



International  
Congress  
**of Health  
Disciplines**



The International Congress of Health Disciplines  
04-05 February, 2026

## Proceedings Book (Full Texts)

Editor  
Assoc. Prof. Merve Keskin



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# International Congress of Health Disciplines



**Online and  
Free of Charge**

**Dates of the Congress**  
**04-05 February 2026**

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**15 January 2026**

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**25 January 2026**

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**02 February 2026**

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## **Contact**

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## **Preface**

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## **Editor's Note**

The **International Congress of Health Disciplines** was successfully held online at 04-05 February 2026. We are delighted to have offered this event free of charge. It was an honor to bring together experts from various fields of health sciences. This Congress aimed to promote interdisciplinary collaboration, encourage knowledge sharing, and advance health sciences at both national and international levels. With a scientific committee comprising nearly 250 scientists from around the world, the congress truly reflected global participation. We extend our special thanks to everyone who contributed and supported the congress.

We look forward to seeing you at our next congress.

Best regards from Türkiye!

Assoc. Prof. Merve KESKİN

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**Kübra BERBER, Özlem ALBAYRAK**

**Changes in Nursing Students' Knowledge Levels and Nursing Diagnoses After Nursing Process Course**

**Özlem ALBAYRAK, Seda DERE İŞSEVEN**

**Intravenous Rehydration Management in a Child with Severe Acute Malnutrition: A Case Report Based on the Nanda–Nic–Noc Nursing Care Model**

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**The Relationship Between Digital Visibility and Academic Impact in Maternal Health Literacy Research: An Altmetric-Based Analysis**

**Nurcan COŞKUN US**



# FULL TEXTS

## Synthesis and Characterization of Some Schiff Bases Derived from Indole as Cytotoxic Agents

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### Abstract

Studies conducted for the treatment of cancer, which is one of the leading causes of mortality worldwide, are still ongoing due to the insufficiency, failure, and side effect profiles of existing treatment methods. In order to develop a solution to this situation, in this study, based on the known anticancer, antioxidant, anti-inflammatory, and antimicrobial effects of hydrazide/hydrazone and indole derived compounds, three 2-(1*H*-indol-3-yl)-*N'*-(substituted benzylidene) acetohydrazide derivatives were synthesized. The synthesis of the compounds and the biological analyses were carried out with meticulous care. The synthesis was carried out through a three-step procedure consisting of esterification, hydrazide and schiff base formation reactions. The obtained compounds were first purified, and their structural determination were performed using <sup>13</sup>C NMR and <sup>1</sup>H NMR, spectroscopic methods. *In vitro* cytotoxicity tests were performed on A549 human lung adenocarcinoma cells and HUVEC human umbilical vein endothelial cells using the MTT assay. The best activity among the compounds was observed in the derivative containing 2-hydroxy-5-chlorophenyl against A549, with an IC<sub>50</sub> value of 111 µM and selectivity index of 2.06. Based on these results and by derivatizing the compounds obtained, it appears possible to synthesize compounds with reduced side effects, increased selectivity, and more potent anticancer activity for future studies.

**Keywords:** schiff bases, indole, cytotoxicity

## Introduction

Cancer arises as a result of mutations occurring in proto-oncogenes or tumor suppressor genes that regulate the cell life cycle, leading to uncontrolled cell proliferation through the activation of carcinogenic oncogenes and the inactivation of tumor suppressor genes. For these mutations to result in the formation of cancerous cells, they must occur in at least half or more of the genes responsible for growth control within the cell (Weinberg, 1996). The release of circulating tumor cells (CTCs) from a primary tumor into the bloodstream and their subsequent dissemination to form secondary tumors in other organs and tissues via the circulatory system is defined as metastasis; while 90% of cancer-related deaths are attributed to metastasis, cancer represents the second leading cause of death worldwide (Wei Li et al., 2025). Chemotherapy, radiotherapy, surgery, immunotherapy, and hormone therapy are the main modalities employed in cancer treatment. During these treatments, issues such as drug resistance of cancer cells, lack of cellular specificity of therapeutic agents, systemic toxicity, low biocompatibility, rapid clearance of drugs from the body, as well as adverse effects including nausea, vomiting, anemia, and hair loss are frequently encountered (Borzooee Moghadam et al., 2023; Di Meglio et al., 2025).

Schiff bases, discovered by the German chemist Hugo Schiff, are organic compounds formed through the condensation reaction of primary amines with aldehydes or ketones under acidic conditions and contain an imine ( $R_1R_2C=NR_3$ ) functional group in their structures. They are also referred to as azomethines. Schiff bases exhibit a wide range of biological activities, including antiproliferative, anticancer, anti-inflammatory, and antidiabetic effects (Nidhi et al., 2025; Deghadi et al., 2026). Their ease of synthesis and practical applicability have made Schiff bases a subject of studies in the fields of medicine, pharmacy, and chemistry. To date, other

imine derivatives such as oximes, hydrazones, azines, thiosemicarbazones, and selenosemicarbazones have been investigated for overcoming multidrug resistance in cancer (A. Podolski-Renić et al., 2024).

Indole is a heterocyclic compound in which a five-membered pyrrole ring is fused to a benzene ring. The compound is known to exhibit anticancer, antiproliferative, antiviral, antibacterial, and anti-inflammatory activities and Anlotinib, used in the treatment of non-small cell lung cancer, and rucaparib, a targeted agent for breast cancer, are among the currently used drugs that contain an indole moiety (N.J. Pravin et al., 2025; G.-P. Gao et al., 2026). Most importantly, indole derivatives exhibit strong anticancer activity against various types of cancer (Z.H. Mahdi et al., 2024). In studies conducted in 2019 by He Z. Et al., indole–thiosemicarbazone derivatives were reported to demonstrate anticancer activity with reduced toxicity and enhanced efficacy and selectivity against MGC803 human gastric carcinoma, EC109 esophageal squamous cell carcinoma, and PC3 human prostate adenocarcinoma cell lines (Z. He et al., 2019).

In this study, based on the indole and Schiff base structures of the compound *N'*-[(*E/Z*)-(2-hydroxyphenyl)methylidene]-2-(1*H*-indol-3-yl)acetohydrazide, which was previously synthesized by Yar et al. and whose cholinesterase inhibitory activity was investigated, two new derivatives were synthesized from this compound, and their anticancer activities were investigated in order to overcome the problems encountered during treatment (Yar et al., 2014).

## Materials and Methods

### Chemistry

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were performed on a Bruker Fourier 400 MHz spectrometer using DMSO-*d*<sub>6</sub> as the solvent. Chemical shifts are reported as ppm, coupling constants (J) in

hertz (Hz), and signal multiplicities are designated as singlet (s), doublet (d), triplet (t), and multiplet (m).

To obtain 2-(1*H*-indol-3-yl) acetohydrazide, the starting material ethyl (1*H*-indol-3-yl)acetate was dissolved in ethanol together with the calculated amount of hydrazine hydrate in a round-bottom flask and the mixture was refluxed with stirring for 4–5 hours. The ending of the reaction was seen by thin-layer chromatography. After finishing, the reaction mixture was allowed to cool to room temperature and the formed precipitate was filtered. The obtained product was crystallized using ethanol in order to proceed with the reaction in a pure and efficient manner. In the second step, the hydrazide derivatives obtained were dissolved in ethanol and reacted with salicylaldehyde, 5-chlorosalicylaldehyde, and 3,5-dichlorosalicylaldehyde in a round-bottom flask under reflux at high temperature for 5–6 hours to obtain the Schiff base derivatives (**ILA1-ILA-3**). The ending of the reaction was monitored by thin-layer chromatography using an ethyl acetate:petroleum ether (3:1) solvent system. The final products obtained were boiled in ethanol with activated charcoal, rapidly filtered while hot, and crystallized.

### Cytotoxicity Studies

The *in vitro* cytotoxicities of the synthesized compounds were determined on A549 human lung adenocarcinoma and HUVEC human umbilical vein endothelial cell lines using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay as described by Mosmann (Mosmann, 1983). This approach allowed us not only to determine the anticancer potential of the compounds but also to evaluate their selectivity toward cancer cells over normal cells (Kassab, 2025). Briefly, cells were seeded into 96-well microplates at a density of  $1 \times 10^4$  cells/well in 200  $\mu$ L of complete growth medium. The cells were allowed to adhere for 24 h

under standard conditions. Subsequently, the cells were treated with the compounds at different concentrations and incubated for an additional 24 h. Then, 20  $\mu\text{L}$  of MTT solution was added to each well, followed by incubation in the dark at 37  $^{\circ}\text{C}$  for 3–4 h. After incubation, the medium containing MTT was carefully removed, and 100  $\mu\text{L}$  of DMSO was added to each well to dissolve the formazan crystals completely. Finally, the absorbance of each well was measured at 540 nm using a microplate reader (BioTek, USA). The obtained results were compared with cisplatin used as the reference drug.

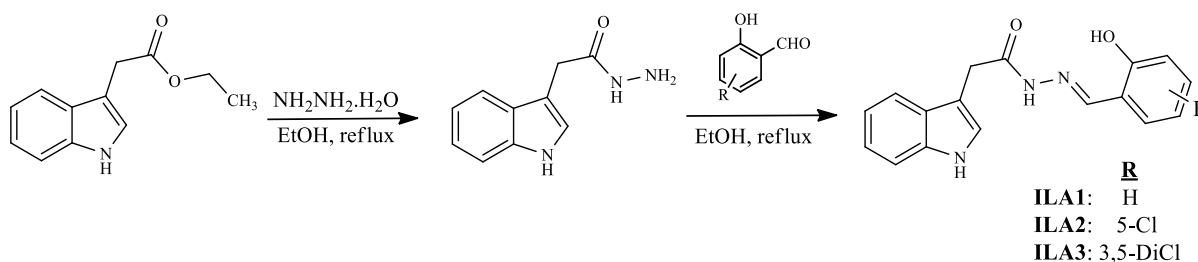
### *In Silico* Studies

The physicochemical properties, lipophilicities, aqueous solubility ratios, and pharmacokinetic properties of the compounds were determined using the SwissADME ([SwissADME](#)) software (Kaya & Yurttas, 2025). The obtained results were evaluated according to Lipinski's rule of five (C.A.Lipinski et al., 2001; Veber et al., 2002).

## Results

### Chemistry

In this study, the reaction steps shown in Scheme 1 were applied, and the compounds ILA-1, ILA-2, and ILA-3 were obtained with yields of 91%, 71%, and 70%, respectively. The structures of the obtained compounds were confirmed using  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectroscopy.



**Scheme 1. Synthesis of the compounds (ILA-1-ILA-3).**

***N'*-[(*E/Z*)-(2-hydroxyphenyl) methylidene]-2-(1*H*-indol-3-yl)acetohydrazide (ILA-1)**

M.P.: 204-205 °C <sup>1</sup>H-NMR (*d*<sub>6</sub>-DMSO) ppm: 3.67 and 4.05 (2s, 2H, CH<sub>2</sub>), 6.90-6.91 (m, 2H, Ar-H), 6.95-7.02 (m, 1H, Ar-H), 7.05-7.09 (m, 1H, Ar-H), 7.22-7.27 (m, 2H, CH=N), 7.35 (t, J: 8.53 Hz, 1H, Ar-H), 7.50 and 7.25 (2d, J:7.55 Hz, 1H, Ar-H), 7.59 (t, J: 8.53 Hz, 1H, Ar-H), 8.29 and 8.42 (2s, 1H, Ar-H), 10.95 and 10.16 (2s, 1H, OH), 11.18 and 10.89 (2s, 1H, NH=C), 11.79 and 11.27 (2s, 1H, indole N-H) <sup>13</sup>C-NMR (*d*<sub>6</sub>-DMSO) ppm: 29.75, 31.87, 108.30, 108.43, 111.77, 111.86, 116.59, 116.79, 118.78, 118.91, 119.08, 119.17, 119.74, 119.94, 120.60, 121.39, 121.52, 124.32, 124.48, 127.12, 127.59, 127.85, 129.86, 131.37, 131.65, 136.48, 136.57, 141.12, 147.23, 156.82, 157.76, 167.43, 172.71.

***N'*-[(*E/Z*)-(5-chloro-2-hydroxyphenyl) methylidene]-2-(1*H*-indol-3-yl) acetohydrazide (ILA-2)**

M.P.: 242-243 °C <sup>1</sup>H-NMR (*d*<sub>6</sub>-DMSO) ppm: 3.67 and 4.04 (2s, 2H, CH<sub>2</sub>), 6.92 (d, J: 8.57 Hz, 1H, Ar-H), 6.98-7.30 (m, 4H, Ar-H, CH=N), 7.35 (t, J: 7.45 Hz, 1H, Ar-H), 7.58-7.74 (m, 2H, Ar-H), 8.24 and 8.39 (2s, 1H, Ar-H), 10.37-10.95 (2s, 1H, OH), 10.90-11.19 (2s, 1H, NH=C), 11.35-11.87 (2s, 1H, indole N-H) <sup>13</sup>C-NMR (*d*<sub>6</sub>-DMSO) ppm: 29.65, 35.89, 29.65, 35.89, 108.24, 108.48, 111.79, 111.86, 118.41, 118.61, 118.80, 118.91, 119.06, 119.13, 121.07, 121.39, 121.52, 122.65, 123.35, 123.71, 124.25, 124.48, 125.43, 127.57, 127.85, 128.06, 130.73, 131.03, 136.46, 136.57, 138.78, 144.86, 155.50, 156.34, 167.61, 173.02.

***N'*-[(*E/Z*)-(3,5-dichloro-2-hydroxyphenyl) methylidene]-2-(1*H*-indol-3-yl) acetohydrazide (ILA-3)**

M.P.: 234-235 °C <sup>1</sup>H-NMR (*d*<sub>6</sub>-DMSO) ppm: 3.71 and 4.04 (2s, 2H, CH<sub>2</sub>), 7.00 (t, J: 8 Hz, 1H, Ar-H), 7.09 (t, J: Hz, 7.0 Hz, 1H, Ar-H), 7.20 and 7.28 (2s, 1H, CH=N), 7.36-7.38 (m, 1H, Ar-H), 7.55-7.69 (m, 3H, Ar-H), 8.24 and 8.37 (2s, 1H, Ar-H), 10.69 and 10.97 (2s, 1H, OH), 10.92-12.16 (2s, 1H, NH=C), 11.56-12.39 (2s, 1H, indole N-H) <sup>13</sup>C-NMR (*d*<sub>6</sub>-DMSO) ppm: 29.81, 31.73, 107.94, 108.04, 111.81, 111.89, 118.84, 118.96, 119.02, 119.13, 121.19, 121.56, 121.82, 122.75, 123.30, 124.27, 124.58, 127.54, 128.81, 130.23, 130.54, 136.50, 136.57, 146.09, 152.58, 167.82, 172.83.

#### Cytotoxicity Studies

The IC<sub>50</sub> values of the synthesized compounds on A549 human lung adenocarcinoma and HUVEC human umbilical vein endothelial cell lines and the calculated selectivity index (S.I.) results are shown in Table 1.

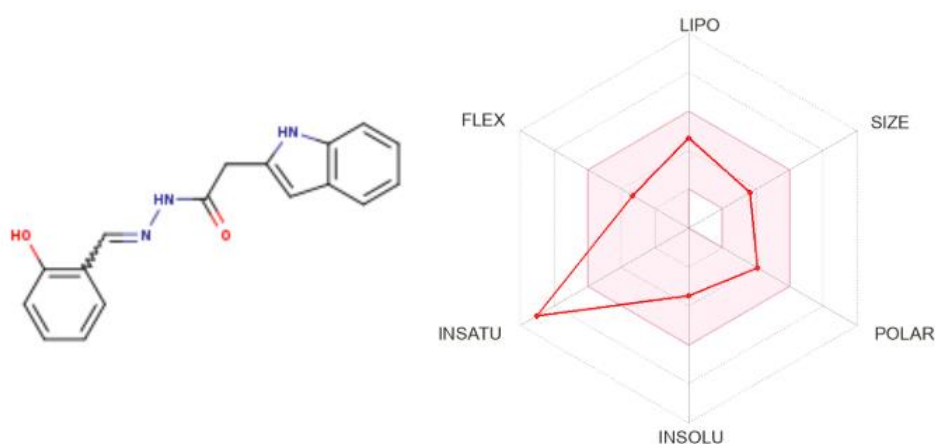
**Table 1.** 50% inhibitory concentrations (IC<sub>50</sub>) of the compounds (μM) after 24h incubation

Compounds	A549 IC <sub>50</sub>	HUVEC IC <sub>50</sub>	S.I.
<b>ILA-1</b>	277.04 ± 18.5	382.6 ± 20.9	1.4
<b>ILA-2</b>	135.5 ± 23.6	215.1 ± 14.6	1.6
<b>ILA-3</b>	258.6 ± 22.5	332.2 ± 8.8	1.3
<b>Cisplatin</b>	24.6 ± 2.0	63.1 ± 1.7	2.6

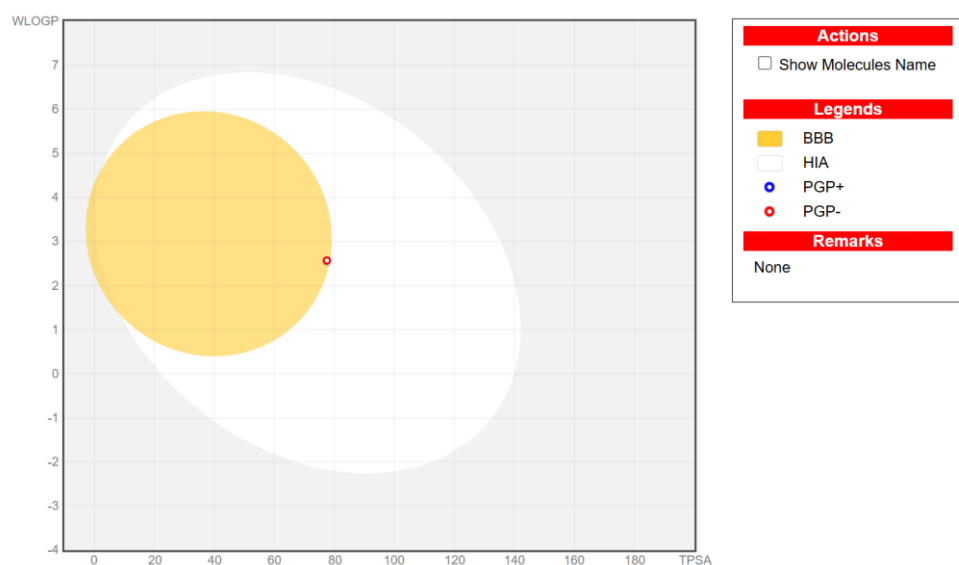
#### *In Silico* Studies

The molecular weight of the ILA-1 compound was found to be 293.32 g/mol, with 3 hydrogen bond acceptor centers and 3 hydrogen bond donor centers, and a TPSA value of 77.48 Å. Its lipophilicity (LogP<sub>o/w</sub>) was calculated as 2.46 based on the average of five lipophilicity values, and its aqueous solubility was determined to be -3.46 according to the LogS value (Figure 1). The compound is an inhibitor of CYP1A2 and CYP2D6. According to the BOILED-Egg model

(Figure 2), it exhibited high gastrointestinal absorption, was able to cross the blood–brain barrier, and was not a P-gp substrate.



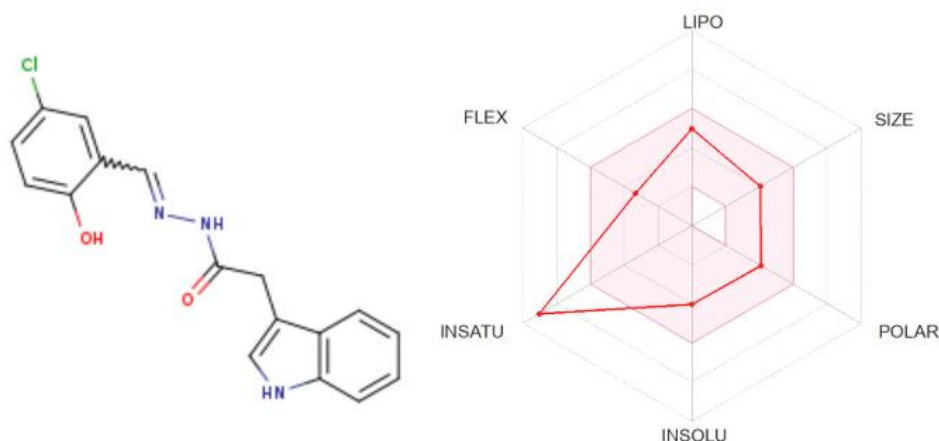
**Figure 1.** Physicochemical space of ILA-1 for oral bioavailability



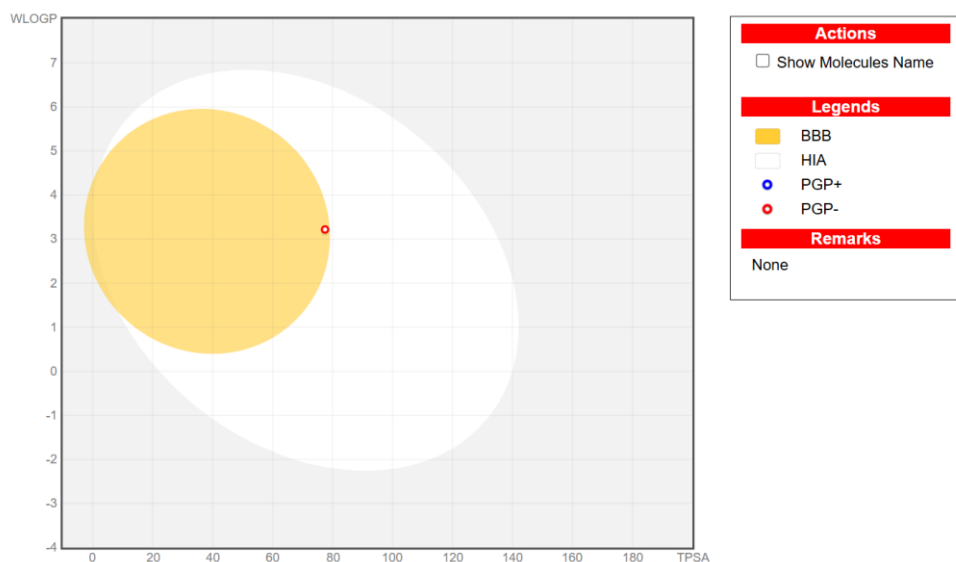
**Figure 2.** Boiled-egg screening of ILA-1

The molecular weight of the ILA-2 compound was found to be 327.76 g/mol, with 3 hydrogen bond acceptor centers and 3 hydrogen bond donor centers, and a TPSA value of 77.48 Å. Its lipophilicity ( $\text{LogP}_{o/w}$ ) was calculated as 2.92 based on the average of five lipophilicity values, and its aqueous solubility was determined to be  $-4.02$  according to the LogS value (Figure 3).

The compound is an inhibitor of CYP1A2 and CYP2D6. According to the BOILED-Egg model (Figure 4), it exhibited high gastrointestinal absorption, was able to cross the blood–brain barrier, and was not a P-gp substrate.



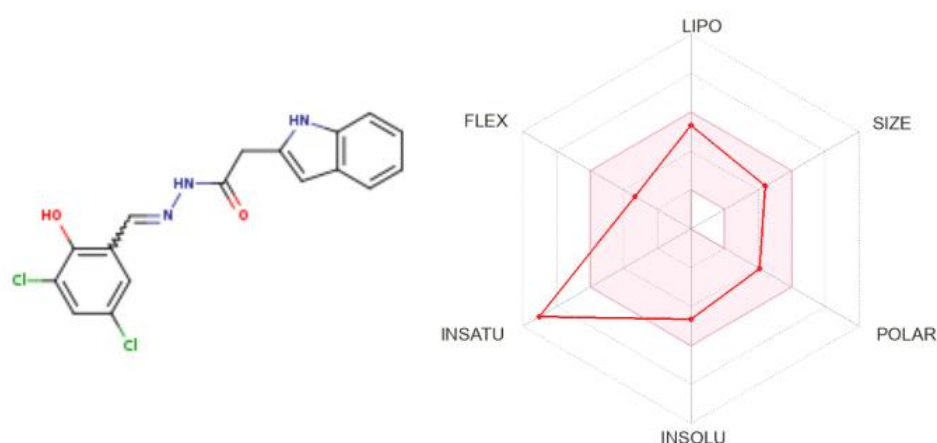
**Figure 3.** Physicochemical space of ILA-2 for oral bioavailability



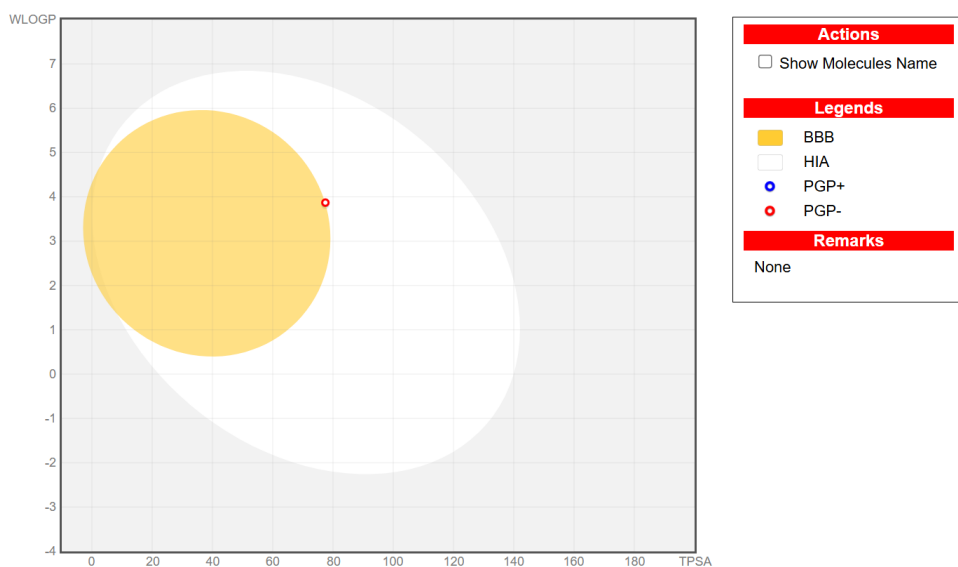
**Figure 4.** Boiled-egg screening of ILA-2

The molecular weight of the ILA-3 compound was found to be 362.21 g/mol, with 3 hydrogen bond acceptor centers and 3 hydrogen bond donor centers, and a TPSA value of 77.48 Å. Its lipophilicity ( $\text{LogP}_{o/w}$ ) was calculated as 3.55 based on the average of five lipophilicity values,

and its aqueous solubility was determined to be  $-4.63$  according to the LogS value (Figure 5). The compound is an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. According to the BOILED-Egg model (Figure 6), it exhibited high gastrointestinal absorption, was able to cross the blood–brain barrier, and was not a P-gp substrate.



**Figure 5.** Physicochemical space of ILA-3 for oral bioavailability

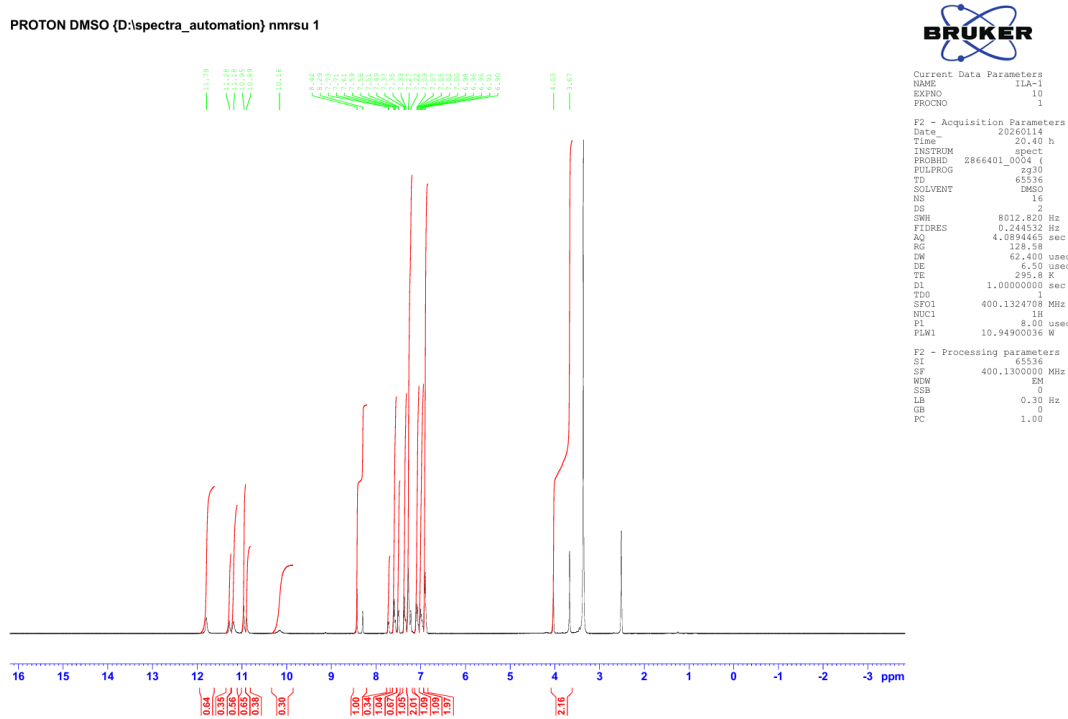


**Figure 6.** Boiled-egg screening of ILA-3

## Discussion

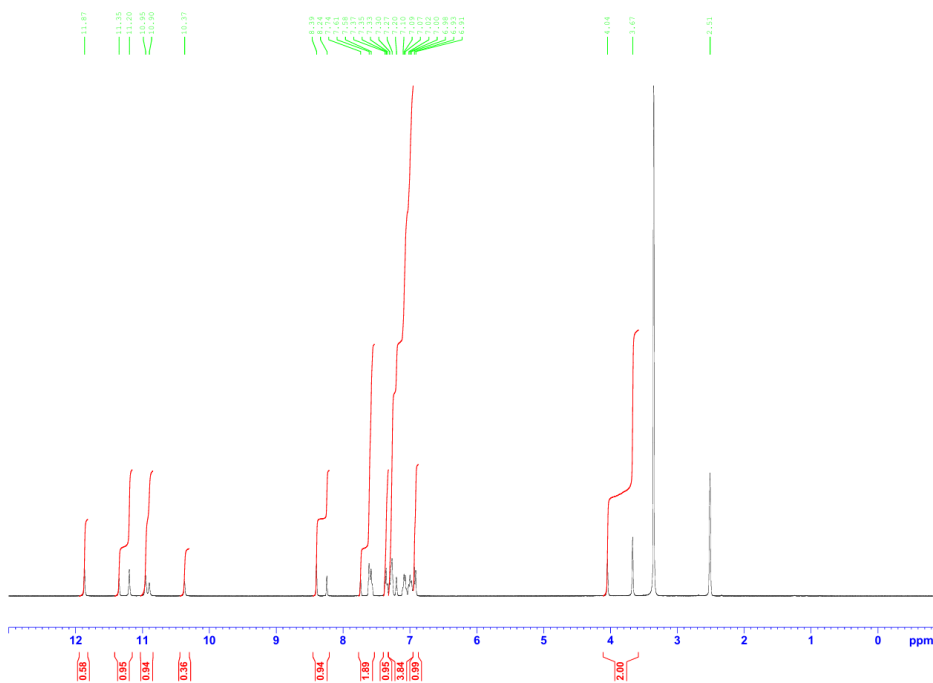
### Chemistry

The spectroscopic results showed that all three compounds were obtained in the form of *E/Z* isomers. As expected, the aliphatic –C–H proton peaks attached to the indole ring were observed in the range of 3.67–4.04 ppm, while the aromatic –C–H proton peaks appeared in the range of 6.90–8.42 ppm (Figure 7-10). Previous studies were utilized for the differentiation of the chemical shift values of the –OH and –NH proton peaks (Yurttas et al., 2017). All compounds exhibited C-NMR values in the range of 29.65–173.02 ppm and contained 34 chemical shift signals. According to the spectroscopic results, the compounds were successfully obtained as intended. This step is of great importance in order to obtain accurate results in cytotoxicity studies.



**Figure 7.** <sup>1</sup>H-NMR spectrum of ILA-1

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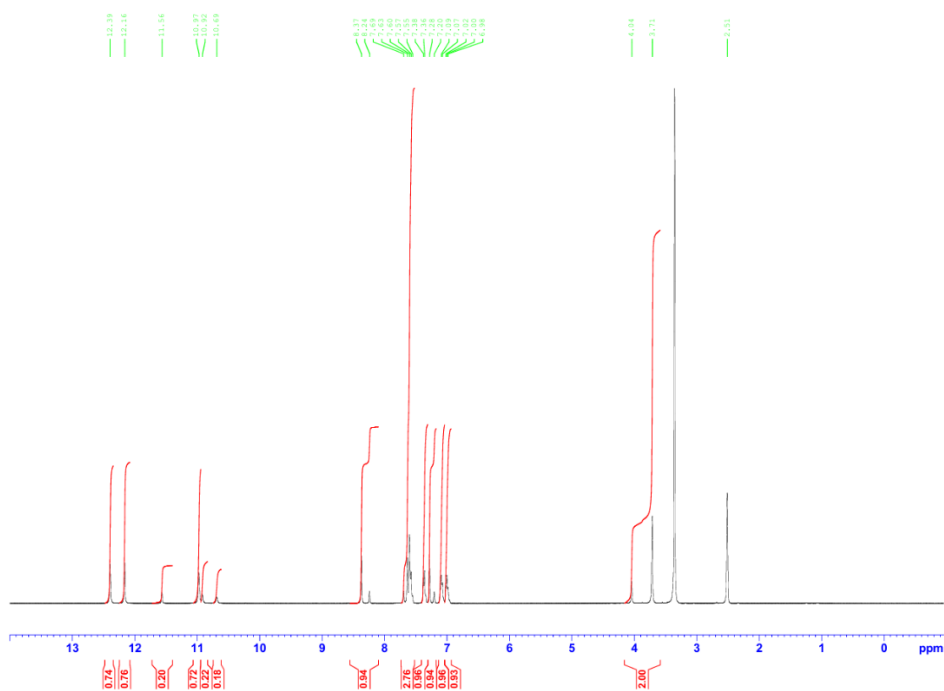
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RG 159.04  
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DE 6.50 usec  
TE 295.7 K  
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TMO 1  
SFO1 400.1324708 MHz  
NUC1 1H  
P1 8.00 usec  
PLW1 10.94900036 W

F2 - Processing parameters  
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Figure 8.  $^1\text{H}$ -NMR spectrum of ILA-2

PROTON DMSO (D:\spectra\_automation) nmsru 3



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F2 - Processing parameters  
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LB 0.30 Hz  
GB 0  
PC 1.00

Figure 9.  $^1\text{H}$ -NMR spectrum of ILA-3

### Cytotoxicity Studies

When the cytotoxic activities and selectivity indices of the synthesized compounds against A549 and HUVEC cell lines were examined, it was observed that the derivative containing 2-hydroxyphenyl exhibited the lowest cytotoxic activity against HUVEC cells with an  $IC_{50}$  value of  $382.6 \pm 20.9 \mu\text{M}$ , but showed the lowest cytotoxic activity against A549 cells, for which high activity was expected, with an  $IC_{50}$  value of  $277.04 \pm 18.5 \mu\text{M}$ . It was observed that the compound ILA-2, obtained by the addition of a Cl group at the 3-position of the 2-hydroxyphenyl ring, provided the best results with an  $IC_{50}$  value of  $135.5 \pm 23.6 \mu\text{M}$  against A549 cells and  $215.1 \pm 14.6 \mu\text{M}$  against HUVEC cells. In the derivative containing 2-hydroxy-3,5-dichlorophenyl, it was observed that the activity significantly decreased against both cell lines used. When the selectivity indices of the compounds were examined, the lowest value was observed in the derivative containing 2-hydroxy-3,5-dichlorophenyl with 1.3, whereas the best result was obtained with the compound ILA-2 containing 2-hydroxy-3-chlorophenyl with 1.6. In future studies, the chlorine group at the 3-position, which increases activity and selectivity, may be replaced with small groups such as fluorine, bromine and methyl, and activity tests may be performed (Shirinzadeh et al., 2020).

### *In Silico* Studies

In the results obtained using SwissADME, it was observed that the molecular weights of all compounds were below 500 Da, the number of hydrogen bond donors was less than 3, the number of hydrogen bond acceptors was less than 10, and the water–octanol partition coefficient ratio was less than 5 (Ibeyaima et al., 2025). No violations of drug-likeness were detected in the compounds, and each of them complies with the drug-likeness rules of Lipinski,

Ghose, Veber, Egan, and Muegge. It was observed that the derivatives containing 2-hydroxyphenyl and 2-hydroxy-5-chlorophenyl were able to cross the blood–brain barrier and were not substrates of P-glycoprotein (P-gp), which limits the passage of drugs into the central nervous system (). The synthesized compounds may contribute to the development of potential drugs that can be used against brain cancers. The inhibition of CYP1A2 and CYP2D6 by the compounds ILA-1 and ILA-2, and the inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 by the compound ILA-3, may increase drug–drug interactions.

### Conclusion

Based on the known anticancer activities of indole and Schiff base structures, the compounds *N'*-[(*E/Z*)-(2-hydroxyphenyl)methylidene]-2-(1*H*-indol-3-yl)acetohydrazide, *N'*-[(*E/Z*)-(5-chloro-2-hydroxyphenyl)methylidene]-2-(1*H*-indol-3-yl)acetohydrazide, and *N'*-[(*E/Z*)-(3,5-dichloro-2-hydroxyphenyl)methylidene]-2-(1*H*-indol-3-yl)acetohydrazide were synthesized and their structures were confirmed by spectroscopic techniques. The *in vitro* cytotoxic activities of the synthesized compounds against different cell types and their selectivity indices were calculated, and the compound ILA-2 showed the best activity with a selectivity index of 1.6. In addition, the pharmacokinetic and physicochemical properties of the compounds were evaluated by *in silico* methods, and all compounds were found to comply with the drug-likeness rules of Lipinski, Ghose, Veber, Egan, and Muegge. In future studies, the number of derivatives will be increased and *in vitro* cytotoxicity experiments and docking studies will be performed.

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## Financial Toxicity in Türkiye: A Systematic Review

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### Abstract

This study aims to systematically review studies on financial toxicity published in Turkish in Türkiye. The study was conducted in accordance with the PRISMA guidelines, and the ULAKBİM TR Index, Google Scholar, and the Council of Higher Education (YÖK) National Thesis Center databases were searched. Studies published between January 2000 and December 2025 were included in the research scope. The keywords used in the search were “financial toxicity,” “economic toxicity,” “financial burden,” “catastrophic health expenditure,” “impoverishing health expenditure,” “cancer,” “disease,” “treatment,” “hospital,” and “chronic disease.” As a result of the search, 227 studies were identified and 22 studies were subjected to full-text review. Three studies that met the inclusion criteria were included in the qualitative synthesis. In all of the examined studies, the financial toxicity levels of cancer patients were measured using the COST scale. In two of the studies, the Turkish validity and reliability analyses of the COST scale were conducted, and the scale was found to be valid in Turkish. When the findings of the studies were evaluated, it was observed that the financial toxicity levels of patients were high. A relationship was identified between financial toxicity and health-related quality of life, treatment adherence, and trust in the health system. As a result, it was determined that studies on financial toxicity in Türkiye are quite limited and that more research on this topic is needed.

**Keywords:** Financial toxicity, financial burden, cancer, systematic review

## **Introduction**

Diseases can have many toxic effects on human health. These toxic effects may also emerge financially. Especially in diseases with high morbidity and mortality, such as cancer, there is a significant financial burden on patients. This situation is defined as financial toxicity (Zafar and Abernethy, 2013).

The long duration of cancer treatment and its high-cost expose patients to greater financial difficulties compared to other diseases. Numerous expenses such as examinations, surgery, medications, equipment, and supportive treatments require substantial financial resources. Depending on the health policies of countries, all or part of these expenses may be covered by insurance or the health system. Even if all medical treatment expenses related to the disease are covered by insurance or the health system, patients may still have to make out-of-pocket payments for other costs such as travel, food, and accommodation. In addition, patients may have to leave their jobs or take leave during the treatment process. Therefore, all these expenses may cause financial toxicity in patients (Pisu and Martin, 2023).

Financial toxicity is also referred to as a side effect of cancer. This situation may negatively affect the quality of life of patients and their families (Nogueira et al., 2020). Due to these effects, the concept of financial toxicity has increasingly become a subject of research in recent years. In particular, studies on this topic have increased over the last decade (Kitaw et al., 2025; Sideris et al., 2025). This situation indicates that it is important to systematically examine studies conducted on financial toxicity.

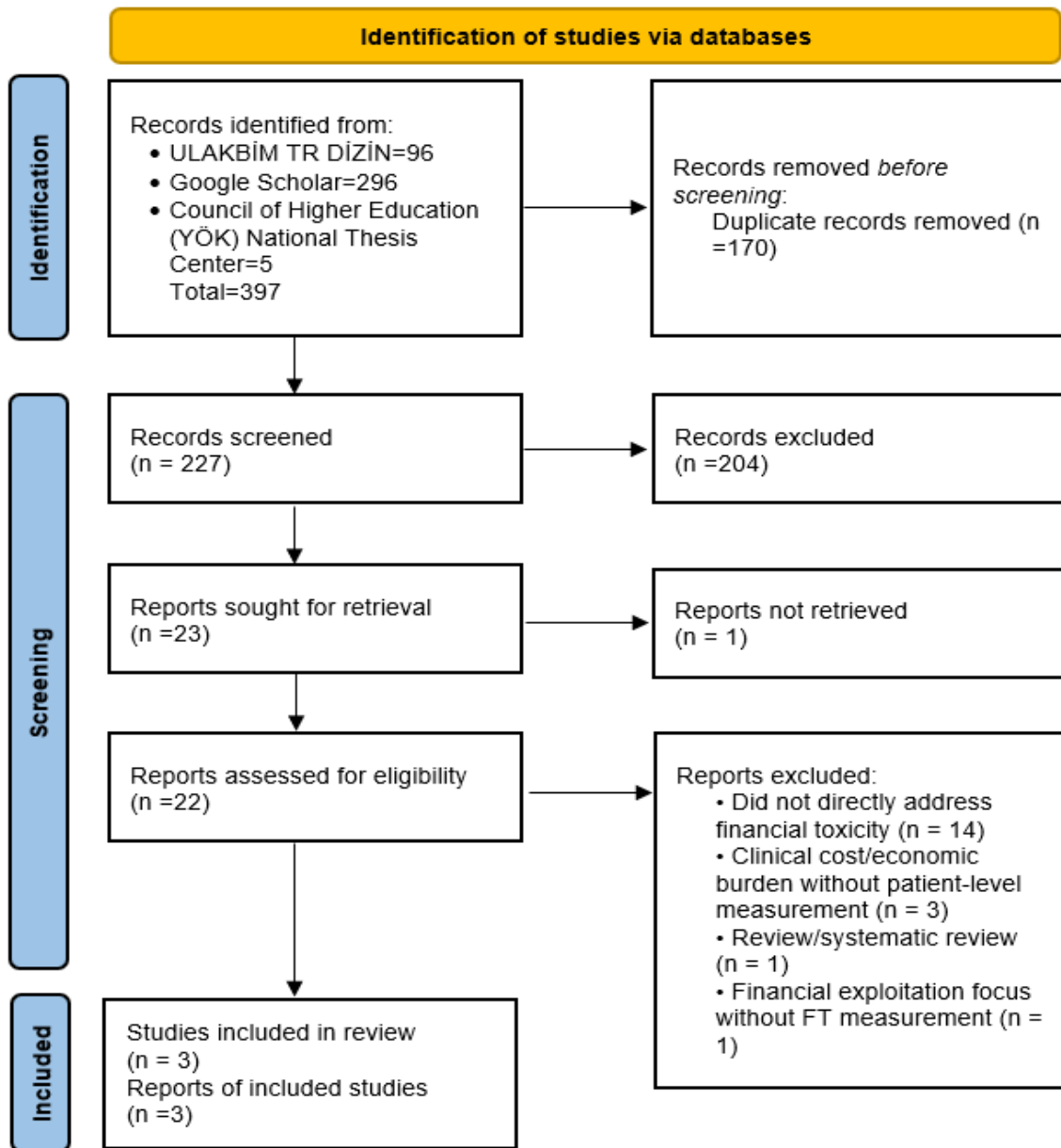
## **Materials and Methods**

This study aims to systematically review studies on financial toxicity published in Turkish in Türkiye. The research was conducted within the scope of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.

The systematic search will be conducted in the ULAKBİM TR Index, Google Scholar, and the Council of Higher Education (YÖK) National Thesis Center databases. In the study, the time period was determined as January 2000–December 2025. The keywords used in the search are “financial toxicity,” “economic toxicity,” “financial burden,” “catastrophic health expenditure,” “impoverishing health expenditure,” “health,” “treatment,” “disease,” “cancer,” “hospital,” and “chronic disease.”

The inclusion criteria of the study are: (1) being published in Turkish, (2) being conducted in Türkiye, and (3) having full-text access. The exclusion criteria are: (1) studies conducted outside Türkiye, (2) studies published in a language other than Turkish, and (3) editorial letters.

The results of the study were reported using the PRISMA flow diagram (Figure 1).



**Figure 1.** PRISMA Flow Diagram

The total number of studies obtained from the databases in the research was 227. After removing duplicates and examining the studies at the title–abstract level, 22 articles were evaluated at the full-text level. As a result of the full-text review, studies that did not directly address the concept of financial toxicity (11), did not include financial toxicity measurement (4), and were

review/systematic review studies (1) were excluded, and 3 studies that met the criteria were evaluated.

## Results

Within the scope of the study, 22 articles were subjected to full-text review, and as a result of the evaluation of the inclusion and exclusion criteria, 3 studies were examined in detail. General information about the studies included in the qualitative synthesis is presented in Table 1.

**Table 1.** Characteristics of Included Studies

Author (Year)	Study Design	Objective	Population	Setting	Sample	Financial Toxicity Instrument	Key Findings
Günçü ve Çınar, 2025	Methodological scale adaptation and validation study	The aim of the study was to adapt the FACIT-COST scale into Turkish and to examine its psychometric properties in women with breast cancer.	Women with breast cancer	University hospital	131	COST	The FACIT-COST scale was adapted into Turkish. The reliability coefficient of the scale (Cronbach's $\alpha$ ) was calculated as 0.92, indicating high internal consistency.
Özyıldız ve Esatoğlu, 2024	Analytical cross-sectional study	The aim of the study was to measure the level of financial toxicity in cancer patients and to examine the relationship between financial burden and trust in the health system.	Patients with lung, breast, and colon cancer	University hospital	105	COST	The level of financial toxicity was found to be high (median=17). A moderate positive relationship ( $r=0.504$ ) was identified between financial toxicity and trust in the health system.
Ürek ve Uğurloğlu, 2021	Analytical cross-sectional and	The aim of the study was to adapt the	Cancer patients	Onkoloj Oncology hospital	316	COST	In the study, the reliability coefficient of

	methodological scale adaptation study	COST scale into Turkish and determine the level of financial toxicity in cancer patients. In addition, it aimed to determine the effect of financial toxicity on quality of life and treatment adherence.					the scale (Cronbach's $\alpha$ ) was calculated as 0.92, and the scale was found to be highly reliable. The level of financial toxicity among patients was found to be moderate (median=21). Additionally, as the level of financial toxicity increased, quality of life decreased and non-adherence to treatment increased.
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Within the scope of the study, two of the examined studies are master's theses (Günçü and Çınar, 2025; Özyıldız and Esatoğlu, 2024) and one is a doctoral thesis (Ürek and Uğurloğlu, 2021). All of the theses examined the concept of financial toxicity in cancer patients from different perspectives. In all three studies, the COST (Comprehensive Score for Financial Toxicity) scale was used to measure financial toxicity. In two studies, the Turkish adaptation and psychometric properties of the COST scale were evaluated.

In the study conducted by Günçü and Çınar (2025), the COST questionnaire was administered to 131 women diagnosed with breast cancer in the province of İzmir. In the study, confirmatory and exploratory factor analyses were conducted to determine the validity of the COST scale. As a result, the reliability coefficient of the scale was calculated as 0.92 and it was determined to have high reliability. It was concluded that the COST scale is a valid and reliable instrument for measuring financial toxicity in women with breast cancer in Türkiye.

In the study conducted by Ürek and Uğurloğlu (2021), in addition to the Turkish adaptation of the COST scale, risk factors, treatment adherence, and health-related quality of life were also examined. The data in the study were obtained from 316 cancer patients hospitalized in an oncology service. Factor analysis was conducted for the adaptation of the COST scale, while correlation and regression analyses were conducted for the other scales. As a result of the study, the reliability coefficient of the COST scale was calculated as 0.92, and it was determined to be valid and reliable. In addition, a negative correlation was found between financial toxicity level and health-related quality of life, and a positive correlation was found between financial toxicity level and non-adherence to treatment.

In the study conducted by Özyıldız and Esatoğlu (2024), it was aimed to determine the level of financial toxicity in cancer patients and to examine its relationship with patients' trust in the health system. In the study, data were collected from 105 patients diagnosed with lung, colon, and breast cancer using the COST scale and the Multidimensional Trust in Health Care Systems Scale. As a result, it was determined that the financial toxicity level of the patients was high and that as the level of trust increased, the level of financial toxicity decreased.

Overall, the validity and reliability analysis results of the COST scale showed that the scale is a valid measurement instrument for measuring the level of financial toxicity in cancer patients in Türkiye. Findings regarding the level of financial toxicity indicate that cancer patients experience financial burden. In addition to the disease process, socioeconomic conditions were also found to be associated with this process. It was determined that financial burden negatively affects the treatment adherence process and health-related quality of life. It was also observed that there is a relationship between trust in the health care system and financial toxicity. As a result, financial toxicity in Türkiye appears to be an important problem for cancer patients,

affecting not only the economic burden on patients but also the treatment process, quality of life, and the level of trust in the health care system.

### **Discussion**

In this study, it was found that there are a limited number of studies examining financial toxicity in Türkiye. In all of the examined studies, the COST scale was used to measure the level of financial toxicity. In two studies, the Turkish adaptation of the COST scale was conducted and its psychometric properties were evaluated. As a result, the Turkish adaptation of the COST scale was found to be valid and reliable. In addition, it was concluded that the level of financial toxicity among cancer patients is high and that socioeconomic factors affect this situation.

These results are consistent with the international literature. When the results of systematic reviews examining financial toxicity in cancer patients are analyzed, it has been determined that cancer creates a significant financial burden on patients and that patients face financial difficulties. The long duration of treatment and the high costs lead to an increase in the direct and indirect health expenditures incurred by individuals (Ehsan et al., 2023; Kitaw et al., 2025; Sideris et al., 2025). When the results of systematic reviews and meta-analyses examining the relationship between financial toxicity and health-related quality of life are analyzed, it has been found that financial toxicity negatively affects quality of life. As financial toxicity increases, health-related quality of life decreases (Pangestu & Rencz, 2022).

Overall, financial toxicity in cancer patients is an important public health problem. Financial toxicity is not only a problem on its own but also affects patients' health-related quality of life, treatment adherence, and their level of trust in the health system. When the literature is examined, systematic reviews conducted on this topic also reveal that financial toxicity is a serious burden for cancer patients (Ehsan et al., 2023; Kitaw et al., 2025; Sideris et al., 2025;

Pangestu & Rencz, 2022). Therefore, it is considered important to conduct more research on financial toxicity in Türkiye.

### **Conclusion**

As a result of the study, it was observed that the number of studies conducted on financial toxicity in Türkiye is limited. However, when the findings of the relevant studies are examined, it has been found that financial toxicity is an important problem among cancer patients and that financial toxicity affects health-related quality of life, treatment adherence, and the level of trust in the health system. This situation reveals the need for better identification of the financial burden and for policies aimed at reducing this burden. Therefore, it is recommended that more comprehensive studies examining the determinants and effects of financial toxicity among cancer patients in Türkiye be conducted.

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## Interpretable Additive Modeling for Heart Disease Prediction: A Reproducible Benchmark on the UCI Cleveland Dataset

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### Abstract

Clinical use of machine learning for cardiovascular risk screening depends not only on discrimination performance, but also on whether model decisions are interpretable and predicted probabilities are trustworthy. This study presents a reproducible, interpretability-first benchmark for binary heart disease prediction using the UCI Cleveland dataset ( $n = 303$ ). The original severity label (“*num*”) was converted into a clinically meaningful binary target by defining disease presence as  $num > 0$ . Predictors were grouped into numeric variables (age, resting blood pressure, cholesterol, maximum heart rate, oldpeak) and categorical variables (sex, chest pain type, fasting blood sugar, resting ECG, exercise-induced angina, slope, number of major vessels, thal). All models were evaluated using the same preprocessing pipeline. Numeric features were imputed with the median and standardized using z-score normalization, while categorical features were imputed with the most frequent category and one-hot encoded. Model performance was assessed using 5-fold cross-validation and reported using both discrimination metrics (AUC, AUPRC) and clinically relevant threshold-based metrics at 0.5 (Accuracy, F1, Sensitivity, Specificity). Probability quality was further evaluated using the Brier score and 10-bin Expected Calibration Error (ECE). Five methods were benchmarked: spline-based logistic GAM (pyGAM), Elastic-Net logistic regression (LR), a shallow decision tree, random forest, and gradient boosting. Hyperparameters were selected through grid search for LR, the decision tree, and GAM. Across the reported metrics (mean  $\pm$  standard deviation), LR and GAM emerged as complementary top-performing models. LR achieved the strongest discrimination, with an AUC of  $0.921 \pm 0.024$  and an AUPRC of  $0.920 \pm 0.031$ , while also maintaining solid threshold-based performance (Acc  $0.858 \pm 0.052$ , F1  $0.838 \pm 0.063$ ) and low probability error (Brier  $0.114 \pm 0.020$ , ECE  $0.113 \pm 0.025$ ). GAM produced the best threshold-based results and the lowest calibration error (Acc  $0.859 \pm 0.019$ , F1  $0.840 \pm 0.023$ , ECE  $0.103 \pm 0.018$ ), remained highly competitive in discrimination (AUC  $0.914 \pm 0.029$ ), and matched LR on the Brier score ( $0.114 \pm 0.019$ ). Rank aggregation across eight metrics showed that LR and GAM were tied for the best mean rank (1.625), highlighting interpretable additive modeling as a strong and publishable baseline for heart disease prediction.

**Keywords:** Interpretable AI, additive models, UCI cleveland, calibration, heart disease prediction.

## **Introduction**

Cardiovascular diseases (CVDs) continue to pose a major global health burden and remain the leading cause of death worldwide. Recent estimates indicate that CVDs were responsible for approximately 19.8 million deaths in 2022, accounting for around 32% of all deaths, with myocardial infarction and stroke causing most of these fatalities (WHO, 2025). Since many individuals remain asymptomatic until a major event occurs, effective prevention relies on timely risk stratification and the early identification of high-risk patients. This makes it possible to initiate lifestyle changes and pharmacologic treatment before irreversible damage develops (Kresejo et al., 2023).

With the growing availability of routinely collected clinical data, machine learning (ML) and deep learning (DL) methods have drawn increasing attention in CVD risk prediction (Oikonomou and Khera, 2023; Deepa et al., 2024; Liu et al., 2025). These approaches are often presented as alternatives to, or extensions of, traditional statistical risk scores. This shift is particularly evident in electronic health record settings, where longitudinal and multivariable modeling can be applied. Evidence syntheses suggest that ML models often show good discrimination for medium- and long-term prediction and may outperform conventional scores in pooled analyses (Jones, 2023). Still, findings vary considerably across studies because of differences in cohorts, predictors, endpoints, and evaluation procedures. These reviews also consistently note that methodological variability and incomplete validation limit clinical confidence, even when reported AUC values appear high.

Despite rapid methodological advances, the clinical uptake of predictive ML in cardiovascular care remains limited because of ongoing concerns about trust, transparency, and the overall strength of evidence (Kresejo et al., 2023). Systematic evaluations of the CVD prediction

literature often describe the field as still being at an early stage, pointing to recurring issues such as limited reproducibility, scarce independent external validation, and inconsistent reporting of key design and evaluation choices (Cai et al., 2024). These limitations make it harder to assess studies rigorously, compare models fairly, and translate findings safely into routine practice. In response, the field has increasingly adopted AI-focused extensions of established prediction-model standards, particularly TRIPOD+AI (Collins et al., 2024) to improve transparent reporting and PROBAST+AI (Moons et al., 2025) to support structured assessment of risk of bias and applicability across both regression- and AI-based models. Taken together, these frameworks reflect a shift away from performance claims based only on leaderboard results and toward more complete methodological reporting and clinically meaningful evidence generation.

A key reason why many seemingly high-performing models fail to translate into practice is that discrimination does not necessarily reflect clinical reliability. The AUC measures how well a model ranks individuals according to risk, but clinical decisions depend on whether predicted probabilities match observed event rates across the full risk spectrum, in other words, calibration (Vickers and Holland, 2021). For this reason, current guidance on the evaluation of clinical prediction models treats calibration as a central objective. It recommends graphical assessment with smooth calibration curves rather than relying solely on grouped points. It also advises reporting quantitative measures such as calibration-in-the-large and the calibration slope (Du et al., 2023; Cheng et al., 2026). At the same time, these guidelines caution that several legacy practices, especially over-reliance on goodness-of-fit hypothesis tests, may lead to misleading conclusions (Van Smeden et al., 2022). Some degree of miscalibration should

also be expected, particularly when case mix, measurement procedures, or outcome prevalence differ between development and deployment settings (Van Smeden et al., 2022).

Even widely used single-number summaries of probabilistic performance should be interpreted carefully. The Brier score is a fundamental proper scoring rule for binary outcomes, but recent methodological discussions have highlighted recurring misunderstandings about what it can and cannot reveal regarding calibration and overall probability quality (Hoessly, 2025). This further supports the need to report complementary diagnostics rather than treating any single metric as conclusive. In practice, robust evaluation increasingly combines calibration curves and calibration parameters with proper scoring rules and, when appropriate, calibration error summaries. Reported results also tend to emphasize sampling variability and the sensitivity of findings to binning choices.

Beyond probability accuracy, models developed for screening and prevention should be evaluated at clinically meaningful operating points. Threshold-based measures such as sensitivity, specificity, and PPV/NPV, together with decision-analytic perspectives such as net benefit from decision curve analysis, connect model outputs to the real consequences of clinical decisions (Hossain and Ahmed, 2023). This is especially important in preventive cardiology, where the harms associated with false negatives and false positives are rarely symmetric. For this reason, discrimination, calibration, and clinical utility analyses are increasingly recommended to be presented together as a coherent body of evidence. This is particularly relevant when the aim is risk-guided intervention rather than retrospective classification alone. Interpretability is a third pillar that often determines whether a model can be used responsibly. In healthcare, complex black-box models may reduce trust and slow adoption. They also make auditing and error analysis more difficult, especially when predictions conflict with clinical

expectations. These risks become even more pronounced when data are limited or biased, and when distributions shift over time. As a result, clinical AI guidance increasingly calls for early-stage evidence that goes beyond accuracy alone. Reporting is also expected to address safety, human factors, and real-world usability, since clinical benefit ultimately depends on how clinicians and AI systems interact within the workflow (Rosenbacke et al., 2024). Interpretable additive models offer a practical balance in this context. Logistic regression provides a transparent baseline, while Generalized Additive Models (GAMs) and modern additive variants can capture nonlinear yet clinically plausible risk patterns and still remain globally interpretable through feature-wise functions (Cui et al., 2020). Recent prediction studies outside cardiology also suggest that additive models can preserve interpretability as decision-support tools while achieving performance close to that of stronger black-box methods (Petch et al., 2022; Wanyonyi et al., 2025). This direction is consistent with the broader shift toward interpretability-by-design in clinical ML.

Within this context, a reproducible, interpretability-first benchmark is valuable for more than simple algorithm comparison. It also promotes methodological discipline. More specifically, it requires models to compete on probability reliability and decision relevance rather than only on separability. The UCI Cleveland Heart Disease dataset remains one of the most widely used public benchmarks for heart disease prediction. It includes 303 instances and is commonly analyzed using a 14-variable feature subset, with a binary outcome of presence or absence derived from the original 0-4 diagnosis field. When combined with modern evaluation practices, it offers a practical testbed for controlled method comparisons. Motivated by this need, a unified and fully specified benchmarking protocol was implemented with consistent preprocessing across all models, and performance was evaluated using 5-fold cross-validation.

Out-of-fold predictions were used to construct ROC, precision-recall, and calibration curves so that all reported curves reflect held-out performance. The benchmark summarizes discrimination through ROC-AUC and AUPRC, threshold-based performance at 0.5 through Accuracy, F1, Sensitivity, and Specificity, and probability quality through the Brier score and 10-bin Expected Calibration Error. Within this standardized framework, an interpretable additive model, namely spline-based generalized additive modeling, is compared with widely used baselines and higher-capacity ensembles, including elastic-net logistic regression, a shallow decision tree, random forest, and gradient boosting. Taken together, this design enables an auditable and reproducible assessment of the discrimination, calibration, and interpretability trade-off, and aligns model selection with clinical expectations for trustworthy risk prediction rather than optimizing AUC alone.

## **Materials and Methods**

### ***Dataset***

This study was based on the UCI Cleveland Heart Disease dataset (Janosi et al., 1988), which is widely used as a public benchmark in clinical risk prediction research. The dataset contains 303 patient records and is commonly analyzed using a standard subset derived from routine demographic and clinical measurements. In this benchmark, a feature set widely reported in the literature was adopted, and variables representing demographics, symptoms, vital and laboratory measurements, exercise testing indicators, and additional clinical descriptors were retained. A concise overview of the predictors used in this study, including their type (numeric or categorical) and the preprocessing operation applied in the unified pipeline, is presented in [Table 1](#).

**Table 1.** Variables included in the UCI Cleveland heart disease benchmark, with feature types and the preprocessing applied in the unified pipeline.

Variable	Clinical meaning	Type	Example values / categories
age	Age (years)	Numeric	continuous
sex	Biological sex	Categorical	{0,1}
cp	Chest pain type	Categorical	{0,1,2,3}
trestbps	Resting blood pressure	Numeric	continuous
chol	Serum cholesterol	Numeric	continuous
fbs	Fasting blood sugar > 120 mg/dl	Categorical	{0,1}
restecg	Resting ECG results	Categorical	{0,1,2}
thalach	Max heart rate achieved	Numeric	continuous
exang	Exercise-induced angina	Categorical	{0,1}
oldpeak	ST depression induced by exercise	Numeric	continuous
slope	Slope of peak exercise ST segment	Categorical	{0,1,2}
ca	Number of major vessels	Categorical	{0,1,2,3}
thal	Thalassemia-related status	Categorical	{0,1,2,3}
<b>Target (y)</b>	Heart disease status derived from “num”	Binary	<b>0 vs 1 (num&gt;0)</b>

The dataset was handled as a tabular binary classification problem. The predictors include both numeric and categorical variables, and some fields contain missing values. For this reason, the dataset offers a practical testbed for benchmarking discrimination performance. It also enables the evaluation of robust preprocessing, probability calibration, and interpretability within a reproducible evaluation protocol.

### ***Target Definition***

The dataset provides the outcome variable “num”, which represents heart disease severity on an ordinal scale from 0 to 4. For clinical screening and consistent benchmarking, this label was converted into a binary target by defining no disease as  $num = 0$  and disease presence as num

$> 0$  ([Table 1](#)). Accordingly, the final target was encoded as  $y = 0$  for  $num = 0$  and  $y = 1$  for  $num \in \{1, 2, 3, 4\}$ .

### ***Predictors and Feature Groups***

The predictors were grouped into numeric and categorical feature sets to reflect the heterogeneous nature of routine clinical variables and to allow type-appropriate preprocessing. The numeric features were age, resting blood pressure (restbps), serum cholesterol (chol), maximum heart rate achieved (thalach), and ST depression induced by exercise (oldpeak). The categorical features were sex, chest pain type (cp), fasting blood sugar (fbs), resting ECG results (restecg), exercise-induced angina (exang), slope, number of major vessels (ca), and thalassemia-related status (thal). This grouping was applied consistently across all models.

### ***Unified Preprocessing Pipeline***

To ensure fair and directly comparable results, all models were trained using the same preprocessing pipeline. Numeric variables were imputed with the median and then standardized using z-score normalization. Categorical variables were imputed with the most frequent category and transformed through one-hot encoding. To prevent data leakage, all preprocessing parameters, including imputation values, scaling statistics, and encoding mappings, were estimated only from the training split within each cross-validation fold and then applied to the corresponding validation split.

### ***Models Benchmarked***

To examine the trade-off between interpretability and predictive performance, an interpretable additive model was benchmarked against common baselines and ensemble methods under a unified protocol. The primary interpretable model was a spline-based logistic Generalized Additive Model (GAM) (Zschech et al., 2022), which captures nonlinear feature-outcome

relationships while preserving additive interpretability. As a transparent baseline, elastic-net logistic regression (LR) (Wu et al., 2022) was included, while a shallow decision tree (Laber et al., 2023) served as a simple nonlinear reference. In addition, two strong ensemble methods that are frequently used in clinical prediction were evaluated: random forest (RF) (Rigatti, 2017) with 600 trees and gradient boosting (GB) (Zhang et al., 2019) with 300 estimators, a *learning rate* of 0.05, and a *maximum depth* of 2.

### ***Hyperparameter Tuning***

Hyperparameters were selected through grid search for the key models to ensure a consistent tuning policy. For LR, the regularization strength ( $C$ ) and the elastic-net mixing parameter ( $l1\_ratio$ ) were tuned. For the decision tree,  $max\_depth$  and  $min\_samples\_leaf$  were adjusted to control model complexity. For GAM, the smoothing parameter ( $\lambda$ ) was searched over a logarithmic range of  $\lambda \in [10^{-3}, 10^3]$  to balance goodness-of-fit with the smoothness of the additive functions (Wood, 2025). The ensemble settings for RF and GB were kept fixed ([Table 2](#)) to provide stable and strong reference baselines.

### ***Evaluation Protocol***

Model performance was assessed using 5-fold cross-validation. In each fold, the models were trained on the training split and evaluated on the held-out validation split. To obtain robust overall curves and avoid overly optimistic reporting, out-of-fold (OOF) predicted probabilities were collected across folds and pooled to generate ROC, precision-recall, and calibration (reliability) curves.

**Table 2.** Benchmark models and key configuration choices.

Model	Role in benchmark	Key configuration
Elastic-net LR	Strong linear baseline	Tuned $C$ , $l1\_ratio$
Logistic GAM (spline-based)	Interpretable additive model	Tuned $\lambda$ (smoothness)
Shallow Decision Tree	Simple nonlinear baseline	Tuned $max\_depth$ , $min\_samples\_leaf$
Random Forest	Ensemble reference	$600$ trees (fixed)
Gradient Boosting	Ensemble reference	$300$ estimators, $lr=0.05$ , $max\_depth=2$ (fixed)

### *Metrics*

The benchmark reports three complementary dimensions of model quality:

1. Discrimination was quantified using ROC-AUC and AUPRC.
2. Threshold-based performance was reported at a fixed threshold of 0.5 using Accuracy, F1-score, Sensitivity, and Specificity.
3. Probability quality was assessed using the Brier score (Yang et al., 2022) and Expected Calibration Error (ECE) (Pavlovic, 2025), computed with 10 bins.

For completeness, Sensitivity and Specificity were calculated from the confusion matrix at a threshold of 0.5 as  $Sensitivity = TP/(TP+FN)$  and  $Specificity = TN/(TN+FP)$ . The Brier score summarizes probability accuracy as the mean squared error between predicted probabilities and the true labels. ECE summarizes calibration by comparing empirical accuracy with mean confidence within probability bins based on a 10-bin partition.

### *Reproducibility Considerations*

A consistent preprocessing, tuning, and evaluation policy was applied across all models to support auditable and reproducible comparisons. The separation between training and validation data was preserved within each fold, and all transformations were learned only from

the training data and then applied to the validation data to prevent leakage. All models were evaluated under the same cross-validation protocol, metric definitions, and curve construction strategy based on pooled OOF predictions. This ensured that the observed differences reflected modeling choices rather than inconsistencies in evaluation.

## **Results**

The benchmark results are summarized using 5-fold cross-validation and reported across three complementary axes: discrimination, threshold-based decision performance, and probability quality/calibration. All comparisons were conducted within a leakage-aware evaluation protocol with stratified splitting to ensure fair and reproducible benchmarking. In addition, pooled OOF predictions were used to visualize ROC/PR behavior and reliability diagrams as complementary model-agnostic checks. The core summary metrics are presented first, followed by a more detailed interpretation of performance.

### ***Overall Performance Summary***

[Table 3](#) presents the core benchmark results as mean  $\pm$  standard deviation across 5 folds. Overall, Spline Logistic GAM and LR (Elastic-Net) emerged as the most consistent top-performing models, although their strengths differed. LR achieved the strongest discrimination, with the highest ROC-AUC and AUPRC, whereas GAM showed the best threshold-based performance at 0.5 and the strongest calibration, reflected by the lowest ECE. More specifically, LR reached the highest ROC-AUC ( $0.921 \pm 0.024$ ) and AUPRC ( $0.920 \pm 0.031$ ), while GAM achieved the best Accuracy ( $0.859 \pm 0.019$ ), the highest F1-score ( $0.840 \pm 0.023$ ), and the lowest ECE ( $0.103 \pm 0.018$ ). Random Forest also remained highly competitive, particularly in calibration, with an ECE of  $0.104 \pm 0.008$ . Gradient Boosting and the shallow tree performed

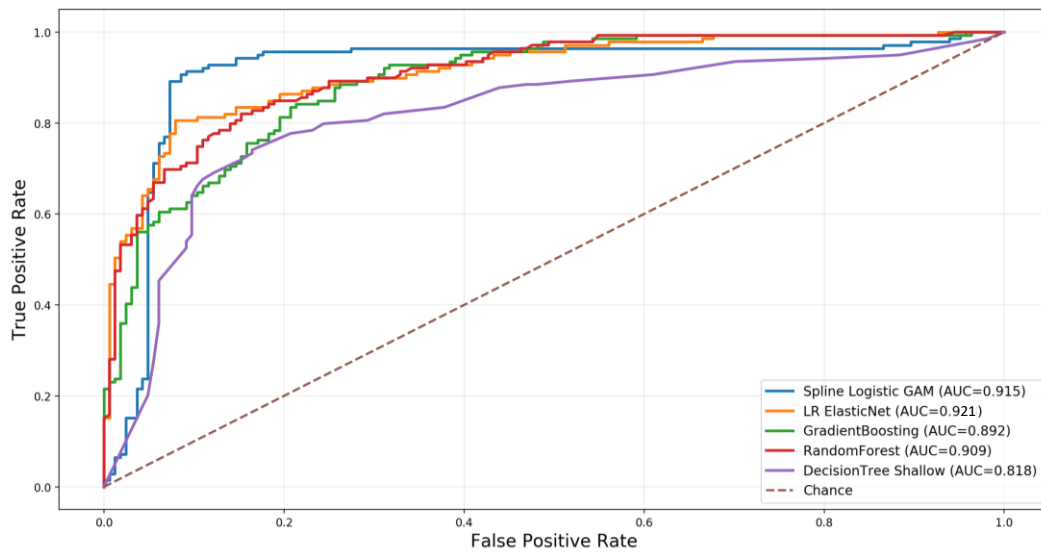
less strongly overall, and the shallow tree showed the clearest decline in both discrimination and probability quality.

**Table 3.** Core results (mean  $\pm$  std across 5-fold CV).

Model	ROC-AUC ↑	AUPRC ↑	Accuracy ↑	F1-Score ↑	Sensitivity ↑	Specificity ↑	Brier ↓	ECE ↓
Spline Logistic GAM	<b>0.915<math>\pm</math>0.029</b>	0.898 $\pm$ 0.031	<b>0.859<math>\pm</math>0.019</b>	<b>0.840<math>\pm</math>0.023</b>	<b>0.807<math>\pm</math>0.032</b>	<b>0.902<math>\pm</math>0.013</b>	<b>0.114<math>\pm</math>0.019</b>	<b>0.103<math>\pm</math>0.018</b>
Elastic-Net LR	<b>0.921<math>\pm</math>0.024</b>	<b>0.920<math>\pm</math>0.031</b>	0.858 $\pm$ 0.052	0.838 $\pm$ 0.063	0.805 $\pm$ 0.081	<b>0.903<math>\pm</math>0.049</b>	<b>0.114<math>\pm</math>0.020</b>	0.113 $\pm$ 0.025
Gradient Boosting	0.894 $\pm$ 0.020	0.882 $\pm$ 0.025	0.799 $\pm$ 0.030	0.775 $\pm$ 0.033	0.755 $\pm$ 0.049	0.836 $\pm$ 0.054	0.140 $\pm$ 0.020	0.127 $\pm$ 0.014
Random Forest	0.909 $\pm$ 0.026	0.904 $\pm$ 0.039	0.825 $\pm$ 0.024	0.805 $\pm$ 0.021	0.784 $\pm$ 0.026	0.860 $\pm$ 0.054	0.122 $\pm$ 0.013	0.104 $\pm$ 0.008
Shallow Decision Tree	0.817 $\pm$ 0.066	0.775 $\pm$ 0.098	0.789 $\pm$ 0.056	0.756 $\pm$ 0.078	0.725 $\pm$ 0.100	0.842 $\pm$ 0.044	0.169 $\pm$ 0.042	0.124 $\pm$ 0.033

### *Discrimination Performance (OOF-ROC)*

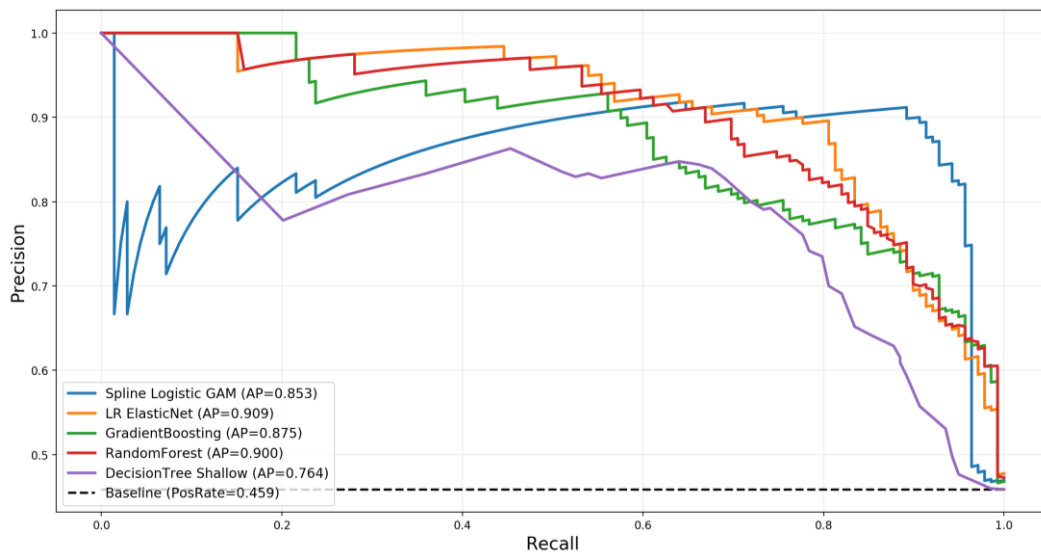
[Figure 1](#) presents the OOF-ROC curves pooled across folds. The curves show that GAM, LR, RF, and GB act as strong discriminators, whereas the shallow decision tree is clearly separated by its lower ROC performance. Consistent with [Table 3](#), LR provides the strongest overall ranking ability, with the highest AUC, while GAM and RF follow closely. This supports the view that interpretability-oriented additive modeling can remain highly competitive in terms of discrimination within a unified, leakage-aware pipeline.



**Figure 1.** Out-of-fold ROC curves for the benchmarked models.

### *Precision-Recall Behavior (OOF-PR)*

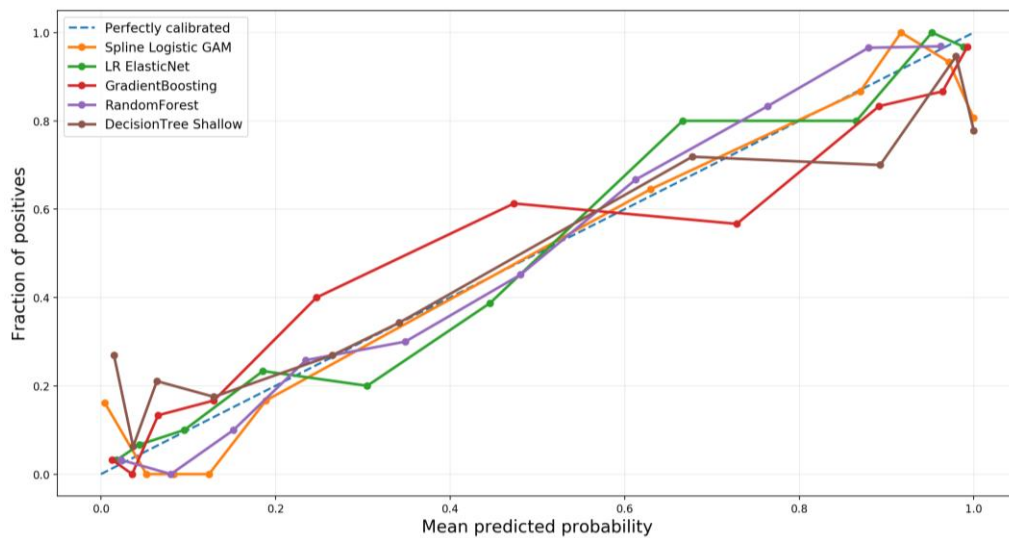
[Figure 2](#) shows the OOF precision-recall (PR) curves, which are particularly informative when positive prevalence is relevant. In the pooled OOF setting, the positive rate is approximately 0.459, providing a meaningful baseline for interpreting the PR curves. LR and RF show the strongest PR behavior, while GAM remains competitive but falls slightly behind LR and RF in pooled OOF PR performance. This suggests a modest trade-off, with GAM showing greater strength in decision stability at a fixed threshold and in probability reliability, rather than in maximizing PR separation alone.



**Figure 2.** Out-of-fold precision-recall curves (baseline positive rate about 0.459).

### *Probability Calibration (Reliability)*

Calibration differences across models are substantial ([Figure 3](#)). The Spline Logistic GAM remains closest to the diagonal overall, which is consistent with its lowest ECE ( $0.103 \pm 0.018$ , [Table 3](#)) and suggests more reliable risk estimates for clinical communication. RF also shows strong calibration, with an ECE of  $0.104 \pm 0.008$ , whereas GB and the shallow tree display more visible deviations from perfect calibration and higher ECE values. These findings are important because they show that high AUC does not necessarily imply well-calibrated probabilities. This again highlights the need to report discrimination and calibration together when developing clinically usable risk prediction models.



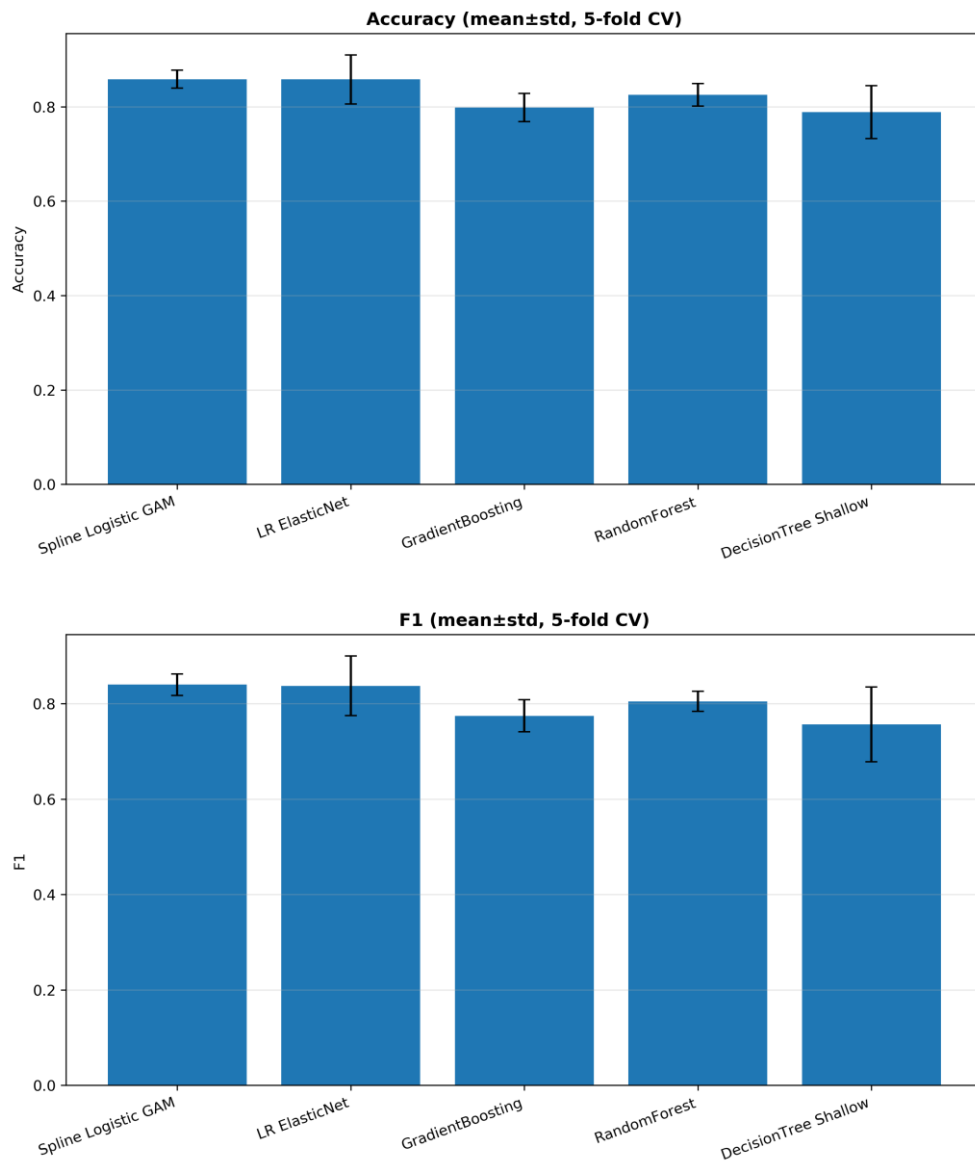
**Figure 3.** Calibration diagrams using pooled OOF predictions.

### *Threshold-Based Performance at 0.5 and Confusion Matrices*

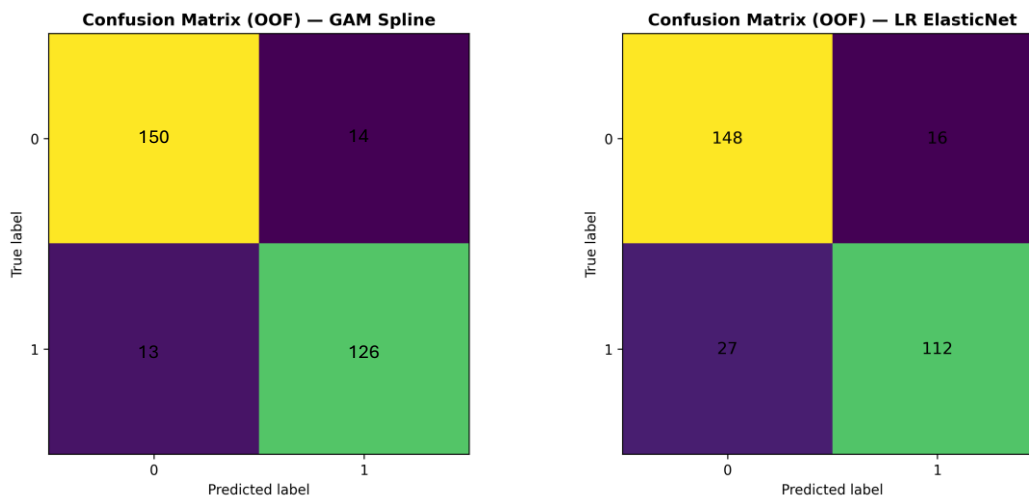
[Figure 4](#) reports threshold-based performance at 0.5 as mean  $\pm$  standard deviation over 5-fold cross-validation. At this clinically interpretable operating point, the spline-based GAM provides the strongest and most stable decision performance, achieving the best Accuracy ( $0.859 \pm 0.019$ ) and F1-score ( $0.840 \pm 0.023$ ) in [Table 3](#). It also maintains a favorable balance between Sensitivity and Specificity (Sens  $0.807 \pm 0.032$ , Spec  $0.902 \pm 0.013$ ), indicating that this improvement is not driven by an overly aggressive tendency to predict positive cases, but by a more consistent trade-off at a fixed cutoff.

The OOF confusion matrices shown in [Figure 5](#) support this interpretation. GAM keeps both types of error low (FP=14, FN=13) while preserving high TN and TP counts (TN=150, TP=126). In contrast, LR ElasticNet shows a higher number of false negatives (FN=27) with a comparable number of false positives (FP=16), suggesting a greater tendency to miss positive cases at the same threshold. This pattern is also consistent with its higher fold-to-fold variability. RF remains slightly behind on threshold-based metrics despite its strong

discrimination and calibration, which suggests that its predicted probabilities may not align as well with the default 0.5 cutoff in the absence of threshold tuning.



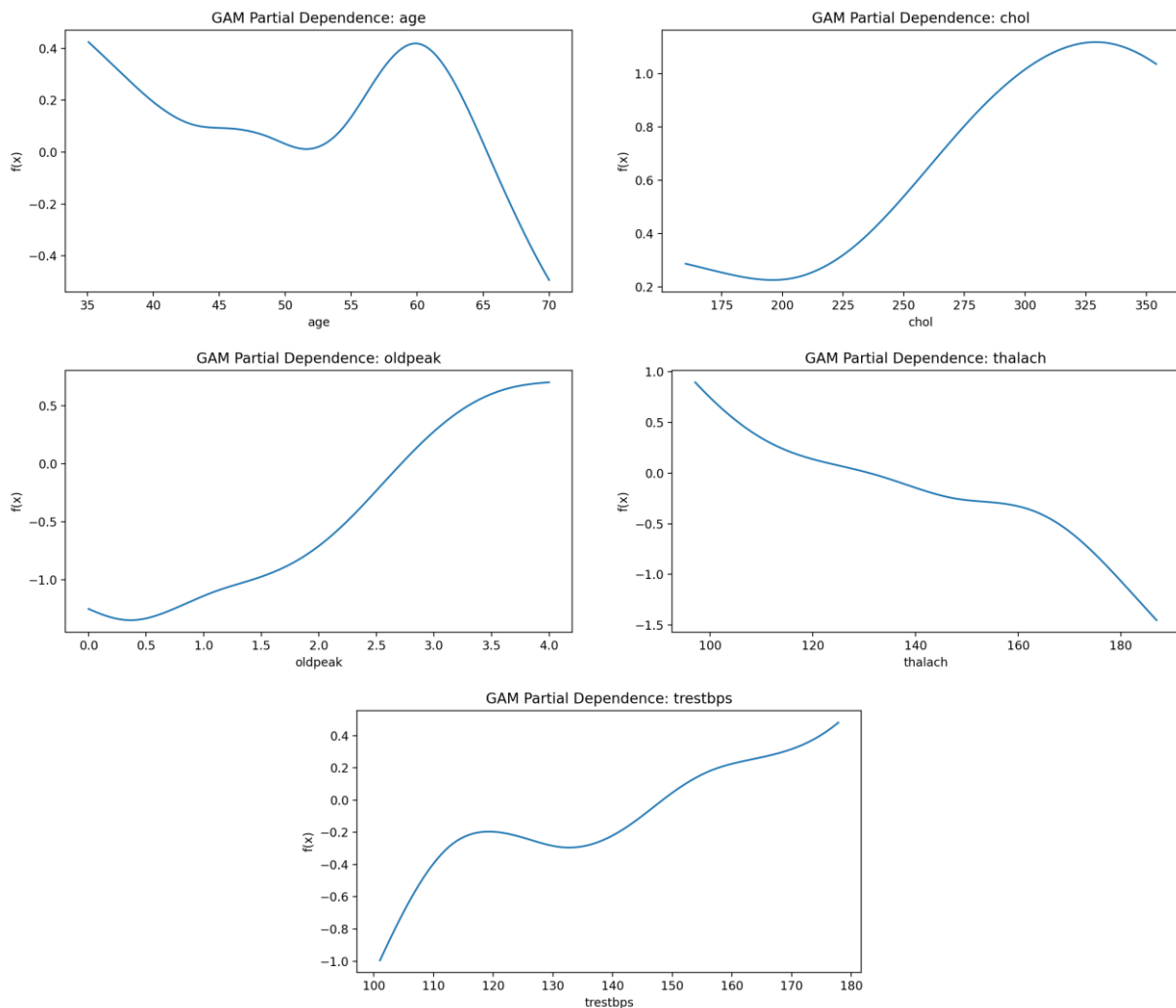
**Figure 4.** Threshold-based comparison at probability threshold 0.5.



**Figure 5.** Confusion matrices at threshold 0.5.

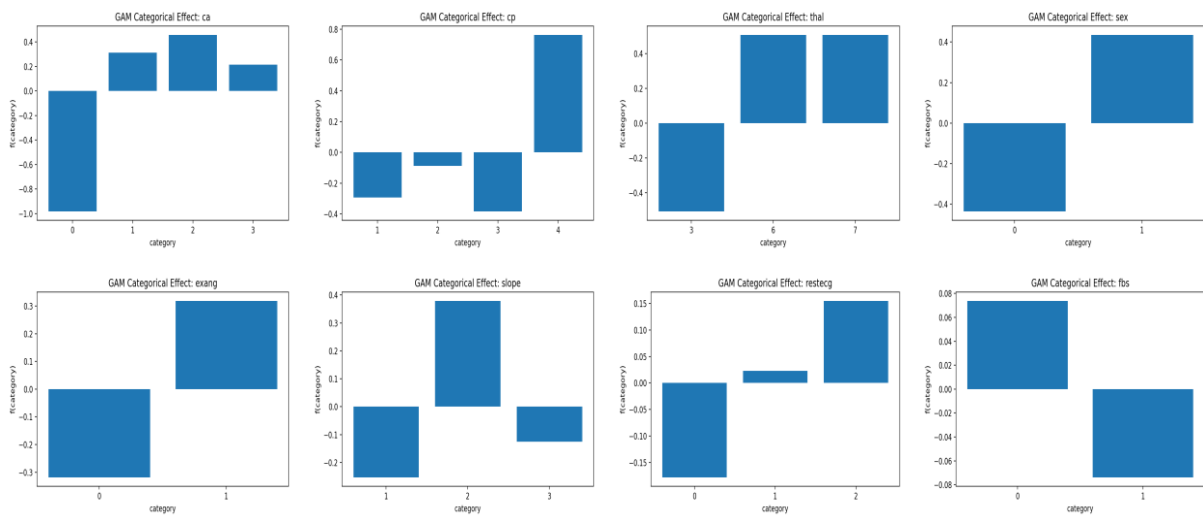
### *Interpretability Results: GAM Numeric and Categorical Effects*

Beyond predictive performance, GAM offers audit-friendly interpretability through additive effects. [Figure 6](#) presents the learned smooth effects for numeric predictors, namely age, trestbps, chol, thalach, and oldpeak, as additive contributions, making risk trends easier to interpret clinically. In particular, oldpeak shows a strong risk-increasing pattern, whereas thalach displays a protective trend at higher values. The effects of age and blood pressure also reveal structured nonlinear relationships that can be examined for clinical plausibility rather than treated as opaque parameters.



**Figure 6.** GAM learned smooth effects for numeric predictors.

[Figure 7](#) presents the categorical effects and directly shows the direction and magnitude of risk for each category. The interpretation is straightforward. Bars above zero shift the prediction toward higher risk relative to the reference level, whereas bars below zero shift it toward lower risk. Variables such as *ca*, *cp*, and *thal* show pronounced category-dependent contributions, supporting transparent reasoning. For example, higher vessel-related categories and specific *thal* or *cp* groups correspond to higher additive risk. This categorical decomposition is especially valuable in clinical review because it allows model-level auditing without the need for post-hoc explanation layers.



**Figure 7.** GAM categorical effects.

### *Combined Ranking Across Metrics*

To summarize performance across multiple criteria, the overall comparison based on the eight reported metrics, covering discrimination, threshold-based performance, and probability quality, shows that Spline Logistic GAM and Elastic-Net LR are the most consistent top performers under the fully specified protocol. In the presentation summary, Spline Logistic GAM and Elastic-Net LR are tied as the best overall models with a *MeanRank* of 1.625 ([Table 4](#)). This supports the intended interpretation that leadership in calibration and decision stability by Spline Logistic GAM, and leadership in discrimination by Elastic-Net LR, can both represent clinically valid best choices depending on whether the main priority is ranking, threshold-based decision support, or calibrated risk communication.

**Table 4.** Mean-rank summary across the full metric suite.

Model	MeanRank ↓ (8 metrics)
Spline Logistic GAM	1.625
Elastic-Net LR	1.625
Random Forest	2.750
Gradient Boosting	4.125

Model	MeanRank ↓ (8 metrics)
Shallow Decision Tree	4.750

## Discussion

This study aimed to move heart-disease risk prediction beyond an AUC-only perspective by establishing an interpretability-first and reproducible benchmark in which models were expected to perform well not only in discrimination, but also in probability reliability and clinically interpretable operating behavior (Alba et al., 2017). Under a unified preprocessing and evaluation pipeline based on 5-fold cross-validation with pooled OOF curves, the results consistently show that transparent additive and linear models can remain competitive with stronger black-box ensembles while offering decision logic that can be audited directly. More importantly, the benchmark shows that a clinically usable screening model should not be defined by ranking performance alone. It should instead be judged by the combined behavior of discrimination, calibration, and threshold-level decision quality.

A central finding of this study is the complementary strengths of GAM and LR across different evaluation dimensions. LR delivers the strongest overall ranking performance, as reflected by ROC-AUC and AUPRC, confirming that a well-regularized linear baseline can be very difficult to outperform on small- to moderate-sized tabular problems when preprocessing is handled carefully and leakage is controlled. GAM, in contrast, provides the most reliable probability estimates, with the lowest ECE, and the best fixed-threshold decision performance, reflected in Accuracy and F1 at 0.5, while still remaining close to LR in discrimination. This pattern is important in practice. In screening settings, clinicians often act on risk thresholds or actionable risk ranges rather than on pairwise ranking alone, which makes calibration and stable threshold behavior essential requirements. The observed tie in mean rank across eight metrics reinforces



the main message of the benchmark: the best model depends on whether the clinical priority is ranking, risk communication, or threshold-based decision support, and additive modeling offers a strong alternative when interpretability and probability trustworthiness are given particular importance.

The calibration analyses further highlight a common pitfall in medical ML: high AUC does not necessarily mean that predicted probabilities are well calibrated. The reliability diagrams show substantial differences in probability quality across models, even among methods with similar ROC behavior, and the ECE and Brier score summaries confirm that probability errors may persist despite strong discrimination. From an implementation perspective, this is not a minor reporting issue. Miscalibrated probabilities can directly affect downstream decisions, such as who is referred for further testing or intervention. The benchmark therefore supports a cautious and clinically aligned position: models intended for risk screening should be evaluated with calibration diagnostics alongside discrimination, rather than treating calibration as an optional addition.

The ensemble baselines provide additional nuance. Random Forest remains highly competitive overall, particularly in terms of calibration error, suggesting that nonparametric ensembling can offer robust probability behavior in this setting. Gradient Boosting performs better than the shallow decision tree, but it does not reach the top-tier combination of discrimination and probability quality achieved by GAM, LR, and RF. The weaker performance of the shallow tree is expected in a small dataset. A single tree is sensitive to sample fluctuations, prone to unstable splits, and generally unable to match the bias-variance balance of regularized linear or additive methods, or that of ensemble averaging. Importantly, these comparisons are meaningful because the benchmark applies a consistent preprocessing pipeline and evaluation design,



which reduces the risk that apparent performance gains stem from differences in data handling rather than from the models themselves.

A major practical advantage of GAM is that it provides model-intrinsic interpretability without the need for post-hoc explanation layers. The learned smooth effects for numeric predictors reveal clinically inspectable risk trends, while categorical contributions show which categories increase or decrease risk under the fitted model. In this benchmark, effects such as the strong risk-increasing pattern associated with *oldpeak* and the protective trend observed at higher *thalach* values reflect clinically plausible relationships that can be reviewed for face validity, discussed with clinicians, and examined for unexpected artifacts. In a similar way, categorical decomposition for variables such as *ca*, *cp*, and *thal* offers a transparent link between discrete clinical states and additive risk contributions. This is useful for debugging, stakeholder communication, and aligning the model's logic with domain knowledge. This *glass-box* behavior is not simply an aesthetic advantage. It also serves as a mechanism for clinical governance by enabling sanity checks and supporting safer translation into practice.

Methodologically, two design choices strengthen the interpretability-first perspective. First, constructing ROC, PR, and calibration curves from pooled out-of-fold predictions ensures that all curves reflect held-out behavior and reduces the risk of overly optimistic visualization. Second, reporting a metric set that clearly separates ranking performance (AUC/AUPRC), threshold-based decisions (Accuracy, F1, Sensitivity, and Specificity at 0.5), and probability quality (Brier score and ECE) makes it easier to understand why models differ instead of reducing performance to a single number. This multi-perspective evaluation is especially valuable in clinical settings, where different stakeholders may prioritize different types of failure. A model with slightly lower AUC but better calibration may be more suitable when risk

communication and probability trustworthiness are the main concern, whereas a model with higher AUC may be preferred for triage ranking when probabilities will later be recalibrated or thresholded more carefully.

Several limitations should be considered when interpreting these findings. The Cleveland dataset is small ( $n=303$ ) and derived from a single source, so the performance estimates, although stabilized through cross-validation, remain sensitive to sampling variability, as reflected in the fold-level standard deviations observed for some models. The benchmark also does not include independent external validation, and for this reason, generalization beyond this dataset should be approached with caution. In addition, threshold-based metrics were reported at a fixed probability threshold of 0.5. This supports comparability across models, but it may not be optimal for clinical utility. In real-world deployment, thresholds should be selected according to prevalence, costs, and clinical workflow. Finally, ECE depends on binning choice and sample size. Although 10-bin ECE provides a reasonable summary, calibration is best interpreted together with reliability curves and, in larger studies, additional calibration parameters.

Future work can build directly on this benchmark without changing its core interpretability-first objective. The most immediate extensions include evaluating the same protocol on larger and more diverse cohorts to assess robustness under dataset shift, incorporating clinically motivated threshold selection or decision-analytic evaluation, and exploring controlled increases in additive model capacity, such as limited interaction terms or monotonicity and sparsity constraints, to preserve interpretability while improving performance when non-additive structure is present. These extensions should preserve the core discipline of the benchmark,



including consistent preprocessing, leakage-aware evaluation, and joint reporting of discrimination, calibration, and decision-relevant metrics.

Collectively, the evidence supports a clear conclusion for heart-disease risk screening in tabular clinical data. Interpretable additive modeling should not be seen as a performance compromise. Instead, it can serve as a strong and publishable baseline that remains competitive in discrimination while offering greater transparency and, in this benchmark, better probability reliability. These properties are directly aligned with clinical expectations for trustworthy prediction.

### **Conclusion**

This study established a reproducible, interpretability-first benchmark for heart disease prediction on the UCI Cleveland dataset (n=303) by evaluating models within a unified preprocessing pipeline and 5-fold cross-validation framework with pooled out-of-fold curves. Across discrimination, threshold-based metrics, and probability quality, spline-based logistic GAM and elastic-net logistic regression (LR) emerged as the most consistent top-performing models. LR showed the strongest discrimination, as reflected in ROC-AUC and AUPRC, whereas GAM delivered the best calibrated and clinically stable performance, achieving the lowest ECE and the highest Accuracy and F1 at the fixed threshold of 0.5.

Taken together, these findings show that interpretable additive models can match or even outperform more complex ensembles when evaluation extends beyond AUC to include calibration and decision-relevant metrics. The results support interpretable additive modeling as a strong and auditable baseline for trustworthy cardiovascular risk prediction and highlight the need for future validation on larger and externally independent cohorts.

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**Competing interest:** The authors declare that they have no competing interests.

## From the Fear of Missing Out to Academic Avoidance: FOMO and Academic Procrastination in Medical Students

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### Abstract

The primary aim of this study was to investigate the association between fear of missing out (FOMO) and academic procrastination among medical students, while the secondary aim was to examine differences in FOMO and academic procrastination according to academic, psychological, and digital behavior characteristics.

This cross-sectional, analytical, single-center study included 203 medical students enrolled at Bilecik Seyh Edebali University Faculty of Medicine during the 2025–2026 academic year. Data were collected anonymously via an online questionnaire including a descriptive characteristics form, the Fear of Missing Out Scale, and the Academic Procrastination Scale–Short Form. Group comparisons were performed using independent-samples t-tests and one-way ANOVA with Tukey post-hoc tests, and correlation was examined using Pearson correlation (SPSS v26). The mean age of participants was  $19.97 \pm 1.91$  years; 55.2% were female. Reliability was high for both scales (FOMO  $\alpha=0.865$ ; academic procrastination  $\alpha=0.890$ ). There were statistically significant differences in FOMO by academic year, digital media use patterns, digital behavior indicators, and recent anxiety level ( $p<0.05$ ), whereas no significant differences were found by GPA, study duration, stress level, and sleep quality ( $p>0.05$ ). Academic procrastination showed significant differences by academic year, GPA, perceived academic success, digital media use, frequency of checking the smartphone while studying, and recent anxiety level ( $p<0.05$ ), with no significant differences by notification status, sleep quality, and stress level ( $p>0.05$ ). A positive correlation was found between FOMO and academic procrastination ( $r=0.310$ ,  $p<0.001$ ). Higher FOMO was associated with increased academic procrastination among medical students, showing a moderate association. Both were related to digital behavior indicators, particularly smartphone-related interruptions during study time. These findings suggest that digital distractions may contribute to academic avoidance behaviors; therefore, strategies aimed at reducing such interruptions may support academic performance among medical students.

**Keywords:** Fear of missing out; Academic procrastination; Medical students, Digital behaviors.

## **Introduction**

The integration of digital communication tools into everyday life has increased individuals' desire to continuously monitor social events, giving rise to the concept of Fear of Missing Out (FOMO), defined as the anxiety stemming from the fear of missing social developments (Przybylski et al., 2013; Blackwell et al., 2017). FOMO is characterized by a persistent need to remain aware of others' experiences and the distress associated with the perception of missing out on rewarding events (Przybylski et al., 2013). This phenomenon has become particularly prevalent among young adults and university students and is closely associated with social media and smartphone use (Balcı & Bal, 2022; Amat et al., 2024; Din & Singh, 2024). Psychometric studies conducted in Türkiye have demonstrated that FOMO is a valid and reliable construct within the cultural context (Gökler et al., 2016). However, despite the availability of culturally validated measurement tools, empirical evidence linking FOMO to academic procrastination outcomes remains limited. Furthermore, these studies indicate that FOMO is a common and measurable phenomenon among university students. This finding suggests that FOMO is not merely an individual perception, but a form of digital anxiety closely linked to contemporary social lifestyles.

An examination of university students' social media use habits reveals that the fear of missing out on social developments may be associated not only with digital dependency behaviors but also with academic processes. University students, particularly young adults, frequently check their smartphones to avoid missing social events, which may lead to interruptions during studying, increased cognitive load, and delays in academic activities. Indeed, it has been reported that FOMO can impair time management by distracting attention and may foster

avoidance behaviors toward academic tasks through increased social media use (Yaman & Kavuncu, 2019). In this context, academic procrastination is defined as the deliberate delay of academic tasks, difficulty initiating tasks, or postponing responsibilities until the last moment (Anggoro, 2023; Li et al., 2023). Most of the procrastination research in the literature has focused on academic procrastination (Çakıcı, 2003; Balkıs et al., 2006; Çeri et al., 2015; Balkıs & Duru, 2009, 2022). Academic procrastination is a widespread tendency that negatively affects students' performance, academic satisfaction, and psychological well-being (Tanrıkulu & Karaca, 2021).

Studies aimed at developing and validating scales to measure academic procrastination indicate that this behavior is highly prevalent among students and has a multidimensional structure (Yockey, 2016; Tanrıkulu & Karaca, 2021; Balkıs & Duru, 2022). Recent research suggests that internet dependence and social media–based attentional distraction may increase academic procrastination behaviors (Çakmak Tolan, 2023). As FOMO creates a motivational drive toward online engagement, it may cause activities requiring sustained attention and self-discipline, such as studying, to be deprioritized. Accordingly, Efeoğlu (2024) reported that FOMO significantly predicts academic procrastination and that digital anxiety–based processes may negatively affect students' academic performance.

Medical students differ from students in many other disciplines in that they are enrolled in an intensive and long-term academic program. Despite their intensive training and high academic demands, the digital anxiety experiences of medical students have received relatively limited empirical attention. Consequently, they may be more vulnerable to digital stimuli that increase attentional distraction. At the same time, factors such as high achievement expectations, examination pressure, and clinical training may render these students more susceptible to both

FOMO and academic procrastination behaviors. Therefore, examining the relationship between FOMO and academic procrastination specifically among medical students may contribute to a better understanding of the impact of digital behaviors on educational performance. This study primarily aimed to investigate the association between levels of FOMO and academic procrastination among medical students, and secondarily to explore differences according to academic, psychological, and digital behavior characteristics.

### **Methods**

This study was conducted using a cross-sectional, analytical, single-center design. The convenience sample consisted of 203 medical students enrolled at Bilecik Seyh Edebali University Faculty of Medicine during the 2025–2026 academic year who voluntarily agreed to participate in the research.

The hypotheses of the study were formulated as follows:

**H1:** There are significant differences in FOMO levels according to university students' gender, academic year, academic achievement, and digital behavior variables.

**H2:** There are significant differences in academic procrastination levels according to university students' gender, academic year, academic achievement, and digital behavior variables.

**H3:** There is a positive relationship between university students' levels of FOMO and academic procrastination.

#### Descriptive Characteristics Form

The descriptive characteristics form was developed by the researchers based on a review of the relevant literature. The form collected data on students' demographic and descriptive characteristics, including gender, age, academic year, academic achievement, daily social media use duration, daily internet use duration, daily smartphone use duration, primary purpose

of internet use, place of residence, daily study duration, frequency of checking smartphones while studying, club membership status, daily sleep duration, smartphone notification settings, perceived anxiety level, and perceived stress level

#### Fear of Missing Out Scale

The Fear of Missing Out Scale, developed by Przybylski et al. (2013), is a 10-item, 5-point Likert-type instrument designed to assess individuals' levels of fear of missing out on social events. Each item is rated on a scale ranging from 1 ("not at all true of me") to 5 ("extremely true of me"), yielding total scores between 10 and 50. Higher scores indicate higher levels of FOMO. The Turkish validity and reliability study of the scale was conducted by Gökler et al. (2016), who reported a Cronbach's alpha coefficient of 0.81.

#### Academic Procrastination Scale – Short Form

To assess academic procrastination behavior, the 5-item short form developed by McCloskey (2011) and adapted into Turkish by Balkis and Duru (2022) was used. The scale is a 5-point Likert-type measure, with items rated from 1 ("strongly disagree") to 5 ("strongly agree"). Higher scores indicate greater tendencies toward academic procrastination. Yockey (2016) reported that the scale has a single-factor structure, with factor loadings ranging from 0.73 to 0.86. The internal consistency of the scale was reported as Cronbach's  $\alpha = 0.87$  (Yockey, 2016), while the Turkish adaptation demonstrated a Cronbach's alpha coefficient of 0.88 (Balkis & Duru, 2022), indicating high reliability.

#### Data Collection Procedure and Ethical Considerations

The study-specific questionnaire was prepared using Google Forms. At the beginning of the survey, participants were clearly informed about the purpose of the study, the voluntary of participation, and their right to withdraw at any time without consequence. All responses were collected anonymously. Ethical approval for the study was obtained from the Non-

Interventional Clinical Research Ethics Committee of Bilecik Şeyh Edebali University with the decision numbered 18 of the 2025/12 meeting.

### **Statistical analysis**

Data were analyzed using IBM SPSS Statistics (Version 26.0). Normality was assessed using Kolmogorov-Smirnov tests, and skewness and kurtosis values, and distributions were considered approximately normal when these values were within the  $-1$  to  $+1$  range. Descriptive statistics were presented as mean  $\pm$  standard deviation for continuous variables and number (percentage) for categorical variables. Between-group comparisons for two-category variables were conducted using the independent-samples t-test. Comparisons of scale scores across variables with more than two categories were performed using one-way analysis of variance (ANOVA), and Tukey's post-hoc test was applied for multiple comparisons. The association between FOMO and academic procrastination scores was examined using Pearson correlation analysis. Internal consistency of the scales was evaluated using Cronbach's alpha. All analyses were conducted at a 95% confidence level, and  $p < 0.05$  was considered statistically significant.

### **Results**

The mean age of the participants was  $19.97 \pm 1.91$  years. Of the students, 112 (55.2%) were female and 91 (44.8%) were male. Regarding academic year, 74 students (36.5%) were enrolled in Year 1, 80 students (39.4%) in Year 2, and 49 students (24.1%) in Year 3.

As shown in Table 1, most participants were female and early-year medical students. Most students reported moderate academic success, studied 1–3 hours per day, and spent more than three hours daily on social media and internet use. Smartphone use during studying and moderate levels of sleep quality, anxiety, and stress were commonly reported.

**Table 1.** Demographic and Academic Characteristics of Medical Students

	n	%
<b>Gender</b>		
Female	112	55.2
Male	91	44.8
<b>Academic Year</b>		
Year 1	74	36.5
Year 2	80	39.4
Year 3	49	24.1
<b>Living Arrangement</b>		
Living with family	11	5.4
Living with friends	21	10.3
Living alone	64	31.5
Dormitory	107	52.7
<b>Grade Point Average (GPA)</b>		
0-55	11	5.4
56-70	117	57.6
71-85	66	32.5
>85	9	4.4
<b>Perceived Academic Success</b>		
Excellent	4	2.0
Good	30	14.8
Moderate	110	54.2
Poor	49	24.1
Very poor	10	4.9
<b>Daily Study Duration</b>		
Never	32	15.8
1-3 hours	144	70.9
4-5 hours	21	10.3
>5 hours	6	3.0
<b>Daily Social Media Use</b>		

<1 hour	15	7.4
1-2 hours	61	30.0
3-4 hours	69	34.0
>4 hours	58	28.6
<b>Daily Internet Use</b>		
1-3 hours	35	17.2
4-6 hours	82	40.4
>7 hours	86	42.4
<b>Daily Smart Phone Use</b>		
<1 hour	9	4.4
1-3 hours	59	29.1
4-6 hours	82	40.4
>7 hours	53	26.1
<b>Aim of Internet Use</b>		
Social media	118	58.1
Messaging	21	10.3
Watching series/films	44	21.7
Gaming	7	3.4
Studying	13	6.4
<b>Frequency of checking mobile phone while studying</b>		
Mostly switched on	60	29.6
Partially switched on	67	33.0
Mostly switch off	35	17.2
Completely switch off	41	20.2
<b>Sleep Quality</b>		
Poor	51	25.1
Moderate	106	52.2
Good	46	22.7
<b>Anxiety Level in the Past 2 Weeks</b>		
Never	23	11.3

Rarely	76	37.4
Often	75	36.9
Always	29	14.3
<b>Stress Level in the Past 2 Weeks</b>		
Never	22	10.8
Low	46	22.7
Moderate	82	40.4
High	53	26.1

**Table 2.** Comparison of FOMO and academic procrastination scores (APS) across socio-demographic and digital behavior characteristics

	FOMO $\bar{X}\pm sd$	test value	p	Comp.	APS $\bar{X}\pm sd$	test value	p	Comp.
<b>Gender</b>								
Female	26.07±8.26	3.036	0.003		15.66±5.66	1.109	0.269	
Male	22.89±6.66				14.78±5.58			
<b>Academic Year</b>								
Year 1	22.79±6.09	4.807	0.008	1-2	15.85±5.70	4.982	0.008	3-1,2
Year 2	26.62±8.63				16.05±5.44			
Year 3	24.20±7.80				13.10±5.63			
<b>Grade Point Average (GPA)</b>								
0-55	24.90±5.20	0.148	0.931		17.00±4.85	5.115	0.002	2-3,4
56-70	24.88±7.89				16.25±5.64			
71-85	24.11±7.54				13.81±5.34			
>85	25.00±10.41				10.88±4.42			
<b>Perceived Academic Success</b>								
Excellent	19.40±8.51	1.862	0.119		11.50±5.96	4.096	0.003	4-1,2
Good	24.22±7.60				14.16±5.75			
Moderate	25.59±8.05				15.21±5.35			
Poor	24.06±5.90				18.00±4.99			

Very poor	21.25±6.94				19.25±7.13			
<b>Daily Study Duration</b>								
Never	25.78±5.77	0.624	0.600		20.25±4.67	13.334	<0.001	1-3; 4-1,2,3
1-3 hours	24.38±8.13				14.63±5.23			
4-5 hours	25.47±7.22				13.38±5.23			
>5 hours	21.83±9.34				10.33±7.33			
<b>Daily Social Media Use</b>								
<1 hour	18.80±7.40	10.001	<0.001	1-3; 4 2-4	9.80±3.96	20.484	<0.001	1-2,3,4; 2-3,4; 3-4
1-2 hours	22.73±7.32				13.19±5.13			
3-4 hours	24.39±7.19				15.15±5.01			
>4 hours	28.46±7.25				18.98±4.92			
<b>Daily Internet Use</b>								
1-3 hours	20.08±6.02	13.868	<0.001	1-2,3; 2-3	13.20±5.38	4.704	0.010	1-3
4-6 hours	23.67±6.43				14.87±5.58			
>7 hours	27.43±8.42				16.47±5.53			
<b>Daily Smart Phone Use</b>								
<1 hour	19.33±7.58	3.465	0.017	1-4	11.33±2.91	6.412	<0.001	4-1,2
1-3 hours	23.23±7.73				13.67±5.13			
4-6 hours	24.91±7.02				15.36±5.83			
>7 hours	26.69±8.27				17.54±5.35			
<b>Aim of Internet Use</b>								
Social media	25.52±7.60	3.577	0.008	5-1,2	15.57±5.68	3.544	0.008	5-1,3
Messaging	26.38±9.28				14.38±5.55			
Watching series/films	23.09±6.51				16.31±5.49			
Gaming	26.28±6.44				15.71±3.90			
Studying	18.23±7.35				10.07±3.90			
<b>Frequency of Checking Mobile Phone While Studying</b>								
Never	20.22±7.91	2.685	0.048	1-3,4	11.66±6.92	12.441	<0.001	1-3,4; 2-3,4
Sometimes	23.77±8.24				13.51±5.16			

Often	25.82±6.72				17.21±4.91			
Usually	27.53±7.69				19.92±5.99			
<b>Frequency of Checking Mobile Phone Notifications</b>								
Mostly switched on	26.06±9.02	3.583	0.015	4-1,2	15.98±6.06	1.784	0.152	
Partially switched on	25.85±7.61				15.94±5.49			
Mostly switch off	23.22±6.35				13.85±5.05			
Completely switch off	21.80±6.05				14.31±5.49			
<b>Sleep Quality</b>								
Poor	24.60±6.49	0.710	0.493		16.27±5.75	1.113	0.331	
Moderate	25.15±8.45				14.87±5.86			
Good	23.52±7.30				15.06±4.88			
<b>Anxiety Level in the Past 2 Weeks</b>								
Never	21.56±8.89	4.870	0.003	4-1,2	12.95±5.99	2.882	0.037	1-4
Rarely	23.23±6.49				15.01±4.99			
Often	25.60±7.98				15.38±6.00			
Always	28.31±7.65				17.44±5.36			
<b>Stress Level in the Past 2 Weeks</b>								
Never	22.81±9.92	1.558	0.201		15.05±7.52	1.932	0.126	
Low	23.76±8.27				16.84±5.69			
Moderate	24.48±7.15				14.37±5.22			
High	26.41±6.95				15.35±5.11			

Table 2 summarizes between-group comparisons of FOMO and APS across socio-demographic and digital behavior characteristics. For FOMO, significant differences were found according to academic year ( $p=0.008$ ), daily social media use ( $p<0.001$ ), daily internet use ( $p<0.001$ ), daily smartphone use ( $p=0.017$ ), primary purpose of internet use ( $p=0.008$ ), frequency of checking the smartphone while studying ( $p=0.048$ ), notification status ( $p=0.015$ ), and anxiety level in the past two weeks ( $p=0.003$ ). Post-hoc comparisons indicated that Year 1 students had

lower mean FOMO scores than Year 2 and Year 3 students, and that higher levels of social media/internet/smartphone use and more frequent phone checking during studying were associated with higher FOMO scores. No significant differences in FOMO were found by GPA, perceived academic success, daily study duration, sleep quality, and recent stress level ( $p>0.05$ ).

For APS, significant differences were found according to academic year ( $p=0.008$ ), GPA ( $p=0.002$ ), perceived academic success ( $p=0.003$ ), daily study duration ( $p<0.001$ ), daily social media use ( $p<0.001$ ), daily internet use ( $p=0.010$ ), daily smartphone use ( $p<0.001$ ), primary purpose of internet use ( $p=0.008$ ), frequency of checking the smartphone while studying ( $p<0.001$ ), and anxiety level ( $p=0.037$ ). Post-hoc comparisons showed that Year 3 students had lower mean APS scores than Year 1 and Year 2 students, and that shorter study duration and greater social media/smartphone use were associated with higher procrastination scores. No significant differences in APS were found by notification status, sleep quality, or stress level (all  $p>0.05$ ).

**Table 3.** Scales descriptive, reliability, and correlation

Scale	Min.	Max.	Mean	SD	Skewness	Kurtosis	Cronbach's $\alpha$	Correlation
<b>FOMO</b>	10.0	50.0	24.64	7.73	0.460	0.332	0.865	r=0.310 p<0.001
<b>Academic Procrastination</b>	5.0	25.0	15.26	5.63	0.015	-0.881	0.890	

As presented in Table 3, the FOMO scale scores ranged from 10 to 50, with a mean of  $24.64 \pm 7.73$ . Academic procrastination scores ranged from 5 to 25, with a mean of  $15.26 \pm 5.63$ . Both scales demonstrated high internal consistency (Cronbach's  $\alpha = 0.865$  for FOMO;  $\alpha = 0.890$  for academic procrastination). Correlation analysis revealed a significant, positive, and moderate association between FOMO and academic procrastination ( $r=0.310$ ,  $p<0.001$ ), indicating that higher FOMO levels were related to higher academic procrastination scores.

### Discussion

Although FOMO is not a novel concept, the digital era has increased attention to it and created opportunities to examine its correlates and consequences (Przybylski et al., 2013; Blackwell et al., 2017). The present study investigated the association between FOMO and academic procrastination among medical students and examined whether these variables differed across academic, psychological, and digital behavior characteristics. In bivariate analyses, FOMO scores were positively correlated with academic procrastination ( $r=0.310$ ;  $p<0.001$ ), indicating that higher FOMO was associated with greater procrastination tendencies.

Consistent with prior research, an increasing number of studies have reported a strong relationship between FOMO and procrastination (Wang et al., 2019; Rozgonjuk et al., 2020; Tandon et al., 2021). Studies in university samples similarly suggest that higher FOMO is accompanied by greater procrastination tendencies (Manap et al., 2023). Supporting this,

academic procrastination has been reported to correlate positively with FOMO in the study by Tang & He ( $r=0.397$ ;  $p<0.001$ ) and by Efeoğlu ( $p=0.256$ ;  $p<0.001$ ) which is consistent with our study. However, many studies address the FOMO–procrastination link within multivariable models, and fewer studies, particularly in medical students, focus on their direct, standalone association. Therefore, our results extend the literature by addressing this association in a high-demand academic group and by considering multiple indicators of digital engagement. In addition, we found that academic procrastination was meaningfully related to academic performance indicators. Students with higher GPA reported lower procrastination, and students who perceived themselves as academically unsuccessful showed higher procrastination than those who perceived themselves as successful. This pattern supports the view that academic procrastination is associated with poorer academic outcomes and may undermine students’ academic satisfaction and well-being (Tanrikulu & Karaca, 2021).

People with FOMO often feel a strong need to keep checking social media to stay updated on what others are doing (Przybylski et al., 2013). This can lead to procrastination because it takes time and attention away from important tasks (Li & Ye, 2022). As a result, FOMO may be linked to students to delay responsibilities they need to complete (Wang et al., 2019). A recent study indicates a close connection between social comparison, social media addiction, and FOMO, and further shows that loneliness and perfectionism may act as mediators in the association between social comparison and FOMO (Piko et al., 2025).

Psychological factors may further intensify these patterns. Social anxiety may lead students to spend more time on social media, which may reduce their ability to complete academic tasks on time (Al-Furaih & Al-Awidi, 2021). Similarly, in the present study, FOMO levels were higher among students who reported higher anxiety in the past two weeks. Prior evidence also

suggests that students with social media addiction may experience higher FOMO, which may in turn be associated with academic procrastination (Li & Ye, 2022). Moreover, students with higher FOMO may use social media more frequently and may become distracted during study time (Shane-Simpson & Bakken, 2024), increasing the risk of academic procrastination. Consistent with this explanation, students with higher FOMO and higher academic procrastination in our sample also reported longer daily social media, smartphone, and internet use. Additionally, evidence indicates that FOMO may drive overuse of social media and smartphones (Elhai et al., 2018; Wang et al., 2019; Akbay et al., 2020). Such overuse may promote procrastination through more frequent interruptions and reduced sustained attention during academic work.

FOMO is associated with anxiety and with perceived deficits in psychosocial needs such as belongingness and social connection (Roberts & David, 2020). Accordingly, FOMO has been linked to negative outcomes such as sleep problems and mental health difficulties, including stress, sadness, and anxiety (Adams et al., 2020). However, in the present study, significant differences were not found in FOMO or academic procrastination by sleep quality or stress level. In addition, the stress and sleep items were assessed using broad self-report categories, which may have reduced sensitivity to detect between-group differences. It is also possible that stress is relatively common in medical students, leading to limited discrimination between groups.

Regarding sociodemographic differences, the literature presents various findings. Some studies reported no significant gender differences (Rozgonjuk et al., 2020; Servidio, 2021), whereas others found significant differences by gender (Przybylski et al., 2013; Zayed, 2024). In the present study, female students reported higher FOMO scores than male students, which is

consistent with studies reporting gender differences. Several studies found a gender difference in academic procrastination (Gür et al., 2018; Coşkun, 2022). However, other studies reported no gender difference in academic procrastination (Şahin, 2020; Zarei & Khoshouei, 2023), similar to our findings. While a study found no differences (Yaman and Kavuncu, 2019), others reported significant variation by class level (Çınar & Mutlu, 2018; Akbay et al., 2020). Similarly, we observed significant differences in FOMO across academic years in our sample. There are also studies showing differences in academic procrastination by class level (Coşkun, 2022; Li et al., 2023), consistent with our findings. There is a study showing that differences in academic procrastination by internet use frequency are similar to our findings (Gür et al., 2018). There are studies showing that FOMO differs according to how often people check calls, messages, e-mails, or social media on their devices (Akbay et al., 2020; Gökler et al., 2016). Differences across studies may reflect cultural context, measurement approaches, and sample characteristics. Therefore, gender effects may not be consistent.

This study should be interpreted considering several limitations. Its cross-sectional, single-center design limits causal inference and generalizability, and the use of self-report measures may have introduced reporting bias. Future multi-center longitudinal studies and intervention research (e.g., reducing smartphone checking while studying) are warranted. Despite these limitations, focusing on medical students is a key strength, and the use of reliable, culturally validated instruments (Cronbach's  $\alpha > 0.86$ ), together with multiple digital behavior indicators, provides a broader view of FOMO and academic procrastination in this context.

## **Conclusion**

In summary, this study demonstrates that FOMO is moderately and positively associated with academic procrastination among medical students and that both constructs are linked to digital

behavior characteristics, particularly smartphone-related interruptions during studying. These findings suggest that digital distractions may contribute to academic avoidance behaviors; therefore, strategies aimed at reducing such interruptions may support academic performance among medical students.

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**Competing interest:** The authors declare that they have no competing interests.

## Comparative Evaluation of the Pharmacokinetics and Drug-Likeness Properties of Certain Flavonoids in Honey 1

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### Abstract:

Honey is a natural food product with high nutritional value due to the many phenolic acids and flavonoids it contains. Apitherapy is known as the medical use of various bee products and is widely used in the treatment of certain diseases and in preventive medicine. In this study, the pharmacokinetic and drug-likeness properties of the flavonoids quercetin and apigenin found in honey were evaluated using *in silico* analysis. The SwissADME website, developed by the Swiss Institute of Bioinformatics, provided information on the physicochemical properties, lipophilicity, water solubility, drug similarity, pharmacokinetic properties, and medicinal chemical properties of two molecules. According to Lipinski's 5 rules, the molecular weights of both molecules were found to be below the <500 g/mol limit. It has also been observed that the topological polar surface areas (TPSA) are below 140 Å<sup>2</sup>. Lipophilicity of the apigenin molecule is higher than that of the quercetin molecule. When their water solubility is considered, the fact that quercetin contains more hydroxyl groups suggests that its water solubility is higher than that of apigenin. It has been observed that the apigenin molecule is more advantageous than quercetin for skin permeation. BOILED-Egg graphic results indicate that apigenin has good gastrointestinal absorption due to its low polarity and high lipophilicity, but neither molecule crosses the blood-brain barrier. Both compounds show appropriate results as CYP1A2, CYP2D6, and CYP3A4 inhibitors, indicating that the molecules have potential drug-drug interactions. The bioavailability score for both molecules is 0.55. The catechol structure present in quercetin's composition may indicate the presence of a reactive motif, but the absence of any warning in apigenin demonstrates that the molecule has a clean profile. General findings indicate that both compounds have acceptable ADME profiles, with apigenin being a more balanced compound for drug development studies and quercetin being a compound with strong biological activity as a reference molecule. By revealing the pharmacokinetic profiles of quercetin and apigenin flavonoids, the results would be beneficial for guiding further and detailed studies that can be conducted *in vitro* and *in vivo* environments.

**Keywords:** honey, flavonoids, pharmacokinetics, drug-likeness, SwissADME.

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<sup>1</sup> This study is a non-derivative and distinct original research.

## Introduction

Honey is one of the highly regarded natural foods due to having rich nutritional value and therapeutic properties since honey has flavonoids and phenolic acids, which contribute to honey's well-studied therapeutic effects, mostly on antioxidant, anti-inflammatory, and antimicrobial effects (Cianciosi et al., 2018). Honey has a notable place among the dietary antioxidant sources as was revealed *in vitro* on samples produced from diverse flora (Gheldof & Engeseth 2002). Antimicrobial effects were studied and it has been found that antimicrobial effects were acting on both prevention and inhibition of growth of different pathogenic microorganisms (Al-Waili et al., 2014). It has been noted that oxidative biomolecular damage leads to progressive development of inflammation, which in turn leads to development of chronic diseases (Lugrin et al., 2014).

Investigations conducted on honey for its anti-inflammatory properties revealed that honey has been effective in reducing edema and reducing pro-inflammatory cytokines, e.g., IL-6, TNF- $\alpha$ , PGE<sub>2</sub>, NO, iNOS, and COX-2 (Hussein et al., 2012; Hussein et al., 2013). It has been reported that honey contains large amounts of flavonoids and phenolic compounds, which particularly include quercetin and kaempferol, along with others such as apigenin, genistein, naringenin, gallic acid, and ferulic acid (Ahmed et al., 2018). Due to the extensive research conducted on honey for its therapeutic properties, it would be beneficial to predict and profile the bioactive substances *in silico* by conducting ADME (Absorption, Distribution, Metabolism, Excretion) profiling and pharmacokinetics assessments. Here, the SwissADME platform was deployed to investigate pharmacokinetics of quercetin and apigenin, which are flavonoids in honey. Different techniques (BOILED-Egg model, Lipinski's Five Rules, Cytochrome P450 enzyme

inhibition prediction algorithms) were used to investigate the therapeutic properties of quercetin and apigenin (Daina et al., 2014, 2017; Daina & Zoete, 2016).

## **Materials and Methods**

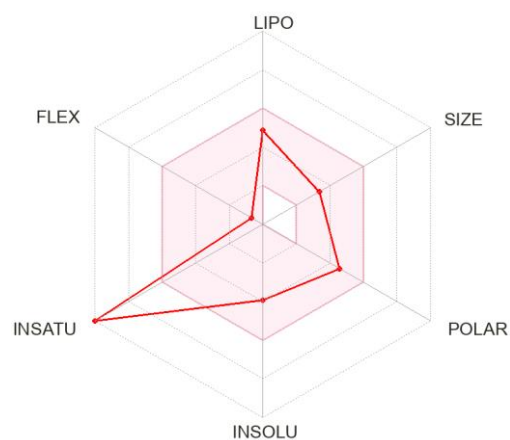
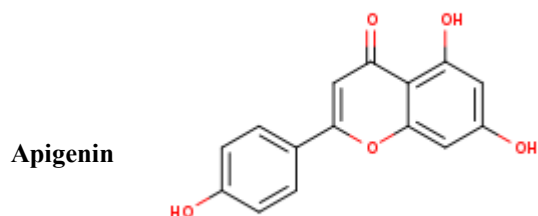
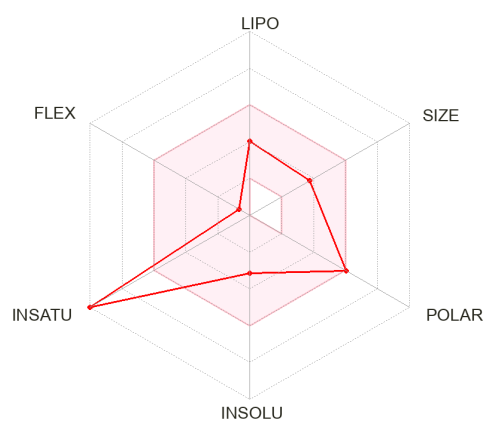
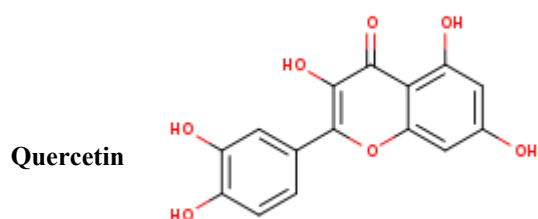
PubChem database (Kim et al., 2025) was used to retrieve the SMILES (Simplified Molecular Input Line Entry System) codes of both quercetin (PubChem CID: 5280343) and apigenin (PubChem CID: 5280443) for to use in the SwissADME online tool, which was an online tool developed and maintained by the Swiss Institute of Bioinformatics for predictive analyses of various compounds such as physicochemistry, pharmacokinetics, and drug-likeness (Daina et al., 2014, 2017; Daina & Zoete, 2016). Computational analyses of the compounds revealed information on following properties: physicochemistry, lipophilicity, water solubility, drug similarity, and pharmacokinetics. Medicinal chemistry properties of the compounds were examined by using bioavailability radar and BOILED-Egg model (Daina & Zoete, 2016) and results were obtained with their visual summaries.

## **Results**

Presented in Figure 1 are the 2D chemical structures and bioavailability radar charts for quercetin and apigenin. The ADME information and medicinal chemistry predictions of quercetin and apigenin are presented in separate tables of Table 1 and Table 2, respectively. Additionally, a model figure 2 is provided that visualizes two fundamental pharmacokinetic properties related to gastrointestinal absorption and brain penetration for two molecules.

### 2D Structure

### Bioavailability Radar



**Figure 1.** Chemical structures of quercetin and apigenin molecules and their bioavailability radar charts

When looking at their chemical structures, quercetin, a flavonol, has 5 hydroxyl groups, while apigenin, a flavone, has 3 hydroxyl groups. The bioavailability radar chart shows the ideal ranges for compounds with drug potential to be taken orally, indicated by the pink area.

Accordingly, quercetin has lower lipophilicity (LIPO) than apigenin, while quercetin has a larger molecular size (SIZE) than apigenin. The fact that the quercetin molecule contains more hydroxyl groups than apigenin also indicates that its polarity (POLAR) is higher compared to apigenin. The presence of aromatic rings in both molecules indicates that the degree of unsaturation is not within ideal limits (Figure 1).

**Table 1.** The ADME properties of quercetin molecule

Physicochemical Properties		Pharmacokinetics	
Formula	C <sub>15</sub> H <sub>10</sub> O <sub>7</sub>	GI absorption	High
Molecular weight	302.24 g/mol	BBB permeant	No
Num. heavy atoms	22	P-gp substrate	No
Num. arom. Heavy atoms	16	CYP1A2 inhibitor	Yes
Fraction Csp3	0.00	CYP2C19 inhibitor	No
Num. rotatable bonds	1	CYP2C9 inhibitor	No
Num. H-bond acceptors	7	CYP2D6 inhibitor	Yes
Num. H-bond donors	5	CYP3A4 inhibitor	Yes
Molar Refractivity	78.03	Log <i>K<sub>p</sub></i> (skin permeation)	-7.05 cm/s
TPSA	131.36 Å <sup>2</sup>	Druglikeness	
Lipophilicity		Lipinski	Yes; 0 violation
Log <i>P<sub>o/w</sub></i> (iLOGP)	1.63	Ghose	Yes
Log <i>P<sub>o/w</sub></i> (XLOGP3)	1.54	Veber	Yes
Log <i>P<sub>o/w</sub></i> (WLOGP)	1.99	Egan	Yes
Log <i>P<sub>o/w</sub></i> (MLOGP)	-0.56	Muegge	Yes

Log $P_{o/w}$ (SILICOS-IT)	1.54	Bioavailability Score	0.55
Consensus Log $P_{o/w}$	1.23	<b>Medicinal Chemistry</b>	
<b>Water Solubility</b>		PAINS	1 alert: catechol_A
Log $S$ (ESOL)	-3.16	Brenk	1 alert: catechol
Solubility	2.11e-01 mg/ml; 6.98e-04 mol/l	Leadlikeness	Yes
Class	Soluble	Synthetic accessibility	3.23
Log $S$ (Ali)	-3.91		
Solubility	3.74e-02 mg/ml; 1.24e-04 mol/l		
Class	Soluble		
Log $S$ (SILICOS-IT)	-3.24		
Solubility	1.73e-01 mg/ml; 5.73e-04 mol/l		
Class	Soluble		

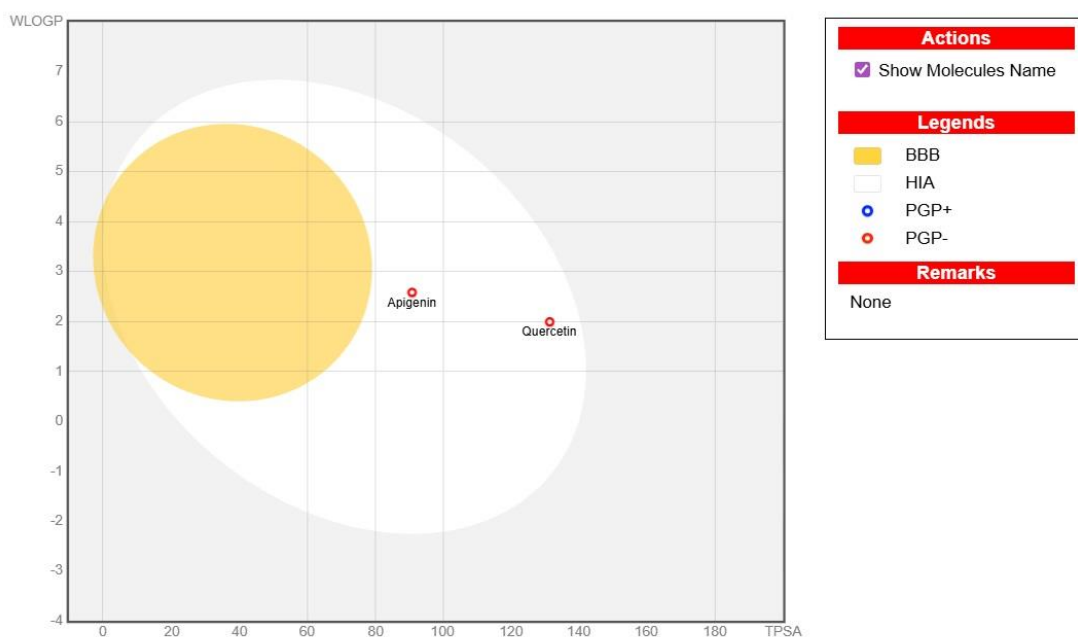
**Table 2.** The ADME properties of apigenin molecule

Physicochemical Properties		Pharmacokinetics	
Formula	C <sub>15</sub> H <sub>10</sub> O <sub>5</sub>	GI absorption	High
Molecular weight	270.24 g/mol	BBB permeant	No
Num. heavy atoms	20	P-gp substrate	No
Num. arom. Heavy atoms	16	CYP1A2 inhibitor	Yes
Fraction Csp3	0.00	CYP2C19 inhibitor	No
Num. rotatable bonds	1	CYP2C9 inhibitor	No
Num. H-bond acceptors	5	CYP2D6 inhibitor	Yes

Num. H-bond donors	3	CYP3A4 inhibitor	Yes
Molar Refractivity	78.99	Log $K_p$ (skin permeation)	-5.80 cm/s
TPSA	90.90 Å <sup>2</sup>	<b>Druglikeness</b>	
<b>Lipophilicity</b>		Lipinski	Yes; 0 violation
Log $P_{o/w}$ (iLOGP)	1.89	Ghose	Yes
Log $P_{o/w}$ (XLOGP3)	3.02	Veber	Yes
Log $P_{o/w}$ (WLOGP)	2.58	Egan	Yes
Log $P_{o/w}$ (MLOGP)	0.52	Muegge	Yes
Log $P_{o/w}$ (SILICOS-IT)	2.52	Bioavailability Score	0.55
Consensus Log $P_{o/w}$	2.11	<b>Medicinal Chemistry</b>	
<b>Water Solubility</b>		PAINS	0 alert
Log $S$ (ESOL)	-3.94	Brenk	0 alert
Solubility	3.07e-02 mg/ml; 1.14e-04 mol/l	Leadlikeness	Yes
Class	Soluble	Synthetic accessibility	2.96
Log $S$ (Ali)	-4.59		
Solubility	6.88e-03 mg/ml; 2.55e-05 mol/l		
Class	Moderately soluble		
Log $S$ (SILICOS-IT)	-4.40		
Solubility	1.07e-02 mg/ml; 3.94e-05 mol/l		
Class	Moderately soluble		

The results presented in Table 1 and Table 2 were evaluated according to Lipinski's five rules (Lipinski et al., 2001). Both molecules have a molecular weight below the <500 g/mol limit (quercetin: 302.24 g/mol, apigenin: 270.24 g/mol) indicate that the molecules are of a suitable size for absorption and distribution in the body. TPSA (Topological Polar Surface Area) values

were measured as 131.36 Å<sup>2</sup> for quercetin, and as 90.90 Å<sup>2</sup> for apigenin compounds. A less than 140 Å<sup>2</sup> TPSA value in compounds was previously reported to improve oral bioavailability (Veber et al., 2002). Therefore, both compounds has the potential of cell membrane permeability and bioavailability. The consensus Log Po/w values were measured for quercetin and apigenin as 1.23 and 2.11, respectively. Since lipophilicity is an indicator of cell membrane permeability, it can be said that apigenin has more lipid solubility compared to quercetin (Daina et al., 2014). It was revealed that quercetin has improved water solubility compared to apigenin in terms of model coefficients from Log S (ESOL), Log S (Ali et al., 2012), and Log S (SILICOS-IT) (Delaney, 2004; Ali et al., 2012). It was revealed that quercetin has -7.05 cm/s Log Kp and apigenin has -5.80 cm/s Log Kp values, and since Log Kp is an indicator for skin permeability (Potts & Guy 1992; Daina et al., 2014), it can be concluded that apigenin has improved skin permeability rating.



**Figure 2.** The BOILED-Egg graphic of the quercetin and apigenin molecule

Potentials of quercetin and apigenin compounds to bypass blood-brain barrier and their ability of gastrointestinal absorption were visualized by using the BOILED-Egg (Brain or Intestinal Estimated) permeation method (Daina & Zoete, 2016). Figure 1 shows the white region indicating gastrointestinal absorption based on the parameters of lipophilicity/fat solubility (WLOP) and polar surface area (TPSA), and the yellow region indicating the ability to cross the blood-brain barrier and enter the central nervous system. The apigenin molecule is closer to the yellow zone due to its low polarity and high lipophilicity. Since neither molecule is within the yellow zone, they cannot cross the blood-brain barrier. Her ikisi de beyaz alanın içerisinde kaldığı için hem quercetin hem de apigeninin bağırsak emilimi vardır. The fact that both compounds yield appropriate results as CYP1A2, CYP2D6, and CYP3A4 inhibitors indicates that the molecules have potential drug-drug interactions. Both molecules passed all drug-likeness filters with zero violations. Furthermore, their bioavailability score of 0.55 suggests that these molecules show promise for becoming drug molecules once optimized. The catechol structure present in quercetin's composition may indicate the presence of a reactive motif, but the absence of any alerts in apigenin indicates that the molecule has a clean profile in terms of reliability in biological tests, chemical stability, and synthesizability.

## **Discussion**

Abundant polyphenols together with rich nutritional value make honey particularly noteworthy natural food that also has notable potential for therapeutic bioactivity, which was mainly attributed to polyphenol abundance it contains (Ranneh et al., 2021). Polyphenols have elevated amounts in plants, particularly in edible vegetables and fruits, and are considered to have pronounced antioxidant properties (Covas et al., 2006). It was reported that honey phytochemistry composition is depending on bees, flora, and climatic conditions (Ranneh et al.,

2021). Among the polyphenols, flavonoids have different subclasses, which include anthocyanidins, flavanols, flavanones, flavonols, flavones, and isoflavones (Shen et al., 2022). Previous research on apigenin revealed alleviation of geriatric muscle atrophy in mice (Wang et al., 2020), and inhibition of oxidative inflammation development (Zhou et al., 2019). The compound quercetin is a flavonol of flavonoids that has reported antioxidant, antiviral, anticancer, and immunomodulatory properties (Aghababaei & Hadidi, 2023). Previous research were indicated that quercetin may activate NKCC1 pathway that leads to antihypertensive effects (Marunaka et al., 2017), and quercetin in particular may be utilized in treatment strategies against allergic disorders (Mlcek et al., 2016). Here, *in silico* analysis of ADME properties of quercetin and apigenin was conducted by using the SwissADME tool. Based on the results, both compounds have the ability of gastrointestinal absorption, can bypass different filters (Lipinski, Ghose, Veber, Egan, and Muegge), have the ability of CYP inhibition, and have the potential for use as oral medication. Results indicate that while quercetin has pronounced water solubility and skin permeability compared to apigenin, it's reliability in biological testing and it's chemical stability were challenged by the PAINS/Brenk warning. Both compounds have favourable ADME profiles, however, results indicate that apigenin may be the more optimal candidate for drug development, while quercetin may be used as a reference bioactive compound.

## **Conclusion**

The present research investigated and evaluated the ADME profiles and their implications of two members of flavonoids in honey, quercetin and apigenin. The SwissADME-based computational analyses revealed notable clinical prospects for these compounds and their similarity to drug-like properties. Since honey and other beekeeping products are notable targets

for innovative life sciences research, novel discoveries would certainly continue, and from the results it can be concluded that both quercetin and apigenin have drug-like potential that warrants further and detailed studies on these compounds.

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## Cytotoxic and Morphological Effects of Syringic Acid on H209 Small Cell Lung Cancer Cells

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### Abstract

Small cell lung cancer (SCLC) represents one of the most aggressive subtypes of lung malignancies, characterized by rapid proliferation and poor therapeutic outcomes. To facilitate the study of SCLC biology and to evaluate the cytotoxic potential of novel agents, the H209 cell line—derived from human SCLC tissue—has been extensively utilized as an in vitro model that closely mirrors the proliferative behavior of this cancer type.

Syringic acid (SA) is a naturally occurring compound known for its diverse biological activities. This study aimed to investigate the cytotoxic and morphological effects of SA on the H209 small-cell lung carcinoma cell line. Cells were treated with increasing concentrations of SA (100, 200, 400, 800, and 1200 µg/mL) for 48 hours. Cytotoxicity and cell viability were assessed using the MTT and Trypan Blue exclusion assays, while fluorescence microscopy with Hoechst 33342 and Propidium Iodide (PI) staining was employed to distinguish viable and non-viable cells. Morphological changes were examined under an inverted light microscope to evaluate dose-dependent alterations in cell structure and adherence. The MTT results revealed a concentration-dependent decrease in cell viability, with approximately 50% cytotoxicity observed at 1200 µg/mL ( $p < 0.001$ ). Lower concentrations (100–800 µg/mL) exhibited gradually reduced inhibitory effects. Trypan Blue and fluorescence staining analyses confirmed the loss of membrane integrity and a decrease in viable cell numbers at higher concentrations. Morphological observations supported these findings, showing reduced cell density and structural disruption in treated groups compared to controls. Collectively, these results indicate that syringic acid exerts a dose-dependent cytotoxic effect on H209 cells, demonstrating potential as a bioactive compound for further in vitro cellular response studies.

**Keywords:** Syringic acid, small cell lung cancer, H209 cells, cytotoxicity, cell viability

## **Introduction**

Small cell lung cancer (SCLC) is a clinically aggressive subtype of lung malignancy distinguished by rapid proliferation, early metastatic dissemination, and poor long-term therapeutic outcomes (Rudin et al., 2021). Although SCLC represents a smaller proportion of lung cancer cases, its aggressive nature and high relapse rates following standard therapies continue to pose significant clinical challenges. These limitations highlight the importance of exploring alternative therapeutic candidates that may contribute to the development of new treatment strategies (Sen et al., 2024).

In vitro cancer cell models are widely employed in early-stage research to assess cellular responses to potential anticancer agents (Antunes et. al., 2022). Among these models, the H209 human SCLC cell line is frequently applied to examine cytotoxic responses and treatment-associated cellular alterations under standardized laboratory conditions. Such models provide valuable preliminary data prior to more advanced experimental approaches (Zhai et al., 2025). Natural compounds have gained growing attention in oncology research because of their structural diversity and wide range of biological activities. Phenolic acids, in particular, have been reported to influence cellular processes related to oxidative stress, inflammation, and cell survival (Asma et al., 2022). Syringic acid (SA) is a plant-derived phenolic molecule that has demonstrated multiple biological activities across various experimental models; however, its specific cellular effects in small cell lung cancer remain insufficiently characterized (Srinivasulu et al., 2018).

Therefore, this study aimed to evaluate the cytotoxicity, viability status, and morphological alterations induced by SA in H209 small cell lung cancer cells using complementary cell-based assays and microscopic analyses.

## **Materials and Methods**

### **Cell Culture**

The H209 human small cell lung cancer cell line served as the in vitro experimental model in this study. Cells were maintained in Iscove's Modified Dulbecco's Medium (IMDM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin to preserve optimal growth conditions. Cultures were incubated under humidified conditions at 37 °C in an atmosphere containing 5% CO<sub>2</sub>. All experiments were conducted using cells within a restricted passage range to maintain experimental consistency.

### **Syringic Acid Treatment**

SA was first dissolved in dimethyl sulfoxide (DMSO) and then serially diluted in complete culture medium to achieve final concentrations of 100, 200, 400, 800, and 1200 µg/mL. The final DMSO concentration in all experimental groups did not exceed 0.5%. Control groups consisted of untreated cells maintained in culture medium and cells treated with the corresponding concentration of DMSO alone. All experimental groups were incubated for 48 hours prior to further analyses.

### **MTT Cytotoxicity Assay**

Cellular metabolic activity was quantified using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay after 48 hours of SA exposure. Upon completion of the treatment period, MTT solution (5 mg/mL) was added to each well and cells were further incubated to enable formazan crystal formation. Formazan crystals were subsequently solubilized in DMSO, and absorbance values were recorded at 570 nm using a

spectrophotometric microplate reader (BioTek, ELx800). Proliferation inhibition rates were calculated relative to untreated control values and expressed as percentage reduction.

### **Trypan Blue Exclusion Assay**

Membrane integrity and viability were further evaluated using the Trypan Blue dye exclusion method after 48 hours of treatment. After treatment, viable and non-viable cells were distinguished according to dye permeability and manually counted under an inverted microscope (Olympus CKX41, 10× magnification). The percentage of viable cells was determined by comparing the number of live cells to the total cell number in each experimental condition.

### **Morphological Analysis**

Morphological evaluation of H209 small cell lung cancer cells was performed using an inverted microscope after 48 hours of SA treatment. Following the incubation period, cells were visually examined to assess treatment-related changes in overall cellular morphology and cell density. Representative images were captured from each experimental group, including SA-treated cells, DMSO-treated control cells, and untreated cells maintained in culture medium, using a 4× objective. All observations and image acquisitions were conducted under identical microscopic settings to enable reliable comparative analysis between groups.

### **Fluorescence Microscopy (Hoechst 33342/PI Staining)**

After 48 hours of SA exposure, H209 cells were stained with Hoechst 33342 and propidium iodide (PI) to differentiate viable cells from membrane-compromised cells. Stained cells were visualized under a fluorescence microscope (Leica DM4000B) equipped with the appropriate

excitation and emission filter sets. Fluorescence images were captured under standardized optical parameters across all experimental and control groups to ensure reliable comparison.

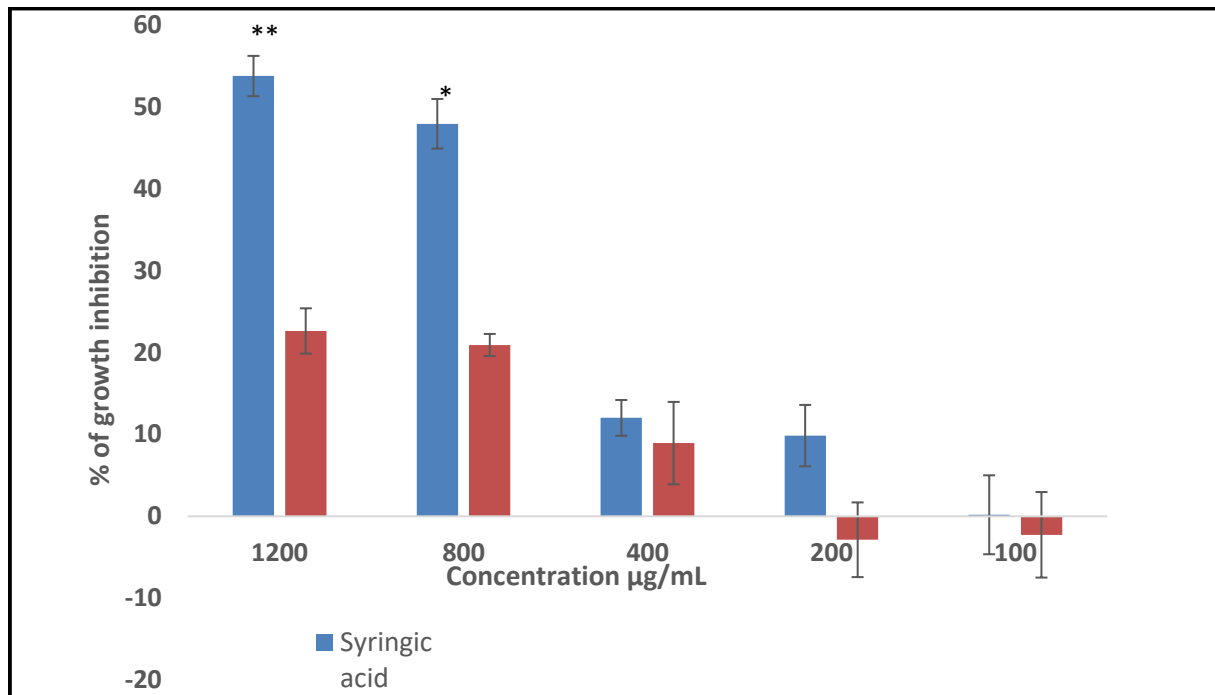
### **Statistical Analysis**

All data are expressed as mean  $\pm$  standard deviation (SD) derived from three independent experimental replicates. Statistical comparisons were conducted using an unpaired Student's t-test in GraphPad Prism software, and p values below 0.05 were interpreted as statistically significant.

### **Results**

#### **Inhibitory Effect of Syringic Acid on H209 Cell Growth**

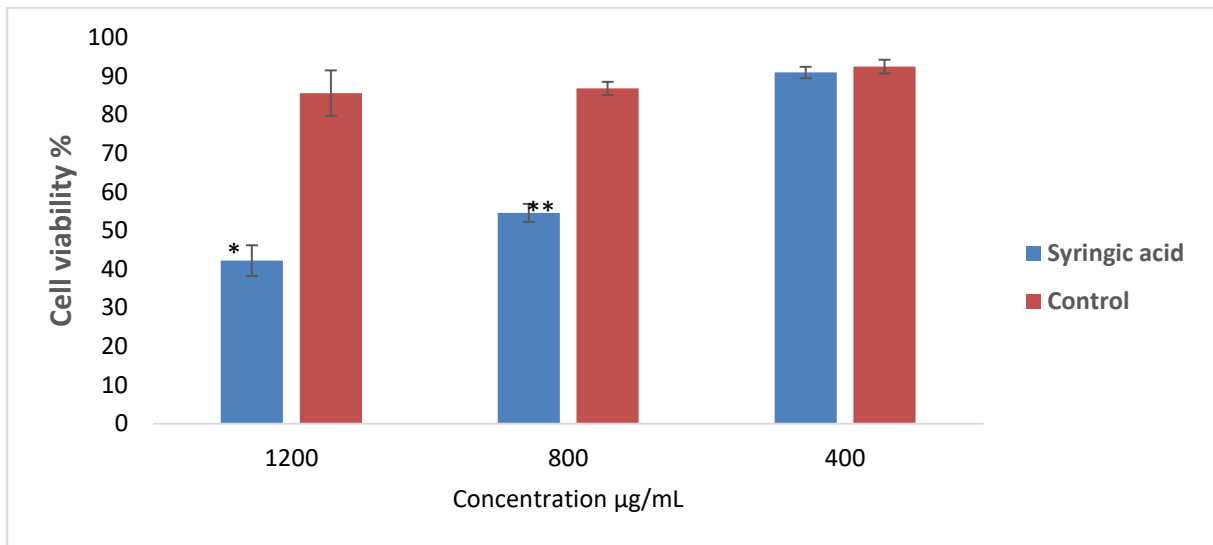
The effect of SA on H209 cell growth was assessed using the MTT assay after a 48-hour exposure period. As illustrated in Figure 1, SA did not produce a statistically significant alteration in proliferation rates at concentrations of 100, 200, or 400  $\mu\text{g}/\text{mL}$  compared with controls. In contrast, exposure to higher concentrations led to a marked suppression of cell proliferation. Specifically, treatment at 800 and 1200  $\mu\text{g}/\text{mL}$  significantly decreased proliferation, with the highest concentration (1200  $\mu\text{g}/\text{mL}$ ) producing approximately 50% inhibition relative to untreated cells (\*\*p < 0.001). These findings demonstrate a dose-responsive antiproliferative effect, reaching statistical significance only at elevated concentrations.



**Figure 1.** Effect of SA on the growth inhibition of H209 cells after 48 hours of treatment. H209 cells were exposed to increasing concentrations of syringic acid (100–1200 µg/mL), and cell growth inhibition was calculated based on MTT assay results. Data are presented as mean ± SD from three independent experiments. SA induced a concentration-dependent increase in growth inhibition at higher concentrations compared with the control group. (\* $p < 0.01$ , \*\* $p < 0.001$ ).

### Effect of Syringic Acid on H209 Cell Viability

Cell viability was determined using the trypan blue dye exclusion method after 48 hours of exposure. As shown in Figure 2, Treatment with 400 µg/mL did not produce a statistically significant reduction in viable cell percentage compared with controls. However, higher concentrations resulted in a pronounced decline in cell viability. Specifically, SA at 800 µg/mL significantly decreased cell viability (\*\* $p < 0.001$ ), while a more pronounced reduction was observed at 1200 µg/mL (\* $p < 0.01$ ). Overall, these data indicate that SA reduces viability of H209 cells in a dose-dependent manner, particularly at elevated concentrations.

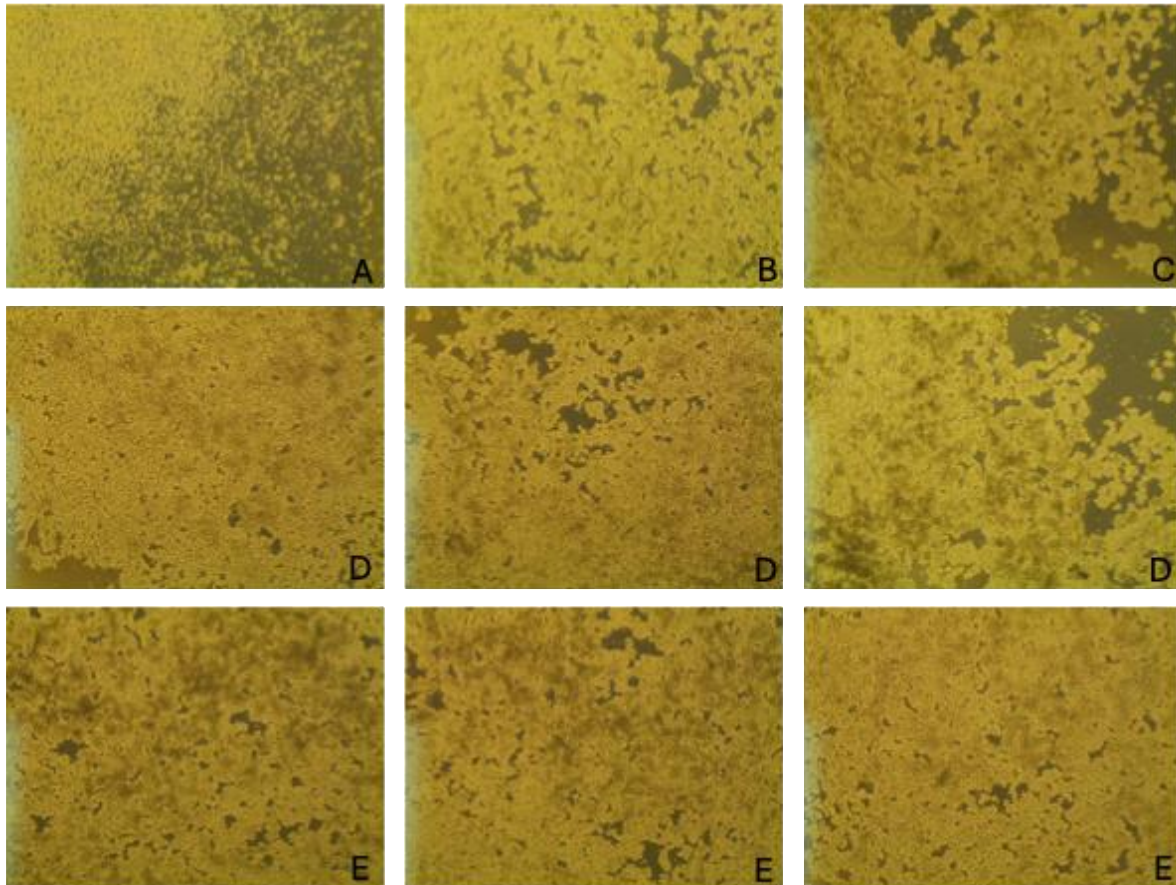


**Figure 2.** Effect of SA on the viability of H209 cells following 48 hours of treatment. H209 cells were treated with SA at concentrations of 400, 800, and 1200 µg/mL for 48 hours, and cell viability was assessed using the trypan blue exclusion assay. Data are presented as mean ± SD from three independent experiments. SA significantly reduced cell viability at higher concentrations compared with the control group ( $p < 0.01$ ,  $p < 0.001$ ). Control cells were treated with vehicle (DMSO) alone.

### Morphological Effects of Syringic Acid on H209 Cells

Morphological changes in H209 cells following SA treatment were evaluated by inverted light microscopy after 48 hours of exposure (Figure 3). Cells treated with a lower concentration of SA (400 µg/mL) exhibited morphological features comparable to those observed in the control groups. In contrast, exposure to higher concentrations resulted in evident alterations in cellular morphology. Treatment with 800 µg/mL SA was associated with a visible reduction in cell density, whereas more pronounced morphological changes were observed at 1200 µg/mL. Control cells treated with DMSO alone displayed morphological characteristics similar to those of untreated cells maintained in culture medium. Collectively, these observations indicate that

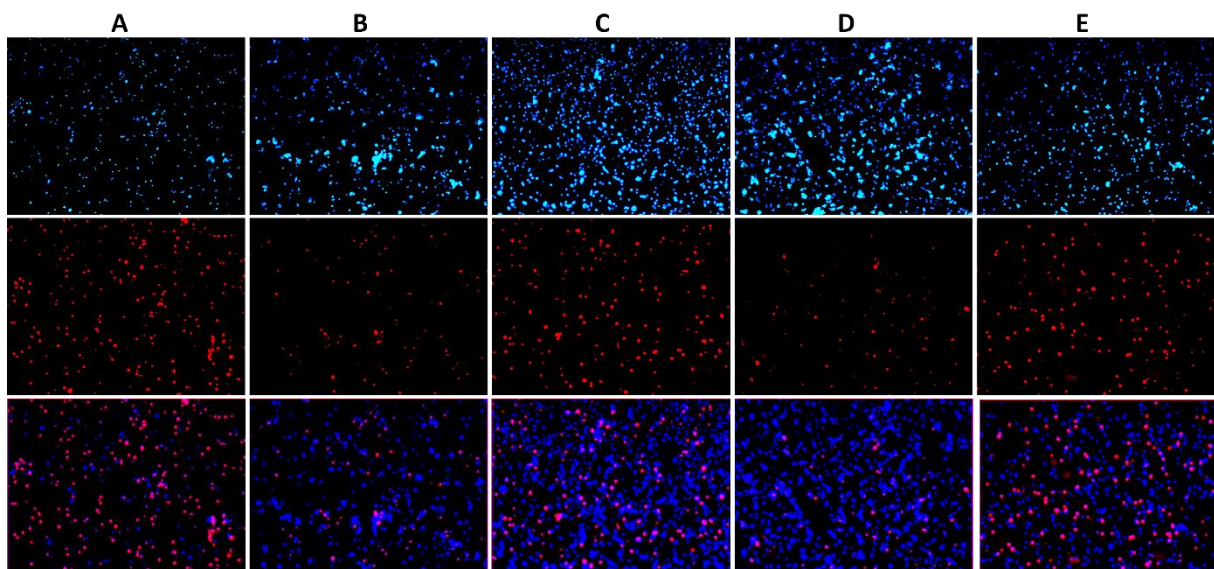
SA induces concentration-dependent morphological alterations in H209 cells at higher concentrations.



**Figure 3.** Representative inverted light microscopy images showing morphological alterations in H209 cells following 48 hours of SA treatment. Cells were treated with SA at the following concentrations: (A) 1200  $\mu\text{g/mL}$ , (B) 800  $\mu\text{g/mL}$ , and (C) 400  $\mu\text{g/mL}$ . Control groups included cells treated with DMSO alone (D) and untreated cells maintained in culture medium (E). Images were captured using an inverted light microscope with a 4 $\times$  objective.

### Effect of Syringic Acid on H209 Cell Viability Assessed by Hoechst 33342/PI Staining

Cell viability and membrane integrity were additionally assessed using Hoechst 33342 and propidium iodide (PI) fluorescence staining after 48 hours of exposure to SA (Figure 4). In the 400  $\mu\text{g}/\text{mL}$  treatment group, most nuclei exhibited Hoechst positivity, while only a limited number of PI-positive cells were observed, comparable to the control groups. Conversely, exposure to higher concentrations resulted in an increased number of PI-positive cells. At 800  $\mu\text{g}/\text{mL}$  SA, a noticeable increase in PI-positive cells was observed, indicating reduced cell viability, while this effect was more pronounced at 1200  $\mu\text{g}/\text{mL}$ , where a substantial proportion of cells exhibited PI positivity. Cells treated with DMSO alone displayed staining patterns comparable to those of untreated cells maintained in culture medium. Collectively, these observations indicate that SA reduces H209 cell viability at higher concentrations, as evidenced by increased PI uptake.



**Figure 4.** Fluorescence microscopy images of H209 cells stained with Hoechst 33342 and Propidium Iodide (PI) following 48 hours of SA treatment. Hoechst 33342–positive nuclei

(blue) and PI-positive cells (red) were visualized using appropriate excitation filters. Cells were treated with SA at (A) 1200  $\mu\text{g}/\text{mL}$ , (B) 800  $\mu\text{g}/\text{mL}$ , and (C) 400  $\mu\text{g}/\text{mL}$ . Control groups included cells treated with DMSO alone (D) and untreated cells maintained in culture medium (E).

### **Discussion**

Small cell lung cancer is an aggressive malignancy defined by rapid proliferative capacity and poor long-term therapeutic outcomes, highlighting the importance of early-stage *in vitro* investigations to identify bioactive compounds with potential cytotoxic activity (Rudin et al., 2021; Sen et al., 2024; Biswas et al., 2025). In the present study, the effects of SA on H209 human SCLC cells were investigated through complementary viability assays and detailed microscopic examinations. The findings indicate that SA induces measurable cytotoxic and structural alterations in H209 cells, particularly at elevated concentrations, with statistically significant growth suppression observed at 800 and 1200  $\mu\text{g}/\text{mL}$  following 48 hours of treatment.

The MTT assay demonstrated statistically significant growth inhibition in H209 cells at concentrations of 800 and 1200  $\mu\text{g}/\text{mL}$  following 48 hours of treatment. At the highest concentration evaluated (1200  $\mu\text{g}/\text{mL}$ ), cell proliferation was reduced by nearly 50%, whereas treatments at lower concentrations did not demonstrate significant effects. Although an exact  $\text{IC}_{50}$  value was not calculated in the present study, the observed inhibitory profile indicates that SA exhibits antiproliferative activity primarily within a higher concentration range. Similar dose-dependent growth inhibition has been reported in colorectal cancer cells treated with SA, where comparable concentration ranges were associated with significant cytotoxic responses (Abaza et al., 2013). When considered in combination, the present findings demonstrate that

the concentration-dependent effect observed in H209 cells is consistent with previously described *in vitro* anticancer properties of SA.

In addition to the MTT findings, the trypan blue exclusion assay further confirmed the cytotoxic effect of SA at higher concentrations. Treatment with 800 and 1200  $\mu\text{g}/\text{mL}$  resulted in a statistically significant reduction in viable cell numbers relative to untreated controls, consistent with compromised membrane integrity. Consistent observations have been reported in colorectal cancer cell systems, in which SA produced dose-responsive growth inhibition, confirmed through MTT and trypan blue analyses (Mihanfar et al., 2021). In that study, SA was shown to induce apoptosis through increased reactive oxygen species production and DNA damage. Although apoptotic markers were not evaluated in the present study, the loss of membrane integrity observed in H209 cells may be partially associated with similar cytotoxic mechanisms.

Morphological evaluation by inverted light microscopy revealed concentration-dependent structural alterations in H209 cells following SA treatment. While cells exposed to 400  $\mu\text{g}/\text{mL}$  maintained morphological characteristics comparable to the control groups, higher concentrations (800 and 1200  $\mu\text{g}/\text{mL}$ ) were associated with a noticeable reduction in cell density and disruption of overall cellular organization. Similar structural alterations have been reported in colorectal cancer cells treated with SA, where dose-dependent growth inhibition and apoptotic changes were observed (Mihanfar et al., 2021). These findings suggest that elevated concentrations of SA induce progressive cellular damage consistent with cytotoxic stress.

Fluorescence microscopy findings obtained using Hoechst 33342 and propidium iodide staining further supported the cytotoxic effect of SA. The increased proportion of PI-positive cells at higher concentrations indicates loss of membrane integrity and reduced cell viability suggesting

progression toward irreversible cellular injury. Although the present study did not directly evaluate specific cell death pathways, previous reports have demonstrated that SA may trigger apoptotic processes in multiple cancer cell types (Mihanfar et al., 2021; Pei et al., 2021). Therefore, the cytotoxic and morphological alterations observed in H209 cells may be associated with similar cellular stress responses.

It is also important to consider that sensitivity to bioactive compounds may vary across different cancer cell types. Differences in proliferative rate and intrinsic cellular characteristics may influence the concentration required to achieve measurable growth inhibition. In this context, the higher concentrations required in H209 small cell lung cancer cells may reflect tumor-specific biological variability rather than diminished anticancer potential of SA, highlighting the importance of considering cell-type dependent responsiveness in vitro studies. SCLC is characterized by rapid doubling time, high proliferative index, and intrinsic chemoresistance, biological features that may necessitate higher in vitro concentrations to elicit significant cytotoxic responses.

It is important to acknowledge certain limitations of this study. The investigation was conducted exclusively in one SCLC cell line (H209), potentially constraining the generalizability of the results across other experimental SCLC systems. Second, although cytotoxic and morphological alterations were clearly demonstrated, specific molecular mechanisms underlying SA-induced cell death were not directly investigated. Mechanistic markers such as reactive oxygen species generation, mitochondrial membrane potential alterations, caspase activation, and cell cycle progression were not investigated in this study. In addition, an exact  $IC_{50}$  value was not calculated, and in vivo validation was beyond the scope of this study. Future investigations involving multiple SCLC cell lines, in-depth mechanistic analyses, and

validation in in vivo systems would provide a more comprehensive understanding of the therapeutic potential of SA in small cell lung cancer.

## Conclusion

The results of the present investigation indicate that SA exerts concentration-dependent cytotoxic and morphological effects on H209 small cell lung cancer cells following 48 hours of exposure. Significant growth inhibition and loss of membrane integrity were observed at higher concentrations, supported by viability assays and microscopic analyses. Although the precise molecular mechanisms were not directly investigated, the findings indicate that SA induces measurable cellular stress leading to reduced viability in this aggressive cancer model. The present data expand the current understanding of the in vitro anticancer properties of SA and offer a framework for future mechanistic exploration and in vivo validation in small cell lung cancer.

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### **Statements and Declarations**

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**Ethical approval statement:** This study was conducted using established human cancer cell lines and did not involve human participants or animal subjects. Therefore, ethics committee approval and informed consent were not required.

**Competing interest:** The authors declare that they have no competing interests.

## Accumulation at the Maternal-Fetal Interface: A Systematic Review on the Effects of Microplastics on the Placental Barrier

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### Abstract

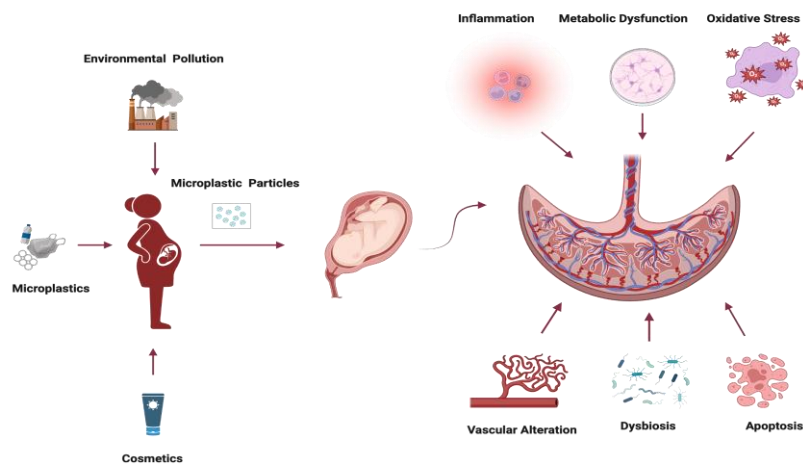
The increasing environmental pollution from microplastics (MP) has raised significant concerns about their potential toxicity, particularly during pregnancy and among sensitive population groups. The placenta serves as a critical metabolic and physical interface organ between the mother and the fetus; however, its capacity to filter emerging pollutants, such as MP, remains as a subject. The primary objective of this study is to systematically review the existing literature to assess the ability of microplastics to cross the placental barrier and to characterize associated histopathological changes at the mother-fetus interface. This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search was conducted in the Web of Science, PubMed, and Scopus databases covering the period 2020-2026. Keywords such as “microplastics,” “placenta,” “maternal-fetal interface,” “histopathology,” and “barrier function” were used. Experimental *in vivo* models and human *ex vivo* placental perfusion studies meeting specific inclusion criteria were analyzed. The synthesized data indicate that MP's, especially those in the range, can cross the maternal-fetal barrier. Histopathological evaluations of the studies reviewed highlight significant accumulation within syncytiotrophoblasts and villous stroma. Identified key cellular mechanisms include induction of oxidative stress, increased apoptosis in trophoblastic cells, and inflammatory infiltration within decidual tissue. Furthermore, structural alterations in the placental vasculature indicate a potential risk for placental insufficiency. In conclusion, current evidence suggests that the maternal-fetal interface is not an impermeable barrier against microplastic contamination. The accumulation of these particles causes cellular stress and structural damage that could compromise placental function and potentially lead to adverse effects. Future research should focus on standardized detection methods in human tissues to fully understand the clinical effects of this threat from a multidisciplinary perspective.

**Keywords:** microplastics, placenta, maternal-fetal interface, histopathology, systematic review

## Introduction

The rapid spread of microplastics (MPs) in the global ecosystem has made it imperative to investigate their potential risks to human health (Bhagat et al., 2021; Campanale et al., 2020; Leslie et al., 2022; Mohamed Nor et al., 2021; Vethaak & Legler, 2021). A study by Ragusa et al. (2021) provided the first evidence of polymer particles in both the fetal and maternal portions of the human placenta (Ragusa et al., 2021). *In vivo* studies in animal models confirm that microplastics are transferred to the fetus via the maternal circulation (Sun et al., 2024; Tian et al., 2025; Zhu et al., 2024; Xue et al., 2024).

In this study, we systematically reviewed the current literature published between 2020 and 2026, evaluating the potential of microplastics to cross the placental barrier and characterizing the histopathological and cellular changes they cause at the maternal-fetal interface. Accordingly, the aim is to synthesize the risks of microplastic accumulation on placental vascular structure and cellular integrity, and to provide a comprehensive perspective on the possible clinical consequences of microplastics.



**Figure 1.** Schematic illustration of the effects of microplastics on the placental barrier and maternal-fetal interface (Created by biorender.com)

## **Materials and Methods**

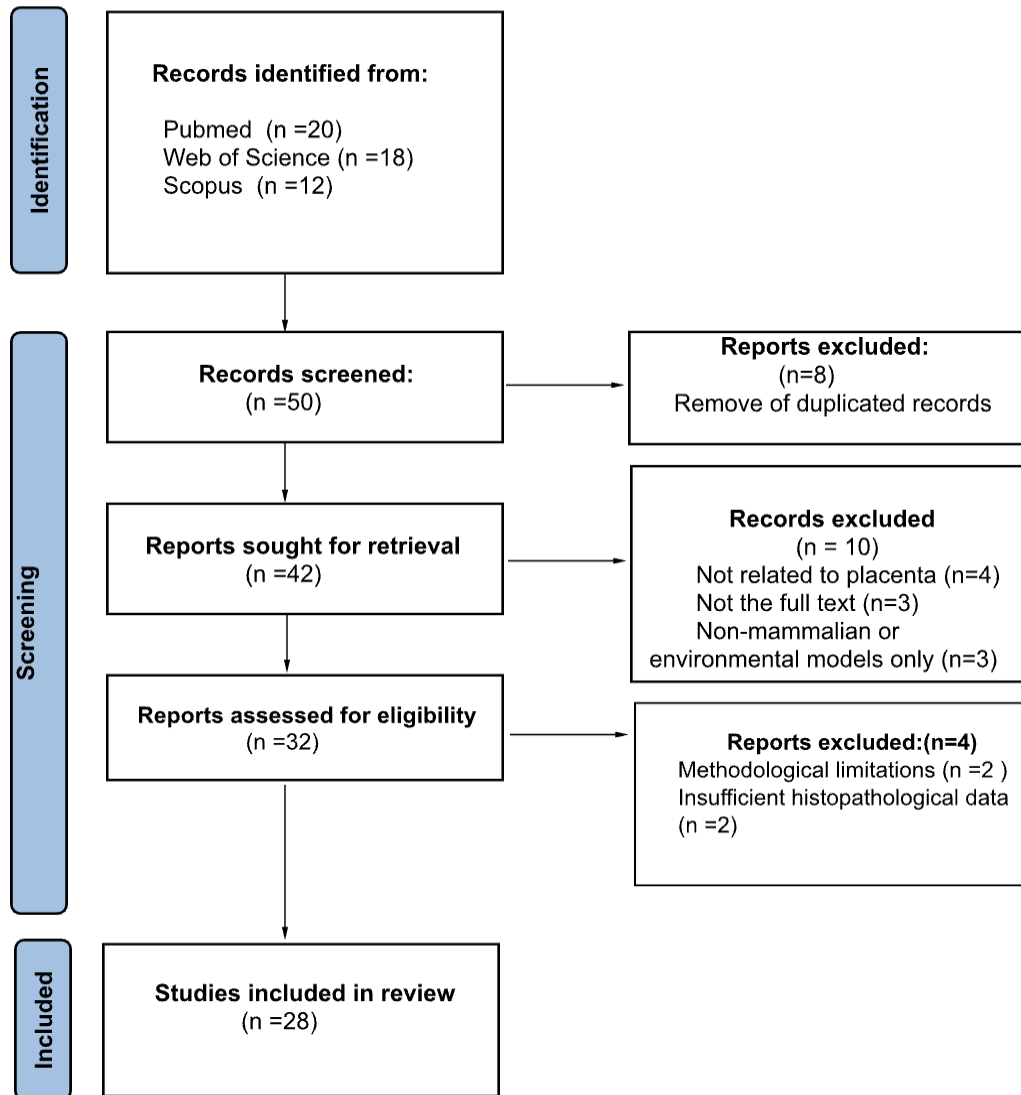
This systematic review was designed and conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1) to analyze the effects of microplastics on the placenta (Page et al., 2021).

As part of the research, a comprehensive search was conducted covering the years 2020-2026 using the keywords and combinations of "microplastics", "placenta", "maternal-fetal interface", and "histopathology" in PubMed, Scopus, and Web of Science databases.

The initial search yielded 50 potential articles on the subject. These articles were evaluated according to the following criteria:

**Inclusion Criteria:** Original research articles directly examining the passage of microplastics across the placental barrier or their histopathological effects, full text availability, and publication between 2020 and 2026.

**Exclusion Criteria:** Review articles, studies conducted only on marine organisms or non-human (non-mammal) models, and publications lacking methodological details. As a result of this screening, 28 articles with the highest methodological quality and data saturation were included in the systematic analysis.



**Figure 2.** PRISMA flow diagram of the study selection process.

## Results

Twenty-eight articles (PubMed: n=12, Web of Science: n=10, Scopus: n=6) that met the criteria determined through systematic searching were analyzed in detail. The effects of microplastics (MPs) on the placenta, as a result of the synthesis of these studies, are presented in Table 1.

**Table 1.** Pathophysiological Effect Analysis of Microplastics on Maternal-Fetal Interface and Syncytiotrophoblasts

<i>Pathological Focus</i>	<i>Main Cellular Target</i>	<i>Key Findings from Synthesized Studies</i>
Presence in placental tissue	Chorionic villi, basal decidua	Microplastic particles (5–10 µm) detected in both maternal and fetal sides of human placenta (Ragusa et al., 2021)
Prenatal exposure evidence	Placenta and neonatal meconium	Microplastics detected in both placental tissue and newborn meconium, indicating fetal exposure (Braun et al., 2021)
Barrier penetration and cellular uptake	Syncytiotrophoblast cells	Experimental studies show nanoplastics can enter trophoblast cells, triggering cellular stress responses (Wan et al., 2024)
Oxidative stress and apoptosis	Mitochondria in trophoblast cells	Increased ROS production, mitochondrial damage, and trophoblastic apoptosis after microplastic exposure (Wan et al., 2024)
Placental inflammation and stress signaling	Maternal–fetal interface (decidua)	Microplastics induce inflammatory responses and oxidative stress in placental tissues (Hu et al., 2022; Wan et al., 2024)
Endocrine and placental dysfunction	Placental endocrine cells	Exposure associated with disrupted placental function and impaired development (Bai et al., 2024)
Vascular impairment and fetal growth restriction	Villous vasculature	Placental dysfunction linked to reduced fetal growth and structural vascular alterations (Bai et al., 2024)
Reduced birth anthropometrics	Whole placenta–fetus unit	Higher placental microplastic levels associated with decreased birth weight and length (Shen et al., 2026)

This table summarizes the main cellular and vascular effects of microplastics at the maternal–fetal interface based on the synthesis of 28 original studies published between 2020 and 2026. The studies summarized in Table 1 consistently indicate that microplastic exposure affects placental function through several interconnected cellular mechanisms. A common finding across experimental models is the induction of oxidative stress, characterized by increased reactive oxygen species (ROS) production and mitochondrial dysfunction in trophoblast cells (Wan et al., 2024; Bai et al., 2024). This oxidative imbalance appears to activate antioxidant

response pathways, including the Nrf2-mediated signaling cascade, while simultaneously promoting cellular apoptosis and inflammatory responses (Dusza et al., 2022; Anifowoshe et al., 2025). In parallel, several studies report disruption of placental barrier integrity through downregulation of tight junction proteins, such as ZO-1 and occludin, leading to increased paracellular permeability (Wang et al., 2025). At the vascular level, microplastic exposure has been associated with the inhibition of VEGF-mediated angiogenic signaling, leading to reduced villous vascularization and impaired placental blood flow (Huang et al., 2022; Yin et al., 2024). Together, these findings suggest that microplastics may compromise placental homeostasis through combined oxidative, inflammatory, and angiogenic pathways.

## **Discussion**

The reviewed studies collectively indicate that microplastic exposure may alter both the structural and functional integrity of the placenta. Experimental and clinical findings suggest that vascular and morphological changes associated with microplastic accumulation can restrict the transfer of oxygen and nutrients from the maternal circulation to the fetus. Such alterations have been linked to adverse pregnancy outcomes, including low birth weight and intrauterine growth restriction (Shen et al., 2026).

At the cellular level, several studies report that nanoplastics, particularly those in the submicron range, can accumulate in placental tissues. This accumulation appears to trigger oxidative stress, inflammatory responses, and metabolic disturbances, potentially compromising trophoblastic function and overall placental homeostasis. Similar observations have been described in both experimental and clinical settings, supporting the consistency of these findings across different study designs (Hu et al., 2022; Wan et al., 2024; de Sousa et al., 2024; Liu et al., 2022).

Moreover, the synthesis of the remaining studies included in this systematic analysis points to a common pattern of placental accumulation, cellular stress responses, endocrine alterations, and unfavorable fetal outcomes following microplastic exposure (Bai et al., 2024; Braun et al., 2021; Garcia et al., 2024; Shen et al., 2026; Wan et al., 2024). Although the extent of these effects varies depending on particle size, concentration, and experimental model, the overall trend in the literature suggests that microplastics represent a potential risk factor for placental function (Amerreh et al., 2022).

## **Conclusion**

In summary, this systematic review finds that microplastic exposure may compromise the structural and functional integrity of the maternal–fetal interface. Evidence from the analyzed studies suggests that microplastics can accumulate in placental tissues, induce oxidative and inflammatory responses, and contribute to vascular and endocrine alterations that may negatively affect fetal development.

Taken together, these results support the view that microplastic accumulation should be considered a potential systemic toxicity factor in pregnancy. Future research should focus on standardized detection methods, well-designed longitudinal clinical studies, and the investigation of possible transgenerational and epigenetic consequences of placental microplastic exposure.

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## Identification of Core Transcriptional Programs and Network Hubs in Breast Cancer

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### Abstract

Breast cancer is one of the most common malignancies among women. It is driven by complex interactions between genetic and environmental factors. Beyond the malignant cells themselves, it is now understood that the non-tumor cell populations within the tumor microenvironment (TME) play a decisive role in disease dynamics. Defining dysregulated gene networks and regulatory mechanisms within these stromal and immune components that drive tumor formation, progression and therapy resistance is critical for effective prevention and management of the disease. The objective of this study was to identify differentially expressed genes (DEGs) and key regulatory networks in non-tumor cell populations within the tumor microenvironment by an integrating transcriptomic dataset. Meta-analysis of RNA-seq datasets was performed to elucidate molecular mechanisms and to identify potential therapeutic targets and biomarkers. The identified DEGs were further subjected to functional enrichment and gene network analyses. Using complementary meta-analytic approaches, a total of 269 DEGs were identified using the Invnorm method, whereas 881 DEGs were detected using the Fisher method. Together, these results provide a more comprehensive and reliable view of the transcriptional landscape of breast cancer. It was observed that the most dysregulated relevant biological processes associated with breast cancer are characterized by metabolic reprogramming, RNA processing, and splicing. Functional enrichment analysis further highlighted key pathways related to RNA regulatory pathways, stress response signaling, cell cycle control and metastasis-related pathways. Additionally, gene regulatory network analysis identified ILF3, HNRNPU, GRN, and GLRX3 as central regulators that play important roles in transcriptional regulation, RNA processing and cellular stress responses enabling cancer cells to adapt to oncogenic and microenvironmental challenges. Collectively, this study enhances our understanding of the molecular landscape of breast cancer by identifying critical hub genes and pathways within non-tumor cell populations of the tumor microenvironment which may serve as a basis for future functional studies and development of genetic strategies to improve clinical outcomes.

**Keywords:** breast cancer, rna sequencing, meta-analysis, enrichment analysis, gene regulatory network

## Introduction

Breast cancer is one of the most common types of cancer worldwide and the leading cause of cancer-related deaths in women. Breast cancer is a polygenic, heterogeneous and multidimensional disease. It is complex because it interacts not only with the tumor microenvironment but also biological networks at the systemic level such as hormonal system, metabolism and immune system. Non-cancerous cells and extracellular matrix components in the tumor microenvironment are now known to play critical roles in the pathogenesis of cancer. Various stromal and immune cell populations and extracellular matrix components within the tumor microenvironment contribute to tumor development, angiogenesis, metastasis, inflammation, and therapy resistance (Hanahan D., 2026) Tumor-associated endothelial cells and neutrophils have been shown to be important regulators in cancer progression.

Tumor associated endothelial cells demonstrate different features, heterogeneity and plasticity than normal endothelial cells. Tumor associated endothelial cells shows decreased expression of adhesion molecules, leading to barrier dysfunction. In addition, they express high levels of inhibitory immune checkpoint molecules, resulting in immune suppression (Amersfoort et al., 2022). Neutrophils, the most abundant immune cells in blood, function as key effectors in infections and acute inflammatory responses. Depending their maturation status, neutrophils can show both anti- tumorigenic or pro-tumorigenic functions. Accumulation of neutrophils contributes to extracellular matrix (ECM) remodeling in distant organs, promoting to pre-metastatic niche formation (Guc et al., 2021). They have critical roles in contributing tumor progression by suppressing anti-tumor immune responses and facilitating metastasis (Zhang et al., 2024).

Despite significant advances in understanding breast cancer pathology, the exact fundamental molecular processes driving breast cancer development and progression remain unclear. A more comprehensive and integrated "omic" approach is essential to elucidate the underlying molecular mechanisms to understand how microenvironmental changes contribute to tumor development. Given the roles of both endothelial cells and neutrophils in the tumor microenvironment, we wanted to investigate whether tumor-associated endothelial cells and neutrophils share a common transcriptional signature. RNA-seq has emerged as one of the most advanced and accurate methods for gene expression analysis, enabling the simultaneous examination of thousands of genes at the transcriptome level. RNA-seq enables a comprehensive analysis of gene expression and molecular networks, providing insights into the complex regulatory mechanisms that control cellular function (Deshpande et al., 2023).

## **Materials and Methods**

### **Data Collection and RNA-seq Analysis**

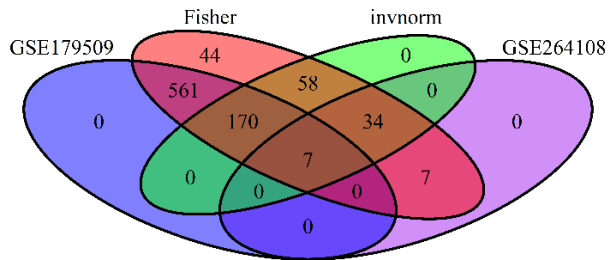
RNA-seq datasets were retrieved from the GEO database (GSE179509 and GSE264108). For meta-analysis, differential expression analysis of RNA-seq data was performed using the DESeq2 package in R (Love et al., 2014). Genes were considered differentially expressed if defined  $P\text{-value} < 0.05$  and  $\text{Fold Change} > 1.5$ . Subsequently, to integrate the P-values obtained from different studies, the fishcomb and invnorm algorithms implemented in the metaRNA-Seq software package were employed (Rau et al., 2014).

### **Functional Genomics: Gene Function and Network Analysis**

Gene Ontology (GO) analysis is an important approach for identifying functional groups of genes that demonstrate similar expression patterns including molecular function (MFs), cellular component (CCs), and biological process (BPs) (Huang et al., 2007). Elucidating gene functions and their associated biological pathways is essential for advancing the understanding of complex traits such as breast cancer. To investigate the functional groups of significant meta-genes in breast cancer, the STRING database was employed. Cytoscape software was used to construct and visualize gene interaction networks to identify protein–protein interactions (Shannon et al., 2003).

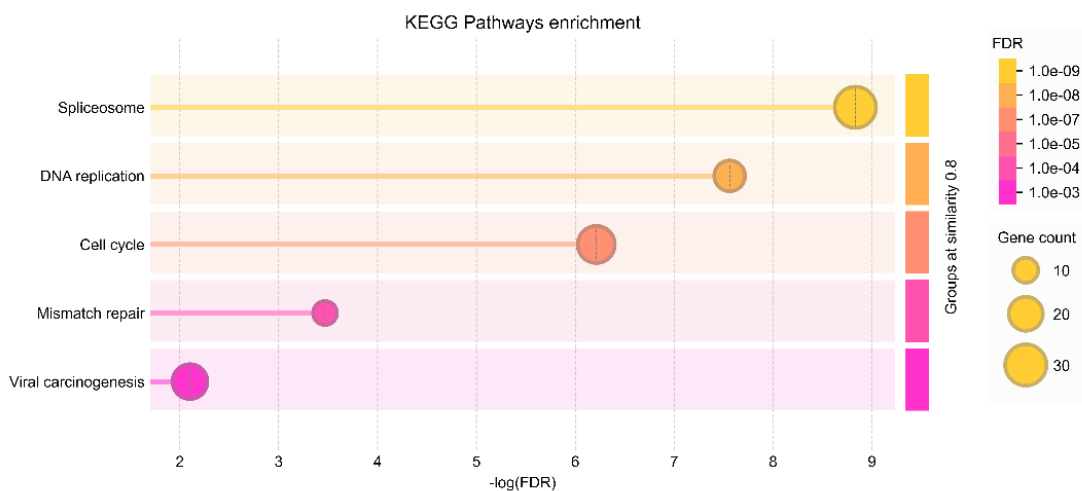
### **Results**

Differential expression analysis of RNA-Seq datasets was performed using the read count matrix and the DESeq2 package. We identified a total of 1293 downregulated and 1291 upregulated genes in GSE179509 dataset, while 29 downregulated and 74 upregulated significant genes in GSE264108 dataset. Several genes, including MMP9, C3AR1, PKM, MSRA, SPINT2 and WIP1 have been reported to be associated with breast cancer development and progression (Joseph et al., 2020; Shu et al., 2021; Zhang et al., 2019). As shown in Figure 1, the meta-analysis identified 269 genes using the Invnorm method and 881 genes using Fisher’s method.



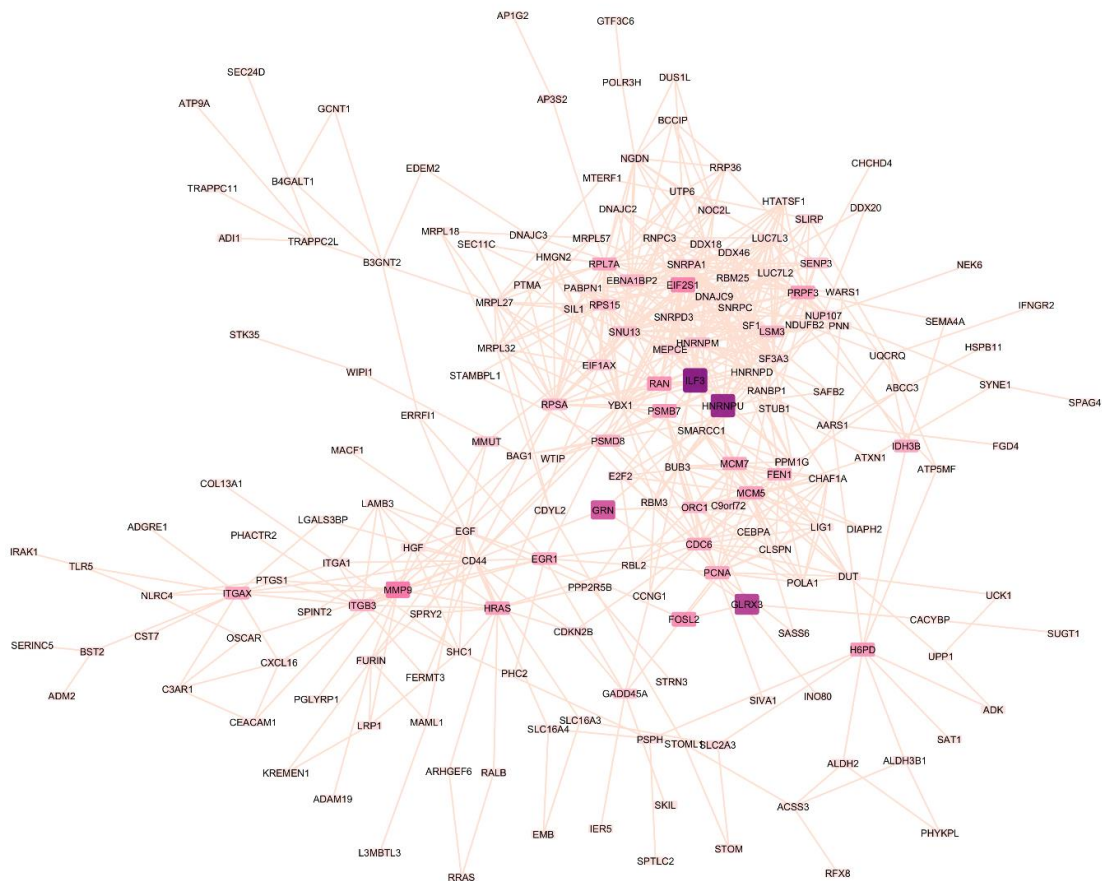
**Figure 1.** Results of meta-analysis using the Fisher and Invnorm approaches

To gain a better understanding of the biological roles 881 genes were analyzed using the STRING database. This analysis identified 171 BPs, 22 MFs, and 69 CCs associated with the studied genes. The key BPs implicated in breast cancer were identified as metabolic reprogramming, RNA processing and splicing. Functional enrichment analysis of the meta-genes further revealed that the spliceosome, DNA replication, and cell cycle represent key signaling pathways involved in breast cancer (Figure 2).



**Figure 2.** Key signaling pathways in breast cancer

The protein–protein interaction network, constructed using Cytoscape, identified key hub genes, including ILF3, HNRNPU, GRN, and GLRX3, which demonstrate the strongest associations with breast cancer (Figure 3). Several genes, including YBX1, FOSL2, GADD45A, EGR1, CEBPA, CD44, MMP9, HRAS, WTIP, TRAPPC11, TRAPPC2L, IRAK1, and SMARCC1 have been implicated in cancer. Collectively, these genes contribute to breast cancer by influencing cell proliferation, DNA repair, migration, metastasis, and critical signaling pathways, highlighting potential targets for therapeutic intervention.



**Figure 3.** Protein–protein interaction network of the common genes

## Discussion

In this study, we performed an integrated meta-analysis of RNA-seq datasets to identify differentially expressed genes and regulatory networks in tumor-associated endothelial cells and neutrophils. We combined two independent datasets using complementary statistical approaches to reduce dataset-specific bias and to increase the reliability of identified candidate genes and pathways. We identified several differentially expressed genes which have been previously implicated in cancer progression such as *MMP9*, *C3AR1*, *PKM*, *MSRA*, *SPINT2*, and *WIP1I*. MMP-9 has important roles in extracellular remodeling, angiogenesis and metastasis (Mondal S et al., 2020). C3AR1 have been reported in immunosuppression in several cancers including ovarian cancer, gastric cancer and osteosarcoma (Huang et al., 2023; Cui et al., 2026). PKM has been shown to affect immune cell infiltration by altering metabolic reprogramming in the tumor microenvironment and contribute to malignant progression (Xue et al., 2025). These differentially expressed genes have roles in metabolic adaptation, extracellular matrix remodeling and immune modulation. All of these biological processes are known to be critical for tumor initiation and progression. Then we performed functional enrichment analysis and found some important biological processes associated with the identified genes such as metabolic reprogramming, RNA splicing and RNA processing. This integrated tumor microenvironment- driven transcriptional analysis showed us stress and metabolic adaptation take place in endothelial and immune cells. Molecular signatures regarding RNA processing and splicing alterations are found to be common in both cell types. Identification of this coordinated regulatory networks helped us to see common differentially expressed genes across non-tumor compartments.

We performed protein–protein interaction (PPI) network analysis to better understand the functional organization of the identified genes. PPI network analysis identified several hub genes such as *ILF3*, *HNRNPU*, *GRN*, and *GLRX3*. These hub genes are involved in RNA binding, transcriptional regulation and cellular stress adaptation (Wang et al., 2025; Han et al., 2022; Xu et al., 2023; He et al., 2016). Moreover, several interacting genes such as *FOSL2*, *GADD45A*, *EGR1*, *CEBPA*, *CD44*, *HRAS*, and *MMP9* have established roles in cell proliferation, DNA damage response, cell migration and survival (Li et al., 2018; Ishiguro et al., 2016; Wang et al, 2021; Pazik et al., 2021). Their integration within a highly connected network suggests coordinated regulation rather than isolated gene effects. This shows the importance of network-based approaches in cancer research and especially in tumor microenvironment studies. Collectively, our findings support the concept that breast cancer progression is driven by the interplay of metabolic alterations, RNA splicing dysregulation and aberrant signaling networks not only in tumor cells themselves but also non-cancerous cells in the tumor microenvironment. The identification of key hub genes and pathways provides a framework for understanding disease mechanisms, defining the role of the tumor microenvironment and identifying potential molecular targets.

## **Conclusion**

This study employed advanced bioinformatics approaches, including RNA-Seq analysis, meta-analysis, gene network, protein-protein interaction network and gene ontology analysis. These analyses have shown that tumor-associated endothelial cells and neutrophils share coordinated transcriptional programs and shared molecular signatures that may contribute to cancer

development. Therefore, their potential as microenvironment-oriented therapeutic strategies should be evaluated in clinical practice.

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## A Systematic Review of the Determination of Heavy Metals and Trace Elements in Tomato (*Solanum lycopersicum*) Varieties

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### Abstract

*Solanum lycopersicum* (tomato) is a plant species that offers significant health benefits for humans. As tomato is an important crop produced in large quantities worldwide, this study aims to review research conducted on the determination of heavy metal and trace element contents in various local tomato varieties commonly cultivated around the world. Knowing the concentrations of heavy metals and trace elements in tomato varieties is crucial to prevent potential health risks to humans that may arise from the growing locations and cultivation conditions of this widely consumed plant. The analysis of heavy metal and trace element contents in *Solanum lycopersicum* has been conducted using results obtained by screening the Google Scholar, Springer, PubMed, Web of Science, Science Direct, and Scopus databases for the period between 2005 and 2025. As a result of the literature review, it has been observed that researchers employed dry ashing, wet digestion, and microwave digestion methods to prepare tomato samples for analysis. The metal concentrations in the digested samples were determined using atomic absorption spectrophotometry and inductively coupled plasma atomic emission spectrophotometry to analyze the metal levels. Systematic literature reviews have revealed that metal concentrations in different tomato varieties vary depending on the digestion techniques used and the soil and environmental conditions in which the samples were grown. Additionally, analyses conducted separately on the leaves, fruits, and seeds of tomato samples have shown that metal levels accumulate most in the fruit portion. It has been reported that the lowest heavy metal levels are found in tomatoes grown far from industrial areas, in uncontaminated soils, and irrigated with clean water, and that these tomato samples contain mineral levels at higher concentrations.

**Keywords:** *solanum lycopersicum*, tomato, heavy metal, trace element, analytical studies.

## Introduction

Tomato (*Solanum lycopersicum*) is an annual, hairy-stemmed, yellow-flowered herbaceous plant with red-yellow-orange, fleshy, and highly seeded fruit (Liu et al., 2022). It ranks among the most widely consumed agricultural products worldwide. Tomatoes, which play an important role in human nutrition, are a fundamental source for processed products in the food industry. This fruit, which has high nutritional value, contains abundant antioxidants and phenolic compounds (Cheynier, 2012). Due to the negative impact of certain environmental factors on agricultural processes, the nutritional content may decrease. In particular, the accumulation of heavy metals in the soil and water sources in tomato plants can cause a decrease in growth and development rates, and heavy metal accumulation above acceptable levels can affect human nutrition in a toxic way (Hadi & Aziz, 2015). Heavy metal accumulation can reach tomato plants from sources such as industrial waste, mining activities, fertilizer use, and contaminated irrigation water. Heavy metal accumulation observed in tomato varieties varies according to geographical and agricultural conditions and causes carcinogenic properties, neurological damage, and irregularities in kidney function (Genchi et al., 2020). At high concentrations, they cause oxidative stress in plants, leading to damage to cell membranes and degradation of lipids (Haider et al., 2021). Although the tomato plant's response to heavy metal stress varies, changes in the concentration of all biologically based compounds, from amino acids to phenolic compounds, can be observed (Younis et al., 2016). Trace elements are necessary for the protection of plant and human health at low doses. High concentrations of trace elements can disrupt the plant's metabolic activities and cause toxic effects on human health. To prevent these toxic effects and ensure food safety, international organizations have set maximum heavy metal limits in foods (Scutarașu & Trincă, 2023). Determining the heavy elements and trace elements

in tomatoes, one of the most widely consumed vegetables in the world, is crucial for public health. Today, sensitive analytical methods such as Atomic Absorption Spectrometry (AAS) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS) are widely used for the detection of these elements (Bressy et al., 2013). The aim of this study is to systematically review recent studies on the determination of heavy metals and trace elements in different tomato (*Solanum lycopersicum*) varieties and to evaluate health risks based on the data obtained.

## **Materials and Methods**

### **Sample Preparation Methods:**

When the studies were examined, it was determined that researchers preferred dry ashing and wet digestion methods to prepare fresh tomato, canned tomato paste, and tomato sauce samples for heavy metal and trace element analysis. In the dry ashing method, samples were typically dried in an oven at 70-85 °C, then incinerated in a muffle furnace at 450–550 °C, and the resulting ash was dissolved with HNO<sub>3</sub> or HCl. This method has generally been preferred in analyses performed using FAAS and GFAAS (Aksu & Yıldız, 2007; Chávez-Servia et al., 2018; Luis et al., 2012). The wet digestion method has mostly been performed using acid mixtures. Dried samples were digested on a hot plate for several hours using HNO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, HClO<sub>4</sub>, H<sub>2</sub>SO<sub>4</sub>, or mixtures thereof. In microwave-assisted acid digestion, a modern and reproducible method, samples were placed in Teflon-coated microwave vessels, HNO<sub>3</sub> + H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, or HF was added, and digestion was performed in a microwave oven at 180–200 °C for 15–30 minutes. After digestion, the solution was filtered and made up to the appropriate volume with distilled water (Birghila et al., 2023; Rodriguez-Iruretagoiena et al., 2015; Shavali-gilani et al., 2025; Urama et al., 2023; Veloo & Tan, 2024). Before dry ashing and wet digestion methods, fresh

samples were washed with distilled water, homogenized, and lyophilized for drying, as described in most literature. In canned samples, digestion was performed immediately after homogenization. In the studies conducted, the methods used for determining heavy metals and trace elements in tomato samples were determined based on the concentration range of the element examined by the researchers, the required sensitivity, the need for multi-element analysis, and laboratory conditions.

### **Flame Atomic Absorption Spectroscopy (FAAS)**

FAAS is based on atomizing the sample in an acetylene flame environment. The atomized elements absorb monochromatic light from an element-specific cathode lamp. The amount of absorption obtained is calculated in direct proportion to the element concentration according to Lambert-Beer's law. Single element analysis can be performed. Operating costs are more affordable compared to other devices. It has been frequently preferred for the determination of macro and microelements such as Cu, Fe, Zn, Mn, Na, K, Ca, and Mg in tomatoes and tomato products (Birghila et al., 2023; Boadi et al., 2012; Luis et al., 2012; Techane et al., 2019).

### **Graphite Furnace Atomic Absorption Spectroscopy (GFAAS)**

It is based on atomizing the sample by injecting it into a graphite tube and applying heating steps. The absorption of light emitted specific to the element is measured during atomization. It is more sensitive than FAAS. The LOD value is generally in the range of 0.1–10 µg/L (ppb), allowing for work with very small sample volumes. As with FAAS, this system, which is based on the measurement of the signal specific to the element being analyzed by the detector, allows for single element analysis. It is frequently preferred in the literature as a device for determining low-concentration toxic metals in tomatoes and tomato products (Al-Lahham et al., 2007; Luis et al., 2012; Shavali-gilani et al., 2025).

### **Inductively Coupled Plasma – Optical Emission Spectrometry (ICP-OES)**

The sample being analyzed is introduced into an argon plasma in aerosol form. At high temperatures, atoms and ions are excited to high energy levels and emit characteristic light as they return to their ground state. This light is collected and separated in an optical system and measured simultaneously with charge coupled device (CCD) or photomultiplier tube (PMT) detectors. Simultaneous determination of more than 70 elements can be performed. It offers a wide range of applications, including food, pesticides, plants, and soil. It enables efficient screening of macro and microelements (Ca, Mg, K, Na, Fe, Zn, Cu, Mn, Al, Ni, Cr, Co, V, etc.). It is a more expensive device than FAAS and GFAAS and has high argon gas consumption (Correia et al., 2018; Urama et al., 2023).

### **Inductively Coupled Plasma – Mass Spectrometry (ICP-MS)**

ICP-MS, widely used in elemental analysis, uses an argon plasma source, as in ICP-OES. The sample is introduced into the argon plasma in aerosol form. Atoms and ions excited to a high energy level are directed to the mass spectrometer. The resulting ions are separated according to their mass-to-charge ratio ( $m/z$ ) using a quadrupole mass analyzer and counted using an electron multiplier detector. This allows for the determination of elements at very low concentrations, even at ppb or ppt levels. It has a wide range of applications, including food, environment, water, soil, plants, pesticides, and metallurgy. It provides efficient screening from macroelements (Ca, Mg, K, Na) to trace elements (Fe, Zn, Cu, Mn, Cr, Ni, Co, V, As, Cd, Pb) and ultra-trace elements. ICP-MS has a lower detection limit than ICP-OES but is more expensive (Rodriguez-Iruretagoiena et al., 2015; Shavali-gilani et al., 2025).

## Results

As a result of the systematic literature review, articles published between 2007 and 2025 on the determination of heavy metals and trace elements in tomatoes (*Solanum lycopersicum*) and tomato products met the inclusion criteria for this review. Sixty percent of the studies focused on fresh fruits, 27% on processed/canned products (sauce, paste), and 13% on soil-plant transfer or contaminated conditions. In the studies reviewed, flame/graphite furnace atomic absorption spectroscopy (FAAS/GFAAS), which is more advantageous in terms of cost and accessibility, was preferred for the determination of heavy elements and trace elements in a significant portion of tomatoes and tomato products (Aksu & Yıldız, 2007; Al-Lahham et al., 2007; Bassey et al., 2014; Birghila et al., 2023; Boadi et al., 2012; Chávez-Servia et al., 2018; Fernández-Ruiz et al., 2011; Luis et al., 2012; Techane et al., 2019; Veloo & Tan, 2024). Recent studies have shown an increase in the use of ICP-MS and ICP-OES techniques, which have lower detection limits and can perform multi-element analysis (Correia et al., 2018; Hashem et al., 2018; Iruretagoiena et al., 2015; Shavali-gilani et al., 2025; Urama et al., 2023). While the dry ashing method was commonly used in previous studies to prepare samples for analysis, current studies prefer the microwave digestion method, which is shorter in duration and offers high reproducibility and accuracy.

## Geographical Distribution and Food Safety Assessment

Heavy metal accumulation in tomatoes may vary depending on the proximity of the growing region to industrial activities. It has been reported that Pb, Cd, and As levels in tomato samples grown in countries such as Spain, Morocco, and Jordan are below international safety limits and do not pose a risk to human health (Al-Lahham et al., 2007; Luis et al., 2012; Rodriguez-Iruretagoiena et al., 2015). However, heavy metal accumulation has been observed in areas with

intensive mining and industrial activities where industrial wastewater is used for irrigation. For example, a study conducted in a mining region in Nigeria (Urama et al., 2023) and in areas in Ethiopia where industrial wastewater mixes with irrigation water (Techane et al., 2019) found that Pb, Cd, and Cr levels exceeded legal limits. A study conducted in Romania found that even in regions where soil heavy metal levels were within acceptable limits, Pb accumulation in fruits was at levels dangerous to human health (Birghila et al., 2023).

### **Effect of Product Type and Processing Method**

Tomatoes are not only consumed fresh but also processed into products such as ketchup and sauce. Analyses of these products have shown that packaging and processing methods increase heavy metal and trace element content. A study conducted in Malaysia found that Pb, Cr, and Ni heavy metal levels in canned sauces were higher than in sauces in glass bottles (Veloo and Tan, 2024). It has been reported that heavy metal levels in canned tomato sauces originating from Iran and Ghana generally remained below the permitted limits, but an increase in Fe and Pb was observed in some brands (Boadi et al., 2012; Shavali-gilani et al., 2025).

### **Physiological Interactions and Variety Differences**

Numerous studies have observed a negative relationship between the heavy metal stress to which the plant is exposed and the nutritional value of the fruit it produces. It has been determined that in tomatoes grown in contaminated soils and soils with high heavy metal concentrations, the synthesis of lycopene and ascorbic acid, which are important antioxidants, is reduced, and consequently, their concentrations are reduced (Hashem et al., 2018; Urama et al., 2023). It has been reported that Ni and Cd elements present in high concentrations in the soil inhibit the uptake of macroelements such as Ca, Fe, and P, which are valuable for plant nutrition (Aksu and Yıldız, 2007; Correia et al., 2018).

## **Discussion**

The systematic literature review conducted has revealed that the accumulation of heavy metals and trace elements in tomatoes and processed tomato products can be investigated with greater precision and the advantage of multi-element determination, thanks to technological advances in analytical methods. Recent studies have shown that ICP-MS and ICP-OES devices, capable of detection at the ppb-ppt level, enable the determination of low-concentration heavy elements and trace elements. These methods, which overcome the limitations of traditional FAAS/GFAAS methods, make significant contributions to the monitoring and control of food safety. It has been observed that industrial activities in the areas where tomatoes are grown and irrigation water are effective in the accumulation of heavy metals and trace elements in tomatoes. This situation clearly demonstrates the need to regulate agricultural policies and industrial compliance, especially in developing countries. It has been observed that heavy metal accumulation in processed tomato products is not only influenced by the conditions under which tomatoes are grown, but also that canning and packaging processes can pose a risk factor. The migration of heavy metals from tin packaging to products highlights the importance of material selection and process validation in the food industry. Heavy metal stress poses a twofold threat by reducing the synthesis of antioxidant compounds in tomatoes and having a toxic effect. Due to the high consumption of tomatoes and processed tomato products worldwide, regular monitoring of heavy metal and trace element levels, control of contaminant sources, and the widespread adoption of sustainable agricultural practices are essential for ensuring food safety.

## Conclusion

This systematic review, based on a literature search, has revealed that the accumulation of heavy elements and trace elements in tomatoes and processed tomato products can now be determined in a multi-faceted and precise manner using advanced instrumental analysis methods. The accumulation of heavy metals in tomatoes is directly related to the environmental characteristics of the growing region. Studies have shown that tomatoes grown in areas with intensive industrial activity and mining contain significantly higher levels of heavy metals. These studies clearly indicate the importance of agricultural irrigation water and soil contamination. Studies have indicated that analyses of tomatoes grown in relatively clean agricultural areas showed low heavy metal accumulation at levels that do not threaten human health. Studies have shown that additional accumulation in processed tomato products can also be affected by canning and packaging processes. Studies have supported that the concentration of heavy metals and trace elements in the soil can physiologically affect all food parameters, especially antioxidants found in tomatoes.

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## Evaluation of Resilience and Related Factors Among Medical Students

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### Abstract

Medical students face multiple stressors including workload, peer relations, financial problems, and performance pressure. Resilience plays an important role in coping with these stressors. This study aimed to evaluate medical students' resilience levels and related factors. This cross-sectional study was conducted in January 2026 among students at Bilecik Şeyh Edebali University Faculty of Medicine. All medical students were invited to participate, and no sampling was performed. After being informed about the study, participants completed an online questionnaire shared via student WhatsApp groups. A total of 258 students (84.8%) who agreed to participate and completed the questionnaire constituted the study group. The questionnaire included sociodemographic characteristics, factors that might be associated with resilience, and the Turkish validated versions of the Brief Resilience Scale (BRS) and the Multidimensional Scale of Perceived Social Support (MSPSS). BRS scores range from 6 to 30, and MSPSS scores from 12 to 84, with higher scores indicating greater resilience and perceived support. Mann–Whitney U, Kruskal–Wallis, and Spearman correlation analyses were used for statistical evaluation. Of the 258 students, 51.9% were female, 48.1% were male. Their ages ranged from 18 to 28 years, with a mean±SD of 19.99±1.63 years. The median BRS score of the students was 19. Higher median scores were observed among males, those reporting good health status, healthy eating, regular exercise, adequate academic performance, and confidence in their medical knowledge and skills ( $p<0.05$ ). Students with poor sleep quality had lower BRS median scores than those with moderate or good sleep quality, and students with less than four hours of weekly extracurricular activity had lower scores than those with more than seven hours ( $p<0.05$ ). A weak positive correlation was found between BRS and MSPSS scores ( $r=0.282$ ;  $p<0.001$ ). Findings indicate that medical students' resilience is associated with individual characteristics, as well as social, academic, and lifestyle factors. Promoting club, art, sports, and volunteer-based activities to enhance students' social interaction, and encouraging programs to strengthen confidence in medical knowledge and skills are recommended. Additionally, raising awareness of healthy lifestyles and creating supportive academic and social environments may help strengthen students' resilience.

**Keywords:** resilience, perceived social support, medical students

## **Introduction**

Resilience is defined as the capacity of an individual to adapt to challenging life experiences by demonstrating mental, emotional, and behavioral flexibility in response to internal and external demands (American Psychological Association, n.d.). In other words, it is the process through which individuals are able to use their existing resources to maintain healthy functioning, develop positive adaptive responses, and preserve their well-being in the face of difficulties (Southwick et al., 2014). Individuals with higher resilience develop more effective coping strategies in stressful situations, and show stronger tendencies toward problem solving and seeking social support, whereas individuals with lower resilience adopt more limited and passive coping approaches (Özbay & Kılıç, 2024; Thompson et al., 2016; Wu et al., 2020).

Medical education is an intensive process in which students are exposed to numerous academic, social, and personal sources of stress, such as excessive workload, difficulties in studying and time management, peer relationships, health problems, financial pressures, career planning, anxiety related to examination performance, and a competitive educational environment (Hill et al., 2018; Nechita et al., 2014). This stress experienced during the educational process may lead to the development of psychological problems and cause negative effects on cognitive functions and academic performance (Dahlin et al., 2005). Indeed, several studies have shown that levels of stress, anxiety, depression, and burnout are high during medical education (Bugaj et al., 2016; Dyrbye et al., 2005; Galán et al., 2011). Therefore, students' coping strategies, together with their levels of resilience, are considered critical determinants in the process of coping with stress (Bugaj et al., 2016).

Resilience is a dynamic construct that may vary from individual to individual and is shaped by life experiences. Rather than being a fixed personality trait, it is a process that develops through

interaction with various factors such as cognitive awareness, self-efficacy, social support, lifestyle, and environmental factors (Azim et al., 2025; Connor & Davidson, 2003; Southwick et al., 2014; Wu et al., 2020). Identifying individual, social, and environmental factors associated with resilience in medical students exposed to intense stressors during the educational process may contribute to the development of targeted interventions.

In this context; this study aimed to evaluate the levels of resilience and associated factors among medical students studying at a university.

## **Materials and Methods**

### **Study Design and Participants**

This study is a cross-sectional study conducted in January 2026 among students of the Faculty of Medicine at Bilecik Şeyh Edebali University. In the study, it was aimed to reach all students studying at the Faculty of Medicine of Bilecik Şeyh Edebali University, and no sampling was performed. After the students were informed about the aim and content of the study, the link to the questionnaire form transferred to a digital platform was shared via student WhatsApp groups. As participation was based on voluntariness, a total of 258 students (84.8%) who agreed to participate in the study and completed the questionnaire constituted the study group.

### **Data Collection Methods**

In line with the aim of the study, a questionnaire form was prepared based on the relevant literature (Azim et al., 2025; Findyartini et al., 2021; Seo et al., 2021; Thompson et al., 2016). The questionnaire form included certain sociodemographic characteristics of the students, factors that may be associated with resilience, the Brief Resilience Scale (BRS), and the Multidimensional Scale of Perceived Social Support Scale (MSPSSS).

The BRS was developed by Smith et al. (2008), and its Turkish validity and reliability study was conducted by Doğan (2015). The scale is a 6-item, self-report measurement tool with a 5-point Likert-type response format. After reverse coding three items in the scale, the possible scores range from 6 to 30. As the score obtained from the scale increases, the level of resilience increases. In the Turkish validity and reliability study, the Cronbach's alpha value of the scale was reported as 0.83 (Doğan, 2015).

The MSPSS was developed by Zimet et al. (1988), and its Turkish validity and reliability study was conducted by Eker et al. (2001). The scale includes three subdimensions, each consisting of four items (family, friends, and a significant other). It is a Likert-type scale measured on a 7-point rating, with a total possible score range of 12 to 84. As the score obtained from the scale increases, the level of perceived social support increases. The Cronbach's alpha value of the scale was reported as 0.89 for the total scale, while the values for the subdimensions were 0.85 for family, 0.88 for friends, and 0.92 for a significant other (Eker et al., 2001).

### **Statistical Analysis**

The obtained data were analyzed using the SPSS 15.0 statistical package program. Descriptive statistics were presented as mean, standard deviation, median, first and third quartiles for numerical variables, and as number and percentage for categorical variables. To test the normality of the data the Kolmogorov–Smirnov test was applied. Mann–Whitney U test, Kruskal–Wallis test, and Spearman correlation analysis were used for data analysis. A  $p \leq 0.05$  was accepted as statistically significant.

### **Results**

Of the 258 students who constituted the study group, 48.1% were male and 51.9% were female.

Their ages ranged from 18 to 28 years, with a mean $\pm$ SD of 19.99 $\pm$ 1.63 years. Of the students,

58.9% reported not having healthy eating habits, and 56.6% reported having a moderate level of sleep quality. Additionally, 40.7% of the students reported studying more than 2 hours per day, 51.5% reported spending less than 4 hours per week on extracurricular social activities, and 58.5% reported having adequate academic performance (Table 1).

**Table 1.** Distribution of students in the study group according to factors that may be related with resilience

<b>Factors that may be related with resilience</b>	<b>n (%)</b>
<b>Age</b>	
<20	113 (43.8)
≥20	145 (56.2)
<b>Gender</b>	
Female	134 (51.9)
Male	124 (48.1)
<b>Place of residence</b>	
Home – with family/friends	52 (20.1)
Home – alone	76 (29.5)
Dormitory	130 (50.4)
<b>Health status</b>	
Moderate	136 (52.7)
Good	122 (47.3)
<b>Healthy eating</b>	
No	152 (58.9)
Yes	106 (41.1)
<b>Regular exercise</b>	
No	198 (76.7)
Yes	60 (23.3)
<b>Sleep quality</b>	
Poor	55 (21.3)

Moderate	146 (56.6)
Good	57 (22.1)
<b>Daily study time</b>	
<1 hour	53 (20.5)
1–2 hours	100 (38.8)
>2 hours	105 (40.7)
<b>Weekly extracurricular social activity time</b>	
<4 hours	133 (51.5)
4-7 hours	74 (28.7)
>7 hours	51 (19.8)
<b>Academic performance</b>	
Inadequate	107 (41.5)
Adequate	151 (58.5)
<b>Confidence in medical knowledge and skills</b>	
No	56 (21.7)
Yes	202 (78.3)

Students' BRS scores ranged from 6 to 30, with a median score of 19.0. Higher median scores were observed among males, those reporting good health status, healthy eating, regular exercise, adequate academic performance, and confidence in their medical knowledge and skills ( $p<0.05$ ). In addition, the median BRS score was lower among students with poor sleep quality compared to those with moderate and good sleep quality, and among students whose weekly extracurricular social activity time was less than 4 hours compared to those with more than 7 hours ( $p<0.05$ ) (Table 2).

**Table 2.** Comparison of students' BRS scores according to factors that may be related with resilience

Factors that may be related with resilience	BRS Median (IQR) <sup>a</sup>	p
<b>Age</b>		
<20	20 (16.5-23)	0.105*
≥20	18 (16-22)	
<b>Gender</b>		
Female	18 (14.75-22)	<b>0.008*</b>
Male	20 (17-22.75)	
<b>Place of residence</b>		
Home – with family/friends	19 (17.25-22)	0.735**
Home – alone	19 (14.25-23.75)	
Dormitory	19 (17-22)	
<b>Health status</b>		
Moderate	18 (16-22)	<b>0.006*</b>
Good	20 (17-23)	
<b>Healthy eating</b>		
No	18 (16-21)	<b>0.002*</b>
Yes	20 (17-24)	
<b>Regular exercise</b>		
No	18 (16-22)	<b>0.003*</b>
Yes	21,5 (17.25-24)	
<b>Sleep quality</b>		
Poor	17 (13-19)	<b>&lt;0.001**</b>
Moderate	19 (17-22)	
Good	21 (18-24)	
<b>Daily study time</b>		
<1 hour	19 (16-23.5)	0.831**
1–2 hours	19 (16-22)	
>2 hours	18 (17-22)	
<b>Weekly extracurricular social activity time</b>		
<4 hours	18 (16-21)	<b>0.003**</b>
4-7 hours	19 (16-23)	
>7 hours	21 (18-24)	
<b>Academic performance</b>		
Inadequate	18 (15-22)	<b>0.049*</b>
Adequate	19 (17-22)	
<b>Confidence in medical knowledge and skills</b>		
No	16 (13-19.75)	<b>&lt;0.001*</b>

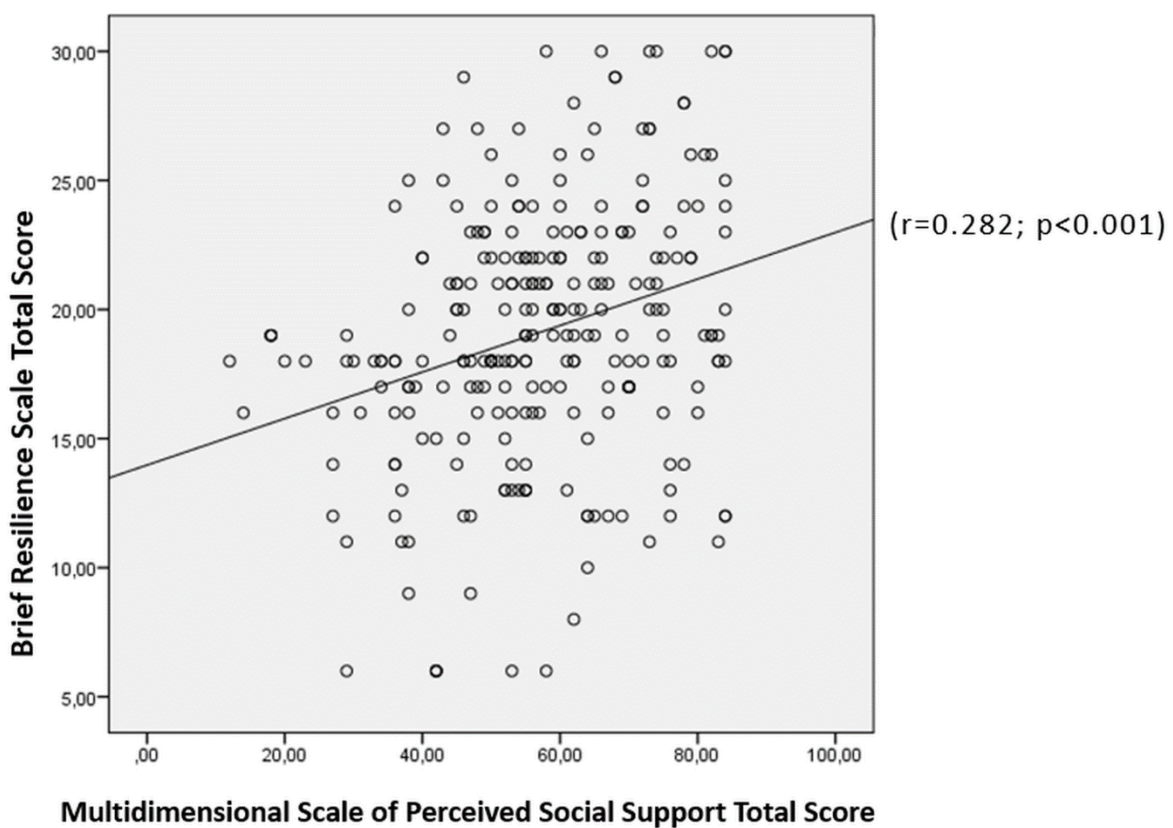
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Yes 20 (17.75-23)

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<sup>a</sup> IQR: interquartiler range (Q1–Q3) \*Mann-Whitney U test \*\*KruskalWallis test

Students' MSPSS scores ranged from 12 to 84, with a median score of 56.0. A weak positive correlation was found between BRS scores and MSPSS scores ( $r=0.282$ ;  $p<0.001$ ) (Figure 1).



**Figure 1.** Scatter plot showing the relationship between BRS and MSPSS scores of students

## Discussion

Resilience plays an important role in supporting mental wellbeing by enabling individuals to recover and adapt to stressful or challenging experiences (Southwick et al., 2014). However, the demanding nature of medical education may at times weaken students' resilience (Hill et al., 2018; Thompson et al., 2016). The present study focuses on identifying the factors that

influence resilience among medical students in order to better understand the dynamics that may strengthen this capacity.

In the study, the level of resilience was found to be lower in female students compared to male students. Similarly, studies conducted with medical students in different countries have reported that female students have lower levels of resilience (Beg et al., 2024; Healy et al., 2023; Kristoffersson et al., 2024; Zila-Velasque et al., 2024). Possible reasons for this finding may include female students' greater perception of examination anxiety and competition, as well as their more pronounced tendency to internalize stressful situations (Azim et al., 2025). In addition, the association of masculinity with strength, resilience, and independence within gender norms may have led male students to express their difficulties less and to perceive their resilience as higher (Gök & Koğar, 2021).

The impact of sleep quality on emotion regulation and mental distress (Palmer & Alfano, 2017), the positive effect of regular physical activity on resilience (Qiu et al., 2025), and the potential link between diet, psychological distress, and resilience have been demonstrated (Whatnall et al., 2019). In addition, extracurricular activity participation has been reported to have beneficial effects on students' mental health (Denovan & Macaskill, 2017; Mukesh et al., 2023). The study found that sleep quality, regular exercise, healthy eating, extracurricular activity, and overall health status were related to resilience. Consistent with these findings, several studies among medical students have reported that poor sleep quality, unhealthy eating habits, low physical activity, limited extracurricular activity time, and lower perceived health status increase psychological strain and reduce resilience (Ahmed et al., 2025; Dai et al., 2023; Damiano et al., 2021; Duncan et al., 2023; Yusoff et al., 2011; Zila-Velasque et al., 2024). Thus, lifestyle

behaviours appear to constitute an important dimension of resilience within the context of medical education.

Self-efficacy is known to be a fundamental cognitive resource that strengthens individuals' capacity to cope with difficulties and facilitates more adaptive responses to academic or personal stressors (Cassidy, 2015). Studies reporting that low academic performance is associated with lower resilience and higher levels of burnout also support this relationship (Findyartini et al., 2021; Mahroon et al., 2018). In the present study, similarly, resilience levels were found to be higher among students who evaluated their academic performance as adequate and those who reported greater confidence in their medical knowledge and skills. These findings suggest that academic self-efficacy and perceived professional competence are important individual resources that strengthen medical students' resilience.

Social support is accepted to enable individuals to perceive stressful events as more manageable, strengthen self-esteem and a sense of control, and increase resilience by supporting effective coping strategies (Satterwhite & Luchner, 2016; Southwick et al., 2016). The study found that as students' levels of perceived social support increased, their levels of resilience also increased. Similarly, Liu and Cao (2022) reported in their study conducted with medical students that social support was positively associated with resilience and that higher levels of social support strengthened resilience, particularly during the online learning process. In addition, Dyrbye et al. (2010) reported that medical students classified as resilient had higher levels of perceived social support. Therefore, social support may represent a crucial interpersonal resource that helps maintain resilience within demanding educational environments.

## Conclusion

Findings indicate that medical students' resilience is associated with individual characteristics, as well as social, academic, and lifestyle factors. Accordingly, promoting club, art, sports, and volunteer-based activities to enhance students' social interaction, and encouraging programs to strengthen confidence in medical knowledge and skills are recommended. Additionally, raising awareness of healthy lifestyles and creating supportive academic and social environments may help strengthen students' resilience. Such comprehensive approaches may contribute substantially to fostering a more balanced and sustainable adaptation process for medical students within the demanding conditions of medical education. Future studies may be multicenter, longitudinal studies targeting the effectiveness of these interventions.

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**Ethical approval statement:** Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Bilecik Şeyh Edebali University (Approval No: 3, Date: December 25, 2025), and administrative permission was also obtained for this study.

**Competing interest:** The author declare that she has no competing interests.



## **A Systematic Review of Studies on Medical Documentation and Secretarial Programs and Profession**

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### **Abstract:**

With the increasing digitalization of health systems, health information systems have become widespread and medical secretaries have become more important. This study aims to examine academic research on the profession and education of medical secretaries, in line with the growing importance of the profession. In this context, articles were evaluated according to various characteristics. The systematic review was conducted in accordance with the PRISMA guidelines. The search was carried out using the DergiPark and TRDizin databases. Following the inclusion and exclusion criteria determined within the scope of the search, 18 articles were included in the evaluation. The analyzed studies were assessed in terms of publication year, research method, and findings. In this regard, it was found that most of the articles addressed topics such as medical secretary education, student experience, professional competence, and professional perceptions. In the majority of the reviewed articles, quantitative methods were used, and data were mostly collected through survey techniques. It was also determined that recent studies have focused more on topics such as digitalization and artificial intelligence. Through this systematic review, a general overview of academic studies conducted in the field of medical secretarial work has been presented, thereby revealing trends in the field. In line with the findings obtained, it is considered that this will contribute to the strengthening of educational curricula and professional competencies.

**Keywords:** Medical Documentation and Secretarial, Systematic Review, Health Education, Professional Competency, Health Information Management

## **Introduction**

With the global rise of digitalization, the health sector has also been affected, and it has become an indispensable tool. Especially within the framework of data-based management, the profession of medical documentation and secretarial work has become much more important.

In this context, the training programs offered in the field are also considered significant.

This study aims to examine academic research conducted in the field of medical secretarial work through the systematic review method. In this regard, a search was carried out in the DergiPark and TRDizin databases, limited to the determined keywords. The articles obtained from the search were analyzed in terms of publication characteristics, methods used, sample groups studied, and the themes addressed. In the later stages of the study, detailed information will be provided about the research method, findings, and results.

## **Materials and Methods**

This systematic review was conducted within the framework of PICOS principles. The population of the study consisted of medical secretary students, graduates, and employees. The studies examined within the scope of the systematic review covered educational activities, practices, and competencies related to the profession. In different studies obtained, comparisons were also made between different student groups and private/public healthcare institutions. Quantitative, qualitative, mixed-method, and literature review studies were included in the systematic review. The outcome variables of the research included education, experience, professional perception, career preference, job satisfaction, and digital skills.

Systematic reviews are a reproducible method used to identify, analyze, and synthesize evidence from all studies conducted (Karaçam, 2013, p. 27). The PRISMA 2020 Checklist (Page et al., 2021) was used in the reporting of the systematic review.

In order to appropriately answer the research question during the literature search, strategies were developed that included inclusion and exclusion criteria related to language, level of evidence, study date, data sources, and keywords. Accordingly:

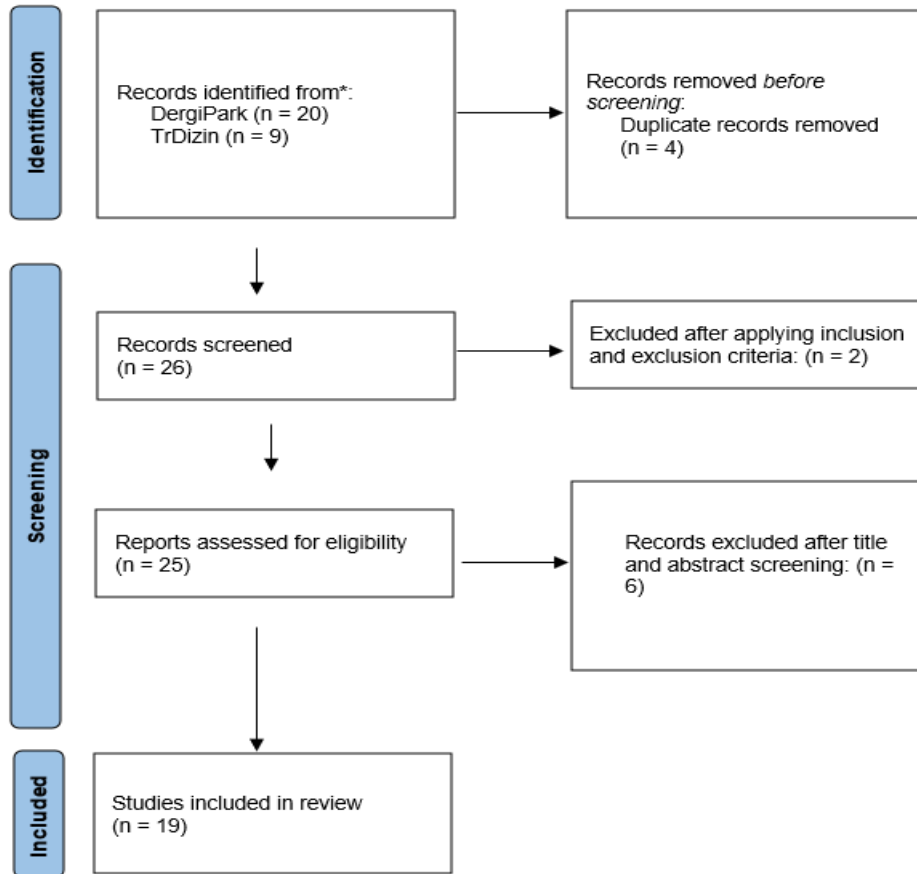
- Studies conducted in the field of medical documentation and secretarial work were included, while studies on other subjects were excluded.
- The literature search was conducted in the DergiPark and TRDizin databases using keywords determined in English. These databases were chosen because of their broad coverage and ability to access all published studies. The English keywords used in the research are listed below.

These are:

- “medical documentation and secretarial work,” “medical secretary,” and “medical documentation”
- Sources were obtained electronically according to the inclusion and exclusion criteria. All research articles retrieved from the databases were uploaded into the Mendeley program to avoid duplication, identify articles containing the research keywords, and classify sources according to research topics. Since the study is a systematic review, ethical committee approval was not required.

## **Results**

In the systematic review conducted, a total of 29 results were obtained from the databases within the framework of the search strategy, as shown in Figure 1. After removing 4 duplicate studies, the titles and abstracts of 26 studies were evaluated. As a result of the evaluation, 6 studies were found to be outside the scope of the research topic, and 18 studies were included in the systematic review (Figure 1).



**Figure 1:** PRISMA Flow Diagram

Within the scope of this systematic review, a total of 19 studies were included in the analysis as a result of the search conducted in the DergiPark and TR Dizin databases. It was observed that most of the reviewed studies were published in recent years and focused on topics such as education, professional competencies, and perception of the profession in the field of medical documentation and secretarial work (Table 1).

**Table 1:** Studies Included in the Systematic Review

No	Author	Year	AİM	Method	Sample	Theme	Type of Medical Emergency	Main Findings
1	(Ataklı et al., 2005)	2005	To evaluate cognitive skills of candidates	Quantitative	Students	Cognitive tests	Cognitive skills	Memory and attention were important for the profession
2	(Semercioğlu et al., 2012)	2012	To compare job satisfaction levels of medical secretaries	Quantitative	Medical secretaries	Questionnaire	Job satisfaction	Job satisfaction differed by institution type
3	(Tengiz & Süral, 2015)	2015	To evaluate students' learning processes through portfolio studies	Qualitative	MDS students	Portfolio analysis	Education	Portfolio applications supported students' professional learning processes
4	(Kaplan & Köksal, 2017)	2017	To examine the structure of MDS education in Türkiye	Descriptive	Education programs	Document analysis	Education	Differences were observed in program curricula
5	(Çoban Budak & 2018)	2018	To determine computer literacy levels of students	Quantitative	MDS students	Questionnaire	Digital skills	Students showed varying levels of computer literacy
6	(Erdoğan, 2018)	2018	To explore perceptions about the medical secretary profession	Qualitative	Medical secretaries	Interviews	Professional perception	The profession plays an important role in healthcare services
7	(Ersözlü et al., 2018)	2018	To determine computer, use levels among medical secretaries	Quantitative	Medical secretaries	Questionnaire	Digital skills	Computer skills varied among employees
8	(Gültekin, 2018)	2018	To examine the importance of ethics in medical secretary services	Review	Literature	Literature review	Ethics	Ethical principles are critical for patient confidentiality

9	(Acar et al., 2020)	2020	To determine problems related to education and professional practice in MDS	Quantitative	Students / graduates	Questionnaire	Education / Profession	Mismatch between education and professional practice was identified
10	(Gültekin & Şeşen, 2021)	2021	To determine career decidedness among MDS students	Quantitative	University students	Survey / scale	Career	Career decisions were influenced by various factors
11	(Çetin et al., 2021)	2021	To examine job satisfaction and burnout levels	Quantitative	Medical secretaries	Scales	Job satisfaction	A relationship between job satisfaction and burnout was found
12	(Kaya & Karaşin, 2022)	2022	To determine students' opinions about online education during the pandemic	Quantitative	Students	Questionnaire	Education	Students reported mixed opinions about online education
13	(Gültekin, 2022)	2022	To identify learning strategies used by students	Quantitative	Students	Scale	Education	Students used different learning strategies
14	(Senel Tekin, 2023)	2023	To examine the historical development of the MDS profession	Review	Literature	Document review	Professional history	The profession developed alongside health information management
15	(Çolaklar et al., 2023)	2023	To examine curricula of distance education MDS programs	Document analysis	Programs	Document analysis	Education	Differences were found in program content
16	(Ancin & Gülşen, 2024)	2024	To examine students' internship experiences	Qualitative	Students	Interviews	Education	Internships contributed to the development of professional skills
17	(Özdemir Aydın, 2025)	2025	To examine the role of patient file studies in education	Qualitative	Students	Document analysis	Education	Patient file practices contributed to learning

18	(Can kurt aran , 2025)	2025	To determine students' awareness of AI applications in education	Quantitative	Students	Questionnaire	Technology	Students had limited awareness of AI applications
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Following the systematic review, it was observed that the majority of the studies were conducted using quantitative research methods. In the articles employing quantitative techniques, surveys and scales were identified as the primary data collection tools. In addition, a small number of qualitative studies were included, which generally used interviews and document analysis as data collection methods. There are also studies in the form of reviews and literature analyses.

When examining the sample groups of the evaluated articles, it was determined that students were the most frequently studied group. Apart from students, some articles also included medical secretaries and administrative staff working in various units of healthcare institutions. This indicates that significant research has been conducted on the educational process and professional development.

From a thematic perspective, the majority of the analyzed studies focused on the student experiences, competencies, and professional perceptions of medical documentation and secretarial students. In addition to these themes, topics such as job satisfaction, professional burnout, digital skills, distance education, ethics, and artificial intelligence were also addressed. When recent studies are specifically considered, it was found that subjects such as artificial intelligence and distance education were included. In the context of some studies, it was also emphasized that medical secretaries play an active role in administrative and clinical processes and undertake important responsibilities.

## Conclusion

In this study, academic research conducted in the field of medical documentation and secretarial work was systematically analyzed, and the existing literature and general trends were revealed. It was determined that a significant portion of the studies evaluated within the scope of the analysis focused on educational activities, experiences, and professional competencies. In addition, although quantitative methods were predominantly used, qualitative and other methods were also included in the articles.

Recent technology-based studies show that current topics are being followed, and it is thought that digital skills such as artificial intelligence will increasingly become areas of research. This situation may indicate that the position and role of medical secretaries will undergo transformation.

Based on the findings obtained from the systematic review, it is recommended that future research be conducted using various methods. In particular, studies in the fields of artificial intelligence and digitalization are considered to be effective in the context of professional competencies, education, and professional perceptions.

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## Microplastic Exposure and Associated Histopathological Changes: A Systematic Review

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### Abstract

As plastic pollution becomes a critical global environmental issue, scientific concerns about the adverse effects of microplastics (MP) on living metabolism and tissue integrity are rapidly increasing. The primary objective of this study is to systematically review the existing literature on histopathological changes and potential mechanisms of toxicity caused by MP exposure in living tissues, and to present the current level of evidence regarding their effects on organ systems. This systematic review was prepared according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search covering the last decade (2016-2026) was conducted using the Web of Science, PubMed, and Scopus databases. Specific keywords such as “microplastics,” “histopathology,” “tissue damage,” “cellular toxicity,” and “oxidative stress” were used in the search strategy. Following a thorough screening of titles and abstracts, studies that met specific inclusion criteria were selected for detailed analysis. When data from the reviewed studies were synthesized, it was observed that MP tend to accumulate particularly in the digestive system, liver, and kidney tissues. In histopathological evaluations, the most frequently reported findings associated with MP exposure included inflammatory cell infiltration, cellular degeneration and degradation.

**Keywords:** Microplastics, histopathology, systematic review, environmental health, tissue damage

## **Introduction**

Plastic pollution has become one of today's most critical global environmental issues due to the intense pressure it exerts on ecosystems and the unpredictable threats it poses to human health. Microplastics (MP), which are produced when macro-sized plastic waste accumulating in the environment breaks down through physical, chemical, and biological processes, are now recognized as affecting not only marine and terrestrial ecosystems but also directly impacting living metabolism. The complex interactions of these particles with biological systems have sparked growing scientific concern (Campanale et al., 2020; Ragusa et al., 2021 ). The bioaccumulation process, which begins with the entry of MP into living organisms via respiration, digestion, and the skin, also poses a risk of systemic toxicity. Understanding the cellular mechanisms triggered by these particles, which accumulate in tissues after exposure, is vital for accurate analysis of environmental health risks. Histopathological examinations, in particular, provide one of the most fundamental assessment tools for demonstrating the direct structural damage, cellular degeneration, and tissue responses caused by this exposure at the microscopic level (Bai et al., 2024; Wan et al., 2024). A review of developments in the literature over the last decade (2016-2026) shows a rapid increase in data on the effects of MP on organ systems. However, there is still a need for systematic synthesis of these findings and a comprehensive perspective on the histopathological reflections of exposure. This study aims to systematically review the existing literature and evaluate the effects of MP exposure on tissue integrity, the affected organ systems, and the possible mechanisms of toxicity underlying this damage. It is intended that the synthesized data presented here will clarify the current level of evidence on the biological effects of MP(Lee et al., 2025; Marcelino et al., 2022) .

**Materials and Methods** A systematic review of the literature from 2016 to 2026 reveals that MP are not

merely a component of environmental pollution but also actively interact with biological tissues. A synthesis of data from the studies reviewed indicates that these particles exhibit a non homogeneous distribution within the body and tend to accumulate in specific organ systems (Campanale et al., 2020). The digestive system, liver, and kidney tissues appear to be the primary sites of accumulation, likely due to their roles in uptake, metabolism, and filtration processes. The most prominent histopathological changes observed in these tissues include widespread inflammatory cell infiltration and varying degrees of cellular degeneration and degradation. These structural impairments clearly demonstrate that MP elicit a persistent immune response and compromise cellular integrity in vital organs. This accumulation observed in filtration organs, such as the liver and kidneys, has critical consequences for overall metabolic health (Marcelino et al., 2022). The presence of these foreign particles within the parenchymal tissue triggers a chronic oxidative stress state, which is central to the cellular damage detected in the tissues. The presence of inflammatory cells highlights that the body recognizes MPas active xenobiotic threats, initiating a process that can extend from local tissue responses to organ dysfunction. The histopathological findings of cellular degradation suggest that MP toxicity is not limited to physical presence but also intensifies the degenerative process in tissue architecture through chemical interactions. In conclusion, the current evidence indicates that MP exposure causes significant cellular stress and structural damage to organ systems (Kadac-Czapska et al., 2024; Wang et al., 2023). While the digestive and filtration systems form the focus of research, the systemic nature of MP distribution necessitates more in-depth investigations into intergenerational effects and the long-term consequences of chronic low-dose accumulation. Standardized detection and quantification methods in human tissues are needed to advance the field and clarify clinical implications. Future research should

prioritize long-term clinical observations and mechanistic studies at the tissue level to determine the lasting effects of this multidisciplinary environmental threat on human health and development. This accumulation observed in filtration organs, such as the liver and kidneys, has critical consequences for overall metabolic health. The presence of these foreign particles within the parenchymal tissue induces a chronic oxidative stress state, which is central to the cellular damage observed in the tissues (Tiao et al., 2023). The presence of inflammatory cells emphasizes that the body recognizes MP as an active xenobiotic threat, initiating a process that can extend from local tissue responses to organ dysfunction. The histopathological findings of cellular degradation suggest that MP toxicity is not limited to its physical presence but also intensifies the degenerative process in tissue architecture through chemical interactions (Guraka et al., 2024). The current evidences indicates that MP exposure causes significant cellular stress and structural damage to organ systems. While the digestive and filtration systems form the focus of research, the systemic nature of MP distribution necessitates more in-depth investigations into intergenerational effects and the long-term consequences of chronic low-dose accumulation. Standardized detection and quantification methods in human tissues are needed to advance the field and clarify clinical implications. Future research should prioritize long term clinical observations and mechanistic studies at the tissue level to determine the lasting effects of this multidisciplinary environmental threat on human health and development.

## **Results**

The synthesis of studies evaluated in the systematic review indicates that MPs do not exhibit random distribution in biological tissues but rather tend to accumulate in specific organ systems. The findings confirm that MP accumulate at high concentrations, particularly in the digestive tract, liver, and kidneys (Deng et al., 2017). The accumulation in the digestive system is directly

related to oral intake, the primary route of exposure, whereas the concentrations in the liver and kidneys are explained by these organs' roles as the primary sites of filtration, detoxification, and elimination (Prata et al., 2020). Histopathological evaluations demonstrate that MP accumulation causes specific, repeatable structural damage at the tissue level. The most frequently reported findings associated with MP exposure in the reviewed literature include widespread inflammatory cell infiltration, cellular degeneration, and tissue degradation in different models (Lu, Y et al., 2016). The presence of an inflammatory response is considered a foreign body reaction, and MP are known to cause chronic immune activation in parenchymal tissue. Degenerative changes at the cellular level indicate that MP exposure is not limited to structural accumulation but also disrupts tissue architecture and cellular integrity (Wright & Kelly, 2017). A comprehensive analysis of the data indicates that oxidative stress is the primary driver of the observed tissue damage. The presence of MP particles triggers the production of reactive oxygen species (ROS) at the tissue level, thereby suppressing cellular defense systems and exacerbating histopathological patterns characterized by degradation and degeneration (Hwang et al., 2019; Ullah et al., 2023). Consequently, the histopathological damage caused by MP in target organs ranges from mild to severe and may compromise organ function.

## **Discussion**

The data from the systematic review clearly demonstrate that MP exposure is not merely an environmental contamination issue but a systemic biotoxicity factor capable of causing serious functional impairments at the tissue level. The intense accumulation observed in elimination and filtration organs, such as the digestive system, liver, and kidneys, indicates that these organs function as biological reservoirs for MP, thereby jeopardizing the body's fundamental homeostatic processes (Bora et al., 2024). The constant interaction of tissues with high

metabolic activity, such as the liver and kidneys, with these particles exceeds the detoxification capacity of parenchymal cells, thereby increasing the risk of chronic organ failure. The widespread histopathological inflammatory cell infiltration is morphological evidence that the body perceives MP as persistent, foreign, and xenobiotic threats. This foreign body reaction triggers a chronic process that is not limited to local inflammation but also disrupts tissue architecture and leads to functional cell loss (degradation). In particular, findings of cellular degeneration indicate that MP exposure causes mitochondrial damage, irreversibly disrupting tissue integrity through excessive production of reactive oxygen species (ROS). This mechanistic picture clearly demonstrates how environmental pollution translates into a histopathological cellular stress response (Mahmud et al., 2024). The synthesized data indicate that, when combined with MP's potential to cross critical barriers, such as the maternal-fetal interface, exposure poses a transgenerational threat. The accumulation and damage observed in sensitive barrier cells, such as syncytiotrophoblasts, suggest that MP may directly affect not only adults but also the developing fetus, potentially leading to serious clinical conditions, such as placental insufficiency. This situation highlights the importance of evaluating MP toxicity from an interdisciplinary perspective, particularly with regard to its lasting effects on reproductive health (Braun et al., 2021; Zurub et al., 2024). While the current literature confirms the destructive effects of MP accumulation on tissue repair and organ function, more human-tissue-focused studies are needed to determine the clinical limits of this threat. Although the lack of standardized detection methods impedes full assessment of the clinical implications of MP exposure, the existing histopathological evidence clearly indicates the need to reshape environmental health policies. Future research should focus not only on the acute effects of MP but also on the chronic and epigenetic changes resulting from their long-term, silent

accumulation in tissues. Conclusion The results of this systematic review reveal that MP exposure is not merely a physical accumulation issue in living tissues but also poses a systemic threat leading to significant structural and functional impairments. Synthesizing the decade of literature reviewed (2016- 2026), it has been confirmed that MP tend to accumulate in vital organs, including the digestive system, liver, and kidneys, creating a persistent pathological burden in these tissues. The most frequently observed histopathological findings, namely, inflammatory cell infiltration, cellular degeneration, and tissue degradation, are clear evidence of the chronic toxicity triggered by MP at the parenchymal level. The study shows that oxidative stress and inflammation cascades underlie the tissue damage caused by MP exposure, ultimately compromising the functional capacity of organs. Consequently, it is imperative that MP be recognized as active xenobiotic agents and that environmental health policies be updated accordingly. Future research must focus on standardized detection methods in human tissues and long-term exposure outcomes to clarify the clinical dimensions of this multidisciplinary threat.

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## The Effect of Antenatal Care Coverage on Birth Indicators in Turkey's Nomenclature of Territorial Units for Statistics-1 Regions\*

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### Abstract

Antenatal care (ANC) coverage is a key indicator for improving maternal and newborn health. Although ANC coverage is high in Turkey, significant regional differences in cesarean section (CS) rates persist. This study examines the relationship between ANC coverage, hospital births, CS, and primary cesarean sections (PCS) among live births across Nomenclature of Territorial Units for Statistics-1 (NUTS-1) regions in Turkey (2020-2024).

This cross-sectional ecological study used aggregated data from 12 NUTS-1 regions in Turkey. Data were obtained from Health Statistics Yearbooks (2020-2024) published by the Turkish Ministry of Health, yielding 60 observations (12 regions × 5 years). Descriptive statistics were calculated as mean ± standard deviation. Pearson correlation analysis assessed relationships between ANC and birth indicators for each region. Multivariate regression analysis (GLM Multivariate) with year as covariate was applied. Statistical significance was set at  $p < 0.05$ .

ANC coverage remained consistently high ( $\geq 99\%$ ), but CS and PCS proportions varied considerably. Western regions showed higher rates. Nationally, CS among live births increased from 57.19% (2020) to 61.20% (2024); PCS peaked in 2022-2023 before declining in 2024. Correlation analyses revealed heterogeneous relationships. In Eastern Marmara, strong negative correlations were observed between ANC and CS ( $r = -0.951$ ;  $p < 0.05$ ) and PCS ( $r = -0.919$ ;  $p < 0.05$ ). However, multivariate regression showed no statistically significant ANC effect on birth indicators in most regions. Despite uniformly high ANC coverage, substantial regional variations in CS rates persist, indicating that factors beyond coverage—service delivery models, facility type distribution, and sociodemographic/institutional determinants—play critical roles. Policy interventions should strengthen care quality rather than quantity alone. Recommendations include systematic implementation of Robson Ten Group Classification, routine monitoring, strengthening Vaginal Birth After Cesarean (VBAC) services, and multi-component quality improvement packages targeting low-risk groups in private facilities. Future studies incorporating individual and institutional determinants will refine intervention strategies.

**Keywords:** antenatal care, cesarean section, primary cesarean, NUTS-1 regions.

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\* This work is not derived from a thesis.

## **Introduction**

ANC is a fundamental public health service in terms of protecting the health of mothers and babies during pregnancy, identifying potential risks early on, and ensuring and supporting safe childbirth (T.C. Sağlık Bakanlığı, 2018; World Health Organization [WHO], 2016; Yavuz et al., 2025). The World Health Organization (WHO) recommends that, in order to ensure a positive pregnancy experience, women receive qualified, timely, and adequate antenatal care throughout their pregnancy, emphasizing that this care should be assessed not only in terms of the number of visits but also in terms of the quality and continuity of the services provided (Çalık et al., 2023; Lattof et al., 2020; WHO, 2016). Effective ANC contributes to reducing maternal and neonatal mortality and morbidity, as well as to making clinical decisions regarding the birth process more rational and evidence-based.

In many countries, expanding ANC coverage is among the priority objectives of health systems; the aim is to reduce inequalities in access to this service, particularly in low- and middle-income countries (Habte et al., 2024). However, the effect of ANC uptake on birth outcomes is not always linear. The literature reports undesirable increases in some birth indicators, particularly CS rates, despite high ANC coverage (Hernández-Vásquez et al., 2020; Piva et al., 2023). This situation indicates that CS should be considered not only in terms of coverage rates, but also in relation to the manner in which healthcare services are delivered, the type of institution, and obstetric practice patterns. When done for the right reasons, CS is an important surgical procedure that saves the lives of mothers and newborns. However, caesarean sections that are not needed or not medically necessary can be dangerous for both the mother and the baby in the short and long term. The WHO says that community-level CS rates above 10–15 percent do not help the health of mothers and newborns in any way (Sanisoğlu et al., 2022). However, in



recent years, a significant increase in CS rates has been observed worldwide, with this increase reaching particularly striking levels in middle- and high-income countries (Bhatia et al., 2020; Vogel et al., 2024).

The WHO states that the CS rate should be around 10 percent on average. Today, CS birth rates are well above this recommended rate, with one in five births worldwide (21 percent) being by CS. The WHO also states that this rate is expected to rise to 29 percent by 2030 (WHO, 2021). According to the Organisation for Economic Co-operation and Development (OECD) data for 2022, Turkey ranks first with a CS rate of 60.8%. Turkey is followed by South Korea with 56.8%, Chile with 51.2%, Mexico with 49.3% and Poland with 41.1%. Again, looking at OECD 2021 data, the country with the lowest CS rate is Israel at 14.7%. It is followed by Iceland at 14.8%, the Netherlands at 15.4% and Norway at 16.0% (OECD, 2021-2022).

Looking at the latest data for our country, CS rates in Turkey have steadily increased. The Turkey Demographic and Health Survey (TDHS) shows that the change in CS rates over the years was 7 percent in the report published in 1993, rising to 14% in 1998, 21% in 2003, 37% in 2008, 48% in 2013, and 52% in 2018 (Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü, 2018). According to the 2024 Health Statistics Yearbook published by the Ministry of Health, the rate of PCS in Turkey is 32.2%, while the proportion of CS births among all births is 61.2%. The same report states that 50.7% of CS births take place in public hospitals, 75.6% in university hospitals, and 77.4% in private hospitals (T.C. Sağlık Bakanlığı Sağlık Bilgi Sistemleri Genel Müdürlüğü, 2024.). Analyses based on Ministry of Health statistics reveal that CS and PCS rates are higher in western regions, while these rates are relatively lower in eastern regions. These regional differences are associated with numerous factors, including socio-economic

structure, access to healthcare services, distribution of institution types (public-private), and clinical practice habits (Birinci & Parpucu, 2023; Golbasi et al., 2022).

The Robson Ten Group Classification System is one of the most widely used ways to keep track of and compare CS rates. This classification divides all births into ten non-overlapping groups that are based on obstetric traits. This allows for a standardised, comparable, and lucid examination of CS rates (Tontus & Nebioğlu, 2020). The Robson classification is based on simple clinical factors such as the number of pregnancies, the mother's history of having a caesarean section, the baby's position, the mother's age at the time of labour, and how labour starts. In this respect, it enables the identification of which groups contribute most to the increase in CS rates. Studies in Turkey based on the Robson classification show that the greatest contribution to the total CS burden comes from Group 5, which includes women with a previous CS history. However, Groups 1 and 2, which consist of low-risk nulliparous women, also play a significant role, especially in the rise of PCS rates (Sanisoğlu et al., 2022; Ulgu et al., 2023). These results suggest that efforts to lower CS rates should target not only high-risk populations but also the clinical decision-making processes associated with low-risk pregnancies.

The link between ANC and CS rates is still a hot topic in the literature. Some studies say that good and enough ANC can lower the number of unnecessary CS, while others say that the amount of ANC is not a major factor in CS rates, especially in high-income areas where services are widely available (Piva et al., 2023; Zahroh et al., 2020). In countries such as Turkey, where ANC coverage is quite high, it is thought that the increase in CS rates cannot be explained solely by the availability of care; the content of service provision, institutional dynamics and regional differences in implementation must be considered together.

In this context, examining the relationship between ANC coverage and birth indicators based on NUTS-1 regions in Turkey is important both for identifying regional differences and for revealing regional patterns in changes in CS rates. This study evaluated the relationship between ANC coverage in NUTS-1 regions during the 2020–2024 period and the proportion of hospital births among live births, the proportion of CS among live births, and the proportion of PCS among live births using aggregated regional-level data. It aims to describe the differences in CS rates observed between regions despite the high ANC coverage level in Turkey from a cross-sectional-ecological perspective.

## **Materials and Methods**

### **Study design**

This study is cross-sectional ecological research conducted to evaluate the relationship between ANC coverage and birth indicators in NUTS-1 regions in Turkey during the 2020-2024 period. Aggregated regional-level data were used in the study, and the unit of analysis is NUTS-1 regions.

### **Data source**

The data used in this study were obtained from the Annual Health Statistics published by the Ministry of Health of the Republic of Turkey. The data has been compiled from the national health statistics database published on the Ministry of Health's official website (T.C. Sağlık Bakanlığı, 2020-2024). This database contains routine service statistics reported by all public and private health institutions, collected under the coordination of the General Directorate of Health Information Systems of Turkey.

### **Study population and sample**

The study universe covers the 12 NUTS-1 regions in Turkey (Istanbul, Western Marmara, Aegean, Eastern Marmara, Western Anatolia, Mediterranean, Central Anatolia, Western Black Sea, Eastern Black Sea, North-Eastern Anatolia, Central-Eastern Anatolia and South-Eastern Anatolia). Annual data were collected for each region between 2020 and 2024, with a total of 60 observations (12 regions  $\times$  5 years). The number of observations per region is  $N=5$ .

### **Variables**

The following indicators were used in the study:

#### ***Independent variable:***

- ANC coverage (%): The proportion of women who received antenatal care from qualified health personnel (doctor, midwife, nurse) at least once during pregnancy, relative to the total number of women who gave birth to live births.

#### ***Dependent variables:***

- Percentage of births occurring in hospitals (%): Percentage of births occurring in healthcare facilities out of total live births
- Percentage of CS births: Percentage of births occurring by CS out of total live births
- Percentage of PCS births among live births: Percentage of first-time CS births among women with no prior history of CS among total live births

#### ***Control variable:***

- Year: Continuous covariate representing the years 2020–2024

### **Statistical analysis**

The data were analysed using IBM SPSS Statistics 27 software. Descriptive statistics are presented as mean  $\pm$  standard deviation.

The relationship between ANC coverage and birth indicators was assessed separately for each NUTS-1 region using Pearson correlation analysis. The significance of the correlation coefficients was tested using a two-tailed test, and  $p < 0.05$  was considered statistically significant.

To assess the effect of prenatal care coverage on birth indicators, GLM Multivariate was applied with the year variable included as a covariate in the model. Separate models were established for each region, and the model results were reported using the F statistic, p-value, and partial eta-squared ( $\eta^2$ ) effect size. The level of statistical significance was set at  $p < 0.05$ .

For interregional comparisons, a heat map was created to visualise the correlations between ANC coverage and birth indicators. Time trends across Turkey are shown using line graphs.

### **Ethical issues**

The study was conducted using publicly available and aggregated secondary data and does not contain personal data at the individual level.

### **Results**

While the ANC coverage rate remained high across all NUTS-1 regions between 2020 and 2024, the proportion of CS deliveries among live births and the proportion of PCS deliveries among live births were particularly higher in western regions (Table 1).

**Table 1.** ANC coverage ( $\geq 1$  Visit) by NUTS-1 regions, proportion of hospital births, CS and PCS among live births, (2020–2024)

NUTS-1 Region	ANC Coverage (%)	Proportion of Live Births Occurring in Hospital (%)	Proportion of Live Births Delivered by CS (%)	Proportion of Live Births Delivered by PCS (%)
Istanbul	99.45 $\pm$ 0.06	98.26 $\pm$ 0.44	62.16 $\pm$ 1.37	34.42 $\pm$ 1.74
West Marmara	99.70 $\pm$ 0.12	95.84 $\pm$ 0.57	65.98 $\pm$ 2.19	38.46 $\pm$ 3.01
Aegean	99.76 $\pm$ 0.06	98.98 $\pm$ 0.66	67.34 $\pm$ 1.74	37.22 $\pm$ 2.02
East Marmara	99.66 $\pm$ 0.11	97.52 $\pm$ 0.67	62.32 $\pm$ 1.07	33.90 $\pm$ 1.61
West Anatolia	99.66 $\pm$ 0.06	99.20 $\pm$ 0.76	58.94 $\pm$ 2.55	32.18 $\pm$ 2.29
Mediterranean	99.62 $\pm$ 0.08	99.16 $\pm$ 1.66	68.64 $\pm$ 1.19	33.38 $\pm$ 1.57
Central Anatolia	99.76 $\pm$ 0.09	97.02 $\pm$ 1.11	56.26 $\pm$ 1.73	31.08 $\pm$ 3.91
West Black Sea	99.71 $\pm$ 0.02	97.68 $\pm$ 1.23	68.00 $\pm$ 1.79	36.88 $\pm$ 1.40
East Black Sea	99.74 $\pm$ 0.05	97.02 $\pm$ 1.15	65.98 $\pm$ 1.79	34.42 $\pm$ 1.94
North-East Anatolia	99.75 $\pm$ 0.05	93.96 $\pm$ 1.44	45.02 $\pm$ 3.79	23.22 $\pm$ 2.34
Middle East Anatolia	99.72 $\pm$ 0.04	95.90 $\pm$ 1.15	46.94 $\pm$ 2.78	23.40 $\pm$ 1.44
South-East Anatolia	99.67 $\pm$ 0.15	96.82 $\pm$ 1.56	50.06 $\pm$ 2.60	20.78 $\pm$ 1.20

**Footnote:** Values are presented as mean  $\pm$  standard deviation.

The proportion of CS deliveries among live births increased across Turkey between 2020 and 2024 (57.19% to 61.20%); the proportion of PCS deliveries among live births rose between 2022 and 2023 but fell in 2024 (Table 2).

**Table 2.** Change in ANC coverage and birth indicators in Turkey by year (%) (2020–2024)

Year	Proportion of Live Births Occurring in Hospital (%)	Proportion of Live Births Delivered by CS (%)	Proportion of Live Births Delivered by PCS (%)	ANC Coverage (%)
2020	97.33	57.19	30.64	99.71
2021	96.94	58.55	31.75	99.73
2022	97.10	59.23	33.17	99.62
2023	97.42	60.18	33.18	99.67
2024	97.08	61.20	31.61	99.68

The correlations between the proportion of births occurring in hospitals with ANC, the proportion of live births with CS, and the proportion of live births with PCS vary by region, with the strongest and most significant negative relationship observed in Eastern Marmara (Table 3).

**Table 3.** Correlation analysis between ANC coverage and birth indicators in NUTS-1 regions (2020–2024)

NUTS-1 Region	Proportion of Live Births Occurring in Hospital-ANC (r)	Proportion of Live Births Delivered by CS-ANC (r)	Proportion of Live Births Delivered by PCS-ANC (r)
Istanbul	-0.4469	-0.4521	-0.2362
West Marmara	0.5846	-0.7000	-0.7000
Aegean	-0.6110	-0.8737	-0.8310
East Marmara	-0.5563	-0.951*	-0.919*
West Anatolia	-0.8353	-0.8484	-0.8335
Mediterranean	0.7397	0.0670	-0.3523
Central Anatolia	0.0912	0.5960	0.5407
West Black Sea	0.4234	0.2859	0.3793
East Black Sea	0.3214	0.3607	0.5016
North-East Anatolia	-0.6773	-0.5317	-0.5403
Middle East Anatolia	-0.0050	0.1513	0.3046
South-East Anatolia	-0.8465	-0.6282	-0.5178

**Footnote:** The table shows the Pearson correlation coefficient. \* $p < 0.05$  (two-tailed).

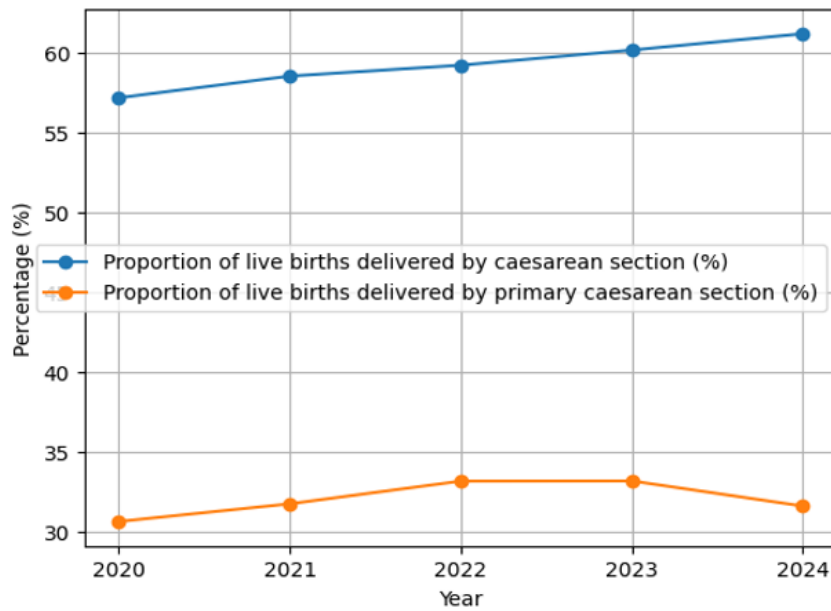
In multivariate analysis, the effect of ANC on the proportion of hospital births among live births, the proportion of CS among live births, and the proportion of PCS among live births is not significant in most regions (Table 4).

**Table 4.** Multivariate regression analysis showing the effect of ANC coverage in NUTS-1 regions on birth indicators (2020–2024)

NUTS-1 Region	Proportion of Live Births Occurring in Hospital— F; p ( $\eta^2$ )	Proportion of Live Births Delivered by CS—F; p ( $\eta^2$ )	Proportion of Live Births Delivered by PCS—F; p ( $\eta^2$ )
Istanbul	0.791; 0.468 (0.283)	0.389; 0.597 (0.163)	0.015; 0.914 (0.007)
West Marmara	1.546; 0.340 (0.436)	3.298; 0.211 (0.623)	6.124; 0.132 (0.754)
Aegean	0.158; 0.730 (0.073)	1.563; 0.338 (0.439)	0.710; 0.488 (0.262)
East Marmara	0.073; 0.812 (0.035)	1.523; 0.343 (0.432)	0.062; 0.826 (0.030)
West Anatolia	1.934; 0.299 (0.492)	16.775; 0.055 (0.893)	10.871; 0.081 (0.845)
Mediterranean	1.910; 0.301 (0.489)	14.741; 0.062 (0.881)	0.000; 0.988 (0.000)
Central Anatolia	3.033; 0.224 (0.603)	0.132; 0.751 (0.062)	3.749; 0.192 (0.652)
West Black Sea	0.631; 0.510 (0.240)	16.328; 0.056 (0.891)	4.640; 0.164 (0.699)
East Black Sea	0.059; 0.830 (0.029)	0.750; 0.478 (0.273)	0.076; 0.809 (0.037)
North-East Anatolia	1.260; 0.378 (0.387)	0.655; 0.503 (0.247)	2.236; 0.273 (0.528)
Middle East Anatolia	0.004; 0.956 (0.002)	1.098; 0.405 (0.354)	8.090; 0.105 (0.802)
South-East Anatolia	1.350; 0.365 (0.403)	5.597; 0.142 (0.737)	1.188; 0.390 (0.373)

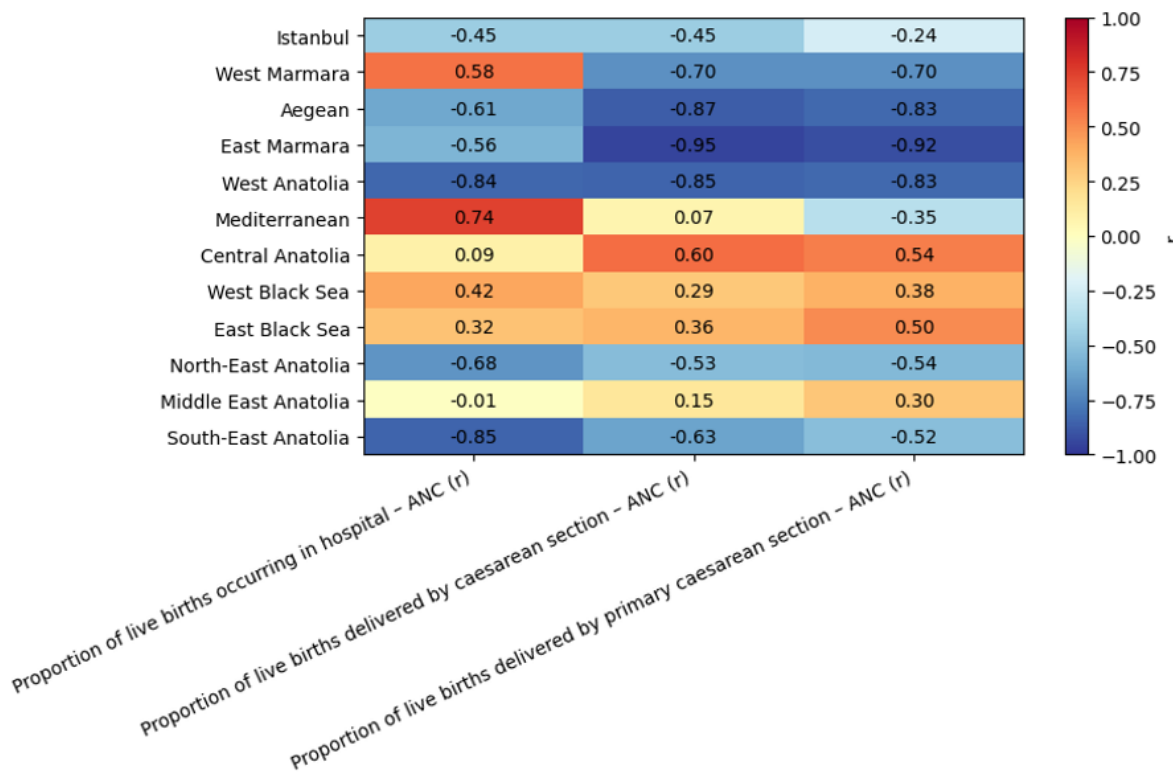
**Footnote:** The values were taken from the SPSS GLM Multivariate → Tests of Between-Subjects Effects table. The Year covariate is included in the model design; N=5 for each region (2020–2024).  $p < 0.05$  was considered significant.

In Turkey, the proportion of CS deliveries among live births increased between 2020 and 2024, while the proportion of PCS deliveries among live births peaked in 2022–2023 and decreased in 2024 (Figure 1).



**Figure 1.** Change in the proportion of CS and PCS in live births by year (%) (2020–2024)

The heat map visually highlights the regional heterogeneity of the relationships between ANC and birth indicators, with the proportions of CS/PCS in live births showing a distinct negative pattern in Eastern Marmara (Figure 2).



**Figure 1.** Heatmap of correlations between the proportion of hospital births within live births, the proportion of CS and PCS within live births in NUTS-1 regions (2020–2024)

## Discussion

This study provides a comprehensive overview of the regional distribution of birth indicators in a context of high ANC coverage by jointly evaluating the proportion of hospital births among live births, the CS rate, and the PCS rate in NUTS-1 regions during the 2020–2024 period. Regional descriptive findings indicate that ANC coverage was very high and relatively homogeneous across all regions; however, CS and PCS rates diverged significantly between regions, being particularly high in western regions. This pattern suggests that regional differences in CS indicators may not be explained solely by the ‘coverage’ of ANC. The service delivery model, the composition of institution types (public/private), and socio-demographic/institutional factors may be more decisive (Birinci & Parpu, 2023; Bhatia et al.,

2020; Hernández-Vásquez et al., 2020; Piva et al., 2023; Zahroh et al., 2020; Zhang et al., 2025).

### **Regional differences and temporal trends**

It is known that Turkey ranks among the countries with the highest CS rates in the world. National analyses conducted using the Robson Group Classification indicate that rates range from approximately 52–60 per cent and that groups 1–5—particularly Group 5, which includes women with a history of CS—contribute significantly to the overall CS burden (Golbasi et al., 2022; Sanisoğlu et al., 2022; Tontus & Nebioğlu, 2020; Ulgu et al., 2023). Regional and hospital-based findings also frequently report rates above 55 per cent in tertiary centres; this indicates that Group 5 is the primary determinant on an ongoing basis and that the contribution of preterm births (Group 10) may increase over time (Buhur & Erdem, 2023; Golbasi et al., 2022; Guner & Yeniocak, 2025; Keskin et al., 2023).

Differentiation by institution type is also noteworthy. Robson-based national audits reveal that CS rates are higher in private (and some university) hospitals across almost all groups, compared to public and private facilities. The inclination towards caesarean section is particularly significant in private hospitals among women experiencing their first childbirth (Groups 1–2) (Birinci & Parpucu, 2023; Sanisoğlu et al., 2022; Tontus & Nebioğlu, 2020; Ulgu et al., 2023). In this context, notwithstanding the elevated coverage level of ANC, the enduring disparities in CS/PCS underscore the necessity for multifaceted explanations that intersect with the institutional-financial dynamics of maternity services and socio-economic inequalities (Bhatia et al., 2020; Hernández-Vásquez et al., 2020; Piva et al., 2023; Zahroh et al., 2020; Zhang et al., 2025).

Time trends across Turkey show that the CS rate increased steadily from 2020 to 2024 (57.19→61.20) and that the PCS rate rose in 2022–2023 before declining in 2024. These findings are consistent with the literature emphasising that CS rates in Turkey are significantly above the range recommended by the WHO. National assessments based on the Robson classification indicate that the overall CS rate has been in the range of approximately 54–58 per cent in recent years (Sanisoğlu et al., 2022; Ulgu et al., 2023). Analyses based on Ministry of Health data indicate that the CS rate rose to 60.5 per cent in 2022 and that more than half of CSs were primary procedures (Birinci & Parpucu, 2023). CS is higher in private and university hospitals compared to public institutions, reaching levels of 70–77 percent in some subsamples (Birinci & Parpucu, 2023; Sanisoğlu et al., 2022; Ulgu et al., 2023).

Hospital-based and regional studies corroborating this burden, influenced by women with a prior caesarean section history (Robson Group 5) and low-risk nulliparous singleton term pregnancies (notably Groups 1–2), underscore the potential for ‘overuse’ beyond medical necessity (Eminov & Eminov, 2024; Guner & Yenioçak, 2025; Keskin et al., 2023; Sanisoğlu et al., 2022; Ulgu et al., 2023).

The drop in the PCS rate in 2024 should be seen as a sign that there may have been changes in how doctors practise, how patients are referred, the types of cases they see, or efforts to improve the institution. The literature emphasizes the importance of using the Robson monitoring system not only as a descriptive framework but also as a fundamental component of continuous quality improvement in reducing PCS in Turkey. National data reveal that PCS remains high and that Robson Groups 1–4 account for a large proportion of the total CS burden. Group-specific rates are particularly striking in private hospitals (Ulgu et al., 2023). Robson-based audits in Turkey and the Black Sea region highlight Groups 1, 2 and 5; they recommend standardisation of

indications, more selective use of induction and active promotion of VBAC (Keskin et al., 2023; Guner & Yeniocak, 2025; Sanisoğlu et al., 2022; Ulgu et al., 2023).

At the implementation level, routine Robson scoreboards, multidisciplinary regular reviews and measurable reduction targets in low-risk nulliparous women can strengthen the traceability of interventions and institutional accountability (Abidi et al., 2025; Ulgu et al., 2023; Vogel et al., 2024). Evidence indicating that multi-component quality improvement packages can safely reduce CS in Robson 1 and 3 (Kondo et al., 2025), when considered alongside programmatic approaches incorporating non-clinical interventions (Dumont et al., 2020; Vogel et al., 2023; Vogel et al., 2024; Zahroh et al., 2020) together suggest that integrating Robson-based monitoring and supervision into routine management and, in particular, adapting packages targeting Robson 1–2 in private healthcare facilities appears to be a strategic focus area for reducing unnecessary PCS (Ulgu et al., 2023).

### **Methodological assessment and limitations**

Correlation analyses have shown that the relationship between ANC and birth indicators is not homogeneous across regions. The relationship varies by region in terms of both direction and magnitude. Particularly noteworthy is the strong and significant negative relationship observed in Eastern Marmara between ANC and the CS rate ( $r = -0.951$ ;  $p < 0.05$ ) and between ANC and the PCS rate ( $r = -0.919$ ;  $p < 0.05$ ). However, it should be remembered that correlations do not indicate causality. The observed patterns may be shaped by co-varying health system characteristics, service delivery patterns, and institutional practice differences.

In such regional-level associations, ecological fallacy and correlation–causation confusion emerge as two key methodological risks. Aggregated indicators may inaccurately classify individual exposure, and the magnitude or direction of the relationship may appear different

from its true nature (Geissbühler et al., 2021; Kakampakou et al., 2025; Shih et al., 2023). Methodological evidence indicates that individual-level causal effects typically require individual-level data and multilevel models. You are more likely to get false results when you only look at aggregate indicators (Geissbühler et al., 2021; Kakampakou et al., 2025). The monitoring strategy of the WHO's new ANC model also supports shifting from contact indicators like "number of visits" to quality-adjusted criteria that include the content and experience of care. It also emphasises that contact-outcome relationships should not be over-interpreted as causal links (Lattof et al., 2020). Therefore, correlations between ANC and birth indicators are considered in this study as hypothesis-generating findings, serving as a starting point for testing contextual mechanisms.

GLM Multivariate analysis found that the effect of ANC on the proportion of hospital births, caesarean section rate, and home birth rate was not statistically significant in most regions. The observation of high effect sizes with borderline p-values in some regions suggests that the relationship between ANC and birth indicators may be context-sensitive. However, due to the short time series and low number of observations, the 'no effect' result should be approached with caution. In the study, the number of observations per region being N=5 limited statistical power, especially in multivariate models. Analyses conducted with longer time series and/or data structures including individual and institutional-level determinants will contribute to a clearer testing of the relationship (Collins & Watt, 2021; Heckman et al., 2022; Lakens & Caldwell, 2021; Ledolter & Kardon, 2020; Pek et al., 2024; Serdar et al., 2020).

The inability to directly incorporate individual risk factors (maternal age, parity, obstetric risk profile) and structural determinants such as institution type into the model due to ecological

design constraints is considered a fundamental limitation that restricts causal interpretations (Kanankege et al., 2023; Li, 2025; Roumeliotis et al., 2021; Villeneuve & Goldberg, 2020).

### **Policy recommendations**

Even in a context where ANC coverage is high and relatively homogeneous across regions, the marked variation in CS and PCS rates offers important policy implications. The upward trend in CS rates across Turkey indicates that current approaches must target not only ‘access to coverage’ but also the content/quality dimension of care and the organisational-institutional dynamics of maternity services.

The WHO's ‘positive pregnancy experience’ approach reframes ANC around women's wellbeing, respectful communication and the timely provision of evidence-based interventions. Supporting this framework with tools such as mHealth and strengthening the quality of care in line with current recommendations is important for understanding the variations seen in outcomes despite high coverage levels (Habte et al., 2024; Kpordoxah et al., 2023; Soni et al., 2023).

The systematic application of the Robson classification in strategies aimed at reducing CS (Abubeker et al., 2020; Akadri et al., 2023; Giaxi et al., 2022; Guner & Yeniocak, 2025) and multi-component quality improvement approaches integrated with monitoring and feedback (Abidi et al., 2025; Vogel et al., 2024) stand out. To enhance the traceability of this approach, it may be advisable to incorporate quality indicators reflecting the safety and experience of obstetric care, along with CS rates according to general/primary and Robson groups, into routine monitoring systems (Fournier et al., 2025; Koc et al., 2024; Parajulee et al., 2025; Ramani et al., 2021; Zhu & Ma, 2025). Thus, an evidence-based and context-adaptable

improvement pathway can be established that contributes to preventing both underuse and overuse in maternity care.

## **Conclusion**

This study examined the relationship between ANC coverage and birth indicators at the NUTS-1 region level in Turkey during the 2020–2024 period, revealing that despite high ANC coverage levels, significant regional differences in CS and PCS rates persist. The findings show that although ANC coverage is quite high and homogeneous across all regions, CS and PCS rates are concentrated at higher levels, particularly in western regions.

Across Turkey, the proportion of CS births among live births showed an upward trend between 2020 and 2024, while the proportion of PCS births peaked in 2022–2023 and declined in 2024, presenting a notable temporal pattern. Regional correlation analyses revealed that the relationships between ANC and birth indicators were heterogeneous, with significant negative relationships found only in some regions (particularly Eastern Marmara). However, the fact that the effect of ANC on birth indicators is not statistically significant in most regions in multivariate regression analyses suggests that differences in CS rates are driven by determinants beyond the scope of ANC.

These findings indicate that the high rates of CS and regional variations in Turkey cannot be explained solely by the accessibility of antenatal care; the manner in which healthcare services are delivered, the distribution of facility types, clinical practice habits, and sociodemographic/institutional factors play a significant role. Therefore, policy and intervention strategies must go beyond increasing the quantity of ANC and focus on the quality of care and the organisational structure of maternity services.

In this context, it is important to systematically and routinely implement the Robson On Group Classification System nationwide, monitor CS rates, and develop targeted quality improvement approaches aimed at reducing PCS, particularly in low-risk groups. Supporting VBAC, strengthening monitoring and feedback mechanisms, and multi-component intervention packages that also include private healthcare institutions can contribute to reducing unnecessary CS. In the future, studies supported by multi-level analyses incorporating individual and organisational determinants will enable the design of more effective and context-sensitive interventions.

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## **Epidemiology of In-Flight Medical Emergencies (IMEs) in Commercial Aviation and Evaluation of Cabin First Response Protocols: A Systematic Review**

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### **Abstract:**

Medical emergencies occurring during flights are an important issue in terms of aviation medicine and emergency health services, and with the increase in passenger numbers, the likelihood of such events has also risen. The aim of this study is to systematically review the existing literature on medical emergencies during commercial flights, evaluating the types, characteristics, and management approaches of these events. Within this scope, a total of 25 studies identified through database searches were analyzed. Most of these studies consisted of observational research, surveys, and review articles. Findings indicate that in-flight medical events are mostly mild to moderate in severity and can generally be managed with the resources available on board. The most frequently reported medical conditions include syncope or presyncope, gastrointestinal complaints, and respiratory problems, while cardiac arrest and severe cardiovascular events are less common but critical. The studies also reveal that initial intervention during flights is usually performed by cabin crew, with healthcare professionals on board contributing when appropriate. In conclusion, strengthening aeromedical training for cabin crew, ensuring effective use of emergency medical equipment available on aircraft, and developing technological support systems such as telemedicine may contribute to more effective management of medical emergencies during flights.

**Keywords:** In-flight medical emergencies, Aviation medicine, Telemedicine support, Commercial aviation, Systematic review



## **Introduction**

Commercial aviation has become the epicenter of global mobility and strategic networks in the modern world. In recent years, it has experienced a significant increase in terms of both passenger capacity and flight ranges. However, this substantial growth has turned in-flight medical emergencies (IME), which involve multi-layered variables that are quite difficult to control, into one of the most critical agenda items of aviation management. This is not merely a statistical increase; concurrently, these cases—as revealed by meta-analysis data covering approximately 1.5 billion passengers—now draw a tangible risk profile for public health and flight safety that cannot be ignored (Nascimento et al., 2021). The fact that an average of 127 cases are encountered per million passengers clearly summarizes the seriousness of the situation. Therefore, this volumetric growth is forcing not only the first response capabilities within the cabin but also the management protocols of international authorities, which have become invariant, towards a fundamental paradigm shift (Kim et al., 2025).

The aircraft cabin is a highly difficult environment for intervention during emergencies due to physical challenges such as limited medical equipment and restricted space for movement. Since cabin pressure in commercial flights is adjusted to an altitude of approximately 8000 feet, the oxygen level in the environment is lower compared to sea level. This condition can lead to an increase in pulmonary pressure even in healthy passengers (Turner et al., 2015). In situations requiring urgent intervention, such as neurological crises, the absence of necessary rescue medications in onboard first-aid kits significantly complicates the treatment process (Asadi-Pooya & Hosseini, 2022). Furthermore, low humidity and pressure differences can lead to a rapid deterioration in the health status of passengers with chronic diseases. For this reason, any

health problem encountered during flight requires a much more difficult and complex management process compared to standard ground-based interventions (Nable et al., 2015).

The management of these challenging processes in the air is no longer left solely to the initiative of the personnel on board. Ground-based telehealth (telehealth / telemedicine) systems are becoming an important part of operational safety. Recent studies reveal that telehealth systems optimize decisions such as aircraft diversion and/or emergency landing, which are costly for airlines, by eliminating diagnostic uncertainty (Battineni et al., 2024; Kim et al., 2025). Otherwise, airline companies may face economic burdens brought by items such as fuel dumping and delay compensations due to a single diversion decision (Alves et al., 2025). This current study aims both to question the efficiency of medical intervention protocols and to demonstrate the strategic value of technological integration in this process by passing the data obtained in the literature through a systematic filter.

## **Materials and Methods**

The PICOS framework of this study, which aims to systematically review the existing literature on medical emergencies during commercial flights, is as follows:

### **P (Population)**

- Passengers traveling on commercial flights
- Especially elderly passengers and individuals with chronic diseases

### **I (Intervention / Exposure)**

- In-flight medical emergencies (IMEs) occurring during flights
- Intervention methods: cabin crew first aid, volunteer healthcare professionals, telemedicine support, use of onboard medical equipment

#### C (Comparison)

- Cases with no intervention or non-standard practices
- Telemedicine-supported vs. unsupported management
- Standardly equipped aircraft vs. aircraft with equipment differences
- Cases with vs. without flight diversion

#### O (Outcomes)

- Clinical outcomes: mortality, morbidity, success of stabilization
- Operational outcomes: flight diversion decisions, delays, costs
- Legal/ethical outcomes: responsibility sharing, legal regulations
- Effectiveness of reporting and recording systems

#### S (Study design)

- Systematic review (in accordance with PRISMA guidelines)
- Included studies: observational studies, systematic reviews, official reports (2016–2025)
- Excluded: case reports, military/cargo/general aviation studies, non-English publications

A systematic review is a type of study that uses reproducible methods to identify, select, and synthesize all available evidence (Karaçam, 2013, p. 27). The research was planned, conducted, and reported in accordance with the PRISMA 2020 Checklist (Page et al., 2021), which is used in the reporting of systematic reviews and ensures quality standards.

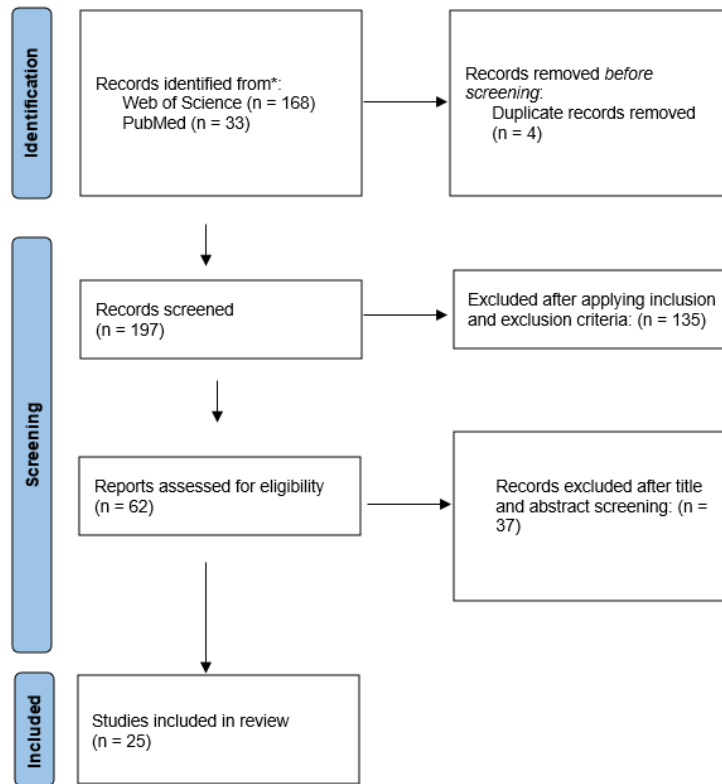
In order to appropriately answer the research question during the literature search, strategies were developed that included inclusion and exclusion criteria related to language, level of evidence, study date, data sources, and keywords. Accordingly:

- Studies conducted in the aviation sector were included, while those conducted in other institutions were excluded.

- Studies carried out between 01.01.2015 and 31.12.2025 were included. The reason for selecting these dates was to access more recent studies. It was considered that including current studies would enhance the quality of the research.
- The literature search was conducted in the Web of Science and PubMed databases using keywords in English. These databases were chosen because of their broad coverage and ability to access all published studies. The English keywords used in the research are listed below:
  - (in-flight medical emergency or inflight medical emergency or medical emergency during flight or medical events during flight or IME) AND (aviation or flight or airline or aircraft or aviation medicine) AND (cabin crew or flight attendant or first aid or emergency response or protocol)
- Full-text articles on aviation management and health constituted the data sources.
- Sources were obtained electronically according to the inclusion and exclusion criteria. All research articles retrieved from the databases were uploaded into the Mendeley program to avoid duplication, identify articles containing the research keywords, and classify sources according to research topics.
- Since the study is a systematic review, ethical committee approval was not required.

## **Results**

In the systematic review conducted, a total of 201 results were obtained from the databases within the framework of the search strategy, as shown in Figure 1. After removing 4 duplicate studies, the titles and abstracts of 197 studies were evaluated. As a result of the evaluation, 135 studies were found to be outside the scope of the research topic, and 25 studies were included in the systematic review.



**Figure 1:** PRISMA Flow Diagram

Within the scope of this systematic review, 25 articles were evaluated by examining medical emergencies occurring during flights. It was observed that the studies were generally reviews and observational studies, while some were survey research, retrospective analyses, and training/simulation studies. When the geographical distribution of the articles was assessed, most were found to be conducted in the United States, Europe, and Asia (Table 1).

**Table 1:** Studies Included in the Systematic Review

No	Author	Year	Country	Study Design	Data Source	Population	Type of Medical Emergency	Key Findings	Outcome Measure
1	Chandra et al.	2015	International	Observational study	Flight data	Airline passengers	Various emergencies	Inflight emergencies occur approximately once per several hundred flights.	Incidence of emergencies
2	Lim et al.	2016	Singapore	Review	Literature review	Physicians	Various emergencies	Ethical and medical considerations for physicians assisting during flights were emphasized.	Clinical and ethical recommendations
3	Peterson et al.	2017	International	Observational study	Flight medical event data	Passengers and cabin crew	Various emergencies	Medical volunteers often assist cabin crew during inflight emergencies.	Outcomes of first aid interventions
4	Peterson et al.	2017	USA	Cross-sectional survey	Physician survey	Physicians	Various emergencies	Physicians reported limited familiarity with onboard medical equipment.	Physician experience and confidence

5	Martin-Grill et al.	2017	USA	Review	Literature review	Airline passengers	Multiple emergencies	Physicians may be called upon to assist with inflight medical events.	Management recommendations
6	Lim et al.	2017	Singapore	Commentary	Editorial	Physicians	Inflight emergencies	Ethical and practical considerations for managing inflight emergencies were discussed.	Ethical guidance
7	Delaune et al.	2017	USA	Review	Literature review	Airline passengers	Multiple emergencies	Physicians assisting inflight should focus on stabilization until landing.	Management approach
8	Sethi et al.	2018	USA	Review	Literature sources	Airline passengers	Neurologic emergencies	Neurological events such as seizures and stroke can occur during flights and require rapid assessment and diversion decisions.	Types and management of neurologic inflight emergencies
9	Dowdall	2018	USA	Narrative review	Literature review	Airline passengers	Multiple emergencies	Cabin crew training and medical kits are essential in managing inflight emergencies.	Management strategies
10	Peterson et al.	2018	USA	Review	Literature review	Airline passengers	Multiple emergencies	Updated emergency medical kits can improve inflight care.	Equipment adequacy

11	Chan et al.	2018	Canada	Review	Literature review	Airline passengers	Various emergencies	Practical recommendations for physicians assisting in inflight emergencies were proposed.	Clinical recommendations
12	Lim et al.	2020	Singapore	Cross-sectional survey	Questionnaire survey	Primary care doctors	Various emergencies	Many physicians reported limited confidence in managing inflight emergencies.	Knowledge and confidence levels
13	Fraser et al.	2020	USA	Commentary	Opinion article	Physicians	Bias in emergency response	Gender and racial bias may affect identification of physicians during emergencies.	Perception of bias
14	Thiel et al.	2021	Europe	Observational study	Aviation medical records	Pilots with insulin-treated diabetes	Hypoglycemia risk	Insulin-treated pilots can safely operate aircraft under strict monitoring protocols.	Safety outcomes of diabetic pilots
15	StatPearls authors	2021	USA	Review	Literature review	Airline passengers	Multiple emergencies	Syncope remains the most frequently reported inflight medical emergency.	Epidemiology and management

16	Patel et al.	2023	USA	Educational simulation study	Emergency medicine training program	Emergency medicine residents	Various inflight emergencies	Simulation-based curriculum improved resident preparedness for inflight medical emergencies.	Educational outcomes and training effectiveness
17	Li et al.	2023	China	Cross-sectional study	Survey	Cabin crew	Various emergencies	First aid and aeromedical training improves crew readiness for inflight incidents.	Training effectiveness
18	Banaszek et al.	2024	Poland	Cross-sectional survey	Questionnaire survey	Cabin crew	Anaphylaxis	Cabin crew showed moderate knowledge regarding recognition and management of anaphylaxis.	Knowledge level score
19	Sand et al.	2024	International	Review	Literature review	Airline passengers	Multiple inflight emergencies	Syncope, gastrointestinal issues, and respiratory problems are among the most frequent inflight emergencies.	Overview of management strategies
20	Zhang et al.	2024	China	Retrospective study	Airline medical event reports	Airline passengers	Multiple emergencies	Most inflight medical events were minor, with syncope being the most common.	Incidence and characteristics of emergencies

21	Brown et al.	2024	International	Review	Literature sources	Airline passengers	Cardiovascular events	Cardiovascular complications remain a significant concern during air travel.	Cardiovascular risk during air travel
22	Ahmed et al.	2025	International	Review	Literature review	Airline passengers	Various emergencies	Telemedicine may improve inflight emergency management and decision making.	Potential impact of telehealth
23	Smith et al.	2025	USA	Observational study	Airline medical event database	Airline passengers	Multiple emergencies	Most inflight events are managed onboard without diversion.	Event frequency and outcomes
24	Johnson et al.	2025	International	Review	Literature review	Airline passengers	Sudden cardiac arrest	Early use of AED significantly improves survival during inflight cardiac arrest.	AED effectiveness
25	Wang et al.	2025	China	Engineering study	Experimental simulation	Aircraft cabin systems	Medical communication	Audio-visual localization technology may help identify medical responders during emergencies.	System performance

## Discussion

Intervention processes for medical events encountered on board during flights and the operational consequences of these situations play a decisive role in aviation safety. According

to the data, at least one physician is present as a passenger on approximately 85% of commercial flights. It is shown that in 48% of emergency cases, assistance is obtained from volunteer healthcare professionals such as physicians, paramedics, or nurses (Alves et al., 2025; Epelde, 2025). Ground-based telehealth systems increase the accuracy of decisions made based on the severity of the case by providing professional support to the cabin crew on board and prevent unnecessary costs for the airline (Battineni et al., 2024; Kim et al., 2025). While approximately 7.3% of cases result in the aircraft being diverted from its route (diversion), 25.8% of the ill passengers are referred to the hospital after the flight (Alves et al., 2025; Nable et al., 2015). It is emphasized that the accurate recording of the procedures applied during the initial intervention process at the time of the incident is of critical importance in terms of both clinical success and the management of legal responsibilities (De Caprariis & Di Maio, 2021).

The high rate (32.7%) of fainting (syncope) incidents, which ranks first as the most frequently encountered case type, is a direct result of the low-humidity and hypobaric environment inside the cabin (Epelde, 2025; Nable et al., 2015). In the study conducted by Turner et al. (2015), it was experimentally demonstrated that the lack of oxygen within the cabin at an altitude of 8000 feet causes an increase in pulmonary artery pressure, creating serious cardiovascular stress, particularly in elderly passengers. Furthermore, it is understood that barotraumas occurring due to pressure differences during the takeoff and landing processes of the aircraft are the most prominent clinical manifestation causing a decrease in labor force among passengers and aviation personnel (Lindfors et al., 2021). These findings prove that in the management of in-flight emergencies, it is of critical importance to include not only standard clinical symptoms but also physiological changes occurring due to cabin altitude in the diagnostic process.



The operational reflections of in-flight medical events are a critical issue for airline management, particularly due to the high costs incurred by airline companies in the event of aircraft diversion decisions. Nable et al. (2015) stated that the encountered cases resulted in the diversion of the aircraft from its route. The accuracy of these decisions depends largely on ground-based medical consultation services. Kim et al. (2025) and Battineni et al. (2024) emphasize that the use of advanced telehealth systems prevents high costs by avoiding unnecessary landings, increases operational efficiency, and provides decision support to medical volunteers on board. In the study conducted by Alves et al. (2025), it is confirmed that diversion decisions are not only a clinical necessity but also a strategic management process optimized with technological infrastructure and ground support.

The biggest factor affecting the intervention decisions of volunteer healthcare workers is the fear of legal liability and medical malpractice. Regulations such as the Aviation Medical Assistance Act (AMAA) implemented by the USA provide legal protection for volunteers, except in cases of gross negligence. However, many volunteer specialists still experience hesitation due to the fear of being sued (De Caprariis & Di Maio, 2021; Nable et al., 2015). Especially for medical students and nurses, the uncertainty of legal boundaries further increases these moral dilemmas (Braverman, 2021; Bukowski & Richards, 2016). Within the scope of the evaluation I conducted from an aviation management perspective; it is seen that the underlying reason for this hesitation is not only the existence of legal gaps but also the lack of standardization in registration forms and intervention protocols among airline companies. This lack of common practice development increases the 'making a mistake' perception of volunteer healthcare professionals and restricts the management of operational safety at full capacity. The fundamental suggestion I offer from an aviation management perspective is the creation of an

internationally standardized 'Volunteer Intervention Form' valid across all airlines. With this standardization and digitalization step, the dilemma of volunteer healthcare personnel regarding 'will I get into trouble?' (malpractice concern) will be reduced, and it will make the level of flight safety management more efficient and robust.

### **Conclusion**

This systematic review evaluated the literature on medical emergencies occurring during commercial flights. The findings showed that medical events were generally mild to moderate in severity and could be managed with the resources available on board.

In line with the findings, it is considered important to strengthen cabin crew training in first aid and aeromedical practices, and to ensure the effective use of emergency kits and automated external defibrillators on aircraft. Future research focusing on the epidemiology of in-flight emergencies and a more detailed examination of intervention strategies will provide significant contributions.

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## How Does Transcultural Nursing Education Affect Cultural Sensitivity and Perceptions Toward Immigrants Among Nursing Students?\*

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### Abstract

The present study sought to evaluate the impact of a transcultural nursing course on nursing students' levels of intercultural sensitivity and their negative attitudes towards immigrants.

The present descriptive study, which employed a pretest–posttest design, was conducted with a sample of 34 nursing students enrolled in the Faculty of Health Sciences, Department of Nursing at Recep Tayyip Erdoğan University, who were undertaking the Transcultural Nursing course. The data were collected using a Personal Information Form, the Intercultural Sensitivity Scale, and the Negative Attitudes Toward Immigrants Scale. The scales were administered at the commencement and conclusion of the course period. The analysis was conducted utilising the SPSS 23.0 statistical software. A subsequent statistical analysis revealed no statistically significant difference between the total scores on the Intercultural Sensitivity Scale before and after the intervention ( $p>0.05$ ). However, post-test scores demonstrated significant increases in the subdimensions of confidence in communication and attentiveness in communication ( $p<0.05$ ). In contrast, a significant decrease was observed in the subdimensions of respect for cultural differences and enjoyment of communication in the post-test ( $p<0.05$ ). Furthermore, a substantial decrease was identified in the total post-test scores of the Negative Attitudes Toward Immigrants Scale ( $p<0.05$ ), suggesting a reduction in negative attitudes towards immigrants following the course. The transcultural nursing course has been demonstrated to be an effective intervention in modifying nursing students' negative attitudes towards immigrants. However, changes in intercultural sensitivity were observed in different directions at the subscale level. These findings suggest that intercultural sensitivity is a multidimensional construct and that short-term educational interventions may not influence all dimensions simultaneously.

**Keywords:** intercultural sensitivity, perceptions toward immigrants, nursing students, transcultural nursing.

## **Introduction**

Migration is a multidimensional phenomenon that occurs when individuals move across an international border or within a country and refers to population mobility regardless of its cause, duration or form. In this context, refugees, forcibly displaced individuals and people who relocate for economic reasons are considered as part of the migration process (Ceylan & Çetinkaya, 2022; Günay et al., 2019). Although there is no single internationally agreed definition of migration, the concept of migration mostly defines an individual's voluntary departure from his/her place to obtain better living conditions without any coercive factor (Ceylan & Çetinkaya, 2022).

As a natural consequence of the phenomenon of migration, individuals carry their own cultural values, beliefs and behavioral patterns to the new living spaces they settle in; this situation paves the way for the encounter of different cultures and the formation of multicultural social structures (Bilgiç & Şahin, 2019). In recent years, Turkey has been among the countries that have been exposed to intensive migration movements, especially from Syria and Afghanistan, and this process has brought about various difficulties in the provision of health services. Communication problems in health institutions, cultural differences, low socioeconomic conditions and limitations in access to services are among the main challenges (Baksi et al., 2019; Ceylan & Çetinkaya, 2022). In addition, it is reported that negative perceptions, exclusionary attitudes and hate-based behaviors at the social level have increased in migrant receiving societies (Günay et al., 2019). It is emphasized that migration, especially irregular migration, creates social and psychological pressures on both migrant individuals and host communities.



Culture is considered as a set of values, beliefs, attitudes and behaviors that are learned, shared and transmitted from generation to generation by the society in which individuals live. Culture is a basic building block that shapes the life of the individual and every individual inevitably exists in a cultural context (Bulduk et al., 2011, 2017). The fact that societies have become more culturally heterogeneous with the globalization process has made it necessary to take cultural differences into account in the planning and delivery of health services. In this context, intercultural sensitivity is becoming increasingly important in the effective and qualified provision of health care services (Bulduk et al., 2011; Markey et al., 2012).

Intercultural sensitivity is defined as the ability of health professionals to recognize the cultural values, belief systems and health-related practices of individuals, to develop an attitude toward understanding these differences and to shape the care process in accordance with the cultural characteristics of the individual (Bulduk et al., 2011). The fact that nurses are the professional group that interacts most intensively and continuously with patients among the healthcare team increases the responsibility in this field even more. Nurses are expected to communicate effectively and provide care to individuals with different cultural and religious backgrounds with a holistic approach (Baksi et al., 2019; Ceylantekin & Öcalan, 2016). Patients' cultural values and practices are one of the basic components of holistic nursing care, and ignoring these elements may negatively affect the quality of care.

The nursing profession, as a professional discipline that aims to provide healthcare services to all individuals regardless of cultural differences, adopts respecting the cultural values of the individual being cared for as a basic principle. Developing cultural sensitivity in immigrant patient care is critical in terms of both ethical principles and quality of care (Bilgiç & Şahin, 2019). Accordingly, supporting nursing students' cultural sensitivity skills and evaluating their

perceptions toward immigrants play a decisive role in improving the quality of care they will provide in the future. In this study, it was aimed to examine the effect of the education given to nursing students on the development of cultural sensitivity skills and to evaluate the perception toward immigrants.

### **Materials and Methods Type of Research**

The present study was conducted as a descriptive research study with a pretest–posttest design. The objective of the study was to evaluate the effect of the Intercultural Nursing course on nursing students' intercultural sensitivity and negative attitudes toward immigrants.

### **Research Population and Sample**

The population of the study consisted of 36 second-year students enrolled in the Intercultural Nursing course at Recep Tayyip Erdoğan University, Faculty of Health Sciences, Department of Nursing. The sample comprised 34 students who voluntarily agreed to participate in the study.

### **Data Collection Tools**

The collection of data was conducted using the following instruments: the Personal Information Form, the Intercultural Sensitivity Scale (ISS), and the Negative Attitudes Toward Immigrants Scale (NATI).

The Personal Information Form was developed by the researchers to collect socio-demographic and background information about the participants, including age, gender, region of residence prior to university education, experiences of contact with individuals from different cultures and immigrants, and prior education related to cultural care and immigrant care during nursing education.



The Turkish Intercultural Sensitivity Scale (ISS), which was originally developed by Chen and Starosta (2000) and adapted into Turkish by Bulduk, Tosun and Arduç (2011), was utilised to assess nursing students' levels of intercultural sensitivity (Bulduk et al., 2011; Chen & Starosta, 2000). The scale under consideration consists of 23 items and five subdimensions: interaction engagement, respect for cultural differences, confidence in interaction, enjoyment of interaction, and interaction attentiveness. Responses are evaluated using a 5-point Likert scale, ranging from 1 ("strongly disagree") to 5 ("strongly agree"). It is important to note that several items are negatively worded and reverse-coded prior to analysis. Conversely, higher total scores are indicative of higher levels of intercultural sensitivity. In the present study, the internal consistency of the scale was found to be satisfactory, with a Cronbach's alpha coefficient of 0.86.

The Negative Attitudes Toward Immigrants Scale (NATI) was utilised to evaluate nursing students' negative attitudes towards immigrants. The scale was originally developed by Varela et al. (2013) and adapted into Turkish with established validity and reliability by Günay et al. (Günay et al., 2019; Varela et al., 2013). The scale is composed of 12 items and possesses a unidimensional structure. Responses are evaluated using a 5-point Likert scale, ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Conversely, elevated scores are indicative of more negative attitudes towards immigrants. In the present study, the internal consistency of the scale was found to be satisfactory, with a Cronbach's alpha coefficient of 0.86.

### **Data Collection**

At the course's commencement, participants completed the Personal Information Form, the Intercultural Sensitivity Scale, and the Negative Attitudes Toward Immigrants Scale as preliminary assessments. At the conclusion of the course semester, post-test data were obtained

by re-administering the Intercultural Sensitivity Scale and the Negative Attitudes Toward Immigrants Scale. Prior to data collection, all necessary permissions for the use of the measurement instruments were obtained.

### Data Analysis

The data obtained in the study were analysed using SPSS (Statistical Package for the Social Sciences) version 23.0 software. The descriptive statistics were presented in tabular form as numbers, percentages, means and standard deviations. Prior to analysis, the data were examined to ascertain their suitability for statistical testing. Depending on the distribution of the data, appropriate parametric or non-parametric statistical tests were applied to compare pre-test and post-test scores. The level of statistical significance was accepted as  $p < 0.05$ .

### Results

**Table 1.** Socio-demographic characteristics of the participants (n=34)

	Mean±SD (Min-Max.)	n	%
<b>Age</b>	19.82± 1.09(18-23)		
<b>Gender</b>			
Female	29	85.3	
Male	5	14.7	
<b>Place of residence</b>			
Black Sea Region	18	52.9	
Eastern Anatolia Region	4	11.8	
Central Anatolia Region	4	11.8	
Southeastern Anatolia Region	4	11.8	
Mediterranean Region	2	5.9	
Marmara Region	2	5.9	
<b>Contact with other cultures</b>			
Yes	28	82.4	
No	6	17.6	
<b>Coexistence with migrants</b>			

Yes	18	52.9
No	16	47.1
<b>Previous training on cultural care</b>		
No	34	100
<b>Previous training on migrants</b>		
No	34	100

The mean age of the participants was  $19.75 \pm 0.95$  (18-23). 84.4% of the participants were female and 15.6% were male. When the region of residence was analyzed; 53.1% lived in the Black Sea Region, 12.5% in Eastern Anatolia, 11.8% in Central Anatolia, 9.4% in Southeastern Anatolia, 6.3% in the Mediterranean and 6.3% in the Marmara Region. 81.3% of the participants reported previous contact with other cultures and half of the group reported having lived together with immigrants. It was observed that the participants answered “no” in all cases of previous training on cultural care and training on migrants (Table 1).

**Table 2.** Comparison of Pre-Test and Post-Test Scores of Turkish Intercultural Sensitivity Scale and Negative Attitudes Toward Immigrants Scale

	<b>Pre-test</b>	<b>Post-test</b>	<b>p</b>	<b>test</b>
	<b>Ort±SS</b>	<b>Ort±SS</b>		
	<b>Med (Min-Max)</b>	<b>Med (Min-Max)</b>		
Responsibility in Communication	25.70±3.48 26(16-33)	27.11±2.93 27(22-33)	.061	-1.940
Respect for Cultural Differences	22.47±3.57 22(14-28)	18.61±3.12 18(14-29)	.000	3.945
Confidence in Communication	16.52±3.42 17(6-24)	17.97±2.30 18(13-25)	.025	-2.343

Enjoying Communication	11.14±1.89 11(7-15)	8.50±2.21 8(5-14)	.000	5.227
Being Attentive in Communication	10.97±1.78 11(7-14)	11.82±1.69 12(6-15)	.047	-2.060
ISS Total	86.82±10.19 89(60-105)	84.02±8.17 83(71-106)	.248	1.176
NATI Total	46.44±8.52 44(35-75)	38.91±11.05 39(24-91)	.006	2.929

Table 2 shows the comparison of students' pre-test and post-test scores. It was observed that the post-test values tended to increase in the sub-dimension of responsibility in communication, but this difference was not statistically significant ( $p=.061$ ). In the sub-dimension of respect for cultural differences, there was a significant decrease between the pre-test and post-test in favor of the post-test ( $p=.000$ ). Significantly higher scores were found in the post-test in the sub-dimensions of being confident in communication ( $p=.025$ ) and being careful in communication ( $p=.047$ ). In the sub-dimension of enjoying communication, the post-test scores were significantly lower ( $p=.000$ ). There was no significant difference in the total score of the Intercultural Sensitivity Scale ( $p=.248$ ). Significantly lower values were found in the total score of the Negative Attitude Toward Immigrants Scale (NATI) in the post-test ( $p=.006$ ).

## Discussion

This study evaluated the effect of an intercultural nursing course on students' perceptions of immigrants and their cultural sensitivity.

The fact that the majority of the participants in this study were female (84.4%) and the mean age was in the young adult group ( $19.75\pm 0.95$ ) is consistent with similar studies conducted with nursing students. In studies conducted with nursing students in Turkey, it is reported that the sample is predominantly composed of women and the average age usually ranges between 19-

22 years (Bilgiç & Şahin, 2019; Kabu Hergül et al., 2022). The fact that more than half of the participants lived in the Black Sea Region seems to be related to the geographical location of the institution where the study was conducted.

However, the fact that the sample includes students from different regions provides diversity in terms of evaluating intercultural sensitivity. The fact that 81.3% of the students had been in contact with different cultures before and about half of them stated that they had been together with immigrants shows that intercultural interaction is not completely foreign to the students. Similarly, it is emphasized in the literature that contact with individuals from different cultures is an important factor that increases cultural sensitivity (Bulduk et al., 2017; Kabu Hergül et al., 2022).

It is noteworthy that all participants in the study stated that they did not receive any training on cultural care and immigrants. This finding shows that nursing students' knowledge and skills in intercultural care are largely based on personal experiences. In studies conducted in Turkey, it has been reported that nursing students and nurses do not receive adequate formal education on intercultural care and therefore have difficulties in practice (Ceylan & Çetinkaya, 2022; Kırgöz et al., 2024).

In the pre-test-post-test comparisons, an increasing trend was observed in the post-test scores in the sub-dimension of responsibility in communication, but this difference was not statistically significant. The limited change in behavioral and internalization dimensions such as responsibility in communication with short-term interventions is consistent with previous studies (Bulduk et al., 2017).

Although the finding of a significant decrease in the respect for cultural differences sub-dimension in favor of the post-test can be considered as a negative finding at first glance, this

can be explained by increased awareness. It is thought that after the intervention, students started to question their previous superficial and idealized perceptions of cultural differences and became more aware of their own prejudices. In the literature, it is stated that awareness-based interventions may initially lead to temporary decreases in sensitivity scores and that this is a developmental process (Bulduk et al., 2011; Ceylan & Çetinkaya, 2022).

One of the positive aspects of the study is that significant increases were found in the sub-dimensions of being confident in communication and being careful in communication in the post-test. This result shows that students developed a more conscious and cautious approach in intercultural communication. Similar findings reveal that especially communication skills can be improved with training in intercultural sensitivity studies (Bilgiç & Şahin, 2019; Kabu Hergül et al., 2022).

The significant decrease in the post-test scores in the sub-dimension of enjoyment of communication may be related to the students' realization of the difficulties of intercultural communication more clearly. It is thought that language barriers and misunderstanding anxiety in communication with immigrants cause students to perceive communication as a less enjoyable process. As a matter of fact, it has been reported that language and communication barriers are the most common problems experienced by nurses and students caring for immigrant patients (Ceylan & Çetinkaya, 2022; Kırgöz et al., 2024). The fact that no significant change was found in the total score of the Cultural Sensitivity Scale can be explained by the different directional changes observed in the sub-dimensions. The increase in some sub-dimensions and the decrease in others may have caused the total score to stabilize. This shows that cultural sensitivity is a multidimensional structure and short-term interventions may not affect all dimensions simultaneously (Bulduk et al., 2011).

On the other hand, a significant decrease in the total score of the Negative Attitudes Toward Immigrants Scale in the posttest is one of the strongest findings of the study. This result shows that awareness and knowledge-based interventions are effective in reducing students' negative attitudes toward immigrants. In the literature, it is emphasized that attitudes can change in a shorter time compared to sensitivity levels (Günay et al., 2019).

### **Conclusion**

This study revealed that intercultural sensitivity levels of nursing students differed in terms of sub-dimensions and that a short-term intervention did not provide a simultaneous increase in all sensitivity dimensions. Although no significant change was found in the total cultural sensitivity score, significant increases were found in the sub-dimensions of self-confidence in communication and caution in communication, whereas a decrease was observed in the sub-dimensions of respect for cultural differences and enjoyment of communication. These findings suggest that students realized the difficulties of intercultural interaction more realistically and their cultural awareness evolved from a superficial acceptance to a more critical level. In addition, the significant decrease in negative attitudes toward immigrants indicates that attitudes can change in a shorter period of time compared to cultural sensitivity.

It is recommended that intercultural care and migrant health issues should not be addressed only at the theoretical level in nursing undergraduate programs, but should be supported by practice and experience-based, long-term and repetitive trainings; in addition, it would be useful to disseminate awareness and empathy-based approaches and to evaluate the effects of these trainings with follow-up and qualitative methods.

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**Competing interest**

The authors declare that they do not have any competing interests.

## Changes in Nursing Students' Knowledge Levels and Nursing Diagnoses After Nursing Process Course

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### Abstract

The objective of the present study was twofold: firstly, to ascertain the knowledge levels of students enrolled in the Nursing Process course with regard to the nursing process itself; and secondly, to examine the diagnoses they identified on the basis of case studies. The research was conducted in a single-group pre-test–post-test quasi-experimental design. The present study was conducted with a sample of 20 second-year students enrolled in the Nursing Process course at a university in northern Turkey between March and June 2025. The students received instruction on the nursing process and nursing diagnoses. The data were collected using a Personal Information Form, a Knowledge Test, and a Sample Case.

The mean age of the students was 20.55 years ( $\pm 1.36$ ), and 55% of the participants were female. The mean pre-knowledge test score was  $57.80 \pm 12.75$ , and the mean post-knowledge test score was  $67.80 \pm 10.34$ . A statistically significant increase in post-course knowledge test scores was found in both male and female students ( $p < 0.05$ ). While the most frequently identified nursing diagnoses by students in the pre-test assessment were “Risk for infection”, and “Disruption Sleep Pattern”, the post-test assessment revealed that “Risk for Infection”, “Decreased Activity Tolerance”, “Risk for Adult Falls” and “Lack Self-Care” diagnoses were identified more frequently, and new, more detailed nursing diagnoses reflecting the clinical situation were added to the diagnostic process. The present study determined that the nursing process course had a positive impact on students' knowledge level and nursing diagnosis identification skills. The findings emphasise the significance of delivering nursing process instruction in a manner that is case-based and oriented towards practice.

**Keywords:** nursing education, nursing process, nursing diagnosis and case-based learning.

## **Introduction**

Nursing is a healthcare discipline that involves the practical application of theoretical knowledge and skills. The nursing process itself is recognised as one of the most significant instruments for the translation of theoretical nursing knowledge into practical application (Biol, 2013; Olmaz & Karakurt, 2019; Tasdemir & Kizilkaya, 2013). In numerous countries worldwide, the nursing process is utilised in the delivery of professional nursing care. The significance of the effective utilisation of the nursing process is especially emphasised in the practice standards of the United States and Canada. In Turkey, the Nursing Law (2007) stipulates that nurses are obliged to identify individuals' health needs and the community's health needs, to plan, implement and evaluate nursing care in accordance with the nursing process. The nursing process is defined as a scientific problem-solving method (Nursing Process, 2016). The nursing process is defined as a systematic problem-solving method that incorporates critical thinking, creativity and decision-making processes. It is a process that requires research to identify the healthcare needs of healthy and sick individuals, and to provide individualised care. (Basit, 2020; Dikmen et al., 2015; Körpe et al., 2019; Tasdemir & Kizilkaya, 2013). The nursing process, a fundamental component of individualised patient care, comprises five sequential stages: data collection, nursing diagnosis, planning, implementation, and evaluation (Basit, 2020; Biol, 2013; Kaçmaz & Tektaş, 2023; Körpe et al., 2019; Olmaz & Karakurt, 2019; Tasdemir & Kizilkaya, 2013).

The classification system and type of diagnosis employed in the expression of nursing diagnoses exerts a significant influence. The nursing diagnoses employed in the nursing process are delineated by the North American Nursing Diagnosis Association Taxonomy (NANDA), an organisation comprising nursing educators, theorists, and practitioners operating within the



United States and Canada. The primary objective of the NANDA is to formulate and develop diagnostic terminology for utilisation by professional nurses (Karaca & Durna, 2019). Consequently, the accurate, systematic, and effective utilisation of NANDA nursing diagnoses is of critical importance for conducting the nursing process on a scientific basis and enhancing the quality of care.

### **Research Aim**

The study aims to determine the level of knowledge of students taking the nursing process course and to examine the diagnoses they determine based on the case.

### **Materials and Methods Type of Research**

This research was conducted in a single group using a pre-test-post-test quasi-experimental design.

### **Location and Time of the Study**

The research was conducted at the Department of Nursing, Faculty of Health Sciences, Recep Tayyip Erdoğan University, Rize Province, between March and June 2025.

### **Research Population and Sample**

The population of the study consisted of 20 second-year students enrolled in the elective Nursing Process course during the spring semester of the 2024-2025 academic year at the Department of Nursing, Faculty of Health Sciences, Recep Tayyip Erdoğan University. The Nursing Process course is a 2-credit, 3 ECTS elective course. This course is conducted with 7 weeks of theory followed by 7 weeks of presenting the care plans created by the students.

### **Data collection tools Personal Information Form**

This form includes the students' age and gender.

### **Knowledge Test**

This is a 25-question, 5-choice multiple-choice test created by the researcher using literature to measure students' knowledge of the nursing process (Birol, 2013; Çiğdem Keski, 2009; Kaplan, 2016; Olmaz, 2016; Olmaz & Karakurt, 2019; Üçkardeş, 2021). Necessary corrections were made to the form based on expert opinions, and then it was implemented. The test duration was 30 minutes, and each question was worth 4 points. The test was administered in writing. In the evaluation of the test, answers were assessed as "correct-incorrect," and the number of correct answers was taken as the basis. The maximum score possible is 100 points, and the minimum is 0 points.

### **Sample Case**

The case used in this study was taken from a book prepared for use in nursing education (Özer & Balcı Akpınar, 2023). Based on this sample case, students were asked to determine nursing diagnoses using the steps of the nursing process and to create an appropriate nursing care plan.

### **Data Collection**

The elective course on the nursing process is taught over 14 weeks, with two hours of class per week, using theoretical and case study presentation methods. The first seven weeks cover general information related to the nursing process. In the other seven weeks, students present case studies. This research was conducted by administering a pre-test in the first week and a post-test in the last week. After informing the students taking the course about the research at the beginning of the semester, those who volunteered to participate in the study were given a "Personal Information Form," an "Knowledge Test," and a "Sample Case" to complete. Data collection tools were collected through face-to-face observation. In the last class of the semester, the post-test was completed by giving the same "Knowledge Test" and "Sample Case"

again. The correct diagnoses determined for the sample case given were taken into consideration for the evaluation.

### Data Analysis

The statistical analysis of the data was performed using the SPSS 24.0 statistical package program (Statistical Package for Social Sciences). In the study, frequency, number, percentage, arithmetic mean, standard deviation, and chi-square test were used to evaluate the data and analyze the demographic characteristics of the student- -nurses.

**Table 1.** Demographic data

	Mean±SD Min.-Max.	n	%
<b>Age</b>	<b>20.55±1.36</b> <b>(19-23)</b>		
<b>Pre-test Knowledge Test</b>	<b>57.80±12.75</b> <b>(36-72)</b>		
<b>Post-test Knowledge Test</b>	<b>67.80±10.34</b> <b>(52-88)</b>		
<b>Gender</b>			
Female		11	55
Male		9	45

The average age of participants was 20.55±1.36, and most were female (55%). The average pre-test score was 57.80±12.75, while the average post-test score was 67.80±10.34. (Table 1)

**Table 2.** Comparison of gender and knowledge test scores

<b>Knowledge Test Scores</b>				
	<b>Pre-test</b>	<b>Post-test</b>	<b>t</b>	<b>p</b>
	<b>Mean±SD</b>	<b>Mean±SD</b>		
<b>Famale</b>	61.82±11.51	71.27±9.93	-2.296	0.045
<b>Male</b>	52.89±13.08	63.56±9.68	-2.499	0.037
<b>Total</b>	<b>57.80±12.75</b>	<b>67.80±10.34</b>	-3.455	<b>0.003</b>

Female participants' pre-test scores were 61.82±11.51, while their post-test scores increased to 71.27±9.93, and this increase was found to be statistically significant ( $t(10)=-2.296$ ;  $p=.045$ ). A significant increase was also observed in male participants between the pre-test (52.89±13.08) and post-test (63.56±9.68) scores ( $t(8)=-2.499$ ;  $p=.037$ ). When the entire group was evaluated, a significant increase in knowledge test scores was observed ( $t(19)=-3.455$ ;  $p=.003$ ). (Table 2)

**Table 3.** Diagnoses identified pre-course and post-course

<b>Pre-course Diagnosis</b>	<b>No</b>	<b>Post-course Diagnosis</b>	<b>No</b>
Risk for Bleeding	9	Risk for Bleeding	12
Risk for Infection	15	Disturption Sleep Pattern	18
Risk for Adult Falls	14	Risk for Adult Falls	14
Impaired Skin Integrity	4	Impaired Skin Integrity	5
Disturption Sleep Pattern	15	Disturption Sleep Pattern	10
Acute Pain	4	Acute Pain	7
Lack Self-Care	11	Lack Self-Care	12
Decreased Activity Tolerance	7	Decreased Activity Tolerance	15
Anxiety/Death anxiety	3	Anxiety/Death anxiety	3
Fatigue	2	Fatigue	3
Imbalanced nutrition: less than body requirements	10	Imbalanced nutrition: less than body requirements	10

Impaired spontaneous ventilation	2	Impaired spontaneous ventilation	3
Risk of Constipation	2	Risk of Constipation	1
Risk for unstable blood glucose level	2	Risk for unstable blood glucose level	4
Risk for impaired oral mucous membrane integrity	6	Risk for impaired oral mucous membrane integrity	7
<b>Total</b>	<b>106</b>		<b>124</b>

The most frequently identified nursing diagnoses in the pre-course assessment were "Risk of Infection" (n=15) and "Disturption Sleep Pattern" (n=15), while the most frequently identified diagnoses in the post-course assessment were "Risk of Infection" (n=18) and "Decreased Activity Tolerance" (n=15) (Table 3).

### Discussion

This study was conducted to examine the effect of the nursing process course on students' knowledge level and ability to identify nursing diagnoses. The findings show that the course significantly improved both cognitive gains and clinical reasoning and diagnostic competence. The study found that the students' pre-test knowledge scores were at an intermediate level, and that there was a statistically significant increase in their knowledge level after the course. This finding suggests that the structured and step-by-step teaching approach of the nursing process course reinforced the students' theoretical knowledge. Similarly, the literature reports that the systematic teaching of the nursing process increases students' knowledge level and clinical decision-making skills. This result is consistent with the findings of the study and supports the educational effectiveness of the course (Akansel & Palloş, 2020; Dikmen et al., 2015; Sahin & Khorshid, 2021; Şen Atasayar & İşeri, 2023).

In the comparison by gender, it is noteworthy that both female and male students showed a significant increase in their post-test scores. The fact that female students' pre-test and post-test

scores were higher than those of male students may be related to female students in nursing education adapting earlier to the care process and patient-centered approach topics. However, the fact that significant development was observed in both genders is important in terms of showing that the effect of the course emerged independently of gender. This suggests that the course content and teaching methods are inclusive and effective.

Another noteworthy finding of the study is the development in students' nursing diagnosis skills. When the nursing diagnoses determined before and after the course were examined, the increase in the total number of diagnoses from 106 to 124 in the final diagnosis was quite significant. This increase shows that the participants' knowledge level has improved, as well as their clinical reasoning, problem identification, and patient needs recognition skills. This indicates that students are able to evaluate cases more holistically and analyze patient needs in greater detail. In particular, the marked increase in the accuracy of the "Decreased Activity Tolerance" diagnosis suggests that students' physiological and functional assessment skills have improved.

The fact that the diagnosis of "Risk of Infection" was the most frequently identified diagnosis in both assessment processes indicates that students are highly sensitive to patient safety and infection control issues. This situation can be considered a natural reflection of the frequent emphasis on infection risk in nursing education.

These findings reveal that case presentations and active student participation are effective in nursing process education. The literature frequently emphasizes that case-based learning develops students' critical thinking, clinical reasoning, and accurate nursing diagnosis skills (Altınbaş & İster, 2020; Çiğdem Keski, 2009; Kaplan, 2016; Şen Atasayar & İşeri, 2023; Yoo & Park, 2014)

### **Limitation**

The fact that the study was conducted in a single-group quasi-experimental design and the limited sample size can be considered a limitation in terms of generalizability. However, despite this, the meaningful results obtained are strong in terms of revealing the educational value of the nursing process course. It is recommended that future studies be planned with larger samples, control groups, and multi-center research.

### **Conclusion**

In conclusion, this study clearly shows that the nursing process course increases students' knowledge level and improves their nursing diagnosis skills. In line with these findings, it is strongly recommended that nursing process teaching in nursing education be structured, case-based, and practice-oriented from the early stages. Overall, it was found that both the number and variety of nursing diagnoses identified by students in the post-course diagnosis process increased.

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**Competing interest:** The authors declare no conflict of interest.

## Intravenous Rehydration Management in a Child with Severe Acute Malnutrition: A Case Report Based on the NANDA–NIC–NOC Nursing Care Model

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### Abstract

Severe acute malnutrition (SAM) continues to represent a critical contributor to pediatric morbidity and mortality, particularly when accompanied by acute gastroenteritis and dehydration. Pathophysiological adaptations observed in malnourished children—including diminished myocardial mass, altered renal function, and disrupted electrolyte homeostasis—necessitate highly cautious and individualized intravenous (IV) fluid therapy. Inappropriate or excessive fluid administration may precipitate severe complications such as heart failure, pulmonary edema, and significant electrolyte disturbances. Within this context, pediatric nurses assume a central role in comprehensive assessment, continuous monitoring, and the safe execution of rehydration protocols. The present case report aims to describe the structured nursing management of IV rehydration in a child diagnosed with severe acute malnutrition using the NANDA–NIC–NOC nursing care framework. An 18-month-old male patient was admitted to the emergency department with a four-day history of persistent diarrhea, recurrent vomiting, decreased oral intake, and lethargy. Clinical examination revealed sunken eyes, reduced skin turgor, delayed capillary refill, and a weight- for-height Z-score below  $-3$ . Vital signs demonstrated mild tachycardia and borderline hypotension. Laboratory evaluation indicated mild hyponatremia and metabolic acidosis. Controlled IV rehydration was initiated in accordance with World Health Organization guidelines. Nursing diagnoses, interventions, and measurable outcomes were systematically identified and implemented using standardized nursing classifications. Following structured nursing interventions focused on fluid balance regulation, electrolyte surveillance, and hemodynamic monitoring, progressive clinical stabilization was achieved. No evidence of fluid overload or cardiac compromise was observed. Laboratory parameters improved gradually, and oral feeding was safely reintroduced. The structured integration of standardized nursing language enhanced clinical reasoning, facilitated organized care delivery, and supported patient safety. The NANDA–NIC–NOC model provides an effective and evidence-based framework for managing IV rehydration in pediatric patients with severe acute malnutrition.

**Keywords:** severe acute malnutrition, intravenous rehydration, pediatric nursing, nanda, nic

## **Introduction**

Severe acute malnutrition remains a persistent global public health concern and is strongly associated with elevated childhood morbidity and mortality rates, particularly in resource-limited settings (World Health Organization [WHO], 2013). Children affected by SAM exhibit compromised physiological reserves, increased susceptibility to infection, metabolic instability, and impaired adaptive responses to dehydration (Trehan & Manary, 2015).

Fluid management in malnourished children requires a fundamentally different clinical approach compared to well-nourished pediatric populations. Reduced myocardial mass, impaired renal concentration capacity, and electrolyte imbalance significantly increase vulnerability to fluid overload and heart failure during intravenous rehydration (Maitland et al., 2011). Consequently, cautious fluid administration accompanied by intensive nursing surveillance is imperative.

Standardized nursing care frameworks, particularly the NANDA–NIC–NOC model, promote systematic assessment, evidence-based intervention planning, and measurable outcome evaluation. The application of standardized nursing language supports structured clinical reasoning and enhances care quality in complex pediatric scenarios (Moorhead et al., 2018).

This case report aims to examine the nursing management of intravenous rehydration in a child with severe acute malnutrition within the NANDA–NIC–NOC framework and to underscore the pivotal role of pediatric nursing in preventing adverse outcomes.

## **Materials and Methods**

This study was conducted as a descriptive case report in a tertiary-level emergency department. An 18-month-old male child presented with a four-day history of diarrhea and vomiting, accompanied by reduced oral intake and lethargy. There was no history of chronic disease or

congenital anomaly. Physical examination demonstrated sunken eyes, decreased skin turgor, dry mucous membranes, and delayed capillary refill. Anthropometric evaluation revealed a weight-for-height Z-score below  $-3$ , confirming severe acute malnutrition.

Vital sign assessment showed mild tachycardia and borderline hypotension. Laboratory analysis identified mild hyponatremia and metabolic acidosis. Based on comprehensive clinical and laboratory findings, a diagnosis of severe acute malnutrition with moderate dehydration was established.

Intravenous rehydration therapy was initiated according to WHO (2013) recommendations for children with SAM. Fluid selection and infusion rates were carefully determined and administered under close monitoring.

The nursing care process was structured using the NANDA International classification system (Herdman et al., 2021). Nursing interventions were selected from the Nursing Interventions Classification (Bulechek et al., 2018), and patient outcomes were evaluated using the Nursing Outcomes Classification (Moorhead et al., 2018).

## **Results**

The primary nursing diagnosis identified was Deficient Fluid Volume related to excessive gastrointestinal losses and insufficient intake, as evidenced by clinical dehydration signs and laboratory abnormalities.

Planned NOC outcomes included:

- Fluid Balance
- Electrolyte and Acid–Base Balance
- Vital Signs Stability

Selected NIC interventions consisted of:

- Controlled Fluid Management
- Continuous Electrolyte Monitoring
- Frequent Vital Signs Assessment
- Coordinated Nutrition Support

Following carefully regulated IV fluid administration and continuous clinical monitoring, the patient demonstrated progressive stabilization. Hydration parameters improved, heart rate normalized, and laboratory abnormalities gradually resolved. Importantly, no signs of pulmonary edema, cardiac overload, or hemodynamic instability were observed. Oral feeding was reintroduced in a controlled manner.

### **Discussion**

The management of dehydration in children with severe acute malnutrition demands a cautious and highly individualized approach due to altered physiological compensatory mechanisms. Previous evidence indicates that rapid or excessive fluid resuscitation may increase mortality risk in this population (Maitland et al., 2011). Therefore, vigilant monitoring and structured nursing intervention are essential to minimize complications.

The NANDA–NIC–NOC model facilitated systematic identification of patient needs, targeted intervention planning, and measurable outcome evaluation. The integration of standardized nursing language enhances clinical documentation, strengthens interdisciplinary communication, and improves patient safety (Müller-Staub et al., 2015).

This case illustrates the critical contribution of pediatric nurses in early complication detection, safe IV rehydration management, and adherence to evidence-based guidelines in malnourished children.

## Conclusion

Intravenous rehydration in children with severe acute malnutrition requires meticulous assessment, cautious fluid administration, and comprehensive nursing surveillance. The NANDA–NIC–NOC framework provides a structured, evidence-based model that supports safe and effective pediatric nursing practice in high-risk clinical situations.

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### **Ethical approval statement**

This study was conducted as a single case report without experimental intervention. Ethics committee approval was not required. Written informed consent was obtained from the child's legal guardian prior to publication. No identifiable patient information is included in this manuscript.

### **Competing interest**

The author declares that there are no competing interests.

## Investigation of the Relationship Between Swallowing Performance and Sleepiness in Patients with Parkinson's Disease\*

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### Abstract

Our study aimed to determine the relationship between swallowing performance and sleepiness in patients with Parkinson's disease. A total of 89 patients were evaluated for eligibility, and patients with a diagnosis of sleep disorder or psychiatric illness (n=2), those who had undergone laryngeal region surgery (n=5) or nodules (n=1), or those who had undergone salivary gland botox (n=2) were excluded. A total of 79 Parkinson's patients (44 females, 35 males; age: 67.33±8.31 years; Body Mass Index (BMI): 28.04 kg/m<sup>2</sup>, IQR 6.92) were included. The median duration of Parkinson's disease in patients was determined as 49,00 months (IQR: 60). Swallowing performance was assessed using the Turkish Eating Assessment Tool (T-EAT-10), daytime sleepiness by the Epworth Sleepiness Scale (ESS). Data normality was evaluated with the Kolmogorov–Smirnov test, and correlations were analysed using Spearman coefficients. The distribution of patients according to the Hoehn–Yahr scale showed that 14 patients were in stage 1, 11 in stage 1.5, 17 in stage 2, 14 in stage 2.5, 15 in stage 3, 2 in stage 3.5, 5 in stage 4, and 1 in stage 5. A moderately positive and significant correlation was found between swallowing performance and daytime sleepiness (r=0.306; p=0.006). A weak positive correlation was found between Parkinson's disease duration and T- EAT-10 scores (r=0.265; p=0.018). This study showed that greater swallowing impairment is associated with excessive sleepiness in Parkinson's disease. These results emphasize the necessity of evaluating swallowing performance and sleep together during clinical follow-up, as this integrated approach may better support quality of life in Parkinson's disease.

**Keywords:** parkinson, swallowing, sleepiness, dysphagia, sleep

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\* This study is not derived from a thesis.

## **Introduction**

Parkinson's disease is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms (Halli-Tierney, Luker, & Carroll, 2020). Non-motor symptoms such as dysphagia negatively affect quality of life (Carneiro et al., 2014; Weerkamp et al., 2013). Swallowing disorders are quite common in Parkinson's patients, with an estimated prevalence of approximately 80% (Kalf, de Swart, Bloem, & Munneke, 2012). Swallowing disorders can also accompany the clinical picture even in the early stages (Pflug et al., 2018). This condition predisposes to serious respiratory complications such as malnutrition, dehydration, and especially aspiration pneumonia, and is among the significant causes of morbidity and mortality in Parkinson's disease (Miller, Noble, Jones, & Burn, 2006; Suttrup & Warnecke, 2016).

Impairments in swallowing function can negatively affect not only nutritional safety but also sleep architecture. It was shown that sialorrhea changes were significant in Parkinson's patients in the intermediate-and high-risk obstructive sleep apnea syndrome (OSAS) (Özkutlu, Demir, Ünlüer, & Sonkaya, 2025). These breathing events such as snoring has been shown to predict the occurrence of daytime sleepiness (Braga-Neto, da Silva-Júnior, Sueli Monte, de Bruin, & de Bruin, 2004). A study conducted on Parkinson's patients reported a close relationship between excessive daytime sleepiness and the development of swallowing disorders (Marano et al., 2020). However, understanding the nature of the relationship between swallowing performance and daytime sleepiness is essential for developing a comprehensive rehabilitation program.

In this context, our study aims to investigate the potential relationship between swallowing performance and sleepiness in Parkinson's patients.

### **Materials and Methods Design**

This prospective cross-sectional study received ethical approval from the Ankara Yıldırım Beyazıt University Ethics Committee (approval no: 06/808) and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

### **Patients**

Participants were recruited from the Movement Disorders and Parkinson's Disease Outpatient Neurology Clinic and included individuals aged  $\geq 18$  years who had been diagnosed with Parkinson's disease by an experienced neurologist in accordance with the 2015 Movement Disorder Society diagnostic criteria (Postuma et al., 2015). Participants were excluded if they had a diagnosed sleep disorder or other neurological disease; non-Parkinsonian conditions that could influence swallowing function (including musculoskeletal disorders, advanced pulmonary disease, history of throat-related surgery, thyroid-related conditions, cancer, dementia, or depression); reliance on enteral nutrition via nasogastric tube or gastrostomy; or prior botulinum toxin injections to the salivary glands. A total of 89 patients were evaluated for eligibility, and 79 Parkinson's patients were included in the study (Figure 1.).

### **Clinical assessment**

A physiotherapist collected demographic data, including age, anthropometric measurements, and educational status, together with clinical information such as disease duration and severity, comorbidities, and current medication use.

### **Assessment of Swallowing Performance**

Patients swallowing performance was assessed using the Turkish Eating and Swallowing Assessment Tool (T-EAT-10) (Belafsky et al., 2008; Demir, Serel Arslan, İnal, & Karaduman, 2016). The T-EAT-10 is a 10-item questionnaire scored on a scale of 0 (no problems) to 4

(severe problems), with a total score ranging from 0 to 40 points. A score of 3 or higher is considered abnormal, while a score of 16 or higher indicates suspected aspiration.

### **Assessment of Sleepiness**

Patients sleepiness was assessed using the Epworth Sleepiness Scale (ESS) (Izci et al., 2008; Johns, 1991). The scale consists of 8 items, each rated on a scale from 0 (never doze off) to 3 (very likely to doze off). As the score increases, the individual's perceived daytime sleepiness increases.

### **Statistical analysis**

IBM SPSS Statistics (version 25) was utilized for all statistical procedures. Categorical data, including sex and Hoehn–Yahr classification, were presented as frequencies. Continuous variables showing normal distribution (age) were described using mean  $\pm$  standard deviation, while variables without normal distribution (body mass index (BMI), duration of Parkinson's disease, T-EAT-10, and ESS scores) were summarized using median, interquartile range. The Kolmogorov–Smirnov test was applied to evaluate distribution normality, and Spearman correlation analysis was performed to determine relationships between variables.

### **Results**

The study included 79 patients with PD. Among the patients, 55.7% were women (n= 44) and 44.3% were men (n= 35). Patients had a mean age of  $67.33 \pm 8.31$  years, with a median BMI of  $28.04 \text{ kg/m}^2$  (IQR: 6.92). The median duration of Parkinson's disease in patients was determined as 49.0 months (IQR: 60). The distribution of patients according to the Hoehn–Yahr scale showed that 14 patients were in stage 1, 11 in stage 1.5, 17 in stage 2, 14 in stage 2.5, 15 in stage 3, 2 in stage 3.5, 5 in stage 4, and 1 in stage 5. The median ESS and T-EAT-10 scores were 10.0 (IQR: 8) and 4.0 (IQR: 5), respectively. A moderately positive and significant correlation was found between swallowing performance and daytime sleepiness ( $r=0.306$ ;

$p=0.006$ ). A weak positive correlation was found between Parkinson's disease duration and T-EAT-10 scores ( $r=0.265$ ;  $p=0.018$ ).

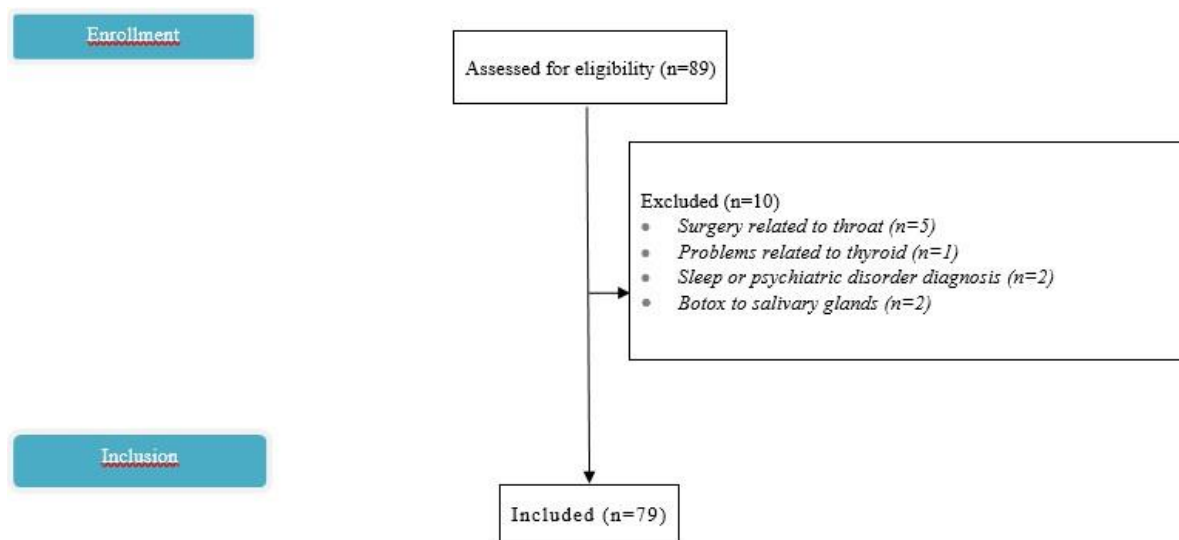


Figure 1. |Flowchart of the Study

**Figure 1.** Flow chart of the study

## Discussion

This study revealed that impairment in swallowing performance is associated with sleepiness in Parkinson's disease. In this study, the number of female patients exceeded that of male patients. However, Parkinson's disease is known to be more prevalent in men. This difference is thought to stem from the nigrostriatal circuit and the potential neuroprotective effect of estrogen (R. Patel & Kompoliti, 2023). The mean age of the patients was over to 65. This finding is consistent with the well-established epidemiological trend where the prevalence of Parkinson's disease increases with advancing age (Ma, Erb, & Moore, 2025; Reeve, Simcox, &

Turnbull, 2014). The high BMI of our sample is quite important for our results. A high BMI in Parkinson's patients may be clinically significant in terms of sleep. Since overweight and obesity are important risk factors for OSAS (Schwartz et al., 2008), sleepiness may be more severe in Parkinson's patients with a high BMI.

The median disease duration in our sample was 49 months (IQR: 60), reflecting considerable variability. Although the distribution was skewed, the trend indicated that longer disease duration was associated with greater swallowing difficulty, which is in line with previous findings reporting disease duration over 3 years as a risk factor for dysphagia (Shilimkar, Londhe, Sundar, & Darole, 2020). This supports our finding of a weak positive correlation between the duration of Parkinson's disease and T-EAT-10 scores.

The wide distribution of Hoehn–Yahr stages 1–5 in our sample and the inclusion of both early and advanced stage patients suggests that swallowing and sleep problems may also be seen in the early stages of the disease. A study reported that dysphagia was more common in the first years ( $\leq 2$  years) after Parkinson's diagnosis compared to the control group; this suggests that swallowing problems are not limited to advanced stages but can also occur in the early stages (Santos-García et al., 2025).

Similarly, it has been shown that excessive daytime sleepiness in Parkinson's patients can begin 10 years before motor symptoms (Pont-Sunyer et al., 2015), and may be related to the severity of the disease (Feng et al., 2021).

We found a moderate positive correlation between swallowing performance and sleepiness. This correlation may be related to dysphagia resulting from delayed pharyngeal swallowing, impaired swallowing-breathing coordination, and delayed protective closure of the airway during the pharyngeal phase observed in Parkinson's patients (B. Patel, Legacy, Hegland, Okun, & Herndon, 2020). This impaired pharyngeal muscle coordination may lead to OSAS (Wang,

Chua, Chan, & Tan, 2025); sleep fragmentation and intermittent hypoxemia associated with OSAS are thought to result in excessive daytime sleepiness (Tankéré et al., 2025). In this context, it is conceivable that impaired swallowing performance contributes to increased daytime sleepiness via OSAS, forming a common underlying mechanism.

## Conclusion

These findings indicate that greater impairment in swallowing performance is associated with excessive sleepiness in Parkinson's disease, suggesting possible shared mechanisms. Longer disease duration is accompanied by more severe swallowing impairment. Although causality cannot be inferred from this cross-sectional design, the results highlight the need for comprehensive clinical follow-up including both swallowing and sleep evaluations to support patient quality of life.

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## From Functional Food to Treatment: A Histopathological Perspective on the Protective and Curative Role of Honey \*

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### Abstract

Honey has been consumed as a highly valued food source for centuries; however, its value as a functional food has increased in recent years due to its potent bioactive compounds. Nevertheless, honey is a heterogeneous product with a variable composition depending on its botanical origin, geographical region, and production conditions. Beyond its nutritional value, honey's therapeutic potential to prevent tissue damage and accelerate repair mechanisms has attracted growing interest in the medical sciences. The main objective of this study is to evaluate the protective and healing effects of honey across different tissue-damage models, particularly through histopathological changes and cellular responses. This systematic review was conducted by searching the Web of Science, PubMed, and Scopus databases for studies published between 1986 and 2026, in accordance with the PRISMA guidelines. Relevant experimental in vivo studies were selected using the keywords “honey,” “histopathology,” “mucosal protection,” “wound healing,” and “inflammation.” A literature review indicates that topical application of honey significantly reduces tissue damage in models of gastric ulcers, colitis, and skin wounds. Histopathological studies consistently report that honey protects mucosal integrity by increasing goblet cell mucus production and reducing hemorrhagic lesions. At the cellular level, application of honey has been shown to reduce inflammatory cell infiltration and connective tissue edema. Furthermore, honey has been reported to accelerate re-epithelialization, increase angiogenesis, and reduce scar formation by regulating collagen organization. In conclusion, microscopic findings reveal that honey is a multifaceted biological agent that modulates inflammatory processes and supports tissue architecture. However, the use of different types of honey across studies and the lack of standardized composition data constitute significant limitations. Therefore, comprehensive statistical analyses were not feasible, and the findings were evaluated using a comparative approach informed by the literature.

**Keywords:** functional food, histopathology, tissue protection, wound healing.

## **Introduction**

Honey is a natural substance that has been used for centuries as both a nutritional product and a complementary therapeutic agent. In addition to its high carbohydrate content, honey contains various bioactive components, including phenolic compounds, flavonoids, enzymes, organic acids, and other biologically active molecules, which contribute to its therapeutic properties (Bonsignore et al., 2024; Coşkun, 2022). These compounds are responsible for the antioxidant, antimicrobial, and anti-inflammatory properties of honey, which have attracted increasing attention in experimental and clinical research (Yaghoobi et al., 2013).

Honey is not chemically uniform. Its composition depends on botanical origin, location, climate, harvest time, and processing. These factors affect its biological activity and therapeutic use. As a result, studies about "honey" may use products with different biochemical profiles. This makes direct comparison between studies difficult.

Animal studies suggest honey may help tissue regeneration and wound healing. In skin wound models, topical honey reduces inflammation, accelerates epithelialization, and improves tissue structure. Honey-containing formulations also protect tissues in gastrointestinal and mucosal injury models.

Furthermore, honey-derived and related bee products, such as propolis, may help regeneration. Used alone or in combination with natural compounds, propolis has improved biochemical and histopathological outcomes in experimental models of liver injury (Singh et al., 2026). Certain polysaccharides from honey also regulate cellular defenses and support epithelial barrier integrity (Song et al., 2024).

Many experimental studies explore honey's role in tissue repair and regeneration. The available evidence, however, is spread across different models and tissues. A comprehensive review is needed to understand honey's therapeutic potential in tissue healing.

This systematic review aims to evaluate experimental studies on honey's effects on histopathological tissue damage and healing. We also gather available evidence about its regenerative and protective effects.

## **Materials and Methods**

### **Study Design**

This study was conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aimed to identify and synthesize experimental studies investigating the effects of honey on histopathological tissue damage and healing processes.

### **Search Strategy**

A comprehensive literature search was conducted in the Web of Science Core Collection and PubMed databases to identify relevant studies examining the histopathological effects of honey on tissue damage and healing processes.

The search strategy included combinations of the following keywords:

'honey' and 'histology OR histopathology OR tissue healing OR tissue repair'

The search covered publications from 1986 to 2026. No initial restrictions were applied regarding language, country, institution, or journal during the search phase to ensure comprehensive coverage of the literature.

## **Study Selection**

The study selection process followed the PRISMA screening procedure. All retrieved records were first screened based on titles and abstracts, and full texts were evaluated when necessary to determine eligibility. Duplicate records identified across databases were manually removed before the screening process. Studies were included if they were experimental in vivo investigations examining the effects of honey on tissue damage or healing processes with histological or histopathological evaluation and available full-text access. Studies focusing only on chemical composition analysis, lacking histological assessment, or not directly related to tissue injury or healing were excluded. Editorials, conference abstracts, book chapters, short reports without full-text access, and duplicate publications were also excluded. Relevant data were systematically extracted from the included studies, including author and publication year, country of origin, experimental model, tissue type, method of honey administration, histopathological findings, and main outcomes related to tissue healing. The extracted information was synthesized qualitatively to identify common experimental approaches, tissue responses, and the reported regenerative or protective effects of honey.

## **Results**

Following the literature search conducted in the Web of Science Core Collection and PubMed databases, a total of 87 studies met the inclusion criteria and were included in this systematic review. Among these, 44 studies were retrieved from Web of Science and 43 from PubMed. All included publications investigated the effects of honey on tissue injury and healing processes using histological or histopathological evaluation methods, primarily within experimental in vivo models.

Overall, the included studies indicate that research investigating the biomedical effects of honey has increased over time, particularly within experimental biomedical research. Most studies relied on animal models, with rats being the most commonly used experimental organism, suggesting that current evidence in this field is largely based on preclinical investigations. Across the included studies, honey application was evaluated in various tissue injury models, including wound healing models, liver injury, gastrointestinal damage, and other experimental tissue damage models.

Histopathological evaluations reported in the studies frequently demonstrated beneficial effects of honey on tissue repair processes. The most commonly reported findings included reduced inflammatory responses, improved epithelial regeneration, enhanced tissue organization, and protective effects against oxidative stress-related tissue damage. These findings suggest that honey may contribute to tissue healing through mechanisms involving anti-inflammatory activity, antioxidant effects, and modulation of cellular repair processes.

Several studies also focused on specific monofloral honey types, particularly Manuka honey and Tualang honey, which appeared frequently in the literature due to their distinctive biochemical composition and biological properties. Manuka honey was most commonly associated with studies investigating wound healing, anti-inflammatory effects, and oxidative stress, whereas Tualang honey was frequently examined in experimental animal models evaluating biofilm formation, antioxidant activity, and tissue protection.

Despite the growing number of experimental studies investigating the therapeutic potential of honey, the available evidence remains heterogeneous. Differences in experimental models, honey types, dosage protocols, and reporting of botanical origin or chemical composition limit direct comparisons between studies. Overall, the findings indicate that honey demonstrates

promising protective and regenerative effects at the histopathological level, particularly in experimental models of tissue injury and oxidative stress; however, the majority of the available evidence is derived from animal studies, and further translational and clinical research is needed to confirm these findings.

## **Discussion**

This systematic review highlights the main research trends and evidence regarding the effects of honey on tissue damage and healing processes in experimental studies. When the available literature is considered as a whole, it becomes clear that research in this field is mainly concentrated on wound healing, inflammation control, and tissue regeneration. The frequent use of histological and histopathological evaluation methods indicates that microscopic tissue response remains the primary approach for assessing the biological effects of honey in experimental models.

The current findings suggest that honey application may support tissue healing in different models of tissue injury. However, the therapeutic effects of honey cannot be explained solely by reductions in lesion size. Evidence from experimental studies indicates that honey may influence tissue repair through multiple biological pathways. In particular, the enhancement of the mucosal barrier, suppression of oxidative stress, and reduction of inflammatory cell infiltration are among the main mechanisms proposed to explain the protective and regenerative effects of honey (Fazalda et al., 2018; Samargandian et al., 2017). These findings suggest that honey may function as a biologically active modulator of the tissue-healing process rather than simply acting as a passive protective agent.

Another important observation in the literature is the frequent investigation of certain monofloral honey types, particularly Manuka honey and Tualang honey. These honey varieties appear prominently in experimental studies due to their distinctive phytochemical composition and reported biological activities. However, many studies still evaluate honey as a general biological product without providing detailed information about its botanical origin or chemical profile. Considering that honey is a complex natural substance whose composition can vary significantly depending on plant source, geographic region, season, and production conditions, the use of the general term “honey” without detailed characterization may limit the interpretability and comparability of results.

The literature also indicates an imbalance between clinical observations and experimental evidence at the tissue level. While honey has been widely investigated in clinical contexts related to nutrition and complementary medicine, histopathology-based controlled in vivo experimental studies remain relatively limited. This situation highlights the need for more well-designed experimental research to better understand the mechanisms underlying honey's biological effects.

Nevertheless, caution is necessary when interpreting the available evidence. Many studies treat honey as a single homogeneous product, despite considerable variations in botanical origin, geographic source, and chemical composition. The prominence of specific honey types such as Manuka and Tualang in the literature may also limit the generalizability of positive findings to other honey varieties. In addition, the predominance of animal models and the lack of standardized reporting regarding honey composition represent important methodological limitations that affect the strength of the current evidence. Therefore, although the available findings suggest promising therapeutic potential for honey, the existing evidence remains

insufficient to generalize these effects across all conditions. Future studies using well-characterized honey samples and standardized experimental designs are needed to clarify the relationship between honey composition and its biological effects.

## **Conclusion**

In conclusion, the findings of this systematic review indicate that honey demonstrates promising biological and regenerative potential in experimental models of tissue injury and healing. Histopathological evidence suggests that honey may support tissue repair through mechanisms such as reducing inflammation, modulating oxidative stress, and promoting tissue regeneration. However, the available evidence remains heterogeneous, and the current data are not sufficiently consistent to allow the generalization of these effects across different conditions and honey varieties.

A major limitation in the existing literature is the lack of detailed characterization of honey samples used in experimental studies. Since honey is a complex natural product whose composition varies depending on botanical origin, geographic source, and production conditions, treating honey as a uniform substance may limit the comparability of results. Therefore, future studies should focus on using chemically and botanically well-defined honey samples and should clearly report compositional characteristics.

Furthermore, most of the available evidence is derived from experimental animal models, highlighting the need for more controlled and comparative studies to better understand the mechanisms underlying honey's biological effects. Future research that considers honey as a group of biologically distinct materials classified according to their component profiles may

provide more reliable and comparable results. Such approaches will contribute to a more comprehensive understanding of the therapeutic potential of honey in tissue healing and regenerative medicine.

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## The Relationship Between Digital Visibility and Academic Impact in Maternal Health Literacy Research: An Altmetric-Based Analysis\*

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### Abstract

This study investigates the relationship between digital visibility and academic impact in the field of maternal health literacy research, utilizing Altmetric Attention Scores (AAS) as a measure of digital visibility and citation counts to represent academic impact. Maternal health literacy is essential for enhancing health outcomes, especially during pregnancy and childbirth. The aim of this study is to assess the societal and digital visibility of scientific publications related to maternal health literacy and to examine how these visibility factors are associated with academic impact. A total of 129 publications were identified from the Web of Science database using relevant keywords such as “maternal health literacy,” “maternal HL,” and “pregnancy health literacy.” The publications were analyzed based on their citation counts, obtained through the Dimensions database, and their Altmetric Attention Scores. Publications with at least one citation and an Altmetric Attention Score greater than one were included in the analysis, resulting in a sample of 68 publications. Spearman's rank correlation analysis was employed to assess the relationship between societal visibility and academic impact. The findings indicate a significant, moderate positive correlation (Spearman's  $\rho = 0.48$ ,  $p < 0.001$ ) between digital visibility and citation counts, suggesting that publications with higher digital engagement tend to be cited more frequently. The study highlights the importance of considering both academic and societal visibility in evaluating the impact of maternal health literacy research. These results suggest that digital metrics, such as Altmetric Attention Scores, complement traditional citation-based metrics, offering a broader view of a publication's influence. It is recommended to enhance dissemination strategies to improve the visibility of maternal health literacy research across both academic and digital channels.

**Keywords:** maternal health literacy, digital visibility, academic impact, altmetric attention score, citation count.

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\* This study is not derived from a thesis.

## **Introduction**

Maternal health is one of the most critical indicators of a society's overall health status. In particular, the processes of pregnancy, childbirth, and the postpartum period have profound impacts on women's health, which emphasizes the value of maternal health literacy in improving health outcomes. Maternal health literacy is directly related to women's ability to access, understand, evaluate, and utilize health information regarding pregnancy and childbirth (Nutbeam, 2008). Initially, health literacy was defined as the capacity of individuals to comprehend health-related information and effectively navigate health systems; it has since evolved to include critical and interactive dimensions (Nutbeam, 2000). Maternal health literacy, as a subfield of this broader concept, specifically refers to women's ability to navigate prenatal care services, recognize risk signs, and make appropriate health decisions during pregnancy and childbirth (Renkert & Nutbeam, 2001).

Studies have shown that low maternal health literacy is associated with insufficient prenatal care, late identification of pregnancy complications, higher cesarean rates, and increased maternal and infant morbidity risks (Berkman et al., 2011; Endres et al., 2004). Especially among socioeconomically disadvantaged and migrant populations, maternal health literacy levels are lower, which exacerbates health inequities (Sentell et al., 2012).

Improving maternal health literacy is not only about increasing individual knowledge but also involves ensuring that health systems are structured in a way that is woman-friendly, comprehensible, and accessible (Kickbusch et al., 2013). Therefore, recent health literacy approaches focus not only on individual competence but also on the responsibility of health systems (WHO, 2016).

With the increasing digitization of healthcare, digital health tools have become significant in maternal health literacy research. Mobile health applications, online pregnancy tracking

systems, and social media-based informational content have been shown to facilitate women's access to information and support health literacy (Lupton, 2016; Sayakhot & Carolan-Olah, 2016). However, the accuracy and reliability of digital information can pose new risks, especially for women with low critical health literacy.

In this context, the social and digital visibility of maternal health literacy studies is becoming increasingly important. Research featured in social media, news platforms, and policy documents has been shown to have greater potential to raise awareness of maternal health (Priem et al., 2012). This recognizes the importance of alternative metrics, such as the Altmetric Attention Score, in evaluating the academic impact of maternal health literacy research beyond citation counts. In conclusion, the body of literature on maternal health literacy is growing and crossing disciplines. It focuses on health inequities, women's empowerment, and changing health systems. The evaluation of studies in this field should consider not only citation counts but also the digital and societal impacts of maternal health information to understand its real-world implications.

### **Materials and Methods**

The aim of this study is to assess the digital and societal visibility of publications in the field of maternal health literacy using the Altmetric Attention Score (AAS) and to examine the association between this visibility and academic impact, measured by citation counts. In this study, scientific publications on maternal health literacy were identified using the "Topic" search option in the Web of Science (WoS) database. The search was conducted using the keywords "maternal health literacy," "maternal HL," and "pregnancy health literacy," yielding 129 publications. These publications formed the literature universe for the study. To access academic impact indicators, the publications were matched in the Dimensions database using

their Digital Object Identifiers (DOI). Citation counts for each publication were obtained through Dimensions. The societal visibility of the publications was assessed using the Altmetric Attention Score. For impact-based analysis, publications with at least one citation and an Altmetric Attention Score of at least 1 were included in the study. Based on these criteria, the analysis sample consisted of 68 publications. The relationships between societal visibility and academic impact indicators were examined using Spearman's rank correlation analysis.

### **Research Question**

Is there a significant relationship between the digital and societal visibility (Altmetric Attention Score) and the academic impact (citation count) of scientific publications in the field of maternal health literacy?

### **Limitations**

This study has several limitations. First, the analyses are limited to the literature universe defined within the Web of Science database; publications indexed in other databases (e.g., Scopus or PubMed) were not included in the study. However, this choice was made to ensure a consistent, reproducible definition in the literature. Second, Altmetric Attention Score and citation data were not available for all publications. Therefore, the analysis was restricted to publications that had at least one citation and an Altmetric Attention Score of at least 1. This approach was chosen because including publications without impact indicators would be methodologically inappropriate for the analysis. Third, the study does not aim to establish a causal relationship; instead, it examines the relationship between societal visibility and academic impact at a correlational level. No inference was made regarding whether Altmetric indicators are a cause or consequence of scholarly citations. Finally, this study does not evaluate the content or methodological quality of the publications; it focuses solely on their academic

and societal impact indicators. This limits the interpretation of the findings in the context of publication quality.

## Results

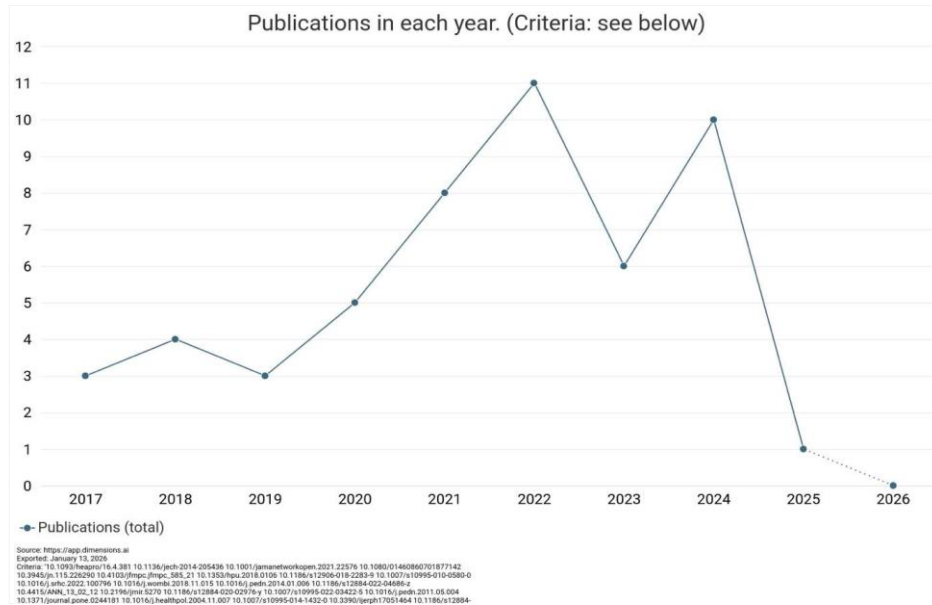
The publications analyzed were published between 2017 and 2025. This indicates that the study focuses on the current literature in maternal health literacy. The Altmetric Attention Scores of the publications range from 1 to 52, suggesting that the levels of digital and societal visibility vary significantly across them. Citation counts range from 1 to 226, indicating a heterogeneous distribution of academic impact across publications. The wide range in both Altmetric Attention Scores and citation counts suggests that the field includes studies that attract varying levels of attention at both academic and societal levels. Citation data were obtained from Dimensions, while Altmetric Attention Score data were retrieved from Altmetric.com. The study's literature universe was defined in the Web of Science (WoS) database using relevant keywords, and the analysis was limited to WoS publications with measurable digital visibility.

**Table 1.** Descriptive Characteristics of Publications Included in the Study (n = 68)

<b>Variables</b>	<b>Description</b>
Publication Years	2017 – 2025
Average Altmetric Attention Score	Digital and social visibility indicator
Altmetric Range	1 – 52
Average Number of Citations	Academic impact indicator
Number of Citations Range	1 – 226
Data Source (Citations)	Dimensions
Data Source (Altmetric)	Altmetric.com
Data Source (Accessible Publications)	Web of Science (WoS)

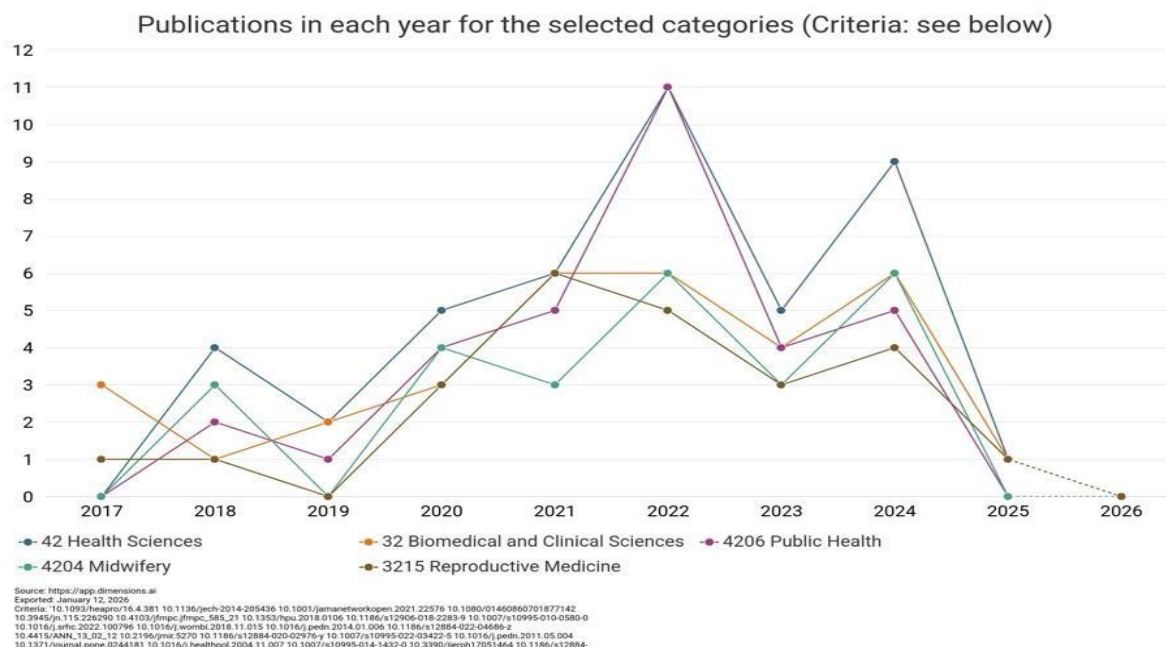


**Table 2.** Number of publications by year



With the popularization of the concept of maternal health literacy, the first studies were published in 2017 and showed a fluctuating increase over time, with the highest number of publications in 2022. The decrease in 2019 may be due to increased attention to COVID-19 publications. The trend of decline in 2025-2026 should not be misleading; the number of publications may be lower than it appears due to early acceptance. As expected, health sciences (58), public health (43), biomedical and clinical sciences (37), midwifery (31), and reproductive medicine/reproductive health (26) are prominent in the research areas.

**Table 3.** Research area categories



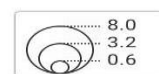
As seen in table 4, the top 10 researchers with the most publications are as follows. As expected, research is concentrated in the USA, where Avital Cnaan has the most publications, totaling 4. Despite having only 2 publications, Georges Karna Kone in Canada received the most citations.

**Table 4.** Researchers - Citation Counts (top 10 researchers with the most publications - citation counts)

No	Researcher	Current Organization	Country	Publications	Citations
1	Avital Cnaan	Children's National Health System	United States	4	92
2	Susmita Pati	State University of New York at Stony Brook	United States	4	92
3	Georgina Amankwah	Ghana Health Service	Ghana	2	36
4	Georges Karna Koné	Université de Montréal	Canada	2	134
5	Larisa Ariadne Justine Barnes	The University of Sydney	Australia	2	88
6	Nancy A. Lockhart	University of Michigan–Ann Arbor	United States	2	36
7	Cheryl Allen Moyer	University of Michigan–Ann Arbor	United States	2	36

	Arbor	States		
8	Eileen K. Fry-Bowers	University of San Diego	United States	2 56
9	Robin Dimatteo	University of California, Riverside	United States	2 56
10	Rosie Nash	University of Tasmania	Australia	2 14

VOSviewer generates a visual representation that presents the journals with the most publications and their networks of relationships. The top five journals with the most publications are listed. The Maternal and Child Health Journal and BMC Pregnancy and Childbirth, each with five publications, occupy the first two places. Next come Women and Birth, International Journal of Environmental Research and Public Health, and Plos One, each with two publications.



**Figure 2.** Inter-journal collaborative network

Springer is in first place with 14 publications, followed by Elsevier with 13 and Sage with 6.

**Table 5.** The most published publishing group

No	Name	Publications	Citations	Citations (mean)
1	Springer Nature	14	317	22.64
2	Elsevier	13	379	29.15
3	SAGE Publications	6	79	13.17
4	Taylor & Francis	5	67	13.4
5	Wiley	4	52	13
6	JMIR Publications	3	68	22.67
7	MDPI	3	55	18.33
8	BMJ	2	84	42
9	Frontiers	2	20	10
10	Hindawi	2	13	6.5

The mission of the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) is to lead research and education to understand human development, improve reproductive health, enhance the lives of children and adolescents, and maximize the potential of all. Therefore, it is expected that this institution would fund the most publications. Second is the Gates Foundation (a non-profit organization run by Bill Gates and Melinda Gates that aims to solve global problems such as malaria and hunger), and third is the European Commission among the funding organizations.

**Table 6.** Funding Organizations

No	Name	Country	Organization Type	Publications	Citations
1	Eunice Kennedy Shriver National Institute of Child	United States	Government	8	194
2	Gates Foundation (BMGF)	United States	Nonprofit	4	158
3	European Commission (EC)	Belgium	Government	3	58
4	National Center for Advancing Translational Sciences (NCATS)	United States	Government	3	97
5	Canadian Institutes of Health Research (CIHR)	Canada	Government	2	134
6	Population Council	United States	Nonprofit	2	24
7	National Institute of Nursing Research (NINR)	United States	Government	2	80
8	Public Health Foundation of India (PHFI)	India	Nonprofit	2	24
9	Health Resources and Services Administration (HRSA)	United States	Government	2	49
10	United Way	United States	Nonprofit	2	46

Looking at the top 10 institutions where the studies were conducted, the University of Pennsylvania in the USA ranks first (with 5 publications). The University of Sydney, Australia, ranks second with three publications. Although the University of Sydney has fewer publications, its impact is evident in the number of citations (314). Hacettepe University, from Turkey, ranks 10th with two publications. The majority of publications originate from Australia, followed by the USA. Publications are frequently from educational institutions (universities). A non-profit organization in India and a healthcare institution in the USA also contributed to the publications.

**Table 7.** Research Organizations

No	Name	Country	Organization Type	Publications	Citations
1	University of Pennsylvania	United States	Education	5	145
2	The University of Sydney (USYD)	Australia	Education	3	314
3	University of California, Los Angeles (UCLA)	United States	Education	3	89
4	Children's Hospital of Philadelphia (CHOP)	United States	Healthcare	3	71
5	Guilan University of Medical Sciences (GUMS)	Iran	Education	3	28
6	Public Health Foundation of India (PHFI)	India	Nonprofit	3	84
7	Monash University	Australia	Education	2	22
8	University of Tasmania (UTAS)	Australia	Education	2	14
9	University of Canberra (UC)	Australia	Education	2	24
10	Hacettepe University	Turkiye	Education	2	15

The top three countries with the most publications are, in order, the USA, Australia, and Iran.

**Table 8.** Countries Where Research Was Conducted

No	Name	Publications	Citations
1	United States	24	670
2	Australia	11	388
3	Iran	6	125
4	Canada	5	206
5	India	5	218
6	China	4	35
7	United Kingdom	3	78
8	Norway	3	78
9	Vietnam	3	13
10	Ivory Coast	2	134

The relationship between social visibility and academic impact was examined using Spearman's rank correlation analysis. The analysis included 68 publications from the Web of Science

database that had at least one citation and at least one Altmetric Attention Score. There is a moderate, positive, and statistically significant correlation between Altmetric Attention Score and citation count (Spearman's  $\rho = 0.48$ ;  $p < 0.001$ ). It was found that publications with high digital/social visibility tend to receive more citations on average.

**Table 9.** Correlation Between Altmetric Attention Score and Citation Count (n=68)

Variables	1	2
1. Altmetric Attention Score	1.00	
2. Citation Count (Times Cited)	0.48*	1.00

Spearman rank correlation coefficients have been reported. \*  $p < 0.001$

## Discussion

The aim of this study is to assess the digital and societal visibility of publications in the field of maternal health literacy using the AAS and to examine the association between this visibility and academic impact, measured by citation counts. This study examines the relationship between digital visibility (measured through the Altmetric Attention Score) and academic impact (measured by citation counts) in maternal health literacy research. The findings reveal a moderate, positive, statistically significant correlation between these two variables, which emphasizes the need to take into account both digital/social visibility and academic impact when assessing the reach and influence of scholarly work. This correlation indicates that research with higher digital and societal visibility tends to accumulate more citations, suggesting that engagement through non-academic channels—such as social media and news platforms—can enhance a publication's reach and scholarly impact.

A significant contribution of this study is the use of Altmetric indicators alongside traditional citation metrics. While citations have long been the gold standard for measuring academic

impact, this study demonstrates that Altmetric data—which captures the broader public and digital engagement—serves as a complementary tool. The findings support previous research suggesting that these alternative metrics provide a more comprehensive understanding of a publication's influence (Kunze et al., 2020; Priem et al., 2012; Llewellyn & Nehl, 2022; Yang et al., 2021). Moreover, the results align with studies that emphasize the growing importance of digital health literacy in the maternal health field, where online tools, such as mobile apps and social media, facilitate access to health information, thereby influencing both digital visibility and academic citations (Lupton, 2016; Sayakhot & Carolan-Olah, 2016).

However, while this study demonstrates a significant correlation, it is crucial to note that digital visibility and academic impact are distinct phenomena. Digital visibility can increase public engagement and awareness, but it does not guarantee that a publication will be cited by other academic works. This finding aligns with research that calls for a nuanced approach to measuring academic influence, recognizing that societal visibility may not always translate directly into academic relevance (Nutbeam, 2008). Further research is needed to explore the specific mechanisms by which digital engagement influences academic citation practices and to investigate whether digital visibility could serve as a predictor for future academic success.

Additionally, this study does not establish a causal relationship between digital visibility and academic impact. The correlation found in this research points to an association, but it does not imply causality. Future studies could explore longitudinal data to better understand the dynamics between these two factors over time. It would also be beneficial to expand the analysis to include publications indexed in other databases, such as Scopus and PubMed, to further validate the findings and ensure a more comprehensive view of the literature.

Finally, while this investigation offers helpful perspectives on maternal health literacy research, it is important to recognize that it does not evaluate the content or methodological quality of the publications included. The focus was solely on their academic and societal impact, which may limit the interpretation of findings in the broader context of publication quality.

## **Conclusion**

This study reveals a meaningful association among digital and societal visibility, and academic impact in maternal health literacy research, using a correlational design. The findings demonstrate that while digital visibility is linked to academic impact, these two factors are distinct and not interchangeable. The results suggest that Altmetric indicators complement traditional citation-based metrics, providing a broader understanding of a publication's influence. Therefore, it is recommended to strengthen dissemination strategies to enhance the visibility of maternal health literacy research, not only within academic platforms but also across digital and societal channels.

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### **Statements and Declarations**

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**Competing interest:** The author declares that they have no competing interests.



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