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Original Article

In silico prediction of paradoxical effect for oxaliplatin in gastric cancer patients based on their transcriptomic profile

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Abstract

Background and purpose: Gastric cancer (GC) is a major global health concern, ranking as the fifth most commonly diagnosed cancer. New treatment strategies like chemoprevention with oxaliplatin (OXA) are emerging, but safety data for GC patients are limited. This *in silico* study aimed to predict potential paradoxical effects of OXA treatment in GC patients using computational analysis.
Experimental approach: RNA-sequencing data from GSE26942, GSE66229, and TCGA-STAD datasets were analyzed. Differential gene expression was identified using GEO2R and DESeq2. Pathway enrichment and protein-protein interaction networks were constructed to pinpoint genes crucial for GC progression. Finally, the R Survival package identified survival-related differentially expressed genes (DEGs). Interactions between OXA and GC-related genes were retrieved from the CTD database and compared with DEGs.
Findings/Results: A total of 151 dysregulated genes were identified across the datasets, comprising 112 downregulated and 39 upregulated genes. Thirteen genes emerged as potential prognostic biomarkers for overall survival. OXA interacted with 97 genes, of which 14 were linked to both OXA and differentially expressed genes in GC. OXA potentially reversed the expression of seven genes associated with GC progression (BIRC5, CAV1, CDH2, IL6, JUN, SERPINB2, TYMS), while promoting the expression of six others (BLVRB, CDKN2A, MAPK3, PLAU, PTGS2, SERPINE1). Notably, SERPINE1 showed a strong correlation with overall survival.
Conclusion and implications: Our findings suggest that a patient's genetic profile, particularly SERPINE1 expression levels, might be crucial for determining the safety and efficacy of OXA treatment for GC.

Keywords: Chemoprevention; Oxaliplatin; Stomach cancer; SERPINE1; Cancer Genome Atlas (TCGA).

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide. The global incidence rate of gastric cancer ranks fifth, with the mortality rate ranking third, thereby imposing a substantial burden on public health (1,2). Gastric cancer is a heterogeneous disease influenced by environment and genetics, including age, sex, race/ethnicity, family history, *Helicobacter pylori* infection, smoking, and diets high in nitrates and nitrites (2-5). Most GC patients are diagnosed at advanced stages. Conventional treatment options are not effective, leading to a poor prognosis with a median overall survival of 10–12 months (6).

The primary method for treating early gastric cancer is endoscopic resection. Surgery is the recommended approach for non-early operable GC, and it should include lymphadenectomy. Patients with stage 1B or higher cancers may experience improved survival with perioperative or adjuvant chemotherapy.

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Advanced GC patients receive chemotherapy in successive stages, beginning with a platinum and fluoropyrimidine doublet in the first line, with a median survival of less than 1 year. Trastuzumab and ramucirumab, as well as nivolumab and pembrolizumab, are among the targeted therapies approved for the treatment of GC (7).

Another proposed approach that could be used in GC patients is platinum-derived chemotherapeutics, which have been shown to significantly improve survival rates and effectively manage local recurrence (8). Furthermore, regimens containing oxaliplatin have demonstrated superiority over other platinum-based therapies (9).

Oxaliplatin belongs to the third generation of platinum compounds and is a cornerstone for the management of advanced GC (10,11). It also primarily manifests its anticancer properties by binding to and impairing DNA, hence hindering DNA replication. The nucleotide excision repair pathway is mostly responsible for fixing DNA damage caused by oxaliplatin. When this pathway is activated, it usually leads to the development of oxaliplatin resistance (12).

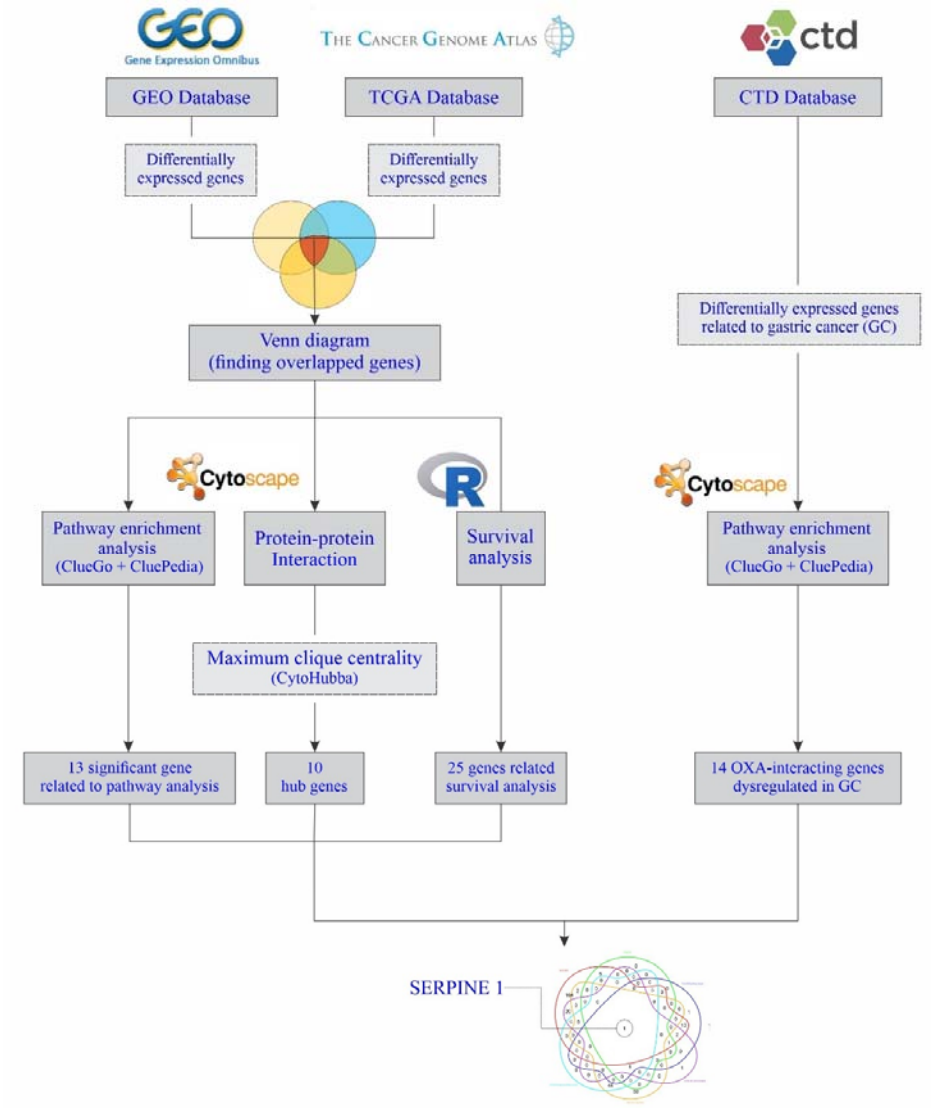

Fig. 1. Workflow of the current study.

Despite the continuous improvements in chemotherapeutic regimens for GC, certain patients still experience adverse effects after chemotherapy. Moreover, most tumor cells develop resistance to chemotherapeutic drugs, resulting in treatment failure. Consequently, the five-year survival rate of patients with advanced GC has not significantly increased in recent years (13). Additionally, oxaliplatin elicits high levels of oxidative stress in cells, causing cell dysfunction and unpredictable effects on the cell. The approach to optimizing the drug's effectiveness while concurrently reducing its side effects is presently under investigation (13,14).

Therefore, our understanding of the safety profile of this treatment in managing GC patients remains unexplored. Hence, the present study aimed to identify potential adverse outcomes triggered by oxaliplatin in GC patients using an *in silico* toxicogenomic approach. The workflow for the current study is shown in Fig. 1.

MATERIAL AND METHODS

Microarray data

The keyword "gastric cancer" was utilized as the primary search term within the Gene Expression Omnibus (GEO) database (ncbi.nlm.nih.gov/geo/), with restrictions on Homo sapiens and Expression profiling by array study type. The results yielded a total of 310 entries, with two gene expression datasets selected for further analysis. These specific gene expression profiles were derived from patients with GC tissues, allowing for comparison with other publicly available GC data. The chosen gene expression datasets were GSE26942 and GSE66229. GSE26942 was conducted on the Illumina HumanHT-12 V3.0 expression beadchip platform GPL6947, whereas GSE66229 was based on the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. The samples collected were divided into two groups: primary GC tissues and normal gastric mucosae, which served as the control group.

The dataset for stomach adenoma and adenocarcinoma [STAD] from The Cancer Genome Atlas (TCGA) was obtained via the Genomic Data Commons Data Portal (GDC). It consists of 343 tumors with clinical data, as well as 30 non-tumor samples.

Identification of differentially expressed genes

The analysis of differentially expressed genes (DEGs) between GC and normal tissues was performed utilizing the GEO2R online analysis tool (http://www.ncbi.nlm.nih.gov/geo/geo2r). The Benjamini-Hochberg adjusted *P*-value and fold change (FC) were calculated and subsequently employed for gene identification that met the cutoff criteria. Specifically, genes that exhibited an adjusted *P*-value of less than 0.05 and |log2 FC| greater than 1 were considered DEGs. The tumor-normal DEGs were identified from TCGA data using the DESeq2 R package (15). A screening threshold was applied with an adjusted *P*-value less than 0.05 and |log2 FC greater than 1 as the cutoff condition. Using the Venn diagram drawing tool from FunRich software (http://funrich.org/), we screened for consistently DEGs among the three gene expression datasets (GEO and TCGA). Additionally, we used the ggVennDiagram package (16) in R (version 4.3.1) to visualize overlapping genes from downstream analyses.

Network analysis

The STRING database was employed to examine the interconnections between genes in a connected network at the protein level (17). The protein-protein interaction (PPI) network was subsequently constructed by removing disconnected nodes and ensuring that the combined scores were greater than 0.4. The PPI network was constructed using Cytoscape (version 3.10.1) (18). We retrieved the network of genes by consistently extracting DEGs from the analyzed expression profiles and uploading them to STRING. Furthermore, we utilized the Cytoscape plugin CytoHubba to rank hub nodes within these networks. Hub genes were identified as genes with the highest maximal clique centrality (MCC) score.

Gene set enrichment analysis

Pathway enrichment analysis was conducted using the ClueGo/CluePedia plugin of Cytoscape. Enrichment analysis of gene-enriched pathway terms was

conducted using Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, and WikiPathways. A *P*-value correction was performed using the Bonferroni step-down method. Using the ClueGo/CluePedia plugin from Cytoscape, we visualized the enriched pathways with a significance cutoff of less than 0.05.

Oxaliplatin interacting genes

For this investigation, we obtained oxaliplatin-interacting genes from the Comparative Toxicogenomics Database (CTD; http://CTD.mdibl.org), a publicly available resource that provides integrated data to enhance our understanding of the connections between chemicals, genes, and diseases (19). The analysis presented here was conducted using the data obtained in April 2024. Additionally, the CTD Chemical-Gene Interaction Query was instrumental in identifying binary interactions between oxaliplatin and key target genes.

Survival analysis

We utilized Kaplan-Meier survival curves to identify differentially expressed genes. Statistically significant thresholds were determined based on a log-rank *P*-value of less than 0.05 and a hazard ratio (HR) not equal to 1. According to the cut-off point, the expression levels of the median DEGs in the TCGA samples were categorized as either high or low. We constructed Kaplan-Meier survival curves using the survival package (https://CRAN.R-project.org/package=survival) in R (version 4.3.1).

Supplementary materials

Table S1 provides interactions between significantly differentially expressed genes and oxaliplatin in gastric cancer retrieved from CTD (define CTD). Available at https://github.com/aniiiiis/RPS-Supplementary-Table-1.

RESULTS

Identification of tumor-DEGs

Two GEO gene expression datasets (GSE26942 and GSE66229) were used. GSE26942 consisted of 12 normal samples and 202 GC samples, while GSE66229 included 100 normal samples and 300 GC samples. In the former group, there were a total of 2564 genes that showed differential expression (423 upregulated and 2,141 downregulated). The latter group exhibited 863 DEGs (277 upregulated and 586 downregulated). On the other hand, according to the TCGA dataset, a total of 12950 genes were found to have different expression levels (4,682 downregulated and 8,268 upregulated). The DEGs from both GEO datasets were compared to those from the TCGA datasets. A Venn analysis was performed to determine the overlap of DEG profiles (Fig. 2). The analysis revealed a total of 151 common DEGs (39 upregulated and 112 downregulated) shared between all three datasets.

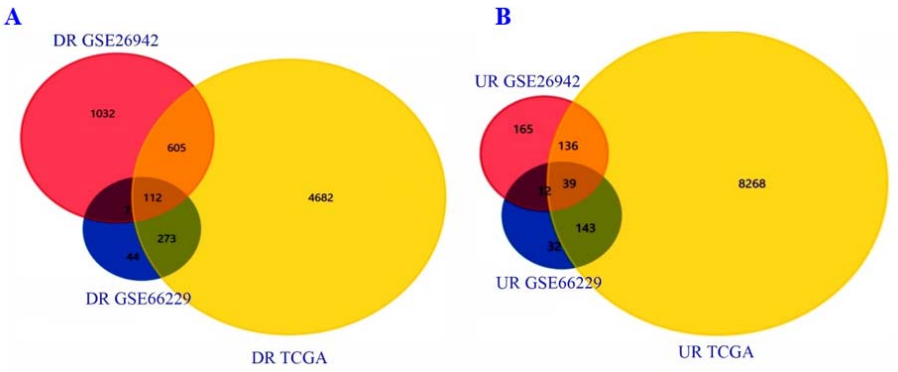

Fig. 2. Venn diagrams of DEGs in gastric cancer versus normal tissue. The Venn diagram displays the number of DEGs in each of the three groups, GSE26942, GSE66229, and TCGA. Venn diagram of overlapped (A) DR genes and (B) UR genes. DEGs, differentially expressed genes; DR, downregulated; UP, upregulated.

Identification of hub genes using PPI network analysis

A network of PPIs was created for the 151 genes that were overlapping differentially expressed genes. By selecting the combined scores > 0.4 and hiding the disconnected nodes, the network consists of 104 nodes and 198 edges (Fig. 3A). For this study, we assessed the hub genes using the MCC score. The MCC algorithm is a method used to analyze the topology of a network and determine the importance of nodes. It has been recognized as the most effective method for identifying hub nodes when compared to other approaches. This method evaluates the significance of a node in a network solely based on its connections with its immediate neighbors (20). These are the top ten genes with the highest MCC score: ATP4A, SPP1, GHRL, SST, KIT, MMP3, CHGA, SERPINE1, PGC, and TFF2 (Fig. 3B).

Pathway enrichment analysis

All 151 common DEGs were subjected to pathway enrichment analysis. The up- and down-regulated DEGs were analyzed separately with the Cytoscape plug-in ClueGo/CluePedia to identify pathway enrichment and gain a better understanding of their function. The enrichment analysis of 39 upregulated genes using KEGG, Reactome, and WikiPathways revealed significant changes in pathways related to "degradation of extracellular matrix", "extracellular matrix organization", "collagen formation", "assembly of collagen fibrils", and "collagen degradation". From these pathways, we identified 8 key genes (MMP3, MMP10, COL10A1, COL11A1, LAMC2, SPP1, SERPINE1, and CEACAM6) as important regulators (Fig. 4A). The same analysis for 112 downregulated genes revealed that these genes were enriched in two functional clusters, including "gastric acid secretion" and "peptide hormone metabolism" (Fig. 4B). From these, 13 genes (KCNE2, KCNJ15, KCNJ16, ATP4A, ATP4B, SST, CHRM3, CCKBR, CHRL, ISL1, MYRIP, CPE, and ERO1B) were identified as important regulators.

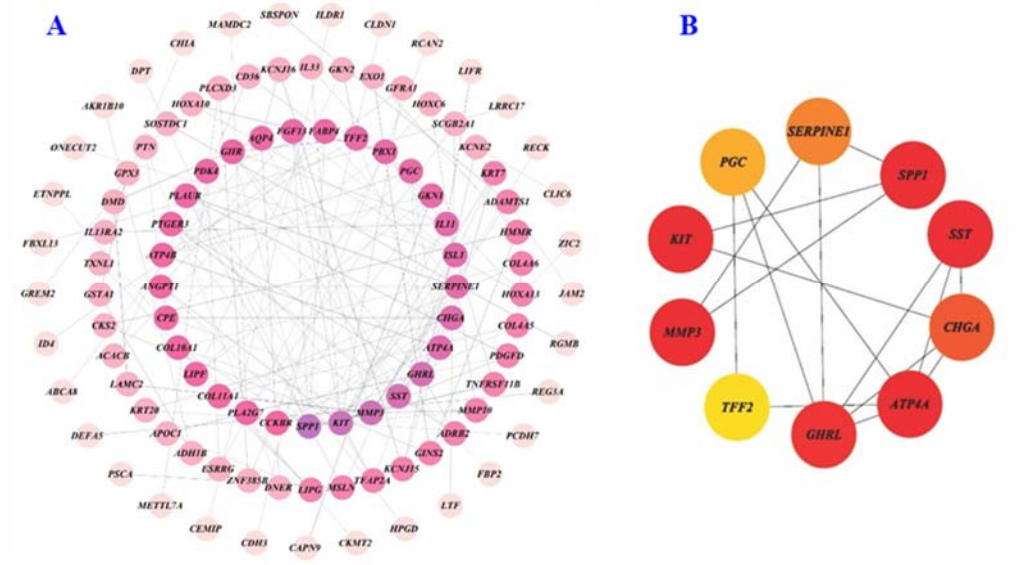

Fig. 3. Protein-protein interaction network of DEGs in gastric cancer. The nodes represent genes (with a combined score of > 0.9), and the edges indicate interactions between their protein products. (A) Colorful nodes represent the degree (number of interacting partners) of a gene; darker colors indicate genes with more interactions, potentially playing a more central role in the network. (B) Top 10 hub genes identified by the MCC Method. Hub genes are genes with a high number of interactions with other genes in a protein-protein interaction network. DEGs, differentially expressed genes

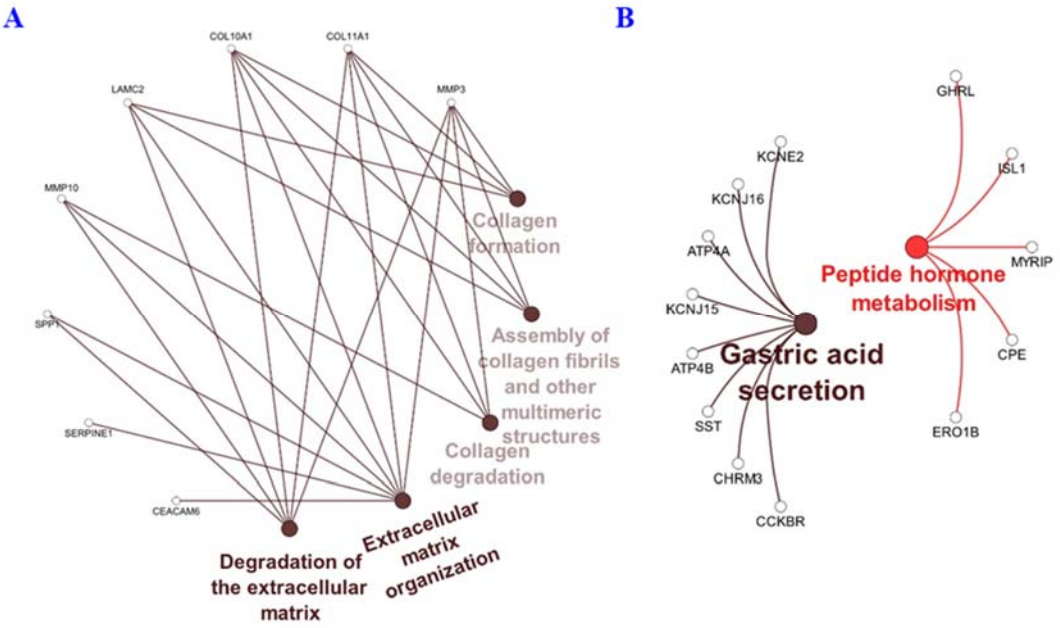

Fig. 4. Pathway enrichment analysis in gastric cancer. KEGG, Reactome, and Wiki Pathways analysis of (A) upregulated and (B) downregulated genes. The color of nodes indicates the *P*-value, and the enrichment shows only significant pathways (*P*-value < 0.05). Darker and lighter color nodes indicate a *P*-value < 0.001 and *P*-value < 0.001-0.05, respectively.

Survival analysis

Using the "survival" R package, a univariate survival analysis was conducted to screen tumor-associated DEGs that are associated with overall survival. A total of 13 genes were identified as significant based on the criteria of log-rank $P < 0.05$, and HR $\neq 1$ was identified. In GC patients, the poorer overall survival was found to be correlated with the increased expression of 5 genes, as well as the decreased expression of 20 genes shown in Table 1. These 25 genes were considered significant and used in further analysis.

Oxaliplatin-interacting genes

Using the CTD Chemical-Gene Query, reactions involving oxaliplatin and genes related to predicted pathways were analyzed. In addition, the impact of oxaliplatin on mRNA expression concerning specific genes was compared, and interactions between oxaliplatin and important genes linked to overall survival were identified. A total of 3861 genes were found to interact with oxaliplatin, according to the source CTD. Out of many genes, 97 were expressed in GC patients. This *in silico* research enabled us to acquire binary linkages of genes that are significant concerning oxaliplatin. It has been observed that oxaliplatin enhances the expression of 56 genes while suppressing 29 genes, which could contribute to the development of GC. Likewise, oxaliplatin significantly increased/ decreased the expression of 7 genes (Table S1). Also, mRNA expression of these genes was evaluated in GC. We observed that the expression of 33 genes was altered in GC patients (Table S1).

Furthermore, pathway enrichment analysis for the set of 97 genes was conducted using ClueGo/CluePedia, as previously described. Obtained results showed these genes were implicated in pathways such as “MAPK3 (ERK1) activation, “interleukin-6 signaling”, “transcriptional activation of p53 responsive genes”, “dissolution of fibrin clot", and “nuclear events stimulated by ALK signaling in cancer” (Fig. 5). Figure 5 reports the importance of 45 genes for pathway regulation. The expression of these 45 genes in GC patients was compared with the type of interaction described between oxaliplatin and the selected genes. Out of the total, only 14 of them exhibited alterations in expression while interacting with oxaliplatin in the stomach cancer datasets analyzed in this work (Table 2).

Table 1. Survival-related genes in gastric cancer patients.

Gene	Up/down-regulated	|Log2FC*|	Log-rank p	Hazard ratio	95% Confidence interval
PDGFD	Down	1.27	0.00008	2.03	1.43, 2.88
SERPINE1	Up	2.21	0.0005	1.8	1.31, 2.63
PLCXD3	Down	1.98	0.0006	1.83	1.30, 2.59
PDK4	Down	2.74	0.0009	1.80	1.27, 2.55
RECK	Down	1.28	0.0009	1.80	1.27, 2.55
GHR	Down	2.17	0.002	1.72	1.22, 2.43
SLC16A7	Down	1.5	0.002	1.75	1.23, 2.48
COL4A5	Down	1.99	0.003	1.69	1.19, 2.40
PCDH7	Down	0.77	0.008	1.59	1.13, 2.25
ANGPT1	Down	1.5	0.012	1.55	1.10, 2.20
LRRC17	Down	0.69	0.012	1.55	1.10, 2.19
CTHRC1	Up	3.46	0.01356	1.54	1.09, 2.17
TEAD4	Up	1.49	0.014	0.65	0.46, 0.92
AFF3	Down	1.74	0.015	1.53	1.09, 2.17
PTGER3	Down	1.51	0.016	1.53	1.08, 2.15
CD36	Down	2.23	0.020	1.50	1.06, 2.11
ADAMTS1	Down	2.07	0.022	1.49	1.06, 2.11
JAM2	Down	1.96	0.022	1.49	1.06, 2.11
CLIC6	Down	1.46	0.022	1.50	1.06, 2.12
DMD	Down	1.96	0.029	1.47	1.04, 2.07
COL10A1	Up	6.87	0.032	1.46	1.03, 2.05
GPX3	Down	2.47	0.038	1.44	1.02, 2.03
ADH1B	Down	2.48	0.040	1.43	1.02, 2.02
CPE	Down	1.29	0.040	1.43	1.02, 2.02
SPP1	Up	3.95	0.045	1.42	1.01, 2.00

*Based on the Cancer Genome Atlas data results.

Table 2. Comparison between the gastric cancer mRNA expression of genes associated with identified pathways, with the Comparative Toxicogenomics Database detected binary interactions between OXA and the same group of genes.

Gene name	OXA-mRNA interaction	mRNA expression in gastric cancer
BIRC5*	Low	High
BLVRB**	Low	Low
CAV1*	High	Low
CDH2*	High	Low
CDKN1A	High/Low	Low
CDKN2A**	High	High
IL6*	High	Low
JUN*	High	Low
MAPK3**	Low	Low
PLAU**	High	High
PTGS2**	High	High
SERPINB2*	High	Low
SERPINE1**	High	High
TYMS*	Low	High

OXA, Oxaliplatin; *, OXA regulates the expression of significant genes in the opposite way to gastric cancer tissue expression; **, OXA promotes the expression of genes in the same way as it was seen in gastric cancer tissue.

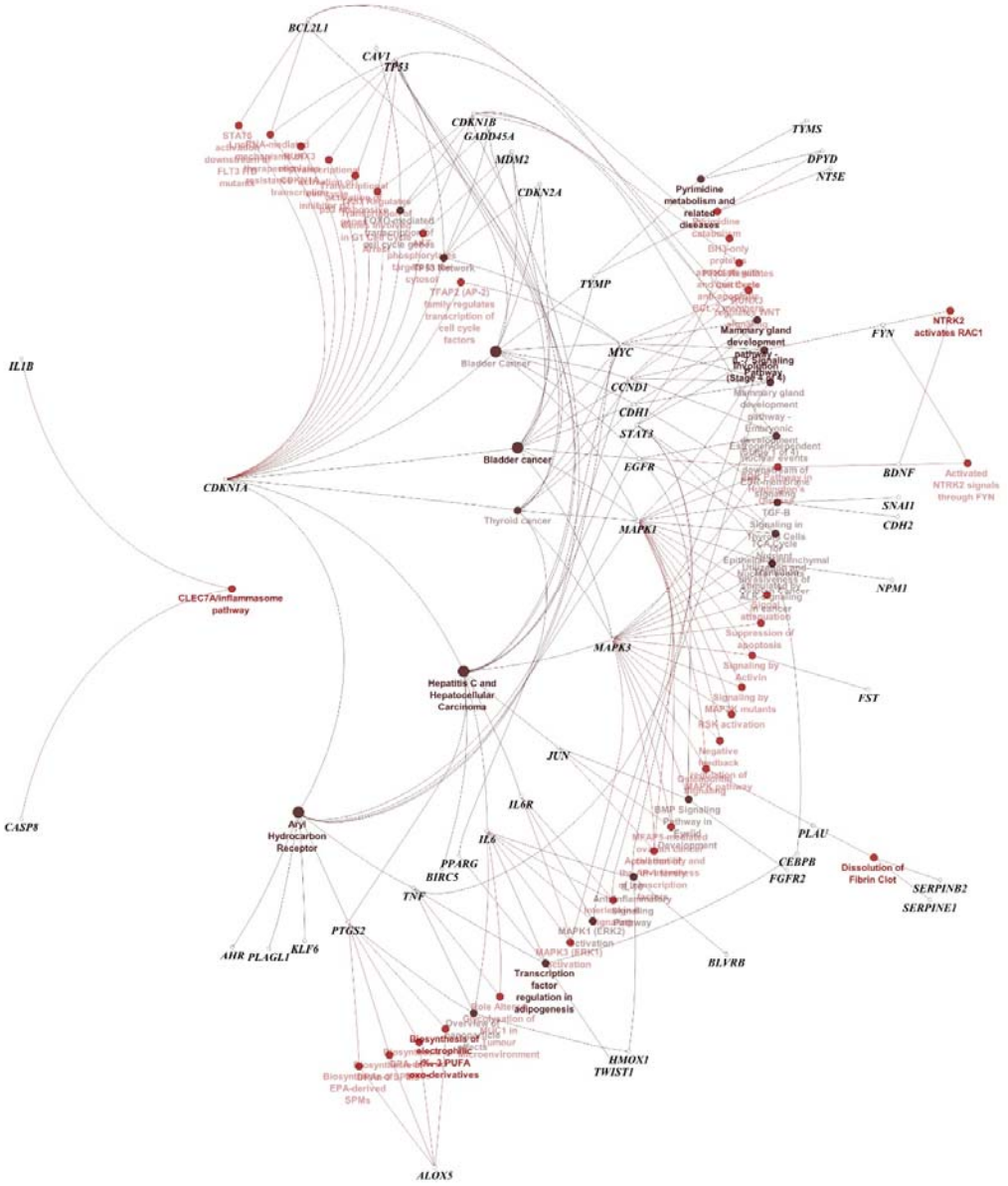

Fig. 5. Pathway analysis of oxaliplatin-interacting gastric cancer dysregulated genes. This figure displays the outcomes of a pathway enrichment analysis for genes that interact with oxaliplatin and are dysregulated in gastric cancer compared to normal tissue as a result of their interaction with oxaliplatin. The list of pathways was extracted from the KEGG, Reactome, and WikiPathways databases.

Common gene between tumor-DEGs and oxaliplatin-interacting dysregulated genes in GC

To identify the set of common genes affected by oxaliplatin and consistently dysregulated in GC patients, we conducted a series of analyses, including differential expression, pathway enrichment, PPI network, and survival analysis. Figure 6A illustrates the intersection of tumor-DEGs and oxaliplatin-interacting dysregulated genes using a Venn diagram. It suggests that SERPINE1 may play a role in driving negative outcomes in GC patients who receive oxaliplatin treatment. According to the data in Table 2, it has been observed that oxaliplatin can enhance the expression of SERPINE1. This gene is considered to be significant and is found among the up-regulated genes in GC. Likewise, it showed a strong and significant relationship to overall survival in patients with GC (Fig. 6B).

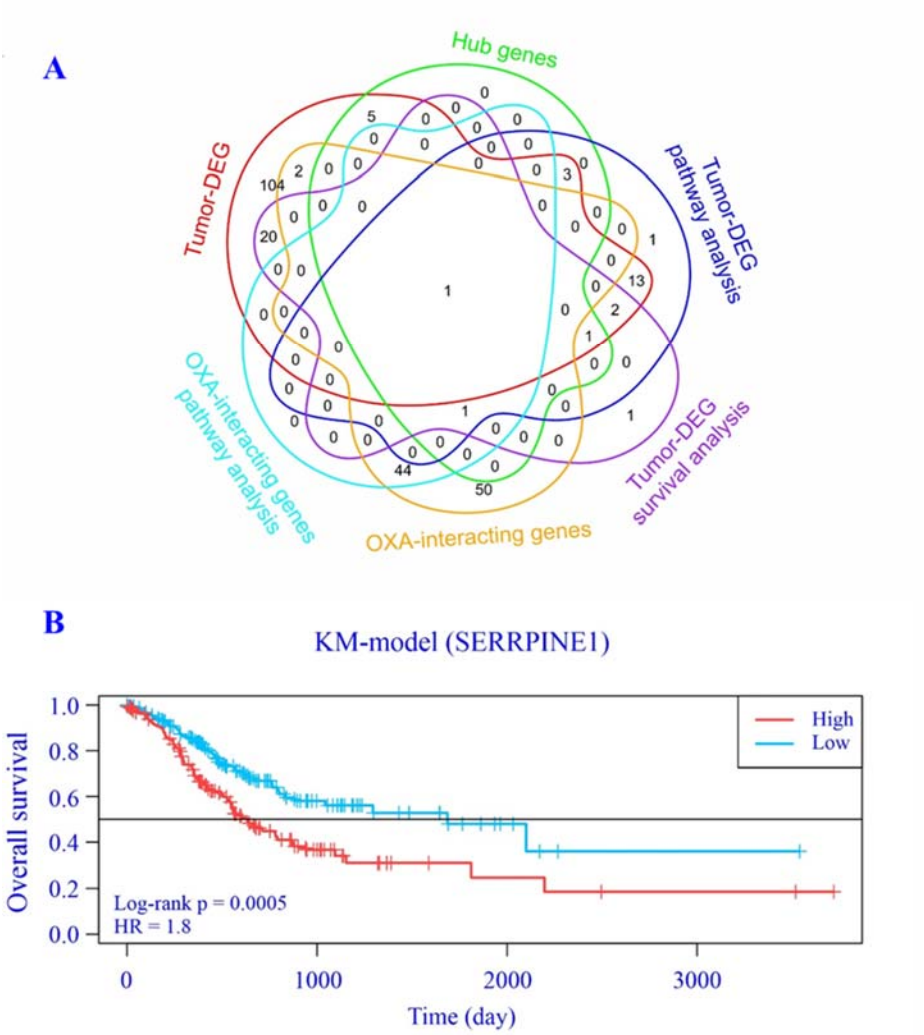

Fig. 6. Venn diagram and Kaplan-Meier curve. The Venn diagram of the distribution of significant genes listed in six analyses. (A) Venn diagram highlighting the overlapping of SERPINE1 in six different analyses. (B) Based on a log-rank $P < 0.05$ and HR#1, SERPINE1 is linked with overall survival. Patients with higher expression of SERPINE1 had significantly poorer survival rates. The threshold for dividing stomach adenoma and adenocarcinoma patients into two groups was established based on the median expression value of each gene. The red and blue lines represent high and low expression of SERPINE1, respectively. A total of 343 tumor samples from patients with stomach adenoma and adenocarcinoma in the Cancer Genome Atlas cohort were examined.

DISCUSSION

The risk-benefit profile of oxaliplatin remains poorly understood. Due to its anticancer properties, oxaliplatin is considered a leading treatment option for GC. it is a member of the third generation of platinum compounds employed in chemotherapy and is progressively emerging as the principal medication for the treatment of advanced GC (21,22). Despite ongoing advancements in chemotherapeutic regimens for GC, certain patients still experience adverse effects after undergoing chemotherapy. Additionally, there are currently no clinically accessible biomarkers that can predict the adverse effects of oxaliplatin. Therefore, we conducted the current *in silico* study to predict the potential molecular mechanisms instigated by oxaliplatin that could lead to unfavorable consequences in GC patients.

We started by using the TCGA and GEO datasets to identify genes that exhibit consistent imbalances in GC tissue when compared to normal tissue. GC tissues showed overexpression of 39 genes and downregulation

of 112 genes, totaling 151 genes. We found a correlation between a lower overall survival rate in patients with GC and the increased expression of SERPINE1, TEAD4, SPP1, CTHRC1, and COL10A1 (n = 5), and the decreased expression of PDGFD, PLCXD3, PDK4, RECK, GHR, SLC16A7, COL4A5, PCDH7, ANGPT1, LRRC17, AFF3, PTGER3, CD36, ADAMTS1, JAM2, CLIC6, DMD, GPX3, ADH1B and CPE (n = 20). Zhu *et al*. suggested that CTHRC1 and SERPINE1 might be new molecular markers for GC that could help predict how well it will do, acting as oncogenes to help GC grow (23). The upregulation of TEAD4 was significantly correlated with adverse prognostic factors, such as increased tumor size, higher tumor grades, and lower survival rates in GC (24). Additionally, reports have highlighted the prognostic role of SPP1 in GC patients (25). Also, the overexpression of COL10A1 was indicative of a poor prognosis for GC, has potential in prognostic evaluation, and expands immunotherapy options for GC patients (26).

Moreover, this research discovered the pathways that are regulated by tumor-DEGs. As anticipated, their primary involvement was in gastrointestinal and metabolic processes, including gastric acid secretion and peptide hormone metabolism. Additionally, they had a role in cancer progression through activities such as degradation of collagen, the extracellular matrix, and extracellular matrix architecture. The aforementioned findings were previously elucidated in the study conducted by Sadegh *et al*. (27). They identified DEGs in the GC, which were primarily enriched in biological processes such as extracellular matrix organization, collagen fibril organization, and extracellular structure organization for the upregulated genes. For the downregulated genes, the DEGs were mainly involved in the positive regulation of peptide hormone secretion (27).

To identify the subset of genes that are often affected by oxaliplatin and consistently dysregulated in GC patients, 2632 genes that interact with oxaliplatin were obtained from the CTD. Among them, 97 genes showed expression in patients with GC. *In silico* analysis allowed us to get binary linkages of genes that are significant for oxaliplatin. Hence, the expression of each gene was compared with the specific type of interaction reported between oxaliplatin and these genes. It was shown that oxaliplatin enhances the expression of 55 genes and suppresses the expression of 29 genes. Also, oxaliplatin significantly increased/decreased the expression of 7 genes from the set (Table S1).

To further explore the potential mechanisms of oxaliplatin-induced toxicity, we identified a set of genes that interact with oxaliplatin. By integrating these genes with the DEGs identified from TCGA and GEO, several key pathways were recognized that may contribute to oxaliplatin-related adverse effects including “MAPK3 (ERK1) activation”, “interleukin-6 signaling”, “transcriptional activation of p53 responsive genes”, “dissolution of fibrin clot”, and “nuclear events stimulated by ALK signaling in cancer”. Among these, a total of 45 genes were identified significant in the control of pathways, as shown in Fig. 5. Out of them, oxaliplatin mediated reversion of the expression of seven significant genes involved in GC, including BIRC5, CAV1, CDH2, IL6, JUN, SERPINB2, and TYMS, which have been indicated playing an important role as tumor suppressor (28-30). While oxaliplatin mediated the progression of GC six genes expression (BLVRB, CDKN2A, MAPK3, PLAU, PTGS2, and SERPINE1), which could explain its oncogenic effects. Chen *et al*. showed that SERPINE1 could promote the occurrence and development of GC, while deletion of SERPINE1 inhibited the progression of GC (31). This analysis aided in identifying biological pathways that have the potential to cause negative outcomes in GC patients who have undergone treatment with oxaliplatin. The identification of SERPINE1 as a hub gene in the PPI network further highlights its central role and biological significance, reinforcing its potential importance in the molecular mechanisms underlying GC.

Due to genetic differences in individuals, some patients have a poor response to chemotherapy. Therefore, it is necessary to identify a biomarker for tracking the response to chemotherapy. For this reason, we searched for a biomarker in our study. We conducted a

series of analyses, including differential expression, pathway enrichment, the PPI network, survival analysis, and the relationship between tumor-DEGs and oxaliplatin-interacting dysregulated genes. It suggests that SERPINE1 may play a role in driving negative outcomes in GC patients receiving oxaliplatin treatment (Fig. 6). Oxaliplatin can enhance the expression of SERPINE1. The upregulation of this gene is considered significant in GC. Likewise, it showed a strong and significant relationship to overall survival. Several studies have demonstrated a correlation between an overexpression of SERPINE1 and a poor prognosis in GC (19,20).

There are distinct advantages to utilizing bioinformatics analysis in the field of toxicology. Large-scale multi-omics datasets, such as those presented in the TCGA, have greatly enhanced our understanding of the characteristics of a wide range of tumors. These cancer datasets provide valuable insights into the characteristics of human cancers at various levels, enabling the development of more precise and effective treatments (32). In addition, these data may help accelerate the development of personalized cancer therapy strategies and predict possible adverse effects for each patient. In toxicological research, some data repositories allow for the initial analysis and identification of chemical gene interactions and disease relationships (33). One of these databases is the CTD (34). By employing a range of methods, researchers can conduct initial toxicology studies that provide insights into the potential adverse effects of the chemical under investigation. These findings then inform subsequent *in vitro* and *in vivo* analyses.

While our *in silico* analysis provides valuable insights, it is important to acknowledge its limitations. Through the utilization of data mining and DEG analysis, we conducted a comprehensive investigation into the pharmacokinetic-toxicological profile of oxaliplatin. Further experimental validation is needed to confirm these findings. Despite these limitations, our study highlights the potential of *in silico* approaches to identify novel biomarkers and therapeutic targets for GC.

CONCLUSION

Oxaliplatin, a chemotherapeutic drug containing platinum, is widely acknowledged as the main medication for treating advanced gastric cancer. However, the safety profile of using oxaliplatin to treat gastric cancer patients has not yet been clearly established. This study used the GEO datasets and the TCGA cohort to find differentially expressed genes in gastric cancer. Then we checked the interaction of these genes with Oxaliplatin, the results revealed that Oxaliplatin (OXA) mediated reversion of GC expression of seven significant genes (BIRC5, CAV1, CDH2, IL6, JUN, SERPINB2, and TYMS) while, oxaliplatin mediated progression of GC expression of six genes (BLVRB, CDKN2A, MAPK3, PLAU, PTGS2, and SERPINE1) which could potentially contribute to the advancement of GC. Therefore, the genomic signature of patients with gastric cancer (GC) could be a crucial aspect to consider when evaluating the risk-to-benefit ratio of oxaliplatin therapy. In addition, SERPINE1 showed a strong correlation with overall survival. Further investigation is required in both preclinical and clinical settings to validate these findings.

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Conflict of interest statement

All authors declared no conflict of interest in this study.

Authors' contributions

H. Khanahmad and A. Khalafiyan designed the study. Development of methodology and writing, review, and revision of the manuscript were done by F. Khara, A. Heydari, M. Fadaie, A. Khalafiyan, H. Khanahmad. H. Khanahmad supervised the study. All authors read and confirmed the finalized article.

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