Bone morphogenetic protein 1: a prognostic indicator and potential biomarker in three cancer types

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Abstract: Background: Bone morphogenetic protein 1 (BMP1) is a metalloprotease that plays a role in activating both transforming growth factor-β (TGF-β) and BMP signaling pathways. TGF-β has been identified as a factor initiating and facilitating cancer development. Consequently, we propose the hypothesis that dysregulation of BMP1 could potentially contribute to the onset and advancement of human cancers. Methods: In this research, we aimed to analyze BMP1 expression level and the associated clinical outcomes across various cancers using online cancer OMICS databases, advanced Bioinformatics tools, and molecular analyses. Results: The outcomes of our web server-based expression analysis indicated an up-regulation of BMP1 in a majority of the human cancers examined. External validation using clinical samples also showed higher expression of BMP1. Moreover, heightened BMP1 expression exhibited a noteworthy correlation with reduced overall survival (OS) duration in Bladder Cancer (BLCA), Kidney Renal Clear Cell Carcinoma (KIRC), and Lung Adenocarcinoma (LUAD) patients. This suggests a substantial involvement of the BMP1 gene in the development and progression of these three types of cancers. The major signaling pathways related with BMP1 enriched genes were “ECM-receptor interaction, Amoebiasis, Focal adhesion, Protein digestion and absorption, progesterone-mediated, PI3K-Akt signaling pathway, and platelet activation”. Moreover, we also explored some interesting correlations among BMP1 expression and its DNA promoter methylation level, CD8+ T immune cells level, and genetic variations. Conclusion: In conclusion, our study has provided some solid basis for BMP1 to be used as a reliable common biomarker for BLCA, KIRC, and LUAD patients.

Keywords: Bone morphogenetic protein 1, analysis, biomarker, cancer

Introduction

Cancer is a multifactorial disease that can originate in any part of the body due to abnormal cell division [1, 2]. In 2023, 1,958,310 new cancer cases and 609,820 cancer deaths are projected to occur in the United States [3]. Despite the substantial improvements in cancer treatment methods, still it is the 2nd leading cause of death worldwide after cardiovascular diseases [4]. Therefore, early and accurate diagnosis and prediction of cancer outcomes are critical to patients, physicians, and researchers for its effective treatment. Because this will help inform about patient illness and to design future treatment strategies [5-7]. For example, an earlier study based on the Australian population has ensured cancer treatment success up to 85% with the help of early detection [8]. Therefore, it is urgently required to discover precise, strong, and reliable diagnostic and prognostic biomarkers that could facilitate early diagnosis and prediction of the prognosis of cancer patients.

Bone Morphogenetic Protein 1 (BMP1) is a member of the astacin family, characterized by three primary domains: an astacin-like Zinc metalloprotease domain, an epidermal growth factor (EGF)-like domain, and three Com-
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The protein encoded by BMP1 is important for the formation of extracellular matrix [9]. Wozney et al. revealed that BMP1 binds with other BMP members of the TGF-β superfamily to stimulate these members, whereas its CUB domain facilitates the protein-protein interactions [10]. Within the extracellular matrix, BMP1 performs the cleavage of TGF-β, releasing TGF-β complexes. These complexes are subsequently targeted by various metalloproteinases, including MMP2, resulting in the release of free TGF. Therefore, the TGF-β signaling pathway and BMP pathways activation are dependent on the BMP1 activity [11]. Previously, BMP1 dysregulation has been documented in gastric cancer [12]. However, systemic pan-cancer research on BMP1 expression in distinct other types of human cancers using data mining, advance Bioinformatics tools, and molecular analyses is still lacking. Recently, advanced Bioinformatics tools, accurate RNA sequencing techniques, and molecular studies exploring genetic basis have speed up the discovery of potential candidate genes involved in cancer development and progression [13-16].

In this study, we conducted a brief examination of BMP1 expression variations and investigated its correlation with the prognosis of diverse human cancers. To this purpose, we utilized well-established databases including UALCAN, TIMER, cBioPortal, Kaplan-Meier Plotter, GEPIA, and CTD, and molecular experiments.

**Materials and methods**

**BMP1 expression analysis**

UALCAN web server (http://ualcan.path.uab.edu/) provides easy access for researchers to analyze OMICS data of more than 31 cancer subtypes. Structurally, UALCAN is based on the PERL-CGI framework and uses JavaScript and CSS to provide higher-quality graphics. Altogether, UALCAN assists the researchers to analyze and understand the gene expression levels of gene(s) of interest in individual TCGA cancer subtype [17]. In this study, we acquired BMP1 mRNA and protein expression data, along with various clinicopathological features, from the TCGA pan-cancer view using the UALCAN web server. Additionally, we utilized UALCAN to evaluate the BMP1 promoter methylation level across different cancer subtypes. For statistical purpose, a student’s t-test was employed and a $p$-value (<0.05) was considered as statistically significant.

**Kaplan-Meier plotter and GEPIA**

In this study, we assessed the clinical prognostic value of BMP1 across various cancer subtypes using online tools such as Kaplan-Meier (KM) plotter, GEPIA, and GENT2. These tools were built to measure the effect of 54 thousand genes and proteins on the survival of 21 types of cancer patients [18, 19]. The GEO and TCGA databases are among the data sources of the KM plotter. A $p$-value (<0.05) was considered as statistically significant.

**Verification of BMP1 genes expressions**

Next, we also verified BMP1 expression in BLCA, KIRC, and LUAD cell lines, and tissues relative to normal tissues using GENT2 online databases [20]. These databases are newly developed for customized and integrated multi-omics analyses of gene(s) of interest across various TCGA datasets. For defining the differential expression of the BMP1 gene, a $p$<0.05 value was used as a cutoff criterion.

**The cBioportal database**

cBioPortal (http://www.cbioportal.org) is an easy to use source resource of cancer OMICS data. It assists the researchers to analyze multidimensional genetic variations in the gene(s) and pathway(s) of interest across multiple TCGA datasets [21]. In our work, cBioPortal was used to investigate the BMP1-associated genetic alterations across defined cancer types.

**Protein-protein interaction (PPI) and pathway enrichment**

In our work, we obtained a PPI network of the BMP1 enriched genes from the STRING web server [22] and visualized it using Cytoscape software [23]. Later on, the KEGG pathway was performed via DAVID tool (http://david.ncifcrf.gov/summary.jsp) [24]. A $p$-value <0.05 was considered as significant.

**BMP1 and immune cells**

TIMER (https://cistrome.shinyapps.io/timer/) is an online database that predicts the levels of various immune cells in distinct cancer types.
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In our work, we used this database to explore the Spearman correlation between BMP1 expression and CD8+ T immune cells across different cancers. A p-value <0.05 was considered as significant.

**BMP1 gene-drug interaction network analysis**

The Comparative Toxicogenomics Database (CTD) [26] was used in our work to construct the gene-drug interaction network for exploring BMP1-associated chemotherapeutic drugs.

**RT-qPCR analysis**

A total of 18 LUAD tissue samples, along with corresponding adjacent controls, were sourced from Nishtar Hospital in Multan, Pakistan, to verify the mRNA expression pattern of BMP1. Ethical approval was obtained from the Pakistan Agriculture Research Center’s ethical committee. TRIzol™ (Takara Biotechnology Co., Ltd.) and additional reagents such as chloroform, isopropyl alcohol, and 75% alcohol were utilized for total RNA extraction from patients’ tissues, comprising nine samples from individuals with GBM and nine normal tissues.

RT-qPCR was executed on the CFX Connect Real-Time PCR Detection System (Bio-Rad, Shanghai, China), integrating amplification and detection steps. Reactions utilized the TB Green Premix Ex Taq II PCR kit (TaKaRa, Dalian, China). All assays were conducted with three biological replicates. Each qPCR reaction was performed in a 20 µL volume comprising 10 µL SYBR Green Master Mix, 0.8 µL of each primer, 2 µL of cDNA sample, and 6.4 µL RNase- and DNase-free water. The primer sequences were as follows: GAPDH-F: 5’-CAGGAGGCATTGCTGATGAT-3’; GAPDH-R: 5’-GAAGGCTGGGGCTCATTT-3’; BMP1-F: 5’-CCAATGGCTACTCTGCTCACA-3’; BMP1-R: 5’-AAGCCATCTCGGACCTCCAC-AT-3’.

**Results**

**BMP1 expression across multiple human cancers and normal controls**

Using the UALCAN web server, we examined the distinct expression patterns of BMP1 in 24 types of cancer tissues and their corresponding paired controls. Notably, a significant (P<0.05) down-regulation of BMP1 was observed in only two types of cancers-Kidney Chromophobe (KICH) and Uterine Corpus Endometrial Carcinoma (UCEC). Conversely, significant overexpression of BMP1 was detected in 22 other cancer types, including Bladder cancer (BLCA), Kidney Renal Clear Cell Carcinoma (KIRC), Lung Adenocarcinoma (LUAD), and several others (Figure 1).

**BMP1 expression and its prognostic potential**

We investigated the correlation between BMP1 expression and Overall Survival (OS) in patients with diverse cancer types using KM plotter, GEPIA, and GENT2 databases. The analysis results revealed a significant (P<0.05) association between BMP1 overexpression and reduced OS in patients with BLCA, KIRC, and LUAD, among the 24 analyzed cancer subtypes (Figure 2). These findings emphasize the substantial involvement of the BMP1 gene in the development and progression of BLCA, KIRC, and LUAD. As a result, the subsequent part of our study will primarily focus on exploring the distinctive role of BMP1 in these three cancers.

**Verification of BMP1 genes expression**

To validate BMP1 gene expression in patients with BLCA, KIRC, and LUAD from another cohort, GENT2 facilitated the detection of BMP1 gene expression levels in BLCA, KIRC, and LUAD tissues, as well as cell lines, in comparison to normal cancer tissues and cell lines. Concurrently, UALCAN assisted in confirming BMP1 expression at the protein level across BLCA, KIRC, and LUAD tissues paired with controls. The analysis results indicated a significant (P<0.05) up-regulation of BMP1 at both mRNA and protein levels in BLCA, KIRC, and LUAD samples, as well as cell lines, relative to controls (Figure 3).

**Associations among BMP1 expression level and diverse clinical variables**

In this study, we utilized the UALCAN web server to examine the associations between BMP1 expression and various clinical variables in BLCA, KIRC, and LUAD patients. Our findings revealed a significant (P<0.05) increase in BMP1 expression across different cancer stages, patient races, ages, genders, and nodal
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DNA promoter methylation level of BMP1

DNA promoter methylation is a crucial mechanism implicated in gene silencing and genetic imprinting [27]. Anomalous methylation patterns in the CpG regions within CpG Islands have been associated with cancers. Consequently, we conducted a promoter methylation analysis of BMP1 in BLCA, KIRC, and LUAD patients using the UALCAN web server. The results revealed significant (P<0.05) hypermethylation of BMP1 in BLCA, KIRC, and LUAD patients compared to their respective paired controls (Figure 7).

Genetic alteration in BMP1

For the analysis of genetic alterations and copy number variations (CNVs) in the BMP1 gene in BLCA, KIRC, and LUAD, we employed the cBioPortal web server. The BMP1 gene exhibited alterations in 7% of examined BLCA and LUAD samples and 2% of KIRC samples, primarily manifesting as deep deletion genetic abnormalities. In summary, our findings suggest that BMP1 overexpression in BLCA, KIRC, and LUAD may not be directly associated with genetic mutations and CNVs, despite the presence of these genetic alterations in a minimal proportion of the analyzed BLCA, KIRC, and LUAD samples (Figure 8).

PPI network and pathway enrichment of BMP1

We obtained a Protein-Protein Interaction (PPI) network of 11 BMP1-enriched genes using STRING (Figure 9A). Utilizing these BMP1-enriched genes as a foundation, we delved into the underlying signaling pathways contributing to the initiation and progression of BLCA, KIRC, and LUAD. To achieve this, the DAVID tool was employed, revealing diverse signaling pathways associated with BMP1-enriched genes, including "ECM-receptor interaction, Amoebiasis, Focal adhesion, Protein digestion and..."
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A

HR = 1.36 (1.02 – 1.83)
log rank P = 0.037

HR = 2.35 (1.73 – 3.18)
log rank P = 1.4e-08

HR = 1.45 (1.08 – 1.94)
log rank P = 0.012

B

Overall Survival

Low BMP1 TPM
High BMP1 TPM
Log rank p=0.031
n(high)=324
n(low)=174

Overall Survival

Low BMP1 TPM
High BMP1 TPM
Log rank p=0.0014
n(high)=146
n(low)=90

Overall Survival

Low BMP1 TPM
High BMP1 TPM
Log rank p=0.035
n(high)=220
n(low)=224

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Figure 2. Association between BMP1 expression and overall survival (OS) in patients with BLCA, KIRC, and LUAD. (A) Features OS analysis through Kaplan-Meier (KM) plotting, while (B) Presents OS analysis via GEPiA (Gene Expression Profiling Interactive Analysis), (C) Consolidates OS meta-analysis through GENT2 (Gene Expression Database of Normal and Tumor tissues 2). A p-value threshold of <0.05 was employed as the cutoff criterion for statistical significance. Bone morphogenetic protein 1 = BMP1, Bladder Cancer = BLCA, Kidney Renal Clear Cell Carcinoma = KIRC, Lung Adenocarcinoma = LUAD.
Figure 3. Expression pattern of the BMP1 across BLCA, KIRC, and LUAD samples and cell lines. A. Provides GENT2-based expression data for BMP1 in BLCA, KIRC, and LUAD tissue samples, shedding light on its expression profiles in clinical specimens. B. Extends the analysis to GENT2-based expression of BMP1 in BLCA, KIRC, and LUAD cell lines, offering insights into its expression dynamics within cell line models. C. Delves into UALCAN-based protein expression data for BMP1 in BLCA, KIRC, and LUAD tissue samples, providing an additional layer of information on the protein-level expression of BMP1 in these cancer types. A p-value threshold of <0.05 was employed as the cutoff criterion for statistical significance. Bone morphogenetic protein 1 = BMP1, Bladder Cancer = BLCA, Kidney Renal Clear Cell Carcinoma = KIRC, Lung Adenocarcinoma = LUAD.
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absorption, progesterone-mediated, PI3K-Akt signaling pathway, and platelet activation” (Figure 9A, 9B; Table 1).

**BMP1 and immune cell levels**

CD8+ T immune cells play a pivotal role in the immune response against cancer [28]. Consequently, in our investigation, we examined the Pearson correlation between CD8+ T immune cells and BMP1 expression levels in BLCA, KIRC, and LUAD using the TIMER database. The findings indicated a notable (P<0.05) negative correlation between BMP1 expression and the infiltrating level of CD8+ T immune cells across BLCA, KIRC, and LUAD samples (Figure 10).

**BMP1-associated drugs**

To investigate potential drugs targeting BMP1, we employed the Comparative Toxicogenomics Database (CTD), and the outcomes were visualized using Cytoscape software. The comprehensive analysis suggested that BMP1 expression could be modulated by various drugs. For example, bacitracin and zoledronic acid drugs are capable of enhancing the expression of BMP1 while valporic acid, colifibrate, and sunitinib are capable of decreasing BMP1 expression level (Figure 11).

**Validation of BMP1 expression on clinical samples**

Importantly, to reinforce the robustness of our findings, we conducted additional validation of BMP1 gene expression using RT-qPCR on clinical samples. The relative expression level of the BMP1 gene was determined using RT-qPCR. BMP1 revealed statistically significant up-regulation in the LUAD sample group as compared to the control group (Figure 12).

**Discussion**

In the current study, we analyzed BMP1 significance as a diagnostic and prognostic biomarker of multiple cancers using a detailed methodology. According to data from multiple databases,
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es, we observed a noteworthy up-regulation of BMP1 in 22 distinct cancer types, and conversely, its down-regulation in 2 other types of cancers. We noted the detrimental impact of elevated BMP1 levels on the OS of cancer patients compared to lower BMP1 levels. The OS analysis of BMP1 expression across these cancers revealed a negative correlation, indicating that its up-regulation was associated with a shorter OS duration for BLCA, KIRC, and LUAD patients, with an overall Hazard Ratio (HR) greater than 1. An earlier study has revealed that higher BMP1 expression is associated with poor prognosis in gastric cancer patients [12]. Collectively, these findings substantiate the notion that BMP1 may play a pivotal role in the onset and progression of BLCA, KIRC, and LUAD. Consequently, our primary focus in this study centers on these three cancers. Furthermore, we noted that elevated BMP1 expression is significantly correlated with various clinical variables in BLCA, KIRC, and LUAD patients, encompassing individual cancer stage, patient’s race, age, gender, and nodal metastasis status.

There are basically four different causes of cancer initiation including genomic, transcriptomic, proteomic, and epigenetic alterations [29, 30]. Majorly, any variation in the genomic region can either suppress or initiate the oncogenic effects [31]. For an examination of the genetic mutation status and copy number variations (CNVs) of BMP1 in BLCA, KIRC, and LUAD, we employed the cBioPortal web server. In the samples analyzed, the BMP1 gene exhibited alterations in 7% of BLCA and LUAD cases, and 2% of KIRC samples, primarily characterized by deep deletion genetic abnormalities. As a result, we postulate that genetic mutations and CNVs are less likely to be contributory factors in the regulation of BMP1 expression across BLCA, LUAD, and KIRC.

Subsequently, we examined the relationship between BMP1 promoter methylation levels...
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Figure 6. BMP1 expression across diverse clinicopathological parameters within LUAD. A. Dissects BMP1 expression in relation to different cancer stages, providing insights into its potential relevance at distinct disease progression points. B. Delves into BMP1 expression across different patient races, shedding light on potential racial disparities. C. Examines BMP1 expression in connection with different patient genders, unraveling any gender-associated variations. D. Investigates BMP1 expression concerning different nodal metastasis statuses, offering valuable information on its potential implications in metastatic processes. A p-value threshold of <0.05 was employed as the cutoff criterion for statistical significance. Bone morphogenetic protein 1 = BMP1, Lung Adenocarcinoma = LUAD.

Figure 7. Promoter methylation level of BMP1 in BLCA, KIRC, and LUAD. A. Provides a detailed examination of BMP1 promoter methylation in BLCA. B. A similar analysis is presented for KIRC. C. Extends the exploration of BMP1 promoter methylation level in LUAD. A p-value threshold of <0.05 was employed as the cutoff criterion for statistical significance. Bone morphogenetic protein 1 = BMP1, Bladder Cancer = BLCA, Kidney Renal Clear Cell Carcinoma = KIRC, Lung Adenocarcinoma = LUAD.
and its expression in BLCA, KIRC, and LUAD. Our findings unveiled a notable positive correlation; challenging the conventional belief that hypermethylation is typically negatively associated with gene expression. It’s important to note that this does not always conform to the general trend, as several studies in the medical literature have identified positive correlations between hypermethylation and gene expression in diverse cancer types [32, 33].

Currently, various BLCA-related biomarkers are being used for its early diagnosis and predicting the prognosis. These biomarkers include NTRK3 [34], P4HB [35], KIF2C, BUB1B, KIF11, CDC2A5, KIFC1, CDC2A8, AURKA, KIF18B, NEK2, KIF18A, NCAPG, NUSAP1, and RACGAP1 [36]. For the early diagnosis and predicting the prognosis of KIRC, different studies have identified multiple key genes such as ACA1, ACADS, ALDH6A1, AUH, HADH, PCCA [37],

Table 1. Detail of BMP1 enriched genes pathway analysis

<table>
<thead>
<tr>
<th>Pathway ID</th>
<th>Pathway Name</th>
<th>Gene count</th>
<th>P-value</th>
<th>Gene name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsa04512</td>
<td>ECM-receptor interaction</td>
<td>7</td>
<td>&lt;0.05</td>
<td>COL1A1, COL1A2, COL5A1, LAMA3, COL5A2, LAMC2, HSPG2</td>
</tr>
<tr>
<td>Hsa05146</td>
<td>Amoebiasis</td>
<td>6</td>
<td>&lt;0.05</td>
<td>COL1A1, COL1A2, COL5A1, LAMA3, COL5A2, LAMC2</td>
</tr>
<tr>
<td>Hsa04510</td>
<td>Focal adhesion</td>
<td>6</td>
<td>&lt;0.05</td>
<td>COL1A1, COL1A2, COL5A1, LAMA3, COL5A2, LAMC2</td>
</tr>
<tr>
<td>Hsa04974</td>
<td>Protein digestion and absorption</td>
<td>5</td>
<td>&lt;0.05</td>
<td>COL1A1, COL1A2, COL5A1, COL7A1, COL5A2</td>
</tr>
<tr>
<td>Hsa04151</td>
<td>PI3K-Akt signaling pathway</td>
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<td>&lt;0.05</td>
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</tr>
<tr>
<td>Hsa04611</td>
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<td>4</td>
<td>&lt;0.05</td>
<td>COL1A1, COL1A2, COL5A1, COL5A2</td>
</tr>
</tbody>
</table>

*Bone morphogenetic protein 1 = BMP1.
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AGXT, PTGER3, SLC12A3 [38], and Linc00342 [39]. Similarly, for the early diagnosis and predicting the prognosis of LUAD, the roles of 9 miRNAs (has-mir-486-1, has-mir-486-2, has-mir-153, has-mir-210, has-mir-9-1, has-mir-9-2, has-mir-9-3, has-mir-577, and has-mir-4732) and 15 genes (EDN1, FOS, IL6, MMP9, CDH1, BIRC5, CDK1, CDKN3, VWF, CD34, UBE2C, AURKA, EGR1, CDKN2A, and CCNB2) are already well described [40, 41].

Nevertheless, none of these, or any other biomarkers, have been universally applied in BLCA, KIRC, and LUAD patients with varied clinicopathological features. In this current study, we highlighted the significant (P<0.05) up-regulation of BMP1 expression in BLCA, KIRC, and LUAD patients across diverse clinicopathological features, including cancer stages, patient race, gender, age, and nodal metastasis status, as compared to normal controls. Moreover, the survival analysis of the BMP1 gene indicated its up-regulation as a prognostic biomarker for BLCA, KIRC, and LUAD. In summary, based on our findings, we posit that elevated BMP1 expression could potentially serve as a novel diagnostic and prognostic tool for BLCA, KIRC, and LUAD patients.

Furthermore, based on the fact that tumor infiltrating immune cells, especially CD8+ T immune cells, contributes to the tumor initiation, development, and progression [42], we found out the correlations among BMP1 expression level and CD8+ T immune cells infiltration via TIMER database. Results of the analysis have shown the notable negative correlations among BMP1 expression and CD8+ T immune cells infiltration across BLCA, KIRC, and LUAD.

Therefore, we also speculated that BMP1 may initiate tumor development by negatively regulating the CD8+ T immune cells immune cells within tumor cells.

We explored that the BMP1-associated genes were linked with some diverse underpinning molecular pathways, such as "ECM-receptor interaction, Amoebiasis, Focal adhesion, Protein digestion and absorption, progesterone-
Pan-cancer analysis of BMP1 could be valuable in formulating novel treatment approaches for BLCA, KIRC, and LUAD.

Conclusion

In this study, our aim was to identify molecular biomarkers crucial for cancer initiation and progression, aiming for effective cancer treatment strategies that minimize risks for patients and reduce the potential side effects of overtreatment. To assess the BMP1 gene’s suitability as a potential diagnostic and prognostic biomarker in cancer development, we examined various aspects, including BMP1 transcriptomic expression levels, DNA methylation levels, mutational status, enriched genes, prognostic capabilities, and gene-drug network interactions. Our findings indicated a significant up-regulation of BMP1 across BLCA, KIRC, and LUAD patients, correlating with reduced overall survival durations. Importantly, our results unveiled the signaling pathways associated with BMP1 that contribute to the initiation and progression of BLCA, KIRC, and LUAD. Consequently, these pathways could be targeted therapeutically to impede the development of BLCA, KIRC, and LUAD. In summary, BMP1 emerges as a potentially common novel diagnostic and prognostic biomarker, as well as a therapeutic target for patients with BLCA, KIRC, and LUAD.

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Disclosure of conflict of interest

None.

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