I^2 = 47.9\%; p = 0.124$). The results revealed that the expression of the PER1 protein was
significantly associated with OS (HR, 0.67; 95% CI, 0.52-0.88; \( p = 0.003 \)) (Figure 2(a)). Patients with a high expression of the PER1 protein had improved prognosis. Only 2 studies reported the association between \( \text{PER1} \) mRNA expression and OS. Among them, Pluquet et al. reported that patients with high expression of \( \text{PER1} \) mRNA in gliomas had significantly higher OS [33]. Hu et al. demonstrated that there was no significant association between the expression of \( \text{PER1} \) mRNA and OS in patients with gastric cancer [34].

3.3. Prognostic Value of \( \text{PER2} \) for OS. A total of 4 studies reported the association between the expression of the \( \text{PER2} \) protein and OS. Due to the heterogeneity (\( I^2, 38.2\%; \ p = 0.183 \)), the fixed-effect model was used. The results revealed that the expression of the \( \text{PER2} \) protein was significantly associated with OS (HR, 0.55; 95% CI, 0.42-0.71; \( p < 0.001 \)) (Figure 2(b)); the high expression of the \( \text{PER2} \) protein demonstrated an improved prognosis. A total of 6 studies reported the association between the expression of \( \text{PER2} \) mRNA and cancer prognosis. The random-effect analysis, which was used as the heterogeneity, was significant (\( I^2, 63.6\%; \ p = 0.017 \)). The results suggested that there was no significant association between the expression of \( \text{PER2} \) mRNA and OS in patients with cancer (HR, 0.92; 95% CI, 0.80-1.06; \( p = 0.247 \); Figure 2(c)).

3.4. Prognostic Value of \( \text{PER3} \) for OS. A total of 3 studies reported the association between the expression of the \( \text{PER3} \) protein and OS; no significant heterogeneity was observed (\( I^2, 0.0\%; \ p = 0.767 \)); therefore, the fixed-effect model was used for the meta-analysis. The results revealed that the expression of the \( \text{PER3} \) protein was significantly associated with OS (HR, 0.47; 95% CI, 0.33-0.66; \( p < 0.001 \); Figure 2(d)). The patients with high expression of the \( \text{PER3} \) protein had an improved prognosis. Only 1 study reported an association between the expression of \( \text{PER3} \) mRNA and OS. Hu et al. suggested that the expression of \( \text{PER3} \) mRNA was significantly associated with OS in patients with gastric cancer [34].

3.5. Sensitivity Analysis. In order to investigate the stability of the pooled HRs for the \( \text{PER1-3} \) proteins, a sensitivity analysis was performed. After removing one study at a time, there was no significant change in the total meta-analysis results of the remaining studies (Figures 3(a)–3(c)), which indicated that the results of the 3 studies are statistically stable and reliable.

In order to investigate the stability of the pooled HRs for \( \text{PER2} \) mRNA, a sensitivity analysis was performed. After removing the study by Hu et al. [34], the meta-analysis demonstrated that the results changed significantly from the original results that did not have statistical significance (HR, 0.92; 95% CI, 0.80-1.06; \( p = 0.247 \)) to the results with statistical significance (HR, 0.63; 95% CI, 0.47-0.85; \( p = 0.002 \)). The heterogeneity changed from the original large heterogeneity (\( I^2, 63.6\%; \ p = 0.017 \)) to homogeneity (\( I^2, 7.6\%; \ p = 0.363 \)). However, after removing the study by other authors at a time, there was no significant change in the total meta-analysis results. These results demonstrate that the great heterogeneity in the present study is caused by the difference between the research of Hu et al. and the quality of the other studies (Figure 3(d)).
3.6. Publication Bias. In order to investigate the publication bias of the present study, funnel plots and Begg’s test analyses were performed (Figures 4(a)–4(d) and 5(a)–5(d)). The results demonstrated that there was no significant publication bias in the present study.

4. Discussion

In the present systematic review and meta-analysis, all the published literature was collected in order to investigate the potential role of the expression level of circadian clock genes in the PER family in predicting the survival and prognosis of human cancer. From the included publications, it was revealed that in the currently published studies assessing the associations between PER gene family expression and cancer prognosis, the primary indicator was OS. Only Wang et al. reported an association between PER1 expression level and disease-free survival (DFS) [30]. Wang et al. [31] reported an association between the PER3 expression level and DFS, while Wang et al. [36] reported an association between the expression level of PER1-3 and progression-free and recurrence-free survival. Therefore, the present study selected the most representative indicator of OS to pursue the research. The research results demonstrated that the protein expression levels of PER1, PER2, and PER3 were significantly associated with the survival and prognosis of patients with cancer. However, there was no significant association between the expression of PER2 mRNA and the survival and prognosis of patients with cancer. PER1 mRNA and PER3 mRNA were not included in the present meta-analysis as there were fewer than three research projects which were included in the study.

The present study analyzed the association between the expression of the PER family of clock genes and cancer prognosis for the first time via systematic review and meta-analysis. The change of gene mRNA expression level is not necessarily consistent with the change of protein expression level [38, 39]; therefore, the present study analyzed the association between the PER gene family mRNA and protein expression level and cancer prognosis. The following results were obtained: patients with cancer that exhibited high-expression levels of the PER1-3 proteins had improved prognosis compared with those with low expression, which suggests that the PER1-3 proteins may be new biomarkers for predicting prognosis in patients with cancer. However, there are few researches exploring the association between PER1-3 mRNA expression levels and cancer prognosis; thus, additional original studies with consistent research standards.
and large sample sizes are needed for further evaluation. Although we have made a comprehensive analysis to the included literature, certain limitations still remain: First, the present study included those literature that can be searched in the PubMed, Cochrane Library, Embase, and Web of Science databases. It should be acknowledged that literature from other databases may have been missed. Secondly, the positive results are often easier to publish than the negative results when regarding the acquisition of data, and thus, the existence of publication bias may cause some errors in the pooled results [40]. Thirdly, the HRs from part of the survival data were extracted using the Kaplan-Meier method. Compared with the data extracted directly from the original articles, there may be some errors in this part of the data, which may also affect the pooled results.

5. Conclusion

The present study identified for the first time that expression of the PER family of clock genes is closely associated with the OS of patients with cancer via the systematic review and meta-analysis. Patients with high expression of PER family protein have better prognosis than those with low expression. The expression level of the PER gene family may be used as novel potential biomarkers to predict cancer prognosis. This provides a basis and the theoretical support required for studies regarding the role of the PER gene family in cancer in the future.

Data Availability

The data used to support the findings of this study are available from the included published articles and the corresponding author upon request.

Conflicts of Interest

All the authors have declared that they have no conflict of interest.

Authors’ Contributions

Kai Yang and Gang Zheng are equal contributors.

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Supplementary Materials

Table S1: literature search strategy. (Supplementary Materials). Table S2: Newcastle-Ottawa scale to assess the quality of the included studies. (Supplementary materials)

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