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Esophageal chemical burns as a risk factor for esophageal malignancies: in-silico analyses – experimental research

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Introduction: Esophageal chemical burns often occur through accidental or intentional oral consumption of chemical agents and lead to severe complications such as esophageal stricture, acute perforation, and even death. Esophageal squamous cell carcinoma is a squamous epithelium tumor that lines the normal esophagus. Additionally, adenocarcinomas are tumors located at the interface between the distal esophagus and the proximal gastric and divided into esophageal adenocarcinoma and gastric-cardia adenocarcinoma. Various conditions, such as chemical burns, are considered risk factors in the disease's pathogenesis. In the in-silico study, the authors aim to present the relationship between chemical burns and esophageal cancer by analyzing bioinformatics genetic data.

Methods: The proper gene set was extracted using the 'GEO' database. The string web tool was utilized to form the gene-interaction network. Gephi and Cytoscape software were applied to achieve network analysis.

Results: According to in-silico data, 26 genes, including NCAPH, DLGAP5, CCNB1, KIF11, KIAA0101, CDCA5, BIRC5, NUF2, BUB1B, RRM2, TTK, CDC20, NUSAP1, CCNB2, CCNA2, MELK, TPX2, PRC1, KIF4A, CENPF, TOP2A, CDK1, ASPM, CEP55, BUB1, KIF20A were extracted that can be regarded as the most critical shared genes between chemical burns and esophageal cancer.

Conclusion: In sum, esophageal chemical burns can be related to the occurrence of esophageal cancer. Moreover, esophageal chemical burn is an external factor that upregulates present genes and can be regarded as a worsening prognosis or risk factor for esophageal cancer.

Keywords: burns, cancer, chemical burns, esophageal cancer, esophageal malignancies

Introduction

Burn injuries are a significant global health concern with far-reaching societal impacts[1,2]. These injuries involve damage to the skin and underlying tissues, usually caused by exposure to fire, electricity, radiation, or chemical agents[3–5]. Furthermore, managing such wounds presents significant challenges due to the pronounced and prolonged systemic dysfunction they cause[6–8]. Hence, chemical burns account for about 10.7% of burns that incidence in the adult population[9], affect the upper gastrointestinal tract, occur through the ingestion of chemical corrosive, and lead to injuries and ulcers in the oral cavity, esophagus, and gastric mucous membrane[10]. Esophageal chemical burns are a significant health concern across various age groups, capable of causing severe injuries to the upper digestive system and esophagus[11]. Esophageal chemical burns typically result from accidentally or intentionally ingesting chemical agents orally and can lead to severe complications such as esophageal stricture, acute

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perforation, and even death. The severity of the damage depends on the type of tissue, the chemical and physical properties (whether acidic or alkaline, solid or liquid) of the caustic substance, and the duration of contact[12]. Complications after chemical burns vary based on chemical properties (acidic or alkaline). In contrast, alkaline substances cause liquid necrosis in the esophageal mucosa and submucosa, while acidic substances lead to coagulative necrosis in the muscular mucosa layer[13]. Also, the acute necrosis phase is associated with reduced tissue perfusion, lipid peroxidation, hydrolysis, active oxygen radicals, and inflammation, which lead to scarring and esophageal strictures[14].

Esophageal cancer, estimated at 400 000 cases annually, is the ninth most common malignancy worldwide and the sixth leading cause of cancer-related death[15]. Based on the origin of cells, esophageal cancer is mainly categorized into squamous cell carcinoma and adenocarcinoma. Other less common forms of esophageal malignancy include melanoma, sarcoma, lymphoma, and carcinoid tumors[16]. Esophageal squamous cell carcinoma is a type of tumor that forms in the squamous epithelium lining of the esophagus. Adenocarcinomas are tumors that occur at the junction between the lower part of the esophagus and the upper part of the stomach. They are further classified as esophageal adenocarcinoma and gastric-cardia adenocarcinoma[17]. Various factors such as lifestyle, genetics, and inflammation are considered risk factors in the pathogenesis of the disease[18]. Chronic inflammation, in particular, plays a critical role in the pathogenesis of numerous malignancies, including esophageal cancer. Long-term exposure to inflammatory triggers (such as burns) leads to the establishment of an inflammatory condition characterized by pro-inflammatory cytokines and cells[19]. Chronic inflammation can disrupt the regulation of cell division, differentiation, and survival of stem cells by secreting cytokines such as epidermal growth factor and angiogenic growth factors like vascular endothelial growth factor and fibroblast growth factor 2. This disruption may lead to the development of cancer[20].

Additionally, there is various clinical evidence indicating a relationship between chemical burns and the incidence of esophageal malignancies[21–23]. In this context, previous studies have shown a history of chemical burns among individuals diagnosed with esophageal cancer. In this regard, Santacruz *et al.*[24], in a case report, revealed that an individual with esophageal malignancy had suffered a chemical burn to the esophagus 50 years prior. Likewise, Singh *et al.*[25] demonstrated that individuals with esophageal cancer often had a history of esophageal mucosal injury caused by corrosive agents such as sodium.

Research questions

This study was conducted to answer the following research questions:

- What are the critical shared genes between chemical burns and esophageal cancer?
- Can esophageal chemical burns be a risk factor for esophageal malignancies?

Aim

However, the relationship between the inflammatory conditions of chemical burns and esophageal cancer is still not well understood. In the in-silico study, the authors aim to present the relationship between chemical burns and esophageal cancer by analyzing bioinformatics genetic data to provide a target for advancing future studies on chemical burn complications.

HIGHLIGHTS

- According to in-silico data, 26 genes, including NCAPH, DLGAP5, CCNB1, KIF11, KIAA0101, CDCA5, BIRC5, NUF2, BUB1B, RRM2, TTK, CDC20, NUSAP1, CCNB2, CCNA2, MELK, TPX2, PRC1, KIF4A, CENPF, TOP2A, CDK1, ASPM, CEP55, BUB1, KIF20A were extracted that can be regarded as the most critical shared genes between chemical burns and esophageal cancer.
- In sum, esophageal chemical burns can be related to the occurrence of esophageal cancer.
- Moreover, esophageal chemical burn is an external factor that upregulates present genes and can be regarded as a worsening prognosis or risk factor for esophageal cancer.

Methods

Extraction of 'gene collection'

In the current study, the gene expression omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) database was utilized to extract related gene sets. GEO is a database managed by the National Center for Biotechnology Information that provides gene expression profiles and RNA methylation profiles. Current high-throughput screening genomics data are supplied from microarray or RNA-Seq experimental data[26]. The keywords 'chemical burns' and 'esophageal cancer' were searched separately in the database. For the identification of proper gene series accessions (GSE), the cases that contained 'intervention protocols' and 'without a control group' were excluded. Also, for extraction of validated and upregulated genes, log foldchange > 1 and P value <0.05 were considered[27].

Identification of shared genes

To detect shared upregulated genes among chemical burn and esophageal cancer, the bioinformatics and evolutionary genomics website (https://bioinformatics.psb.ugent.be/webtools/Venn/) were used to identify shared genes and create the Venn diagram. The Venn diagram is widely used to visually present the unions, intersections, and differences among multiple datasets. Many programs for use in various research fields have generated Venn diagrams[28].

Formation of gene-interaction network

Using the STRING database (https://string-db.org/), the interaction network of the extracted genes was formed. The string is a biological database and web resource that contains information on known and predicted protein–protein interactions. Data in the STRING database is derived from various sources, including experimental data, computational prediction methods, and public text collections[29].

Network analysis

Density analysis

Utilizing Cytoscape software (V 3.9.1), the achieved networks were analyzed. Cytoscape, an open-source tool, visualizes molecular interaction networks and integrates them with gene expression profiles and other state information[30].

Betweenness and degree analysis

The Gephi software (V 0.9.7) was applied to analyze the criteria. Gephi is an open-source tool for analyzing graphs and networks. To display large networks in real-time and to facilitate exploration, Gephi uses a 3D render engine. Data can be processed efficiently using a flexible and multi-tasking architecture, producing valuable visual results[31].

Identification of effective medications

TISIDB

The 'Cancer Informatics and Systems Biology Lab' (TISIDB) (http://cis.hku.hk/TISIDB/) website was applied to recognize effective genes-related medications. TISIDB is a web portal for tumor and immune system interaction, integrating multiple heterogeneous data types[32].

Drug bank

The 'drug bank' (https://go.drugbank.com/) database was used to identify drugs' clinical trials. 'Drug bank' is a database that

Table 1

The sub-network analysis by Gephi.

ID	Label	Degree	Weighted degree	Betweenness centrality	Authority
NCAPH	NCAPH	52	52	1.697759	0.142807
DLGAP5	DLGAP5	52	52	1.697759	0.142807
CCNB1	CCNB1	52	52	1.697759	0.142807
KIF11	KIF11	52	52	1.697759	0.142807
KIAA0101	KIAA0101	52	52	1.697759	0.142807
CDCA5	CDCA5	52	52	1.697759	0.142807
BIRC5	BIRC5	52	52	1.697759	0.142807
NUF2	NUF2	52	52	1.697759	0.142807
BUB1B	BUB1B	52	52	1.697759	0.142807
RRM2	RRM2	52	52	1.697759	0.142807
TTK	TTK	52	52	1.697759	0.142807
CDC20	CDC20	52	52	1.697759	0.142807
NUSAP1	NUSAP1	52	52	1.697759	0.142807
CCNB2	CCNB2	52	52	1.697759	0.142807
CCNA2	CCNA2	52	52	1.697759	0.142807
MELK	MELK	52	52	1.697759	0.142807
TPX2	TPX2	52	52	1.697759	0.142807
PRC1	PRC1	52	52	1.697759	0.142807
KIF4A	KIF4A	52	52	1.697759	0.142807
CENPF	CENPF	52	52	1.697759	0.142807
TOP2A	TOP2A	52	52	1.697759	0.142807
CDK1	CDK1	52	52	1.697759	0.142807
ASPM	ASPM	52	52	1.697759	0.142807
CEP55	CEP55	52	52	1.697759	0.142807
BUB1	BUB1	52	52	1.697759	0.142807

Table 2

Gene-related drugs.

Gene	Drug	Application for carcinoma	Application for gastrointestinal cancers
KIF11	Filanesib	Y	N
BIRC5	Berberine*	Y	Y
	LY2181308	Y	N
	Reserpine	N	N
CDK1	Alvocidib*	Y	Y
	AT7519	Y	N
	Seliciclib	Y	N
RRM2	Cladribine	Y	N
	Imexon	Y	N
	Gallium nitrate	Y	N
	Motexafin gadolinium	Y	N
TOP2	Trovafloxacin	N	N
	Daunorubicin	Y	N
	Etoposide	Y	N
	Dactinomycin	N	N
	Doxorubicin	Y	N
	Norfloxacin	Y	N
	Levofloxacin	N	N
	Ofloxacin	N	N
	Idarubicin	Y	N
	Podofilox	Y	N
	Mitoxantrone	Y	N
	Genistein	Y	N
	Amonafide	Y	N
	Elsamitrucin	Y	N
	13-deoxydoxorubicin	Y	N
	RTA 744	Y	N
	Aldoxorubicin	Y	N
	Amrubicin	Y	N
	Becatecarin	Y	N
	Annamycin	Y	N
	Finafloxacin	N	N
	Moxifloxacin	N	N
	Amsacrine	Y	N
	Dexrazoxane	Y	N
	Valrubicin	Y	N
	Teniposide	Y	N
	Epirubicin	Y	N
	Ciprofloxacin	N	N

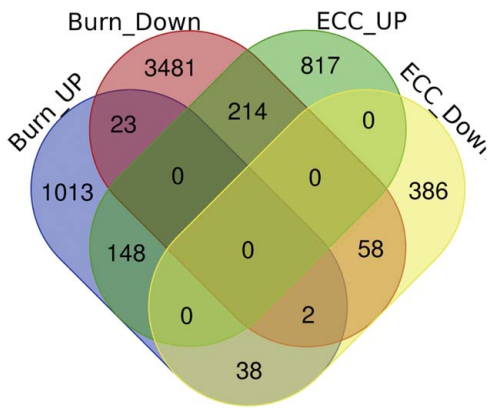

Figure 1. Shared upregulated genes between chemical burns and esophageal cancer.

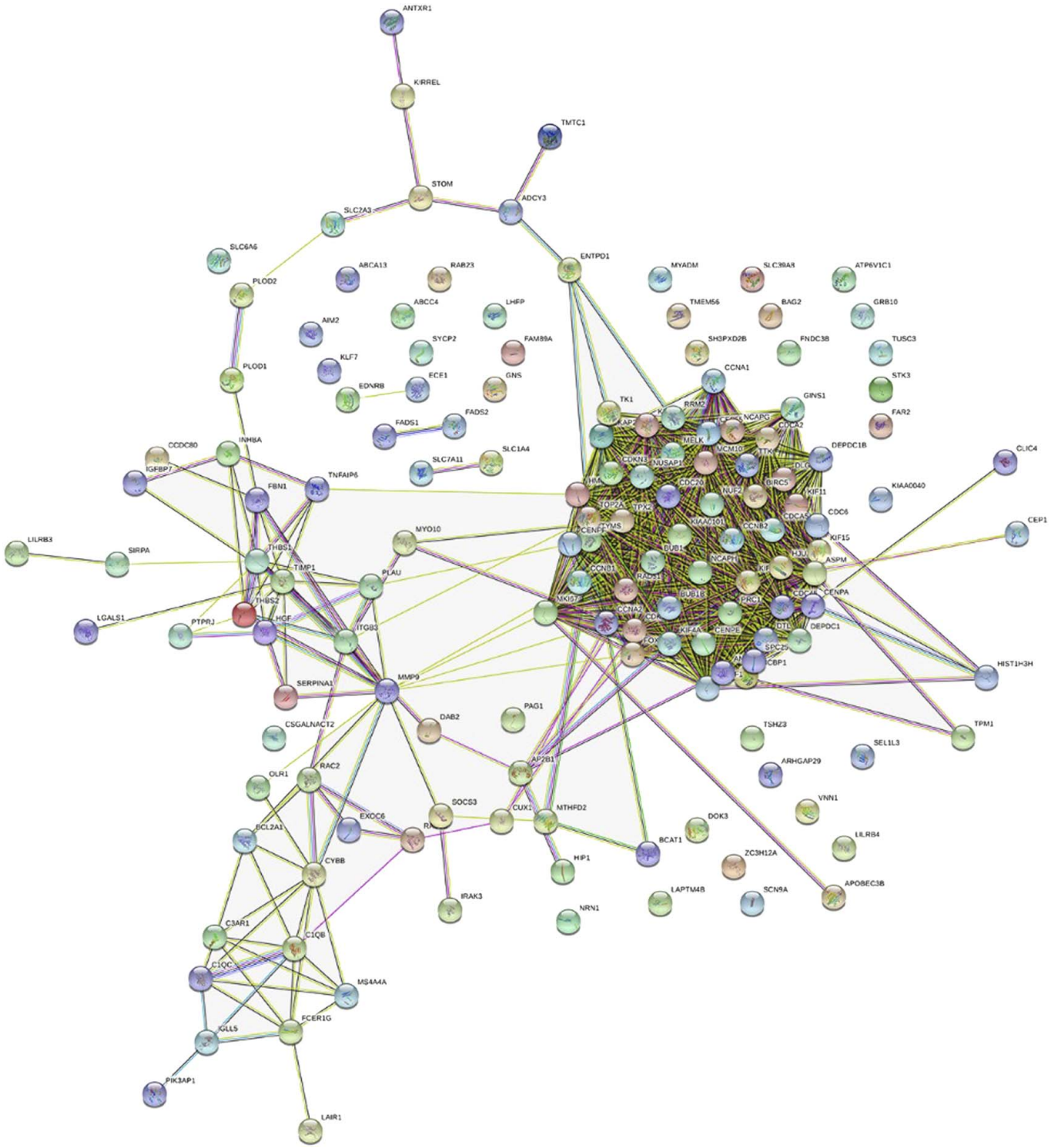

Figure 2. The gene-interaction network is illustrated by the 'string' web tools.

includes comprehensive molecular information, mechanisms, interactions, and targets of drugs[33].

Ethical approval

This article does not contain any studies with human or animal subjects performed by authors and does not require ethical approval or consent.

Results

Gene extraction

Using the GEO database, two GSEs, including GSE75241 and GSE19743, were obtained (Tables 1 and 2), and by applying the criteria, 1179 genes related to esophageal cancer and 1199 genes related to chemical burns were obtained. Additionally, by using

the Venn diagram, 148 genes were identified that upregulated in chemical burn and esophageal cancer (Fig. 1).

Network formation and analysis

Furthermore, using the STRING database, the interaction network of the extracted genes was formed (Fig. 2). Interestingly, the present network contains two sub-networks with various densities. Appling network analysis, the sub-network with a higher density was detected and selected (Fig. 3). Ultimately, the genes with the highest betweenness and degree criteria were selected, which included NCAPH, DLGAP5, CCNB1, KIF11, KIAA0101, CDCA5, BIRC5, NUF2, BUB1B, RRM2, TTK, CDC20, NUSAP1, CCNB2, CCNA2, MELK, TPX2, PRC1, KIF4A, CENPF, TOP2A, CDK1, ASPM, CEP55, BUB1, KIF20A (Table 1 and Fig. 4).

Drug findings

Based on 'TISIDB' and 'drug bank' data, among 26 genes, seven genes have 100 related drugs. Among 100 gene-related drugs, 39 cases are approved for clinical trial. Of 39 cases, 29 have treatment applications for carcinomas, and two medications were used as a treatment for gastrointestinal cancers (Table 2).

Discussion

According to in-silico data, 26 genes, including NCAPH, DLGAP5, CCNB1, KIF11, KIAA0101, CDCA5, BIRC5, NUF2, BUB1B, RRM2, TTK, CDC20, NUSAP1, CCNB2, CCNA2, MELK, TPX2, PRC1, KIF4A, CENPF, TOP2A, CDK1, ASPM, CEP55, BUB1, KIF20A were extracted that can be regarded as the most critical shared genes between chemical burns and esophageal cancer. Overall, the findings indicate that chemical burn injuries can lead to the development of esophageal cancer. This context was described in numerous previous studies. Consistent with the results of the present study, it has been shown that chemical burns can cause esophageal stenosis, which may ultimately result in cancer[34]. Additionally, it has been demonstrated that ethanol induces chemical burns on the esophageal mucosal surface, affects the microbial homeostasis of the oral cavity and esophagus, and leads to damage to the esophageal mucosal barrier[35]. Therefore, it appears that chemical burns can generally be considered a risk factor for esophageal cancer.

Burn injuries can have profound physical and emotional impacts, often giving rise to a range of psychological challenges, with anxiety being a prominent issue[36–38]. Based on histological studies, the current genes have a significant expression in esophageal tissues[39]. Moreover, previous evidence shows that the present genes are potentially over-expressed in gastrointestinal carcinomas[40]. For example, based on evidence, the down-regulation of NCAPH can prevent the proliferation of esophageal cancer cell lines[41]. DLGAP5 has also shown higher expression in esophageal cancer cell lines[42]. Additionally, studies have shown that CCNB1, an oncogene, is linked to promoter methylation, which may related to poor esophageal cancer prognosis[43]. Gao *et al*.[44] also demonstrated that KIF11, acting as a mitogen, can trigger uncontrolled division in various cell types. Additionally,

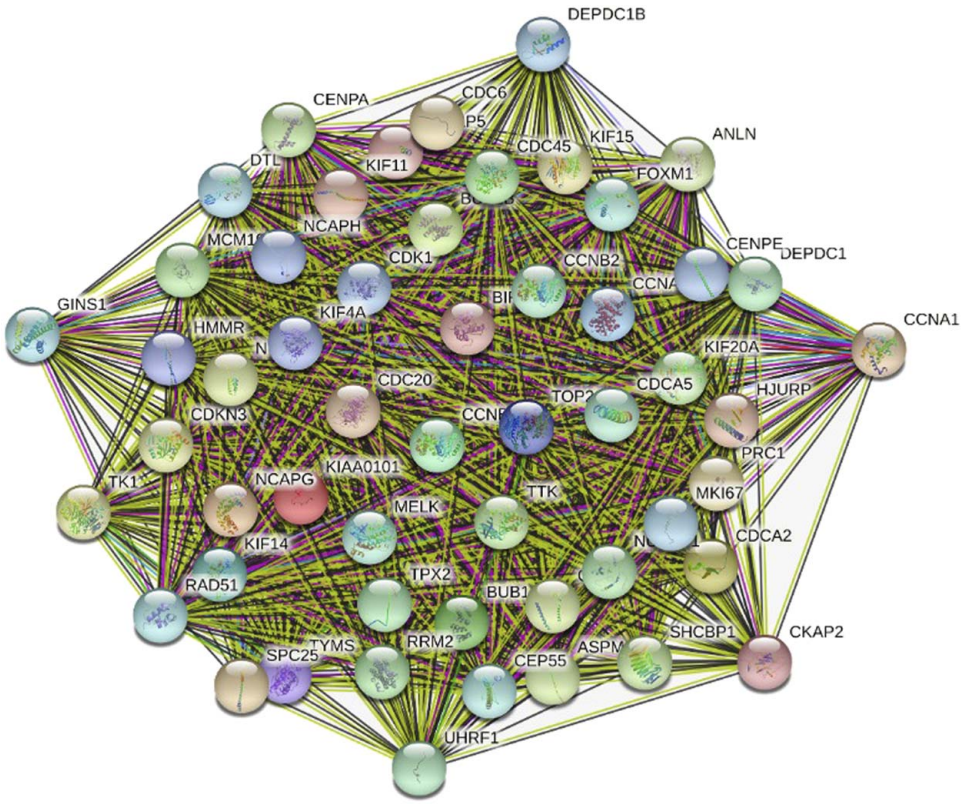

Figure 3. Isolated sub-network with higher density.

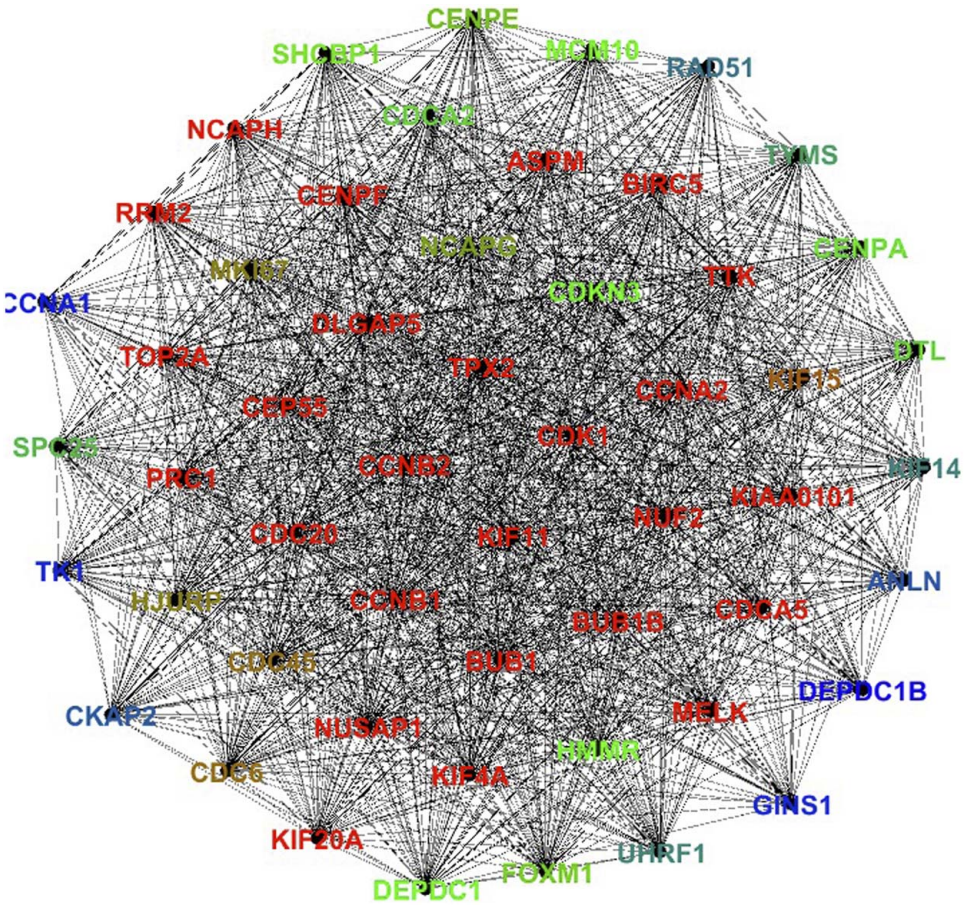

Figure 4. Visual analysis of the obtained sub-network illustrated by Gephi.

Zhang *et al.*[45] demonstrated that KIAA0101 could also result in resistance to anticancer drugs such as cisplatin.

Also, according to 'Enrichr' data, the present gene set is involved in cellular processes such as mitotic spindle organization, microtubule cytoskeleton organization involved in mitosis, mitotic sister chromatid segregation, chromosome condensation, and spindle assembly checkpoint signaling. The current cellular processes are essential in chemical burn wound healing by facilitating and increasing cell division in tissues, causing tissue damage, and releasing cytokines and trophic mediators; the damaged area cells proliferate through mitosis, ultimately leading to tissue regeneration[46–48]. Further, the incidence of chemical burns and subsequent cytokine secretion, cell division, and replication is increased by influencing trophic factors, such as mitotic arrest deficient 2[49]. In addition to the association of mitotic arrest deficient 2 with cancer incidence, it also has a strong relationship with increased risk of all-cause mortality and cancer recurrence[50]. Meanwhile, through induction of inflammation, chemical burns drive dysregulation of the trophic processes and may be related to incidences of esophageal cancer[51,52]. However, the regulation of the genes-related processes can be necessary to prevent the incidence of cancers; subsequently, lack of control leads to the development of cancers and malignancies such as esophageal cancer[53,54], and these genes can be a potential target for managing the complication of chemical burns.

Furthermore, 'Enrichr' data has shown that the gene set can be involved in essential pathways such as the cell cycle, Amp kinase (AMPK) signaling pathway, p53 signaling pathway, and forkhead box transcription factors (FoxO) signaling pathway. Several studies revealed that FoxOs, including differentiation, apoptosis, cell proliferation, DNA damage and repair, and mediators of oxidative stress, mediate a wide range of cellular functions. A growing body of evidence implicates dysregulation of the functioning of FoxO proteins in cancer progression and tumorigenesis[55]. Also, Fields *et al.*[56] demonstrated that chemical burns are a potent carcinogen that lead to oxidative stress in the FoxO signaling pathway and alters the cell cycle. In this regard, through the incidence of chemical burns, FoxO signaling may also upregulated in damaged tissue cells, which lack control of this messaging path and may lead to malignancy.

Additionally, p53 suppresses tumor formation and protects against DNA damage by inducing cell cycle arrest, repair, or apoptosis. Also, nearly 50% of human cancers exhibit impaired tumor suppressor function due to the disruption of the p53 signaling pathway[57]. However, the p53 pathway could be disrupted during severe burn injuries, and Harland *et al.*[58] showed that various burns could disrupt the p53 signaling pathway and lead to carcinoma. Indeed, by down-regulating the p53 pathway, it can be argued that chemical burns may prevent cell cycle arrest, which can exponentially

lead to uncontrolled cell divisions. Furthermore, former studies demonstrated the role of AMPK in cancer pathogenesis through metabolism dysregulation[59]. Based on the evidence, through hypermetabolism, chemical burns impact the AMPK pathway and induce malignancies[60,61].

In the current study, BIRC5 and CDK1 are the target genes for treating various cancers, especially gastrointestinal cancers. Liang *et al.*[62] revealed that BIRC significantly correlates with the prognosis of burn injuries. Shang *et al.*[63] have shown that the downregulation of BIRC5 could inhibit the migration and invasion of esophageal cancer cells. Oparina *et al.*[64] also, a meta-analysis conducted to investigate three cohort studies discovered that an overall increase in the expression of the BIRC5 gene could potentially be linked to a poor prognosis among breast cancer patients. Also, former evidence has shown that Berberine might have antitumor activity on esophageal cancer[65], and Berberine can be regarded as a helpful medication for chemical burns management. However, Mumlek showed that BIRC5 polymorphisms do not significantly impact oropharyngeal squamous cell carcinoma patient survival[66]. Furthermore, the demonstrations indicated that CDK1 is related to the prognosis of cancer and burn injuries[67,68]. Also, alvocidib (the gene-related drug) might be a promising medication for managing chemical burn injuries[69]. Additionally, Mughal *et al.*[41], in a review, indicated that CDK inhibitors such as alvocidib may have potent clinical efficacy on cancer prognosis.

Limitations

The present study is a bioinformatics investigation that explores the genetic relationship between burn injuries and esophageal cancer. However, certain limitations must be acknowledged. First, due to a lack of resources, this study was unable to conduct clinical experimental evaluations. Additionally, the study focused solely on examining gene networks and shared genes despite the possibility that these two conditions may share numerous aspects in transcriptomics or genomics.

Recommendation for future research

Based on the findings of this study, researchers can consider the following research recommendations in the future:

1. Conducting cohort studies in populations affected by chemical burns to confirm the roles of the discovered genes.
2. Investigating shared noncoding RNA between chemical burns and esophageal cancer.
3. Identifying the network, expression patterns, and interactions among the discovered genes.

Implementation for clinical practice

Based on the results, the identified genes could be utilized to create gene therapy medications for treating esophageal cancer. Additionally, these genes could be examined as biomarkers to improve the monitoring of chemical burn wounds. Moreover, the prescribed medicines may be a viable treatment option for managing chemical burn wounds.

Conclusion

Overall, according to the achieved gene expression pathway data, esophageal chemical burns can be related to the occurrence of esophageal cancer. Moreover, esophageal chemical burn is an external factor that upregulates present genes and can be regarded as a worsening prognosis or risk factor for esophageal cancer. At last, the obtained gene network can be considered a therapeutic and research target for a better understanding of the relationship between chemical burns and esophageal cancer incidence.

Ethical approval

This article does not contain any studies with human or animal subjects performed by any authors and does not require ethical approval and consent.

Consent

This article does not contain any studies with human or animal subjects performed by any authors and does not require ethical approval and consent.

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Author contribution

All authors were involved in the study concept and design, data acquisition, data interpretation, drafting of the manuscript, revision of the manuscript, and the final version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

We could not register our manuscript in the Research Registry UIN: www.researchregistry.com due to internet access restrictions and international sanctions. We live in Iran. We hardly even meet the basic needs of our daily life. We do not receive any funding for our research and we cannot pay for our research. Please excuse us from registering this manuscript in the Research Registry UIN: www.researchregistry.com.

Guarantor

Ramyar Farzan (MD).

Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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