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Chemical burn wounds as a risk factor for gastric cancer: in-silico analyses—experimental research

Mohammad Reza Zabihi[a], Mohammad Akhoondian, MSc[b], Mobina Tohidian[e], Samad Karkhah, MSc[c], Pooyan Ghorbani Vajargah, MSc[c], Seyed Amirhossein Mazhari, MD[g], Bahar Farhadi, MD[f,*], Ramyar Farzan, MD[d,*]

Introduction: The present study employs bioinformatics tools to identify shared upregulated genes between chemical burns and gastric cancer.

Methods: Gene Expression Omnibus (GEO) retrieved gene sets for this investigation. GSEs with *P* value less than 0.05 and LOG fold change (FC) greater than 1 were valid and upregulated. Gastric cancer and chemical burn common elevated genes were found using Venn diagram online tools. In the second stage, the "string" visualized gastric cancer elevated genes network, and non-coding RNAs were deleted, and "interaction" greater than 1 was examined to choose important gene nodes. Next, they explored the String gene-interaction network for common genes. To determine the most interacting genes, Gephi (V 0.9.7) used "betweenness centrality" greater than "0" to evaluate the twenty-gene network. TISIDB and drug banks provide gene-related medications.

Results: In the present study, two genes, including ALOX5AP and SERPINB2, were obtained, with the highest centrality among chemical burns and gastric cancer shared genes. Additionally, the current study presented five drugs, including Urokinase, Tenecteplase, DG031, AM103, and Fiboflapon, which can have predicted effects on gastric cancer following chemical burns.

Conclusion: According to current in-silicon analyses, ALOX5AP and SERPINB2 are linked genetic keys between gastric chemical burn and cancer. Considering that burn is an environmental factor that leads to the upregulation of the two genes thus, the chemical burn can be related to the incidence of gastric cancer.

Keywords: burns, cancer, chemical burns, gastric cancer, wounds

Introduction

Burn injuries constitute a widely recognized global health challenge with significant societal implications[1–13]. These injuries cause damage to the skin and underlying tissues, often resulting from exposure to fire, electricity, radiation, or chemical agents[14–30]. Importantly, they cause severe pain and can lead to adverse physical and psychological consequences for affected individuals[31–46]. Moreover, managing such wounds poses formidable challenges due to the pronounced and prolonged systemic dysfunction they induce[47–66]. Chemical burns of the upper gastrointestinal tract can occur through the ingestion of corrosive chemicals, leading to injuries and ulcers in the oral cavity, esophagus, and gastric mucous membrane[67]. Various chemical agents and drugs may cause chemical burns, and the severity of these burns depends on factors such as concentration, volume, and duration of tissue contact[68]. Also, corrosive substances can be classified as acidic or alkaline, causing tissue damage through different mechanisms[69]. With the exception of hydrofluoric acid, acids induce coagulation necrosis by forming a coagulum that restricts tissue penetration, thereby reducing the incidence of

HIGHLIGHTS

- In the present study, two genes, including ALOX5AP and SERPINB2, were obtained, with the highest centrality among chemical burns and gastric cancer shared genes.
- The current study presented five drugs, including Urokinase, Tenecteplase, DG031, AM103, and Fiboflapon, which can have predicted effects on gastric cancer following chemical burns.
- According to current in-silicon analyses, ALOX5AP and SERPINB2 are linked genetic keys between gastric chemical burn and cancer.
- Considering that burn is an environmental factor that leads to the upregulation of the two genes thus, the chemical burn can be related to the incidence of gastric cancer.

[a]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, [b]Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, [c]Department of Medical-Surgical Nursing, School of Nursing and Midwifery, [d]Department of Plastic & Reconstructive Surgery, School of Medicine, Guilan University of Medical Sciences, Rasht, [e]Department of Anatomy and Cell Biology, Shahi Beheshti University of Medical Sciences, Tehran, [f]School of Medicine, Islamic Azad University, Mashhad Branch, Mashhad, Iran and [g]Student Research Committee, Azerbaijan Medical University, Baku, Azerbaijan

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*Corresponding author. Address: School of Medicine, Islamic Azad University, Mashhad Branch, Mashhad, Iran. Tel.: +98 915 111 4296; fax: +98 513 328 259. E-mail: baharrrfrhadi1387@gmail.com (B. Farhadi); Department of Plastic & Reconstructive Surgery, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran. Tel.: +98 911 131 1055; fax: +98 133 332 586. E-mail: ramyar.farzan2001@yahoo.com (R. Farzan).

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full-thickness damage[70]. Conversely, alkalis cause liquefaction necrosis, increasing the likelihood of transmural injuries, often accompanied by peri-esophageal injury and harm to surrounding organs such as the respiratory system[71]. The preferential involvement of the stomach in acid consumption is attributed to eschar development, which limits esophageal injury and reflex pylorospasm, thereby extending gastric contact duration, especially in the prepyloric zone when the amount of corrosive substance ingested is limited[72].

Gastric cancer ranks as the fifth most prevalent cancer and the third leading cause of cancer-related mortality worldwide[73]. Additionally, gastric cancer is twice as prevalent in men as in women[74]. Anatomically, gastric cancer is classified into true gastric adenocarcinomas and gastro-esophageal-junction adenocarcinomas, with histological subtypes including diffuse and intestinal forms[74]. The most common type of gastric cancer is adenocarcinoma, primarily developing through the loss of parietal cells and metaplasia[75]. Gastric metaplasia occurs due to reprogramming of differentiated epithelial cells[76]. Characterized by the presence of a normal cell line in a tissue where it is not typically found, mainly characterized by mucus secretion[77]. Epidemiological studies indicate the impact of inflammation on gastric cancer incidence, with chronic inflammation perpetuating a recurring pattern of metaplasia, a risk factor for gastric cancer development[78]. Inflammation is also associated with the transition of benign cells into malignant ones, as normal epithelial cells undergo epithelial-mesenchymal transition (EMT) to acquire characteristics such as invasion, resistance to apoptosis, and metastasis[79]. This mechanism is evident in embryogenesis, wound healing, and several forms of cancer when dysregulation occurs[80]. Interestingly, chemical burns, as potent sources of inflammation[81], may be associated with gastric cancer incidence[82]. However, while a few case reports have suggested a link between gastric cancer and a history of gastric chemical burns[83,84], the relationship between the two disorders remains poorly understood. Clinical studies have established a connection between different types of ulcers and the development of gastric cancer. For instance, Sonnenberg and colleagues, suggested that stomach acid-induced ulcers, similar to chemical burns, might be associated with gastric cancer[85]. Additionally, research by Parikh *et al*.[86], linked chemical burns caused by iron ions in the gastric fundus with malignancies in this region. Mori *et al*.[87], also demonstrated that L-menthol can induce a condition akin to chemical burns, leading to the transformation of gastric mucosa into atrophic mucosa, potentially contributing to the formation of pathological lesions. In summary, evidence suggests that chemical burns in the stomach area caused by corrosive substances can lead to hyperplasia and the development of neoplasms in gastrocarcinomas.

Overall, this study employs bioinformatics tools to identify shared upregulated genes between chemical burns and gastric cancer. Additionally, the findings of this study can serve as therapeutic and research targets for healing chemical burn wounds.

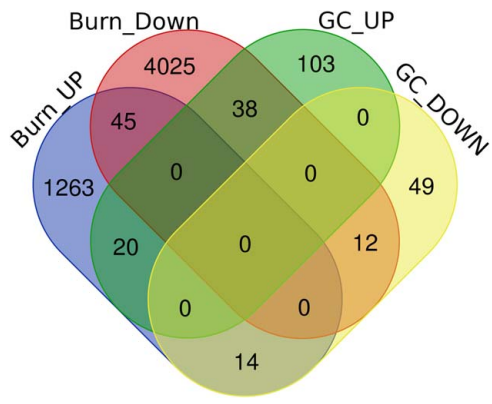

Figure 1. Shared upregulated genes between chemical burns and gastric cancer.

Methods

Gene identification

Gene Expression Omnibus (GEO)

The GEO (https://www.ncbi.nlm.nih.gov/geo/) website was utilized to identify appropriate gene sets. GEO, provided by the Center for Biotechnology Information, offers high-throughput genomics screening data originating from microarray or RNA-Seq experiments[42]. The terms "gastric cancer" and "chemical burn" were used as queries in GEO. Cases with intervention protocols, samples fewer than 10, and lacking a control group were excluded. Finally, GSE19743 and GSE186582 were selected as suitable datasets for investigation in this study.

Venn diagram

To identify shared upregulated genes between gastric cancer and chemical burns, the Venn diagram web tools (https://bioinformatics.psb.ugent.be/webtools/Venn/) were employed. A Venn diagram, a graphical illustration utilizing circles to represent the relationships among items or groups of items, was utilized. Overlapping circles indicate similarities, while non-overlapping circles indicate differences. Venn diagrams visually depict similarities and differences between two concepts[88].

String (V 11.5)

The String (https://string-db.org/) website was used to visualize the network of upregulated genes in gastric cancer. The STRING database aims to include all known and predicted physical and functional interactions between proteins. The upcoming version, V 11.5 of the STRING resource, is expected to include nearly 14 000 species[42].

Study procedure

In this study, appropriate gene sets were extracted using GEO. Among the achieved GSEs, those with a *P* value less than 0.05 and a LOG fold change (FC) greater than 1 were considered to extract valid and upregulated genes. Venn diagram web tools were then utilized to identify shared upregulated genes between gastric cancer and chemical burns. Subsequently, the "string" was used to visualize the network of upregulated genes in gastric cancer. Valuable gene nodes were selected by omitting non-coding RNAs and considering interactions greater than 1[89].

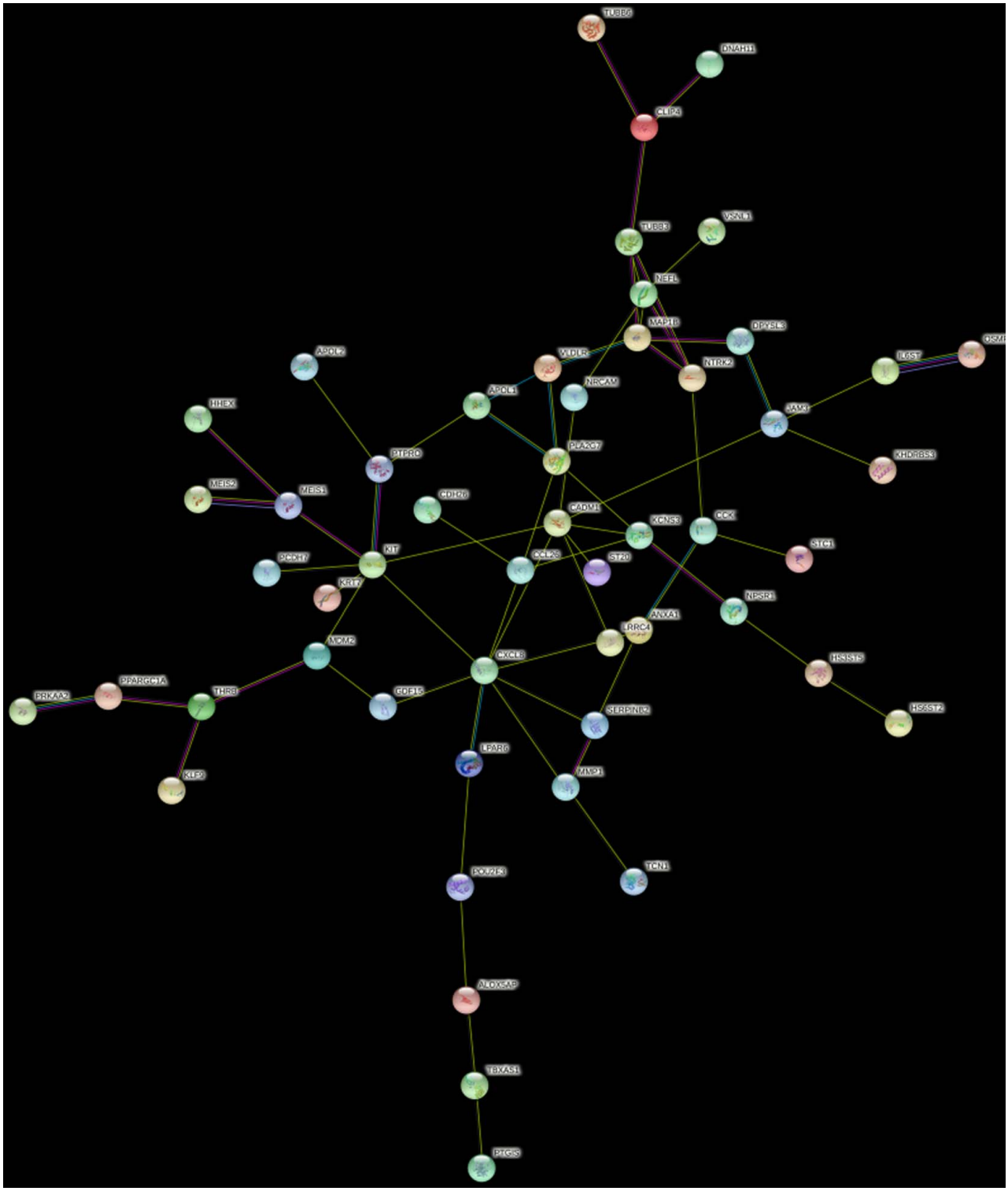

Figure 2. Gastric cancer filtered gene network, criteria; omitted non-coding RNAs and the "interaction" greater than 1.

Network analysis

Gephi software (V 0.9.7)

Gephi software (V 0.9.7) was employed to analyze the gene network and identify the most interacted genes, considering "betweenness centrality" greater than 0. Gephi is an open-source networking analysis program that utilizes a 3D render engine to visualize massive networks in real-time, facilitating exploration. Its flexible design creates opportunities for working with complex datasets and generating high-quality visual output[90]. In this

Table 1

Gephi analysis results.

ID	Label	Degree	Eccentricity	Closeness centrality	Harmonic closeness centrality	Betweenness centrality
ALOX5AP	ALOX5AP	2	9	0.184783	0.228377	98
SERPINB2	SERPINB2	3	6	0.278689	0.337908	7.066667

approach, the authors searched for the obtained shared genes in the gene-interaction network illustrated by String. The Gephi software analyzed the twenty-gene network, identifying the most interacted genes based on "betweenness centrality" greater than 0[90].

Gene-related medications

TISIDB

TISIDB (http://cis.hku.hk/TISIDB/) was used to extract gene-related medication information. TISIDB enables users to examine the role of a particular gene in tumor-immune interaction through literature mining and high-throughput data analysis. Additionally, TISIDB provides a user-friendly interface for browsing, searching, and downloading data[91].

Drugbank

The DrugBank (https://go.drugbank.com/) website was utilized to identify the pharmacological properties of obtained drugs. DrugBank is a unique bioinformatics/chemoinformatics database that combines detailed drug data with extensive drug target information. The database includes over 4100 drug entries, including more than 800 FDA-approved small molecule and biotech drugs, and over 3200 experimental drugs. These drug entries are associated with over 14 000 protein or drug target sequences[92].

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.

Results

Gene set extraction

In this study, two GSEs were obtained, including GSE19743 and GSE186582, and 20 upregulated shared genes between gastric cancer and chemical burns were extracted using Venn diagram web tools (Fig. 1).

Table 2

Gene-related drugs and properties.

Gene	Drugs
SERPINB2	Urokinase
	Tenecteplase
ALOX5AP	DG031
	AM103
	Fiboflapon

Protein-protein interaction network

Subsequently, the "string" was used to visualize the network of upregulated genes in gastric cancer, resulting in 53 nodes that were considered valid and upregulated (Fig. 2).

Network analysis

The 20 obtained genes were examined in the 53-gene-interaction network. Via Gephi software (V 0.9.7), two genes, ALOX5AP and SERPINB2, were identified (Table 1).

Gene-related medications

Gene-related drugs were identified using the "DrugBank and TISIDB" databases, including Urokinase, Tenecteplase, DG031, AM103, and Fiboflapon (Table 2).

Discussion

Burns can range from mild to severe and can be caused by various factors such as heat, chemical exposure, electricity, or radiation[93–110]. Chemical burn wounds can potentially increase the risk of developing certain types of cancer over time. Chronic inflammation and scarring from chemical burns can contribute to the development of cancer, as damaged cells may become more susceptible to mutations that can lead to cancerous growth. It is important to seek medical treatment for chemical burns to prevent complications and reduce the risk of long-term health issues, including an increased risk of cancer. It is also crucial to follow up with regular medical check-ups and screenings to monitor any potential risks associated with chemical burn wounds[85–87]. In our study, we identified two genes, ALOX5AP and SERPINB2, which showed the highest centrality among the shared genes between chemical burns and gastric cancer. Additionally, we identified five drugs (Urokinase, Tenecteplase, DG031, AM103, and Fiboflapon) that may have potential effects on gastric cancer following chemical burns.

ALOX5AP, also known as Arachidonate 5-Lipoxygenase Activating Protein, is a crucial gene involved in leukotriene biosynthesis, playing a role in diseases such as atherosclerotic cardiovascular disease (CVD)[111]. Recent research by Nguyen *et al.*[112] has linked ALOX5AP expression to impairments in burn wound healing. Moreover, evidence suggests its association with prognosis in various cancers[113,114]. SERPINB2, or Serpin Family B Member 2, primarily functions as an extracellular inhibitor of urokinase, significantly upregulated in various inflammatory conditions[115]. Its irregular expression and polymorphism are linked to various human inflammatory diseases[116]. Interestingly, increased SERPINB2 expression correlates with prolonged survival, reduced metastasis, and decreased tumor growth in various cancers[117]. Furthermore, it plays a significant role in wound healing, particularly after

burns[118] and has been shown to regulate collagen stromal regeneration, crucial for healing wounds like chemical burns[119].

Furthermore, according to data from "Enrichr," both genes are involved in Complement and coagulation cascades[42]. Chemical burns can activate these pathways in injured tissue through tissue permeability and inflammatory processes[120]. potentially increasing the risk of disseminated intravascular coagulation (DIC)[121]. The complement system is a critical driver in various burns' pathophysiology[122] and may be associated with inflammation-related carcinomas[123]. including gastric carcinoma[124].

In the current study, three drugs, including Urokinase and Tenecteplase, were detected related to SERPINB2. Urokinase is a type of human Urokinase with a low molecular weight used to treat pulmonary embolism, myocardial infarction, and clear IV lines[125]. While, according to the authors' knowledge, the administration of Urokinase in treating gastric cancer was not investigated, former evidence has shown that Urokinase can be considered a prognostic value[126]. Tenecteplase is a modified recombinant human tissue plasminogen activator used to treat myocardial infarction and pulmonary emboli. Tenecteplase is a tissue plasminogen activator (tPA) created by modifying the complementary DNA sequence of human tPA[127]. Yu *et al*.[128] revealed that Tenecteplase could effectively treat breast cancer.

Moreover, three members of 5-Lipoxygenase-Activating Protein (FLAP) Inhibitors, including DG031, AM103, and Fiboflapon, were obtained related to ALOX5AP. Leukotrienes have been implicated in several disorders, including cardiovascular diseases, cancer, and asthma[129]. papers demonstrated that FLAP is a crucial enzyme in leukotriene production[130]. However, the application of FLAP Inhibitors in cancer treatment was limited[131], and the present drug family can be considered a future research platform for developing anti-cancer drugs.

Limitations

The current investigation marks the inaugural endeavor to utilize a bioinformatics methodology in examining the convergence of gastric cancer and chemical burns, thereby predisposing it to certain constraints. Primarily, the absence of experimental validation stems from limitations inherent in data acquisition. Furthermore, the omission of an analysis on epigenetic facets of gene expression regulation constitutes a notable gap in this study. Additionally, the predictive nature of our research methodology underscores the potential for biased outcomes, warranting careful consideration.

Implications for clinical practice

This study has identified a set of genes shared between chemical burns and gastric cancer, a finding with profound implications for the development of gene therapy targets. Moreover, the regulation of expression in these common genes may hold significant importance in the effective management of chemical burn ulcers.

Recommendations for future research

Given the introduction of drugs tailored to specific genes in this study, the prospect of initiating multiple clinical trials based on these drugs to assess their effectiveness in enhancing outcomes for chemical burns and gastric cancer appears viable. Furthermore, leveraging the identified genes opens avenues for epidemiological studies aimed at elucidating genes associated with gastric cancer.

Conclusion

Based on current in-silico analyses, ALOX5AP and SERPINB2 emerge as pivotal genetic factors that interconnect gastric chemical burns and cancer. Considering burns as environmental triggers that upregulate these genes, particularly ALOX5AP, a plausible association between chemical burns and gastric cancer incidence becomes apparent. Consequently, downregulating ALOX5AP presents a promising avenue for therapeutic intervention and research focus aimed at developing safe approaches to burn wound healing. Additionally, the upregulation of SERPINB2 and its healing role in both chemical burns and gastric cancer underscore its significance as another viable target identified in this study. Strategically managing the upregulation of SERPINB2 in both conditions could potentially enhance injury recovery from chemical burns without eliciting chronic side effects. However, rigorous clinical and cohort trials are imperative to substantiate this hypothesis. Furthermore, given the established link between inflammation and gastric cancer incidence, compounded by the exacerbating effect of chemical burns on this pathological process, interventions that mitigate inflammation hold promise as preventive measures against gastric cancer. The data obtained suggest that FLAP inhibitors could serve as a therapeutic target to ameliorate the long-term complications of chemical burns by virtue of their favorable effects on inflammation inhibition. Nevertheless, comprehensive clinical and cohort research is indispensable to deepen our understanding of this topic.

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

Not applicable.

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Author contribution

Study concept and design by all authors; data acquisition by all authors; data interpretation by all authors; drafting the manuscript by all authors; revision of the manuscript by all authors; the final version of the manuscript is approved by all authors.

Conflicts of interest disclosure

The authors declare no conflict 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.

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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