phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2021.0207
Osong Public Health Res Perspect 2021;12(5):324-332

Original Article

Yes-associated protein 1 as a prognostic biomarker and its correlation with telomerase in various cancers

Hye-Ran Kim[1], Choong-Won Seo[1], Keunje Yoo[2], Sang Jun Han[3], Jongwan Kim[1]

[1]Department of Biomedical Laboratory Science, Dong-Eui Institute of Technology, Busan, Korea
[2]Department of Environmental Engineering, Korea Maritime and Ocean University, Busan, Korea
[3]Department of Biotechnology, College of Fisheries Sciences, Pukyong National University, Busan, Korea

ABSTRACT

Objectives: The aims of this study were to investigate the expression of Yes-associated protein 1 (*YAP1*), its prognostic significance, and the correlation between *YAP1* and telomerase in various cancers.

Methods: The Gene Expression Profiling Interactive Analysis database was used to analyze RNA sequencing data and the survival rate of patients with various cancers in The Cancer Genome Atlas (TCGA) database. PrognoScan was used to analyze the prognostic value of *YAP1* expression in various cancers. Tumor Immune Estimation Resource was used to determine the correlation between *YAP1* expression and telomerase in various cancer types based on TCGA data.

Results: The analysis suggested that *YAP1* was differentially expressed between tissues of various cancers and non-tumor tissues. High *YAP1* expression was also related to a poor prognosis in adrenocortical carcinoma, bladder urothelial carcinoma, and pancreatic adenocarcinoma. Moreover, *YAP1* expression was correlated with the expression of telomerase reverse transcriptase and telomerase RNA component in various cancer types.

Conclusion: These results suggest that *YAP1* is a potential biomarker with prognostic significance and relevance for oncogene research in various cancer types. The correlation between the expression of *YAP1* and telomere-associated genes will help to understand their cancer-promoting mechanisms and interactions.

Keywords: Correlation study; Neoplasms; Prognosis; Telomerase; Telomerase RNA; Yes-associated protein 1

Received: July 26, 2021
Revised: August 31, 2021
Accepted: September 2, 2021

Corresponding author:
Jongwan Kim
Department of Biomedical Laboratory Science, Dong-Eui Institute of Technology, 54 Yangji-ro, Busanjin-gu, Busan, 47230, Korea
E-mail: dahyun@dit.ac.kr

Introduction

Yes-associated protein 1 (*YAP1*) expression and nuclear localization have been found to be increased in various cancers [1–4]. *YAP1* is one of the most important effectors of the Hippo signaling pathway and is involved in crosstalk with other cancer-promoting pathways. The

Hippo pathway plays a crucial role in organ size control and tissue regeneration [5]. The roles of Hippo pathway dysregulation in tumorigenesis and cancer progression have been widely reported [6]. As a potent oncogene activated in many cancers, *YAP1* has a negatively regulated downstream target in the Hippo signaling pathway and functions as a transcriptional coactivator involved in the regulation of cell growth, proliferation, and apoptosis [2,7–9]. *YAP1* plays a key role as a tumor suppressor in the Hippo signaling pathway and enhances gene transcription by binding to transcription factors [10]. Specifically, *YAP1* contributes to cancer development by promoting malignant phenotypes, the expansion of cancer stem cells, and drug resistance of cancer cells. *YAP1* is considered a potent oncogene closely linked to the progression of several cancer types [11,12], and *YAP1* overexpression in cancer cell lines can also promote tumor growth [13,14]. Therefore, *YAP1* promotes tumorigenesis, but the underlying mechanisms by which *YAP1* exerts this effect require further exploration.

Telomeres are cellular nucleoprotein complexes, and their main function is to maintain chromosomal integrity and genomic stability [15]. A telomere is a ribonucleoprotein complex composed of 2 main core subunits: telomerase reverse transcriptase (*TERT*), which constitutes the catalytic subunit, and a functional telomerase RNA component (*TR* or *TERC*) that provides a template for telomerase elongation [16]. A positive correlation between *TERT* mRNA levels and telomerase activity has been reported, suggesting that telomerase is primarily regulated by *TERT* expression [17]. Telomerase is active in adult germ-line tissues, immortal cells [18], and most malignant tumors [19]. *TERT* induces stemness of cancer cells to promote metastasis and recurrence [20]. In cancer cells, the upregulation of *TERT* transcriptional activity has been reported [21]. *TERT* overexpression has been detected in more than 80% to 90% of human cancers [15]. Thus, *TERT* overexpression may represent the mechanism by which cancer cells prevent telomere shortening and become immortal [22]. Zhang et al. [23] recently reported that *YAP1* regulates *TERT* expression, and that hyperactivation of *YAP1* promotes telomerase activity and increases telomeric length, causing an increase in *TERT* expression. They also showed that *TERT* expression was positively correlated with *YAP1* activation in liver cancer tissues. Several studies have reported that *TERT* overexpression contributes to cancer progression [24]. Therefore, *YAP1* promotes *TERT* expression, which may contribute to tumor progression [25]. However, several studies have highlighted the importance of *TERC* in cancer because of findings indicating that *TERC* expression may be highly upregulated in a variety of cancers [26–30]. Although *TERC* is associated with the development of several diseases, its underlying mechanisms in cancer are poorly understood. In addition, the correlation between the expression of *YAP1* and telomerase-associated genes in cancer has not been completely explored.

In the present study, we analyzed *YAP1* expression in normal and different types of tumor tissues based on The Cancer Genome Atlas (TCGA) data using online databases and tools. We also evaluated the prognostic value of *YAP1* expression its correlation with the expression of 2 major telomerase components (*TERT* and *TERC*) in various cancer types on the basis of TCGA data.

Materials and Methods

Gene Expression Profiling Interactive Analysis Database Analysis

The Gene Expression Profiling Interactive Analysis (GEPIA) database (https://gepia.cancer-pku.cn/index.html), which is a web server tool consisting of 8,587 normal and 9,736 tumor tissue samples from the TCGA and GTEx projects [31–33], was used to analyze differences in *YAP1* expression between normal and tumor tissue based on RNA sequencing. We represented expression of the *YAP1* profile across various cancers and paired normal tissues. We also analyzed the survival curves, including overall survival (OS), which refers to the duration of patient survival from the date of disease treatment, and disease-free survival (DFS), which denotes relapse-free survival, according to *YAP1* gene expression by using the log-rank and Mantel-Cox tests for different cancer types via the GEPIA database.

PrognoScan Database Analysis

The PrognoScan database (http://www.abren.net/PrognoScan/), a platform for evaluating potential tumor markers, is widely used to evaluate biological relationships between gene expression and patient prognosis such as OS and DFS [34]. It includes a large-scale collection of publicly available cancer microarray datasets with clinical information. We used this PrognoScan database to analyze the prognostic value of *YAP1* in various cancers based on the hazard ratio (HR) and log-rank *p*-values.

Tumor Immune Estimation Resource Database Analysis

The Tumor Immune Estimation Resource (TIMER) database (https://cistrome.shinyapps.io/timer/) for systematic analysis was used to explore gene correlations in various cancers. The TIMER database consists of 10,897 samples across 32 cancer types from TCGA to estimate the relationship

of cancer signaling pathway genes. Spearman correlation analysis of these samples was performed to determine the relationship between *YAP1* expression and telomerase (*TERT* and *TERC*) [35].

Statistical Analysis

Gene expression data from the GEPIA were explored with online tools. Survival curves were generated with GEPIA and PrognoScan online tools. The correlations of gene expression were evaluated in the TIMER database using Spearman correlation analysis. All results are presented with *p*-values from the log-rank test. Statistical significance of the data (*p*-values) was provided by the program.

Results

mRNA Expression Levels of *YAP1* in Various Types of Cancer

To determine differences in *YAP1* expression between tumor and normal tissue, *YAP1* expression in normal samples and multiple cancer types was analyzed using the GEPIA database. The mRNA expression levels of *YAP1* were higher in cholangiocarcinoma (CHOL), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), glioblastoma multiforme (GBM), pancreatic adenocarcinoma (PAAD), stomach adenocarcinoma, and thymoma (THYM) than in non-tumor tissues (Figure 1A). However, the mRNA expression levels of *YAP1* were lower in adrenocortical

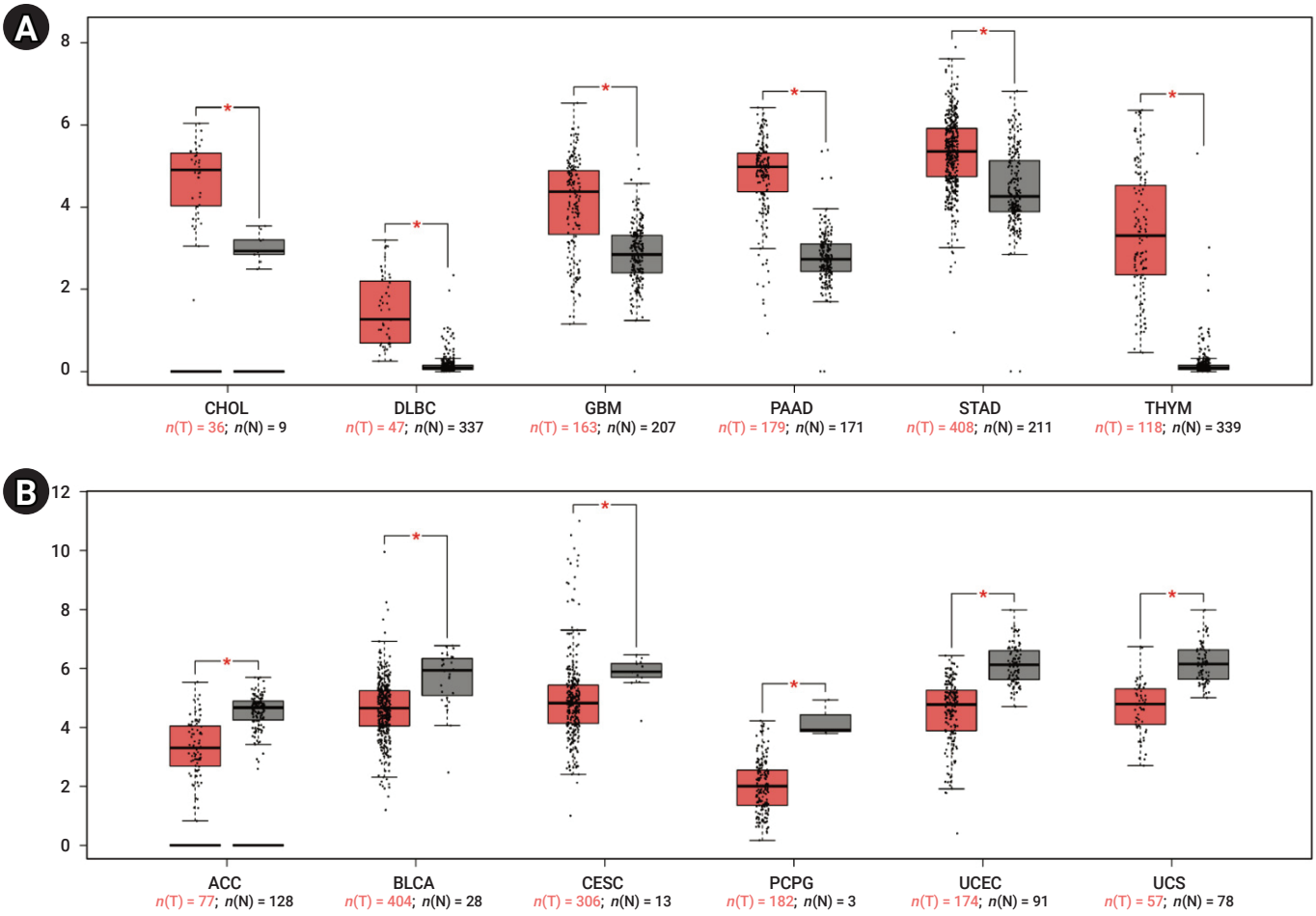

Figure 1. The mRNA expression levels of Yes-associated protein 1 (*YAP1*) in various cancer types. The expression levels of *YAP1* were analyzed using the Gene Expression Profiling Interactive Analysis database.
(A) High expression of *YAP1* in various cancer tissues compared with normal tissues. (B) Low expression of *YAP1* in various cancer tissues compared with normal tissues. *p<0.05. T, tumor; N, normal; CHOL, cholangiocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; GBM, glioblastoma multiforme; PAAD, pancreatic adenocarcinoma; STAD, stomach adenocarcinoma; THYM, thymoma; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; CESC, cervical squamous cell carcinoma; PCPG, pheochromocytoma and paraganglioma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma.

https://doi.org/10.24171/j.phrp.2021.0207

carcinoma (ACC), bladder urothelial carcinoma (BLCA), cervical squamous cell carcinoma, pheochromocytoma and paraganglioma, uterine corpus endometrial carcinoma, and uterine carcinosarcoma than in non-tumor tissues (Figure 1B). These results suggested that *YAP1* was differentially expressed between tissue samples of various cancers and non-tumor tissues.

Prognostic Significance of *YAP1* Expression in Various Types of Cancer

We investigated whether *YAP1* expression was correlated with the prognosis in various cancer types. Therefore, the effect of *YAP1* expression on survival rates was evaluated using the GEPIA and PrognoScan databases. The OS rates of patients with different types of cancers that overexpressed or underexpressed *YAP1* were compared. The results revealed shorter OS with a worse prognosis in patients with high *YAP1* expression than in those with ACC (HR, 0.009; $p = 0.006$) and PAAD (HR, 0.006; $p = 0.005$) who had low *YAP1* expression (Figure 2A, B). Moreover, the DFS rates between patients with low and high *YAP1* expression were compared. High *YAP1* expression was associated with poorer DFS in

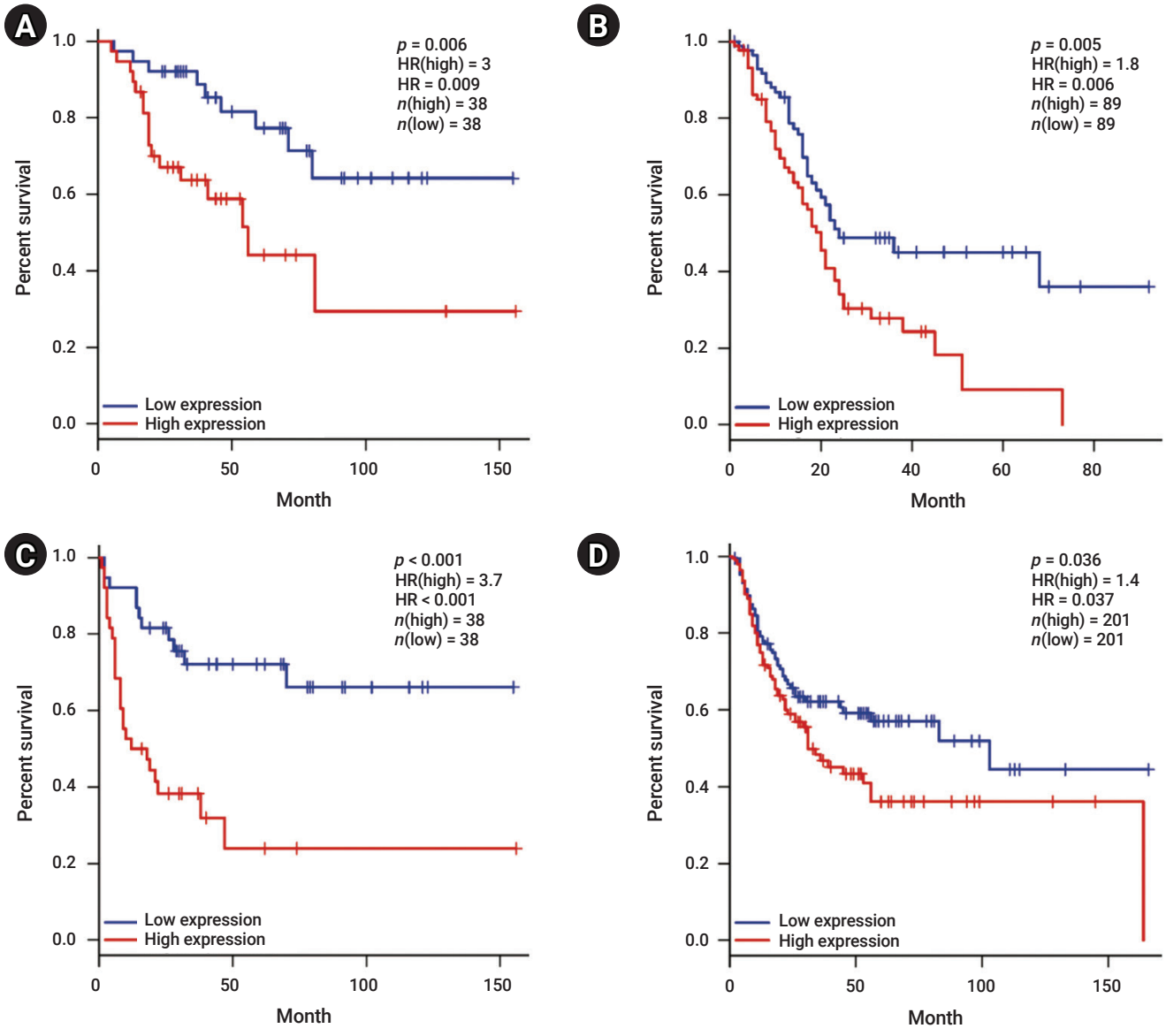

Figure 2. The prognostic significance of high expression of Yes-associated protein 1 (*YAP1*) in different cancer types. *YAP1* expression and survival rates were evaluated using the Gene Expression Profiling Interactive Analysis and PrognoScan databases.
(A, B) Overall survival curves according to *YAP1* expression in adrenocortical carcinoma (ACC) and pancreatic adenocarcinoma.
(C, D) Disease-free survival curves according to *YAP1* expression in ACC and bladder urothelial carcinoma. HR, hazard ratio.

patients with ACC (HR < 0.001; $p < 0.001$) and BLCA (HR, 0.037; $p = 0.036$) (Figure 2C, D). In other cancer types, *YAP1* did not have any prognostic value (Table S1). To further examine the prognostic potential of *YAP1* in different cancer types, we analyzed the PrognoScan database. The analysis indicated a worse prognosis in cancers of the bladder, brain, breast, colorectal, esophagus, and lung (Table S2). These results suggest that *YAP1* expression affects cancer prognosis.

Correlation between *YAP1* Expression and Telomerase in Various Types of Cancer

To determine the correlation between *YAP1* expression and *TERT* and *TERC*, we analyzed the data included in the TIMER database. As shown in Table 1, the analysis indicated *YAP1* expression was negatively correlated with *TERT* in BLCA, breast invasive carcinoma (BRCA), CHOL, colon adenocarcinoma (COAD), brain lower grade glioma (LGG), lung adenocarcinoma (LUAD,), mesothelioma (MESO), prostate adenocarcinoma (PRAD), rectal adenocarcinoma (READ), sarcoma (SARC), testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), and THYM. Moreover, *YAP1* expression was negatively correlated with *TERC* in BLCA, BRCA, DLBC, GBM, head and neck squamous cell carcinoma (HNSC), LUAD, lung squamous cell carcinoma (LUSC), MESO, ovarian serous cystadenocarcinoma (OV), PRAD, READ, TGCT and THYM (Table 2). However, *YAP1* expression was positively correlated with *TERT* activity in OV and uveal melanoma (UVM). These results suggested that *YAP1*

Table 1. Correlations between *YAP1* and *TERT* expression in different types of cancer

Cancer type	R	*p*
Adrenocortical carcinoma	0.10	0.384
Bladder urothelial carcinoma	−0.14	0.005*
Breast invasive carcinoma	−0.14	0.000*
Cervical squamous cell carcinoma and endocervical adenocarcinoma	0.03	0.547
Cholangiocarcinoma	−0.35	0.038*
Colon adenocarcinoma	−0.12	0.012*
Lymphoid neoplasm diffuse large B-cell lymphoma	0.05	0.750
Esophageal carcinoma	0.03	0.729
Glioblastoma multiforme	0.01	0.908
Head and neck squamous cell carcinoma	−0.04	0.326
Kidney chromophobe	0.07	0.604
Kidney renal clear cell carcinoma	−0.08	0.062
Kidney renal papillary cell carcinoma	0.04	0.509
Brain lower grade glioma	−0.28	0.000*
Liver hepatocellular carcinoma	−0.08	0.142
Lung adenocarcinoma	−0.09	0.045*
Lung squamous cell carcinoma	0.01	0.839
Mesothelioma	−0.25	0.022*
Ovarian serous cystadenocarcinoma	0.20	0.000*
Pancreatic adenocarcinoma	−0.08	0.298
Pheochromocytoma and paraganglioma	−0.04	0.636
Prostate adenocarcinoma	−0.24	0.000*
Rectum adenocarcinoma	−0.29	0.000*
Sarcoma	−0.22	0.000*
Skin cutaneous melanoma	0.04	0.397
Stomach adenocarcinoma	−0.08	0.100
Testicular germ cell tumors	−0.18	0.031*
Thyroid carcinoma	−0.13	0.004*
Thymoma	−0.50	0.000*
Uterine corpus endometrial carcinoma	0.01	0.760
Uterine carcinosarcoma	0.08	0.553
Uveal melanoma	0.31	0.005*

The correlation between Yes-associated protein 1 (*YAP1*) and telomerase reverse transcriptase (*TERT*) expression was analyzed by using Tumor Immune Estimation Resource database.
*$p < 0.05$.

https://doi.org/10.24171/j.phrp.2021.0207

Table 2. Correlations between *YAP1* and *TERC* expression in different types of cancer

Cancer type	R	*p*
Adrenocortical carcinoma	−0.07	0.568
Bladder urothelial carcinoma	−0.14	0.005*
Breast invasive carcinoma	−0.18	0.000*
Cervical squamous cell carcinoma and endocervical adenocarcinoma	−0.03	0.587
Cholangiocarcinoma	0.06	0.742
Colon adenocarcinoma	−0.03	0.468
Lymphoid neoplasm diffuse large B-cell lymphoma	−0.31	0.035*
Esophageal carcinoma	−0.07	0.336
Glioblastoma multiforme	−0.18	0.023*
Head and neck squamous cell carcinoma	−0.11	0.016*
Kidney chromophobe	0.18	0.156
Kidney renal clear cell carcinoma	−0.07	0.101
Kidney renal papillary cell carcinoma	−0.07	0.243
Brain lower grade glioma	−0.01	0.748
Liver hepatocellular carcinoma	0.05	0.345
Lung adenocarcinoma	−0.16	0.000*
Lung squamous cell carcinoma	−0.12	0.007*
Mesothelioma	−0.28	0.007*
Ovarian serous cystadenocarcinoma	−0.14	0.012*
Pancreatic adenocarcinoma	−0.12	0.122
Pheochromocytoma and paraganglioma	−0.05	0.484
Prostate adenocarcinoma	−0.18	0.000*
Rectum adenocarcinoma	−0.39	0.000*
Sarcoma	−0.09	0.144
Skin cutaneous melanoma	−0.03	0.588
Stomach adenocarcinoma	−0.07	0.173
Testicular germ cell tumors	−0.23	0.005*
Thyroid carcinoma	−0.04	0.381
Thymoma	−0.56	0.000*
Uterine corpus endometrial carcinoma	0.08	0.071
Uterine carcinosarcoma	0.16	0.236
Uveal melanoma	−0.05	0.642

The correlation between Yes-associated protein 1 (*YAP1*) and telomerase reverse transcriptase (*TERC*) expression was analyzed by using Tumor Immune Estimation Resource database.
*$p < 0.05$.

expression was correlated with *TERT* and *TERC* in different cancer types.

Discussion

In the past decade, previous studies have focused on determining *YAP1* expression to improve the understanding of its prognostic significance and potential effect on various cancer types. *YAP1* is a potent oncogene [24], and its levels are frequently increased in many cancer types [1,14,36–38]. The expression and role of *YAP1* in cancer are cell type-dependent, and its expression may contribute to cancer development [2,6,9,39]. Upregulation of *YAP1* expression has been observed in multiple cancer types. *YAP1* overexpression has been reported in patients with hepatocellular carcinoma (HCC), colorectal cancers, LUAD, ovarian cancer, and prostate cancer [2,3,14,40]. These findings suggest the potential oncogenic role of *YAP1* in multiple cancer types.

Zhang et al. [41] performed the immunohistochemical analyzes of primary esophageal squamous cell carcinoma tumor resection samples from patients, and reported that overexpression of *YAP1* was associated with tumor relative to adjacent tissue samples. In addition, Collak et al. [42] identified overexpression of *YAP1* in nuclear and cytosolic of benign prostates using immunohistochemistry, whereas moderate expression of *YAP1* was found in cellular locations of prostate intraepithelial neoplasia and prostate cancer. These findings show differences in expression levels of *YAP1* across cancer tissue samples, and are consistent with those presented in this study.

In this study, we showed that the prognostic value of *YAP1* expression was significant in various cancer types. Importantly, our data provide evidence that *YAP1* expression is correlated with telomerase (*TERT* and *TERC*) expression in various cancer types. Previous studies have reported that *YAP1* is a prognostic marker for OS and DFS in HCC [2]. *YAP1* expression is a remarkable predictor of poor prognosis in HCC patients with negative keratin 19 cells [9]. *YAP1* expression has also been significantly correlated with a poor prognosis in OV [6,36,43,44]. However, our results showed that *YAP1* expression did not have a prognostic role in various cancers, including HCC and OSC, based on TCGA data. Interestingly, higher expression of *YAP1* predicted poorer OS in patients with ACC and PAAD, and poorer DFS in patients with ACC and BLCA. According to these results, we suggest that higher expression of *YAP1* may be significantly correlated to a poorer prognosis in various cancers.

Telomerase is active in adult germ-line tissues, immortal cells [18], and most types of malignant tumors [19]. It is upregulated during tumorigenesis through the transcriptional regulation of *TERT* in up to 90% of cancers [45–48]. Upregulation of *TERC* is an early event in tumorigenesis, and *TERC* could be more closely correlated with tumor grade than telomerase activity or *TERT* expression [49–55]. *TERC* activity is associated with cancer, but its underlying mechanisms are poorly understood. This is the first study to explore the correlations between *YAP1* expression and telomerase expression (*TERT* and *TERC*) in various cancer types. Our data indicated that *YAP1* expression was

negatively correlated with *TERT* in BLCA, BRCA, CHOL, COAD, LGG, MESO, PRAD, READ, SARC, TGCT, THCA, and THYM. *YAP1* expression was positively correlated with *TERT* in OV and UVM, but negatively correlated with *TERC* in BLCA, BRCA, DLBC, GBM, HNSC, LIHC, LUSC, MESO, OV, PRAD, READ, TGCT, and THYM. Our findings may suggest that *YAP1* expression affects *TERT* and *TERC* expression in different cancer types. However, further investigation should be performed to elucidate the potential role of *YAP1* and telomere-related gene expression, which may contribute to novel research and therapies for treating various cancer types. Our results indicate that *YAP1* expression is correlated with 2 major components of telomerase, and is associated with a poor prognosis in various cancer types.

In this study, we attempted to confirm the clinical value of *YAP1* expression in various cancer types and its effect on telomerase. Although *YAP1* expression was different in many cancer types, the detailed mechanism underlying *YAP1* regulation should be established in future studies.

Conclusion

We suggest that *YAP1* could be a potential prognostic biomarker, which may stimulate novel cancer research. Understanding the correlation between *YAP1* expression and telomerase may provide insights into telomere-related diseases, including different types of cancers. Therefore, future oncology research could seek to understand the biological functions of *YAP1* and the correlation between *YAP1* and telomere-associated gene expression.

Supplementary Material

Table S1. Survival analysis of *YAP1* in different types of cancer using Gene Expression Profiling Interactive Analysis database; **Table S2.** Survival analysis of *YAP1* in different types of cancer using PrognoScan database. Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0207.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
This research was supported by the National Research Foundation Grant funded by the Korean Government (NRF-2021R1C1C1003333 to HSJ).

Availability of Data
All data generated or analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

Authors' Contributions
Conceptualization: SJH, JK; Data curation: SJH, JK; Formal analysis: SJH, JK; Funding acquisition: SJH; Investigation: HRK, KY, CWS; Methodology: HRK, KY, CWS; Project administration: HRK, KY, CWS; Resources: HRK, KY, CWS; Software: HRK, KY, CWS; Supervision: HRK, KY, CWS; Validation: HRK, KY; Visualization: HRK, KY; Writing–original draft: all authors; Writing–review & editing: all authors.

References

1. Wang Y, Dong Q, Zhang Q, et al. Overexpression of yes-associated protein contributes to progression and poor prognosis of non-small-cell lung cancer. Cancer Sci 2010;101:1279–85.
2. Xu MZ, Yao TJ, Lee NP, et al. Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. Cancer 2009;115:4576–85.
3. Zhao B, Wei X, Li W, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev 2007;21:2747–61.
4. Orr BA, Bai H, Odia Y, et al. Yes-associated protein 1 is widely expressed in human brain tumors and promotes glioblastoma growth. J Neuropathol Exp Neurol 2011;70:568–77.
5. Pan D. The hippo signaling pathway in development and cancer. Dev Cell 2010;19:491–505.
6. Harvey KF, Zhang X, Thomas DM. The Hippo pathway and human cancer. Nat Rev Cancer 2013;13:246–57.
7. Zhou Q, Bauden M, Andersson R, et al. YAP1 is an independent prognostic marker in pancreatic cancer and associated with extracellular matrix remodeling. J Transl Med 2020;18:77.
8. Zhao B, Tumaneng K, Guan KL. The Hippo pathway in organ size control, tissue regeneration and stem cell self-renewal. Nat Cell Biol 2011;13:877–83.
9. Van Haele M, Moya IM, Karaman R, et al. YAP and TAZ heterogeneity in primary liver cancer: an analysis of its prognostic and diagnostic role. Int J Mol Sci 2019;20:638.
10. Lamar JM, Stern P, Liu H, et al. The Hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain. Proc Natl Acad Sci U S A 2012;109:E2441–50.
11. Guo L, Chen Y, Luo J, et al. YAP1 overexpression is associated with poor prognosis of breast cancer patients and induces breast cancer cell growth by inhibiting PTEN. FEBS Open Bio 2019;9:437–45.
12. Werneburg N, Gores GJ, Smoot RL. The Hippo pathway and YAP signaling: emerging concepts in regulation, signaling, and experimental targeting strategies with implications for hepatobiliary malignancies. Gene Expr 2020;20:67–74.
13. Wang X, Su L, Ou Q. Yes-associated protein promotes tumour development in luminal epithelial derived breast cancer. Eur J Cancer 2012;48:1227–34.

14. Kang W, Tong JH, Chan AW, et al. Yes-associated protein 1 exhibits oncogenic property in gastric cancer and its nuclear accumulation associates with poor prognosis. Clin Cancer Res 2011;17:2130–9.
15. Pestana A, Vinagre J, Sobrinho-Simoes M, et al. TERT biology and function in cancer: beyond immortalisation. J Mol Endocrinol 2017; 58:R129–46.
16. Lingner J, Cech TR. Purification of telomerase from Euplotes aediculatus: requirement of a primer 3' overhang. Proc Natl Acad Sci U S A 1996;93:10712–7.
17. Li C, Wu MY, Liang YR, et al. Correlation between expression of human telomerase subunits and telomerase activity in esophageal squamous cell carcinoma. World J Gastroenterol 2003;9:2395–9.
18. Shen ZY, Xu LY, Li EM, et al. Telomere and telomerase in the initial stage of immortalization of esophageal epithelial cell. World J Gastroenterol 2002;8:357–62.
19. Hiyama E, Hiyama K. Clinical utility of telomerase in cancer. Oncogene 2002;21:643–9.
20. Liu Z, Li Q, Li K, et al. Telomerase reverse transcriptase promotes epithelial-mesenchymal transition and stem cell-like traits in cancer cells. Oncogene 2013;32:4203–13.
21. Takakura M, Kyo S, Kanaya T, et al. Cloning of human telomerase catalytic subunit (hTERT) gene promoter and identification of proximal core promoter sequences essential for transcriptional activation in immortalized and cancer cells. Cancer Res 1999; 59:551–7.
22. Reddel RR. Telomere maintenance mechanisms in cancer: clinical implications. Curr Pharm Des 2014;20:6361–74.
23. Zhang Q, Liu N, Bai J, et al. Human telomerase reverse transcriptase is a novel target of Hippo-YAP pathway. FASEB J 2020;34:4178–88.
24. Moroishi T, Hansen CG, Guan KL. The emerging roles of YAP and TAZ in cancer. Nat Rev Cancer 2015;15:73–9.
25. Jung SJ, Seo YR, Park WJ, et al. Clinicopathological characteristics of TZAP expression in colorectal cancers. Onco Targets Ther 2020; 13:12933–42.
26. Chiang YJ, Hemann MT, Hathcock KS, et al. Expression of telomerase RNA template, but not telomerase reverse transcriptase, is limiting for telomere length maintenance in vivo. Mol Cell Biol 2004;24:7024–31.
27. Cristofari G, Lingner J. Telomere length homeostasis requires that telomerase levels are limiting. EMBO J 2006;25:565–74.
28. Cayuela ML, Flores JM, Blasco MA. The telomerase RNA component Terc is required for the tumour-promoting effects of Tert overexpression. EMBO Rep 2005;6:268–74.
29. Soder AI, Going JJ, Kaye SB, et al. Tumour specific regulation of telomerase RNA gene expression visualized by in situ hybridization. Oncogene 1998;16:979–83.
30. Kedde M, le Sage C, Duursma A, et al. Telomerase-independent regulation of ATR by human telomerase RNA. J Biol Chem 2006;281: 40503–14.
31. Chen B, Lai J, Dai D, et al. JAK1 as a prognostic marker and its correlation with immune infiltrates in breast cancer. Aging (Albany NY) 2019;11:11124–35.
32. Gu Y, Li X, Bi Y, et al. CCL14 is a prognostic biomarker and correlates with immune infiltrates in hepatocellular carcinoma. Aging (Albany NY) 2020;12:784–807.
33. Tang Z, Li C, Kang B, et al. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res 2017;45:W98–102.
34. Mizuno H, Kitada K, Nakai K, et al. PrognoScan: a new database for meta-analysis of the prognostic value of genes. BMC Med Genomics 2009;2:18.
35. Li T, Fan J, Wang B, et al. TIMER: a web server for comprehensive analysis of tumor-infiltrating immune cells. Cancer Res 2017;77: e108–10.
36. Hall CA, Wang R, Miao J, et al. Hippo pathway effector Yap is an ovarian cancer oncogene. Cancer Res 2010;70:8517–25.
37. Liu T, Liu Y, Gao H, et al. Clinical significance of yes-associated protein overexpression in cervical carcinoma: the differential effects based on histotypes. Int J Gynecol Cancer 2013;23:735–42.
38. Zhang J, Xu ZP, Yang YC, et al. Expression of Yes-associated protein in gastric adenocarcinoma and inhibitory effects of its knockdown on gastric cancer cell proliferation and metastasis. Int J Immunopathol Pharmacol 2012;25:583–90.
39. Park J, Eisenbarth D, Choi W, et al. YAP and AP-1 cooperate to initiate pancreatic cancer development from ductal cells in mice. Cancer Res 2020;80:4768–79.
40. Steinhardt AA, Gayyed MF, Klein AP, et al. Expression of Yes-associated protein in common solid tumors. Hum Pathol 2008;39:1582–9.
41. Zhang Q, Lou L, Cai X, et al. Clinical significance of AJUBA, YAP1, and MMP14 expression in esophageal squamous cell carcinoma. Int J Clin Exp Pathol 2018;11:6018–24.
42. Collak FK, Demir U, Ozkanli S, et al. Increased expression of YAP1 in prostate cancer correlates with extraprostatic extension. Cancer Biol Med 2017;14:405–13.
43. Cho SY, Kim K, Park MS, et al. Expression of Yes-associated protein 1 and its clinical significance in ovarian serous cystadenocarcinoma. Oncol Rep 2017;37:2620–32.
44. Zhang X, George J, Deb S, et al. The Hippo pathway transcriptional co-activator, YAP, is an ovarian cancer oncogene. Oncogene 2011; 30:2810–22.
45. Peters B. Response to Letter to the Editor "Hyponatremia may be an under-recognised complication after desmopressin to reduce uremic bleeding in kidney biopsy". Nephrology (Carlton) 2020;25:584.
46. Yuan X, Larsson C, Xu D. Mechanisms underlying the activation of TERT transcription and telomerase activity in human cancer: old actors and new players. Oncogene 2019;38:6172–83.
47. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. Eur J Cancer 1997;33:787–91.
48. Cong YS, Wright WE, Shay JW. Human telomerase and its regulation. Microbiol Mol Biol Rev 2002;66:407–25.
49. Soder AI, Hoare SF, Muir S, et al. Amplification, increased dosage

and in situ expression of the telomerase RNA gene in human cancer. Oncogene 1997;14:1013–21.

50. Brown DF, Gazdar AF, White CL 3rd, et al. Human telomerase RNA expression and MIB-1 (Ki-67) proliferation index distinguish hemangioblastomas from metastatic renal cell carcinomas. J Neuropathol Exp Neurol 1997;56:1349–55.
51. Morales CP, Lee EL, Shay JW. In situ hybridization for the detection of telomerase RNA in the progression from Barrett's esophagus to esophageal adenocarcinoma. Cancer 1998;83:652–9.
52. Maitra A, Yashima K, Rathi A, et al. The RNA component of telomerase as a marker of biologic potential and clinical outcome in childhood neuroblastic tumors. Cancer 1999;85:741–9.
53. Yashima K, Litzky LA, Kaiser L, et al. Telomerase expression in respiratory epithelium during the multistage pathogenesis of lung carcinomas. Cancer Res 1997;57:2373–7.
54. Yi X, Tesmer VM, Savre-Train I, et al. Both transcriptional and posttranscriptional mechanisms regulate human telomerase template RNA levels. Mol Cell Biol 1999;19:3989–97.
55. Dome JS, Bockhold CA, Li SM, et al. High telomerase RNA expression level is an adverse prognostic factor for favorable-histology Wilms' tumor. J Clin Oncol 2005;23:9138–45.

https://doi.org/10.24171/j.phrp.2021.0207