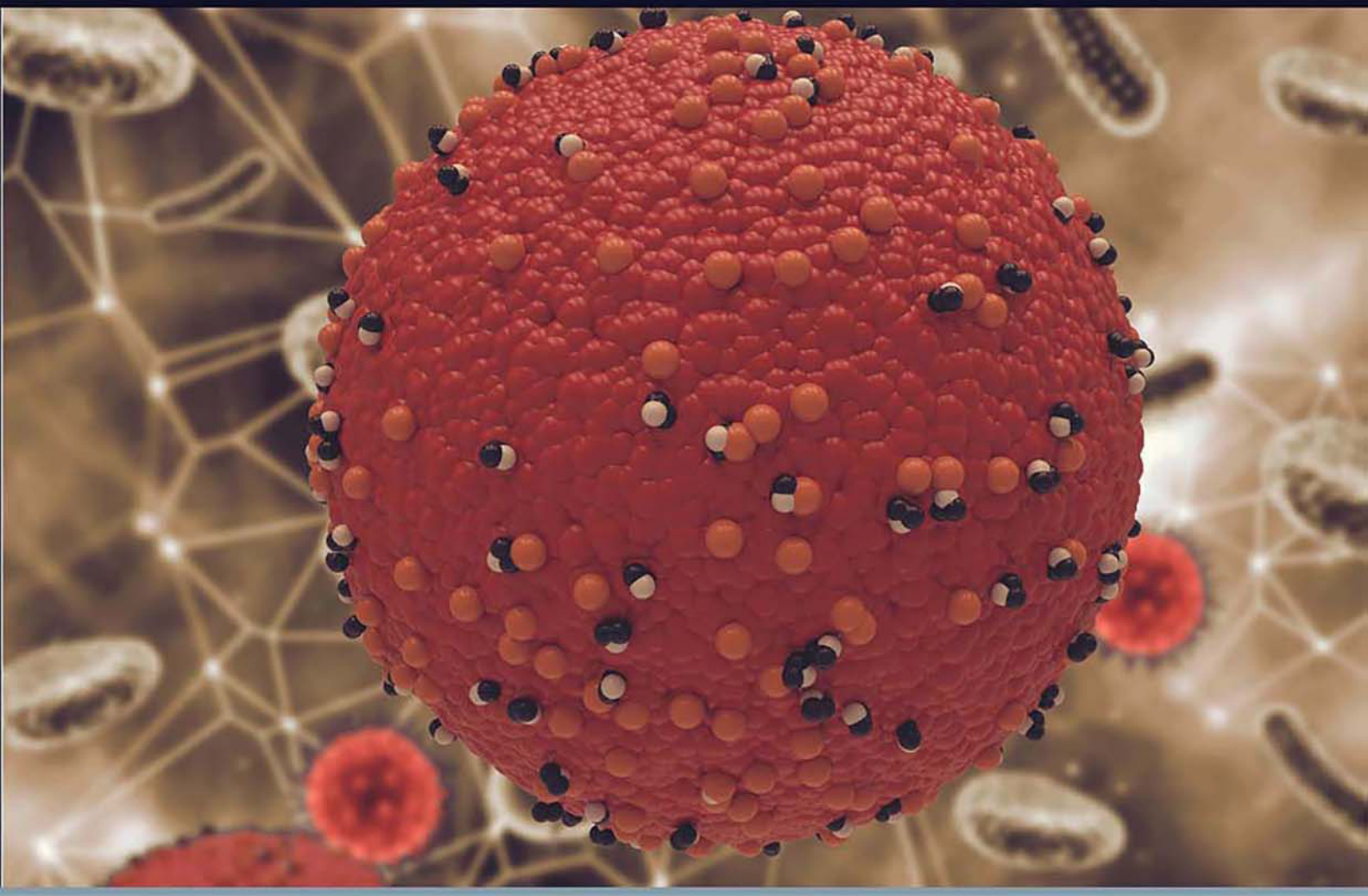
Personalized & Precision Medicine JOURNAL

Medical Journal / 10 year / No. 37 / 500000 Rials / Winter 2025 / ISSN:3115-7874



The Future of Medicine is Personalized

Journal Information

Name: Personalized Medicine Joumal
Abbreviated Name: PMJ
Date of First Issue Published: Februa 2019
Concessionaire: AmitisGen TECH Dev Grou
Release Period: uarterl

Editorial Board Information

Contact Information
Tel: (98)2188985291-3
Fax: (98)2189775181
Email: Editor@pmjournal.ir
Address: No. 2, Italia Street, Tehran, Iran
Poqal code : 1416673744

Personalized & Precision Medicine Journal
Spring 2025,Volume 10, Issue 37

Table of Content

Spring 2025, Volume 10, Issue 37 (1-8) DOI: 10.22034/pmj.2025.2048504.1048

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Exploring the Antidepressant Effect of Aqueous Alcoholic Extract of Purslane Plant (Portulaca Oleracea) on Asthma-induced Depression in Mice: Insights from Open Field and Forced Swimming Tests

Najmeh Khatun Dehnavi [1], **Ali Neamati** [1,*]

[1]Department of Biology, IAUM, Islamic Azad University, Mashhad, Iran.

ARTICLE INFO

Paper Type: Original Article

Submitted: 2025-02-09
Accepted: 2025-06-01

Keywords:
Asthma
Depression
Inflammation
Oxidative stress
Purslane

Corresponding author:
Ali Neamati, Department of Biology, IAUM, Islamic Azad University, Mashhad, Iran.
Email: 0942229630@iau.ir.

ABSTRACT

Asthma is one of the most common chronic diseases in which inflammation plays an essential role in its pathophysiology. One of the secondary effects of asthma is depression, which is probably due to overlapping pathogenic mechanisms. One of the important mechanisms in the treatment of depression and asthma is to pay attention to removing inflammation and reducing oxidative stress. Purslane exerts its anti-inflammatory and antioxidant effects through NFqB and NOS pathways. This study aims to investigate the effect of the aqueous-alcoholic extract of the purslane plant on depression caused by experimental asthma using an Open Field Test and Forced Swimming Test in small laboratory mice.

To investigate the aqueous-alcoholic extract of the purslane plant on depression caused by experimental asthma, 40 Syrian NMRI male mice were divided into 4 groups: control, asthmatic, and asthmatic receiving the extract at a dose of 50 mg/kg and 100 mg/kg. Syrian mice were injected and inhaled ovalbumin to develop asthma, and the control group received PBS solution in the same way. The treated groups received the extract at the same time as asthma induction.

The results show that depression symptoms increased significantly after asthma induction. These symptoms were significantly reduced after the administration of purslane extract in a dose-dependent manner. The results indicated a significant increase in depression in the asthmatic group samples compared to the control group and also a significant decrease in depression in the groups treated with purslane extract compared to the asthmatic group.

How to Cite this Article:
N.Kh. Dehnavi, A. Neamati. "Exploring the Antidepressant Effect of Aqueous Alcoholic extract of purslane plant (Portulaca oleracea) on Asthma-induced depression in Mice: Insights from Open Field and Forced Swimming Tests" Personalized & Precision Medicine Journal, Vol. 10, no. 37, pp. 1- 8.

INTRODUCTION

Asthma is one of the most common chronic diseases in the world, which causes numerous changes in the shape and function of the respiratory system and other body systems, including the immune system, nervous system, and endocrine system (1), and is associated with symptoms such as depression and anxiety (2). According to the statistics of the World Health Organization, the number of asthma patients in the whole world is 300 million and it is expected to reach 400 million by 2025 (3). The average prevalence of asthma in Iran is 13.14%, which is higher than the world average (4). Asthma is a very complex and heterogeneous disease, and genetic factors along with environmental factors play a role in it (5-7).

Studies show that respiratory diseases are associated with the persistence of depression and anxiety, so it is not surprising that there are common pathogenic mechanisms between them (8). Research has shown that patients with asthma are more at risk of depression, and this has been observed to varying degrees in studies (9-14). In asthma, the disorder of nitric oxide metabolism leads to an increase in the production of oxygen-free radicals by eosinophils and other leukocytes. On the other hand, the concentration of natural antioxidants such as glutathione and vitamins C and E decreases in blood cells and lavage fluid (15). Following the reduction of antioxidant

factors, mitochondrial dysfunction and inflammation in asthma, complications such as depression come to a person. The inflammasome is another reason for the development of systemic inflammation that leads to the increase of IL-1β in these two diseases (16). Increased levels of inflammatory markers including IL-6, IL-4, IL-1 and TNFα, C-reactive protein and CD163 (macrophage activation index) have been associated with decreased lung function (17-19).

Purslane is the 8th most used plant in the world, which has a long history of use as an edible and medicinal plant in the list of the World Health Organization. Studies that have recently been conducted on the isolation of homoisoflavonoids and related compounds from purslane indicate that this plant family has biomedical properties such as cough relief, antioxidant, anti-allergic, anti-inflammatory, antihistamine, etc. This plant contains glutathione, coenzyme Q10-omega-3, vitamins (A, B1, B2, C, E), noradrenaline, dopamine and flavonoids such as quercetin and apigenin. Melatonin is also one of the active and unique molecules that can be found in abundance in purslane, and part of the antioxidant properties of purslane extract is due to the presence of this substance (20- 28).

Many studies have been conducted on the anti-inflammatory and antioxidant effects of purslane in various diseases, but so far no research has been done on its effect on depression caused by asthma. This study aims to investigate the effect of the aqueous-alcoholic extract of the purslane plant on depression caused by experimental asthma using an Open Field Test and Forced Swimming Test in small laboratory mice.

MATERIALS AND METHODS

Animals

In this research, 40 Syrian NMRI male mice with an approximate weight of 25 to 30 grams were obtained from the Razi Serum Institute of Mashhad. The samples were kept in 12 hours of light and darkness with free access to water and food at a temperature of 21-23 °C in PVC cages in the animal room of the Islamic Azad University of Mashhad, Faculty of Basic Sciences.

The animals were randomly divided into 4 groups (n = 10), 1) control, 2) asthmatic, 3 and 4) asthmatic receiving water-alcoholic extract of purslane at the rate of 50 and 100 mg per kilogram of body weight. Intraperitoneal face in 6 times. To standardize the test conditions, the samples of the control group received PBS solution intraperitoneally.

Method of preparation of aqueous-alcoholic extract of purslane plant

The purslane plant was identified by herbarium code 10033 by the Islamic Azad University of Mashhad, Faculty of Basic Sciences. Extraction was done by the Soxhlet method. To prepare the extract, 100 grams of dried purslane leaves were used. The solvent consisted of 250 ml of distilled water and 250 ml of 98% ethanol. The extraction continued until the solvent became colorless. Finally, about 24 grams of dry extract was obtained (due to the presence of oily and carotenoid compounds, purslane extract is not completely dry and powder-like). This extract with a certain dose was dissolved in PBS solution and injected intraperitoneally into the animals.

Experimental asthma induction method

To induce asthma, ovalbumin solution (1 mg/kg of ovalbumin powder along with 100 mg of aluminium hydroxide powder and 0.5 ml of PBS solution) was injected intraperitoneally into the samples for three consecutive days. Also, the animals, from day 6 to day 21 In addition to intraperitoneal injection, received this solution by inhalation with the help of a nebulizer and an aerosol device It was used in the inhalation chamber (29, 30).

Behavioral tests

Open Field Test (OFT): This test is used to evaluate behavioral responses such as motor activity, hyperactivity and exploratory behavior as well as measure anxiety. OFT is an indicator of the activity of the dopaminergic and glutamate systems. To perform this test, a white wooden cube with dimensions of 70 x 70 cm with a wall of 40 cm and divided into 25 squares of 14 x 14 cm was used. The behavior of the samples after 21 days of asthma induction was recorded by a video camera and the following parameters were measured for 5 minutes: 1) the duration of residence in central houses (O.F.C.T), 2) the number of central squares travelled (O.F.C.N), 3)) duration of residence in environmental houses (O.F.P.T) and 4) several environmental squares travelled (O.F.P.N).

Forced Swimming Test (FST): This test is one of the most common tests to check the level of depression and its possible mechanism. For this purpose, a glass cylinder with a height of 45 cm and a diameter of 30 cm was used, which contained water of 24 ± 1 degrees Celsius up to a depth of 30 cm. The duration of immobility (F.S.T.F) was measured and recorded with a chronometer for 5 minutes (31).

Data analysis

The results were analyzed using SPSS software and the Kolmogorov-Smirnov test was used to determine the normal distribution of the data. Data measurement was done based on one-way ANOVA followed by the Tukey post hoc test. The data were drawn as a

graph (Mean±SEM) and $p<0.05$ was considered as a statistically significant difference.

RESULTS

Placement time in central houses (O.F.C.T)

The average O.F.C.T in the control group is 41.86±4.53 seconds and in the asthmatic group it is 12.13±4.8 seconds, and there is a significant difference between these two groups at $p<0.01$. This average is 24.62 ± 4.27 seconds in samples treated with a dose of 50 mg/kg, which is not significantly different compared to the asthmatic group. This rate in the samples treated with a dose of 100 mg/kg is equal to 37.88 ± 9.16 seconds, which has a significant increase in $p < 0.01$ compared to the asthmatic group (Fig 1).

Number of shifts in central houses in open box test (O.F.C.N)

The average O.F.C.N in the control group is 29.43±3.7 and in the asthmatic group is 2±0.9, and there is a significant difference between these two groups (p<0.001). This average in samples treated with a dose of 50 mg/kg is equal to 13.33±2.57, which is significantly increased compared to the asthmatic group (p<0.001). This amount in the samples treated with a dose of 100 mg/kg is equal to 15.13 ± 3.73, which has a significant difference (p<0.001) compared to the asthmatic group (Fig 2).

At the time of establishment in O.F.P.T. environmental houses

The average O.F.P.T in the control group is 258 ± 4.53 seconds and in the asthmatic group it is 288.88 ± 4.53 seconds, and there is a significant difference between these two groups ($p < 0.01$). This average in samples treated with 50 mg/kg dose is 277.8 ± 3.74 seconds, which is not significantly different compared to the asthmatic group. This amount in samples treated with 100 mg/kg dose is equal to 268.7 ± 8.45 seconds, which has significantly decreased compared to the asthmatic group at $p<0.05$ (Fig 3).

The number of displacements in peripheral houses in the open box test (O.F.P.N.)

The average O.F.P.N in the control group is 125.71 ± 8.66 and the asthmatic group is 79.37 ± 5.78, and there is a significant difference between these two groups (p>0.001). This average in the samples treated with a dose of 50 mg/kg is 99±10.006, which is not significantly different compared to the asthmatic group. This amount in the samples treated with 100 mg/kg of purslane is 102.82±4.95, which has a significant increase in p<0.05 compared to the asthmatic group (Fig 4).

The duration of immobility in the forced swimming test (F.S.T.F.)

The average immobility time in the control group

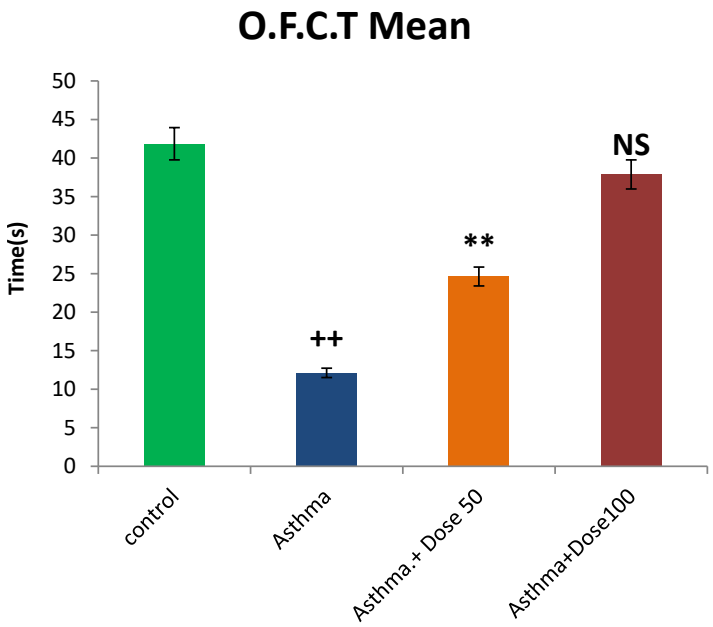


Fig1. Comparison of mean ± standard error, O.F.C.T of control, asthmatic and O.F.T group samples ++ represents the significance of the difference between the asthmatic group and the control group ($p < 0.01$).
** The significance of the difference between the asthmatic group and the recipient of purslane extract for the treatment of depression caused by it is ($p < 0.01$).

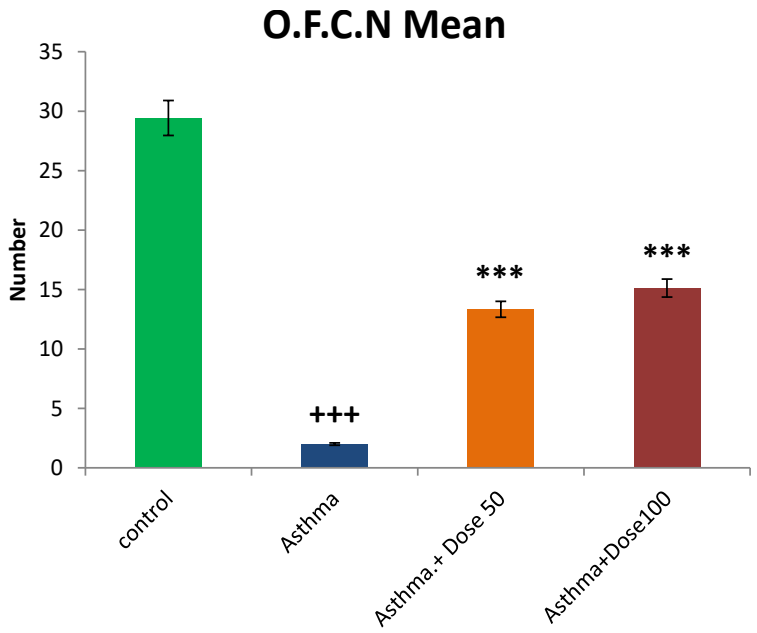


Fig 2. Comparison of mean ± standard error, O.F.C.N of control, asthmatic and treated group samples in O.F.T.
+++ represents the significance of the difference between the asthmatic group and the control group (p>0.001).
*** Indicates the significance of the difference between the asthmatic group and the recipient of purslane extract for the treatment of depression caused by it, at the level of (p<0.001).

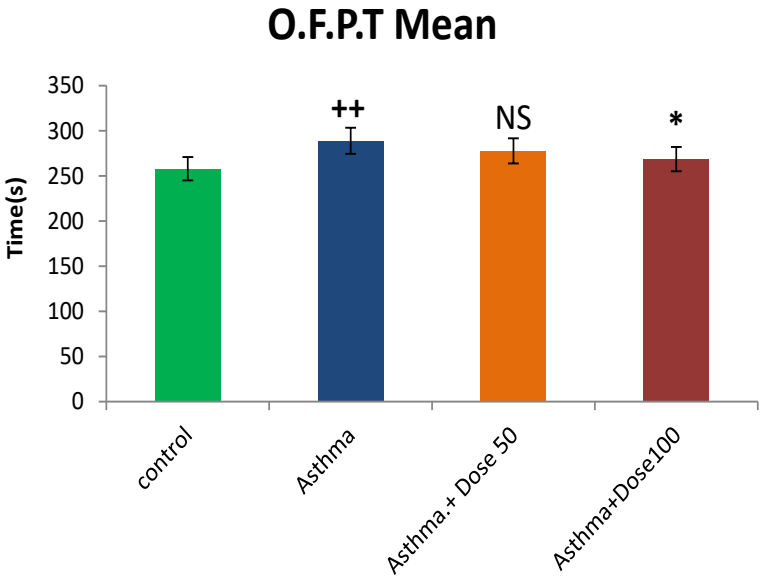


Fig 3. Comparison of mean ± standard error, O.F.P.T of control, asthmatic and treated samples in O.F.T.
++ represents the significance of the difference between the asthmatic group and the control group (p < 0.01).
* The significance of the difference between the asthmatic group and the recipient of purslane extract for the treatment of depression caused by it is (p < 0.05).
= NS indicates no significant difference.

is 12.22±5.82 seconds and in the asthmatic group is 77.33±20.13 seconds, and there is a significant difference between these two groups at $p<0.001$. This average is 33.71 ± 12.15 in the samples treated with 50 mg/kg dose, which is a significant difference at $p<0.05$ compared to the asthmatic group. This amount in samples treated with 100 mg/kg dose is equal to 18.33 ± 3.48 seconds, which has a significant difference of $p<0.001$ compared to the asthmatic group (Fig 5).

DISCUSSION

According to the results of this study, it was

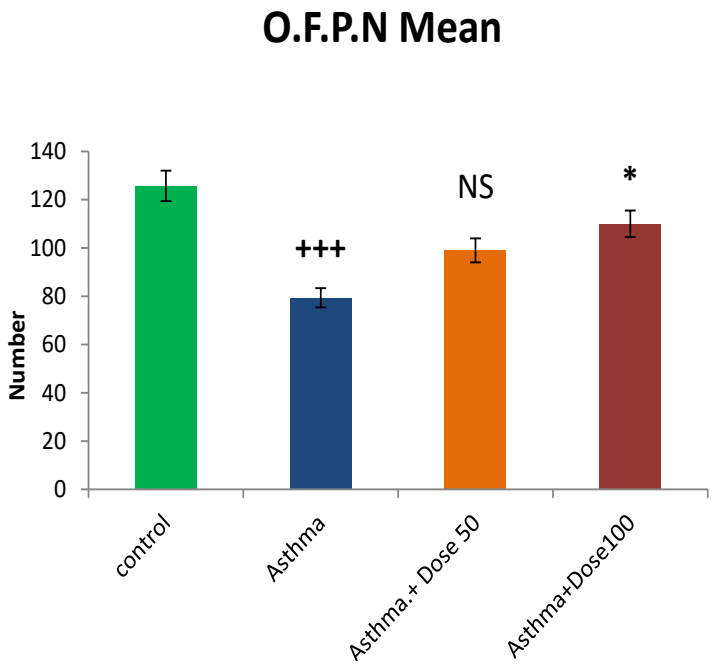


Fig 4. Comparison of mean ± standard error, O.F.P.N of control, asthmatic and treated group samples in O.F.T.
+++ represents the significance of the difference between the asthmatic group and the control group ($p>0.001$).
* The significance of the difference between the asthmatic group and the recipient of purslane extract for the treatment of depression caused by it is ($p<0.05$).
= NS indicates no significant difference.

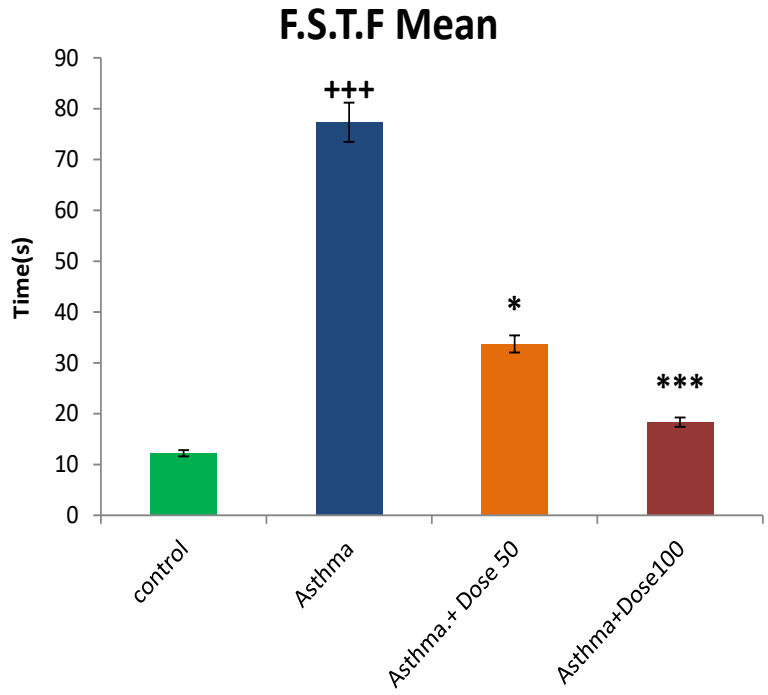


Fig 5. Comparison of mean ± standard error, F.S.T.F of control, asthmatic and treated samples in F.S.T.
+++ represents the significance of the difference between the asthmatic group and the control group ($p>0.001$).
* The significance of the difference between the asthmatic group and the recipient of purslane extract for the treatment of depression caused by it is ($p< 0.05$).
*** Indicates the significance of the difference between the asthmatic group and the recipient of purslane extract for the treatment of depression caused by it, at the level of ($p<0.001$).

observed that the aqueous-alcoholic extract of purslane can significantly reduce the symptoms of depression

factor that controls the expression of inflammatory mediators such as iNOS, COX-2, IL-8, IL-6, IL-1β,

caused by asthma induction. The results of FST and OFT indicate an increase in depression and anxiety in asthmatic samples compared to the control group, which is consistent with other studies. According to the results of this study, the improvement of these symptoms was observed after intraperitoneal administration of purslane aqueous-alcoholic extract. According to the research of Milady et al., the anti-anxiety effects of purslane have been reported to be dose-independent (32).

Recent research has shown that plants that are rich in antioxidant compounds can show anti-anxiety and anti-depressant effects (33). The body's antioxidant defense system includes enzymatic components such as catalase and non-enzymatic components such as vitamins E and C (34). Coenzyme Q10 acts as a strong antioxidant in scavenging free radicals and plays a role in the production of other key antioxidants such as vitamins C and E (35). Omega-3 fatty acids inhibit the production of IL-1β and TNF-α, which are inflammatory mediators in asthma and depression. It also reduces the production of leukotrienes by blocking the metabolism of arachidonic acid. Leukotrienes are potent inducers of bronchospasm, airway edema, mucus secretion, and inflammatory cell migration in asthma (36). Due to their antioxidant and anti-inflammatory properties, flavonoids play a role in modulating Th2-induced inflammation (37). Flavonoids are inhibitors of monoamine oxidases A or B, with quercetin having MAO-A inhibitory activity (38, 25). Also, studies have shown that apigenin is a flavonoid compound with sedative, anti-anxiety and anti-depressant properties that exerts its pharmacological properties by binding to GABA-A receptors (27).

According to the results obtained in this research, depression in the samples with experimental asthma has decreased to a favorable extent, which is probably due to the presence of antioxidants that are abundant in the purslane plant.

According to the results of OFT, experimental asthma induction has led to a decrease in the duration of presence and the number of movements of asthmatic group samples in central houses compared to the control group, which is probably a sign of depression. This decrease in motor activity is probably caused by the decrease in dopamine in the brain (37). Aqueous-alcoholic extract of the purslane plant has led to an increase in the presence of samples in central houses and a decrease in the presence of samples in peripheral houses, which may be due to its effects through synaptic modulation of monoaminergic neurotransmitters in brain regions (36). Also, in this research, we see a significant increase in immobility in the FST in the asthma group compared to the control group, which probably indicates the occurrence of depression due to asthma induction, which is in line with other studies.

One of the important mechanisms in the treatment of asthma and depression is to pay attention to removing inflammation and reducing oxidative stress. The inflammasome is a multi-protein complex that plays a role in the development of systemic inflammation that causes airway depression and hypersensitivity (16). Its activation is a two-step process that leads to the production of IL-1β through the activation of the NFκB pathway (39). NFκB is an oxidative-sensitive factor that controls the expression of inflammatory mediators such as iNOS, COX-2, IL-8, IL-6, IL-1β, and TNFα. NFκB is a transcription factor that plays an important role in proliferation, apoptosis, inflammation and immunity. Melatonin is one of the important antioxidants of purslane, which acts as an anti-inflammatory agent by modulating the NFκB signaling pathway. Also, melatonin modulates the inflammatory pathway by inhibiting the release of TNF-α (40, 39). On the other hand, studies show that antidepressants reduce oxidative stress by inhibiting the expression of pro-inflammatory cytokines such as TNFα (41).

According to the results obtained in this research, the purslane plant has been able to reduce the amount of depression caused by asthma induction due to the presence of these compounds. According to the epidemiological studies and overlap of the common mechanisms between asthma and depression and the antioxidant and anti-inflammatory effects of purslane, while improving the symptoms of depression, it probably also improves the symptoms of asthma. Based on this, the use of purslane in asthmatic patients can be considered a candidate for replacing synthetic drugs after conducting confirmatory studies.

Acknowledgements

The researchers are grateful to all the experts and personnel of the Biology Department of Islamic Azad University of Mashhad who have cooperated in this research.

Authors's Contribution

Ali Neamati: data curation; editing and review. Najmeh Khatun Dehnavi: investigation and writing. All authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable.

REFERENCES

1.Horak F, Doberer D, Eber E, Horak E, Pohl W, Riedler J et al. Diagnosis and management of asthma–Statement on the 2015 GINA Guidelines. Wiener klinische Wochenschrift 2016; 128(15-16): 541-554.

2.Mauad T, Bel EH, Sterk PJ. Asthma therapy and airway remodeling. Journal of allergy and clinical immunology 2007; 120(5):997-1009.

3.Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss M. World Allergy Organization (WAO) white book on allergy. Wisconsin: World Allergy Organisation 2011.

4.Heidarnia MA, Entezari A, Moein M, Mehrabi Y, Pourpak Z. Prevalence of asthma symptom in Iran: a meta-analysis. Research in Medicine 2007; 31(3): 217-225.

5.Kim HY, DeKruyff RH, Umetsu DT. The many paths to asthma: phenotype shaped by innate and adaptive immunity. Nature immunology 2010; 11(7): 577.

6.Martinez FD. Genes, environments, development and asthma: a reappraisal. European Respiratory Journal 2007; 29(1): 179-184.

7.Miller RL, Ho SM. Environmental epigenetics and asthma: current concepts and call for studies. American journal of respiratory and critical care medicine 2008; 177(6):567-573.

8.Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. Archives of general psychiatry 2003; 60(11): 1125-1130.

9.Opolski M, Wilson I. Asthma and depression: a pragmatic review of the literature and recommendations for future research. Clinical Practice and Epidemiology in Mental Health 2005; 1(1): 18.

10.Chun TH, Weitzen SH, Fritz GK.. The asthma/mental health nexus in a population-based sample of the United States. CHEST Journal 2008; 134(6):1176-1182.

11.Dunbar F. Mind and Body: Psychosomatic Medicine 1948.

12.Goldney R, Ruffin R, Fisher L, Wilson D. Asthma symptoms associated with depression and lower quality of life: a population survey 2003.

13.Zielinski TA, Brown ES, Nejte, VA, Khan DA, Moore JJ, Rush AJ. Depression in asthma: prevalence and clinical implications. Primary care companion to the Journal of clinical psychiatry 2000;2(5): 153.

14.Valenç AM, Falcão R, Freire RC, Nascimento I, Nascentes R, Zin WA et al. The relationship between the severity of asthma and comorbidites with anxiety and depressive disorders. Revista Brasileira de Psiquiatria 2006; 28(3):206-208.

15.Sagols E, Priymenk N. Oxidative stress in dog with heart failure: the role of dietary fatty acids and antioxidants. Veterinary medicine international 2011.

16.Haneklaus M, O'neill LA. NLRP3 at the interface of metabolism and inflammation. Immunological reviews 2015; 265(1): 53-62.

17.Baines KJ, Backer V, Gibson PG, Powel H, Porsbjerg CM. Impaired lung function is associated with systemic inflammation and macrophage activation. European Respiratory Journal 2015;45(2): 557-559.

18.Morjaria JB, Babu KS, Vijayanand P, Chauhan AJ, Davies DE, Holgate ST. Sputum IL-6 concentrations in severe asthma and its relationship with FEV1. Thorax, thx 2010.

19.Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. CHEST Journal 2012; 142(1): 86-93.

20.Liu L, Howe P, Zhou YF, Xu ZQ, Hocart C, Zhang R. Fatty acids and β-carotene in Australian purslane (Portulaca oleracea) varieties. Journal of chromatography a 2000; 893(1): 207-213.

21.Samy J, Sugumaran M, Lee KL. Herbs of Malaysia: an introduction to the medicinal, culinary, aromatic and cosmetic use of herbs. Times Editions. 2005.

22.Yan J, Sun LR, Zhou ZY, Chen YC, Zhang WM, Dai HF, Tan JW. Homoisoflavonoids from the medicinal plant Portulaca oleracea. Phytochemistry 2012; 80: 37-41.

23. Okafor IA, Ayalokunrin MB, Orachu LA. A review on Portulaca oleracea (Purslane) plant–Its nature and biomedical benefits. Int J Biomed Res 2014 ; 5(2): 75-80.

24. Brian R.Urban Edibles: Weeds 2012.

25. Jalali sf, baradaran m, mahdinezhad sm, roushan t. Effect of Coenzyme-Q10 in Congestive Heart Failure 2010.

26.Alam MA, Juraimi AS, Rafii MY, Abdul Hamid A, Aslani F, Hasan MM et al. Evaluation of antioxidant compounds, antioxidant activities, and mineral composition of 13 collected purslane (Portulaca oleracea L.) accessions. BioMed research international 2014.

27.Hongyan W, Songli W, Qunce H. Advance in the Research of Portulaca oleracea L. (Wild Vegetable) [J]. Chinese Agricultural Science Bulletin 2004; 2, 010.

28.Simopoulos AP, Tan DX, Manchester LC, Reiter RJ. Purslane: a plant source of omega-3 fatty acids and melatonin. Journal of pineal research 2005; 39(3): 331-332.

29.Keyhanmanesh R, Alipour MR, Ebrahimi H, Aslani

MR. Effects of Diet-Induced Obesity on Tracheal Responsiveness to Methacholine, Tracheal Visfatin Level, and Lung Histological Changes in Ovalbumin-Sensitized Female Wistar Rats. Inflammation 2018; 41(3): 846-858.
30.Ahmadi M, Rahbarghazi R, Soltani S, Aslani MR, Keyhanmanesh R. Contributory anti-inflammatory effects of mesenchymal stem cells, not conditioned media, on ovalbumin-induced asthmatic changes in male rats. Inflammation 2016; 39(6): 1960-1971.
31.Wang Z, Gu J, Wang X, Xie KL, Wan N, Liu D. Antidepressant-like activity of resveratrol treatment in the forced swim test and tail suspension test in mice: the HPA axis, BDNF expression and phosphorylation of ERK. Pharmacology Biochemistry and Behavior 2013; 112: 104-110.
32.MILADI GH, Rashidipour A, Ghorbani R. Antinociceptive effects of the aqueous extracts of Portulaca oleracea seeds in mice 2005.
33.KHOSRAVI H, RAHNEMA M, ASLE RM. Anxiolytic and antidepressant effects of tarragon (Artemisia dracunculus L.) hydroalcoholic extract in male rats exposed to chronic restraint stress 2017.
34.Hosseinzadeh H, Sadeghnia HR. Safranal, a constituent of Crocus sativus (saffron), attenuated cerebral ischemia induced oxidative damage in rat hippocampus. J Pharm Pharm Sci 2005; 8(3): 394-399.
35.Jalali sf, baradaran m, mahdinezhad sm, roushan t. Effect of Coenzyme-Q10 in Congestive Heart Failure 2010.
36. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Experimental biology and medicine 2008; 233(6):674-688.
37.Gonzalez R, Ballester I, López-Posadas R, Suárez MD, Zarzuelo A, Martinez-Augustin O et al.. Effects of flavonoids and other polyphenols on inflammation. Critical reviews in food science and nutrition 2011;51(4): 331-362.
38.Jäger AK, Saaby L. Flavonoids and the CNS. Molecules 2011; 16(2):1471-1485.
39.Favero G, Franceschetti L, Bonomini F, Rodella LF, Rezzani R. Melatonin as an anti-inflammatory agent modulating inflammasome activation. International journal of endocrinology 2017.
40.Kaltschmidt B, Kaltschmidt C. NF-KappaB in long-term memory and structural plasticity in the adult mammalian brain. *Frontiers in molecular neuroscience* 2015; *8*: 69.
41.Novío S, Núñez MJ, Amigo G, Freire-Garabal M. Effects of fluoxetine on the oxidative status of peripheral blood leucocytes of restraint-stressed mice. Basic & clinical pharmacology & toxicology 2011; 109(5): 365-371.

Spring 2025, Volume 10, Issue 37 (9- 19) DOI: 10.22034/pmj.2025.2057922.1056

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

The Positive Impacts of Artificial Intelligence in Anesthesia and Anesthesia Technology

Ezzadeen Hadi Mohammad Al Kaiati[1,*]

[1]Bart Al-Anan Hospital, Sana, Yemen

ARTICLE INFO

Paper Type: Review Article

Submitted: 2025-02-17

Accepted: 2025-05-28

Keywords:
Artificial Intelligence (AI)
Anesthesia
Anesthesiology
Machine Learning
Predictive Tools

Corresponding author:
Ezzadeen Hadi Mohammad Al Kaiati, Bart Al-Anan Hospital, Sana, Yemen.
Email: ezzadeenhadi@gmail.com.

ABSTRACT

Artificial Intelligence (AI) is profoundly transforming healthcare, with its impact becoming increasingly evident across various medical disciplines. The most promising and novel applications of AI are found in anesthesiology, where it is enhancing patient safety, clinical decision-making, and individualized care practices. Anesthesiologists face the complex task of maintaining anesthetic stability throughout surgical procedures, where even variations in patient parameters can lead to adverse outcomes. In this context, AI is emerging as a powerful tool that enhances the precision and effectiveness of anesthetic operations.

The function of AI in anesthesiology includes several essential areas, such as improving operating room safety and tailoring medication dosages to the specific needs of individual patients. AI systems employ advanced machine learning algorithms to examine vast data from real-time physiological monitoring devices, such as heart rate, blood pressure, oxygen saturation, and respiratory rate. These devices can detect subtle changes in vital signs, providing early warnings of potential outcomes and supplying clinicians with evidence-based treatment alternatives.

Moreover, AI is substantially enhancing the personalization of anesthetic administration. By evaluating patient-specific characteristics, including demographics, medical history, and genetic predispositions, AI systems can predict optimal medication dosages, mitigating risks of under- or overdose and enhancing recovery times. Furthermore, AI-driven predictive analytics can forecast patient-specific risks, including the likelihood of adverse reactions or postoperative complications, allowing anesthesiologists to execute preventive measures.

This research aims to analyze the various ways in which AI is enhancing anesthesiology, encompassing sophisticated monitoring systems, predictive tools, and personalized treatment strategies. The advancement of AI significantly enhances anesthetic treatments, promising safer, more efficient, and highly tailored patient care in both surgical and non-surgical contexts.

How to Cite this Article:
E.H.M. Al Kaiati, "EThe Positive Impacts of Artificial Intelligence in Anesthesia and Anesthesia Technology" Personalized & Precision Medicine Journal, Vol. 10, no. 37, pp. 9- 19.

INTRODUCTION

Anesthesia is essential to modern surgery, guaranteeing that patients undergo treatments without pain, worry, or awareness. Over the decades, physicians have perfected the process of sedating or producing coma in patients while preserving vital physiological functions (1, 2). Anesthesiologists depend on their knowledge, expertise, and diverse monitoring systems to maintain this fragile balance throughout surgery. As healthcare systems evolve and embrace data-driven approaches, artificial intelligence signifies a new technological frontier (3). Artificial intelligence is becoming essential in anesthesiology, with substantial opportunity to improve anesthesia in novel ways. Anesthesia equilibrates sedation, analgesia, and essential parameters such as blood pressure, heart rate, and oxygen saturation. Effectively monitoring these factors in real-time while anticipating and addressing changes or dangers during surgery is arduous (4). The expertise and discernment of anesthesiologists have been crucial throughout history. The intricacy of modern surgical methods and the growing amount of data gathered during operations present novel obstacles (5).

Artificial intelligence is becoming an essential tool for tackling these challenges, enhancing human proficiency. Artificial intelligence, particularly machine learning (ML) and deep learning algorithms, can analyze vast quantities of data and discern

patterns that clinicians might miss (6). In the realm of anesthesia, AI can evaluate patient data in real-time, including vital signs, laboratory results, and historical medical information, to provide predictive insights and recommendations. This expertise aids anesthesiologists in making more informed decisions, reducing human error, and improving the safety and efficiency of anesthesia (7).

Artificial intelligence has considerably enhanced anesthesiology, particularly in patient monitoring. Anesthesiologists must monitor patients' vital signs and modify anesthetic dosages during the surgical procedure (8). Traditional monitoring methods provide critical data; nevertheless, anesthesiologists are required to manually adjust parameters according to their evaluation. AI-driven systems can evaluate this data and provide real-time change recommendations. AI algorithms can evaluate heart rate variability, oxygen saturation, and blood pressure to detect hypotension, arrhythmias, and respiratory distress at an early stage (9).

Anesthesiologists can utilize AI monitoring systems to respond more swiftly and accurately, thereby enhancing patient outcomes and reducing adverse events. Advancements in AI enable the oversight and personalization of pharmaceutical distribution (10). Age, weight, medical history, genetics, and immediate physiological responses influence each patient's responsiveness to anesthetic agents. Traditional anesthesia dosing use established formulas or clinical judgment to estimate dosage. However, underdosing may result in consciousness or discomfort during the treatment, while overdose may lead to prolonged drowsiness or other side effects, but AI systems can examine patient data and change anesthetic drug dosages more precisely, ensuring that each patient receives the proper amount of anesthesia (11).

Artificial intelligence can customize anesthetic protocols based on body composition, metabolic rates, and genetic predispositions, thereby reducing the risks associated with conventional doses. Moreover, AI is crucial in predicting possible issues. Artificial intelligence can detect adverse events such as postoperative nausea and vomiting, respiratory depression, and cardiovascular complications during surgery by utilizing previous patient data and predictive analytics (12). These predictive models are constructed using vast datasets that encompass a diverse array of attributes, enabling them to assess certain risks with enhanced accuracy. Artificial intelligence assists anesthesiologists in mitigating patient risk by identifying vulnerable patients promptly and adjusting anesthetic dosages or incorporating additional monitoring techniques (13).

Although AI is altering anesthesia, it is not meant to replace anesthesiologists. AI is intended to enhance the job of these proficient personnel. Anesthesiologists leverage artificial intelligence, together with their extensive knowledge, clinical expertise, and human discernment, to render swifter and more precise decisions (14). AI liberates anesthesiologists to concentrate on clinical decision-making and patient care by executing routine and data-intensive anesthesia administration responsibilities. Anesthesiologists collaborate with AI to enhance patient care and establish a safety net, relying on human expertise for complex decision-making (15).

AI is enhancing anesthesiology through advancements in monitoring, drug administration, and risk evaluation. These innovations are enhancing the safety, efficiency, and personalization of anesthesia. The utilization of AI in anesthesia will undoubtedly increase as healthcare advances, enabling anesthesiologists to provide optimal care with contemporary technology. Artificial intelligence is enhancing human expertise, enabling anesthesiologists to deliver more certain and accurate care, hence improving surgical outcomes (16).

Enhancing Patient Safety Through Predictive Analytics

Anesthesiology's foremost priority is patient safety, as it manages essential physiological functions during surgery, where any departure may lead to grave outcomes. Anesthesiologists have proficiently administered sedation, analgesia, and autonomic modulation for decades using their expertise, experience, and traditional monitoring devices (17). These systems provide real-time vital indicators such as heart rate, blood pressure, oxygen saturation, and breathing rate to aid anesthesiologists in decision-making. Conventional monitors are advantageous; yet, they merely present data without the ability to foresee changes. Modern anesthesiology is undergoing a transformation thanks to artificial intelligence (18).

AI systems demonstrate talents that extend beyond just data presentation, unlike traditional displays. They gather, assess, and scrutinize substantial amounts of real-time patient data to discern patterns and trends that clinicians may neglect. The predictive capacity of AI has the potential to improve patient safety. AI systems can alert clinicians to identify risks before they intensify, enabling preventative measures and preventing negative results. Anesthesiology has advanced considerably with this anticipatory method, providing insights that surpass human perception (19).

Various AI algorithms can forecast a reduction in blood pressure (hypotension) 10 to 15 minutes in advance. Anesthetic drugs often induce hypotension, a significant influence on the circulatory system during anesthesia. Upon detecting hypotension in

a standard setting, the patient may be at risk and necessitate immediate action. AI can alert physicians to small trends and fluctuations in vital signs, enabling them to adjust anesthetic dosages, inject fluids, or do other corrective actions prior to a significant drop in blood pressure. AI's ability to predict hypotension is one way it can aid anesthesiologists in making safe, educated judgments (20).

Artificial intelligence systems can assess oxygen saturation and respiratory patterns to detect hypoxia and respiratory depression. Anesthesia poses risks of respiratory complications, including compromised breathing or oxygenation, particularly in individuals with preexisting respiratory conditions or during high-risk interventions (21). Traditional monitoring techniques may detect hypoxia or respiratory depression too late to avert catastrophic consequences. Conversely, AI can detect nuanced changes in respiratory data, such as reductions in oxygen saturation or anomalies in breathing patterns, and notify clinicians before to the emergence of serious consequences. This enables swift interventions, such as adjusting ventilator parameters or providing supplemental oxygen, which can significantly reduce the risk of adverse outcomes (22).

AI-driven monitoring systems anticipate conditions beyond hypotension and hypoxia. They also evaluate heart rate variability, hydration balance, and temperature. AI technologies provide a holistic view of the patient's physiological state in real-time, allowing anesthesiologists to identify many concerns. This extensive monitoring method represents a notable progression, enabling anesthesiologists to navigate the complexities of anesthesia with enhanced accuracy and agility (23).

The application of AI in anesthesiology signifies a transition from reactive to proactive healthcare. An alternative viewpoint that analyzes, assesses, and predicts functions as auxiliary support. The ability of AI to identify patterns in health data and derive insights from extensive databases of patient outcomes renders it powerful. These computers are taught on comprehensive clinical data to improve their predictions and offer insights derived from a wider range of experiences than any single clinician. Deep learning empowers AI systems to discern nuanced trends or anomalies, granting them a competitive advantage (24).

Artificial intelligence is designed to continuously monitor these indicators, ensuring perpetual patient supervision during procedures. Anesthesiologists may encounter cognitive overload after extended or complex procedures, but AI stays impervious to such effects. It offers clinicians an ongoing safety net by monitoring, processing, and predicting dangers in real-time, enabling them to respond decisively and efficiently under duress (25).

Smarter Drug Delivery and Real-Time Adjustments

The anesthesia procedure lacks standardization. Age, body mass, sex, pre-existing health issues, metabolic rate, and genetic factors affect individual reactions to anesthetic drugs. Selecting the appropriate anesthetic kind, dosage, and administration rate necessitates clinical acumen and expertise. Even the most experienced clinicians may make minor errors that can lead to considerable adverse outcomes, such as under-sedation, resulting in intraoperative awareness and discomfort, or over-sedation, which can prolong recovery time, induce respiratory depression, cause cardiovascular instability, or trigger other complications. This complex balance is where (AI) reveals its most compelling advantages (26).

Artificial intelligence in closed-loop drug delivery systems signifies a leading achievement in anesthesiology. Real-time physiological data from patients is employed to autonomously modify anesthetic medication distribution. Closed-loop systems analyze patient data such as heart rate, blood pressure, oxygen saturation, and electroencephalographic signals (EEG), including the Bispectral Index (BIS) for assessing anesthetic depth, on a per-second basis, in contrast to manual titration techniques (27). AI-driven algorithms assess this data to guarantee the precise administration of anesthetic dosages throughout treatment, hence ensuring patient safety and comfort. Closed-loop devices maintain a stable anesthetic concentration and prevent both over- and under-dosing by responding to patient feedback in real-time. Artificial intelligence surpasses simple automation. Personalized anesthetic delivery is essential. Standard anesthesia techniques generally utilize population-average methods, neglecting specific patient factors that could affect medication responses (28).

AI algorithms can utilize electronic health records, biometric data, pharmacogenomic profiles, and previous anesthetic history to formulate personalized anesthesia programs. Genetic differences in liver enzymes like CYP2D6 or CYP3A4 may affect drug metabolism, leading to unexpected increases or decreases in blood concentrations. Artificial intelligence can evaluate genetic data and real-time physiological information to swiftly discover unexpected reactions or drug sensitivities (29). Customization enhances safety and efficacy. Individuals with a sluggish metabolism are protected from excessive sedation, while rapid metabolizers are defended against insufficient anesthetic. AI can also incorporate medication clearance comorbidities, such as renal or hepatic diseases, hence improving dosing precision and safety. This method reduces intraoperative and postoperative problems, drug interactions, and

recovery time while improving outcomes (30).

Moreover, AI can enhance preoperative planning by analyzing prediction models based on numerous similar patient characteristics. Anesthesiologists can evaluate optimal induction agents, maintenance procedures, and emergence techniques before the patient's arrival. AI can recommend anesthesia approaches that have demonstrated efficacy for similar patient cohorts by leveraging comprehensive information from prior instances, so minimizing variability and enhancing consistency in complex or high-risk patients (31).

In summary, artificial intelligence is transforming the management and personalization of anesthetic medications for individual patients. Employing advanced closed-loop technologies and individualized predictive analytics, AI optimizes drug delivery on a minute-by-minute basis according to each patient's physiological and genetic traits. This reduces side effects, accelerates recovery, and enhances surgical outcomes while increasing anesthetic precision and safety. As artificial intelligence progresses, its incorporation into anesthesia management will certainly become widespread, revolutionizing a crucial component of surgical care (32).

Improving Preoperative Evaluation

Preparing a patient for surgery is a complex procedure that involves more than simple instructions such as fasting or filling out paperwork. The process entails a thorough medical evaluation to determine a patient's suitability for anesthesia, recognize potential dangers, and guarantee optimal readiness for the procedure. Traditional evaluations are labor-intensive and rely on the physicians' knowledge and experience to examine the patient's medical history, test outcomes, imaging, and additional health data. Any neglected aspect may lead to operational difficulties, including anesthetic responses or undetected medical issues that affect outcomes. The growing intricacy of healthcare is making the preparing phase progressively more difficult. Artificial Intelligence is transforming this phase (33).

Artificial intelligence is transforming preoperative assessment by optimizing data analysis, improving precision, and retrieving critical information. Contemporary AI models can analyze extensive datasets in within seconds, whereas physicians may require an hour. This entails analyzing detailed medical histories, diagnostic test outcomes, imaging examinations, and physician documentation to ascertain risks or conditions that could compromise anesthetic or surgical procedures. AI systems can analyze data from diverse sources to assess a patient's health and discover both explicit and subtle risk factors (34).

An essential component of preoperative examination is the assessment of the patient's risk for anesthesia-related problems, sometimes utilizing a scoring system such as the American Society of Anesthesiologists (ASA) physical status classification system. This technique assesses patients based on their medical history, comorbidities, and physical state. An AI model can swiftly deliver an accurate ASA score by examining medical data and detecting diseases such as obstructive sleep apnea, heart failure, and extreme obesity. AI aids anesthesiologists in adjusting anesthetic dosages or choosing safer drugs for individual patients by predicting probable dangers (35).

In addition to predicting ASA values, AI can anticipate the influence of medical problems on anesthetic administration. Individuals with obstructive sleep apnea may necessitate certain anesthetics to avert respiratory issues or challenges in sustaining oxygen levels during sleep. Anesthesia can impose strain on the heart and circulatory system; therefore, patients with heart failure may necessitate careful fluid management and cardiovascular support during surgical interventions. AI models can identify these illnesses and suggest anesthetic strategies based on the patient's risk evaluation. This allows anesthesiologists to make data-driven decisions and adjust anesthetic procedures to improve patient safety and surgical outcomes (36).

A significant benefit of employing AI in preoperative evaluation is its speed and dependability. Clinical practitioners specialize in analyzing patient data; nevertheless, the vast volume of information they must evaluate might result in time limitations and oversight. Artificial intelligence can rapidly examine vast databases, discerning trends and threats. AI can evaluate a patient's medical information, laboratory findings, and imaging results in seconds, thus saving practitioners hours. This speed preserves time and guarantees that no facts are missed, offering clinicians a thorough and up-to-date assessment of the patient's operational readiness (37).

The consistency of AI in employing designated algorithms and criteria ensures the uniformity of preoperative assessments across patients. AI is unbiased, ensuring that every patient is assessed consistently, unlike humans, who may be swayed by weariness, personal biases, or previous experiences. This ensures that all patients receive a standardized and thorough preoperative evaluation, hence mitigating errors in clinical decision-making (38).

Artificial intelligence enhances communication among surgical teams. AI can alert anesthesiologists, surgeons, and nurses to potential complications prior to the patient's entry into the operating room by delivering precise, data-driven suggestions and risk assessments. This collaborative, AI-augmented method improves patient care coordination and proactivity (39).

Artificial intelligence have the capacity to improve

long-term patient outcomes and facilitate swift advancements in preoperative assessments. AI aids clinicians in accurately and promptly detecting risk factors, facilitating preemptive interventions. Preventive techniques include enhancing the patient's medical management before to surgery, adjusting anesthesia protocols to reduce risks, and requesting further testing or consultations. This leads to enhanced efficiency, expedited recoveries, and a decrease in postoperative problems (40).

Ultimately, AI is augmenting the efficacy, accuracy, and consistency of preoperative assessments. Artificial intelligence can forecast risks, compute clinical scores such as the ASA score, and generate personalized anesthetic plans by analyzing comprehensive patient data in real-time. This improves therapy and patient safety by identifying and addressing potential hazards prior to operation. As AI technology advances, its role in preoperative evaluation will certainly expand, optimizing surgical preparation and improving patient outcomes across diverse surgical procedures (41).

Improving Preoperative Assessment

Preparing for surgery encompasses more than merely abstaining from food and completing documentation. It involves a comprehensive medical assessment to ascertain a patient's eligibility for anesthesia, identify risks, and ensure optimal operational preparedness. Conventional assessments are time-consuming and depend on physicians' expertise and experience to evaluate the patient's medical history, test results, imaging, and other health information (42). Any overlooked factor may result in operational challenges, including anesthesia reactions or undiagnosed medical conditions that influence outcomes. The increasing complexity of healthcare is rendering the preparatory phase increasingly challenging. Artificial intelligence is revolutionizing this stage (43).

AI is revolutionizing preoperative evaluation by streamlining data analysis, enhancing accuracy, and extracting essential information. Contemporary AI models can evaluate extensive datasets in within seconds, whereas physicians may require an hour. Uncovering dangers or conditions that could complicate anesthesia or surgery, requires examining thorough medical histories, laboratory findings, imaging scans, and doctor's notes. AI systems can evaluate data from various sources to assess a patient's health and identify both overt and nuanced risk factors (44).

Assessing the patient's risk for anesthesia-related complications via the American Society of ASA physical status categorization system is essential for preoperative evaluation. This system evaluates patients based on their medical history, comorbidities, and physical condition. An AI model can rapidly provide an accurate ASA score by analyzing medical data and identifying conditions such as obstructive sleep apnea, heart failure, and severe obesity. AI assists anesthesiologists in modifying anesthetic dosages or selecting safer medications for specific patients by forecasting potential risks (44).

In addition to predicting ASA values, AI can anticipate how medical conditions may affect anesthetic administration. Individuals with obstructive sleep apnea may require specific anesthetics to prevent respiratory complications or difficulties in maintaining oxygen levels throughout sleep. Anesthesia can exert stress on the heart and circulatory system; hence, individuals with heart failure may require meticulous fluid management and cardiovascular assistance during surgical procedures. AI models can diagnose these disorders and recommend anesthetic treatments tailored to the patient's risk profile. This enables anesthesiologists to make data-informed judgments and modify anesthesia protocols to enhance patient safety and surgical results (45). The rapidity and reliability of AI preoperative assessment render it attractive. Clinical professionals excel at interpreting patient data; however, the extensive volume of information they must analyze can lead to time constraints and oversight. Artificial Intelligence can analyze extensive datasets instantaneously, identifying patterns and potential threats. Artificial intelligence may assess a patient's medical data, laboratory reports, and imaging results within seconds, thereby conserving hours for clinicians. This velocity conserves time and ensures no details are overlooked, providing clinicians with a comprehensive and current evaluation of the patient's operational preparedness. The consistency of AI in implementing established algorithms and criteria guarantees the standardization of preoperative evaluations among patients. AI is impartial, guaranteeing that each patient is evaluated uniformly, in contrast to humans, who may be influenced by fatigue, personal prejudices, or prior experiences. This guarantees that all patients undergo an identical comprehensive preoperative assessment and mitigates clinical decision-making errors (46).

AI enhances surgical team communication. AI can notify anesthesiologists, surgeons, and nurses of potential issues before the patient enters into the operating room by providing clear, data-driven recommendations and risk evaluations. This collaborative, AI-enhanced approach enhances patient care coordination and proactivity. Artificial intelligence has the potential to enhance patient outcomes in the long term and to immediately refine preoperative evaluations. AI assists clinicians in identifying risk variables with greater precision and timeliness, enabling proactive interventions. Preventive strategies encompass optimizing the patient's medical therapy before to surgery, modifying

anesthetic protocols to mitigate hazards, and soliciting supplementary testing or consultations. This results in more efficient processes, quicker recoveries, and a reduction in postoperative complications (47).

Ultimately, artificial intelligence is enhancing the speed, precision, and consistency of preoperative evaluations. Artificial intelligence can predict risks, calculate clinical scores such as the ASA score, and provide individualized anesthetic plans by analyzing extensive patient data in real-time. This enhances treatment and patient safety by recognizing and mitigating any hazards before the surgery. As AI technology progresses, its function in preoperative assessment will undoubtedly increase, streamlining surgical preparation and enhancing patient outcomes across many surgical procedures (48).

Real-Time Monitoring and Intelligent Alerts

A notable and transformative application of Artificial Intelligence (AI) in the operating room (OR) is its ability to enhance patient monitoring. Traditional monitoring systems have been crucial in alerting clinicians to changes in vital signs, such as heart rate, blood pressure, oxygen saturation, and respiration rate. These systems are mostly reactive, alerting physicians only when a certain metric above a predefined threshold, such as when blood pressure falls below a designated level or oxygen saturation drops to critical levels. While these signals are essential for patient safety, their ability to detect urgent issues prior to reaching a critical phase may be limited. AI-enhanced monitoring solutions improve oversight by providing a more sophisticated, predictive approach that enables earlier intervention and more precise management (49). AI-enhanced monitoring systems surpass the basic function of simply alerting when a parameter has achieved a perilous level. These systems are designed to analyze patterns and detect subtle differences in real-time data, offering critical insights into the patient's state prior to the activation of alarms by traditional monitors. Through the continuous analysis of data from several sources—such as electrocardiograms (ECG), blood pressure readings, respiratory patterns, and temperature fluctuations AI systems can identify emerging issues that may not be apparent from singular measurements alone. For example, AI can detect nuanced variations in a patient's heart rate, indicating the initial onset of arrhythmias or ischemic events (reduced blood supply to the heart), even when other vital signs stay within normal ranges. These early warnings are essential for allowing physicians to intervene before to the exacerbation of problems, so preventing potentially life-threatening complications (50).

Standard ECG monitoring may fail to detect an abnormal rhythm or signs of myocardial ischemia if the results are subtle or the patient is asymptomatic. AI-driven ECG monitors can assess the patterns of the heart's electrical activity over time, detecting even little deviations that may indicate the emergence of an issue. This predictive capability enables clinicians to undertake preventative measures, adjusting anesthetic agents or administering medications to stabilize the patient's condition prior to a critical state. Prompt recognition and action significantly improve patient outcomes, especially in complex procedures where cardiovascular stability is essential (51). In addition to enhancing early detection, AI plays a crucial role in reducing false alarms, a common issue in traditional monitoring systems. In the operating room, false alarms may arise from multiple sources, including motion artifacts (patient movement), technical faults, or brief fluctuations in vital signs that do not indicate a legitimate problem. Although these false alarms are primarily intended to protect patients, they can be vexatious and lead to alarm fatigue—a condition in which doctors become desensitized to frequent alerts, occasionally dismissing or postponing responses to legitimately critical signals. This desensitization may ultimately result in delayed or inappropriate responses during a genuine emergency (52).

AI-enhanced monitoring systems mitigate this problem by evaluating the context of vital sign variations, distinguishing between genuine physiological changes and clinically irrelevant anomalies. For example, AI can identify that a temporary drop in blood pressure may be attributed to the patient's shift in position or a specific stage of anesthesia, rather than an actual cardiovascular failure. By removing these false positives, AI reduces unnecessary alarms and allows clinicians to focus on the most crucial and time-sensitive events, hence improving productivity and alleviating stress in the operating room setting (53).

This enhanced monitoring alleviates physician fatigue, especially during extended or complex procedures that need prolonged focus. Anesthesiologists and surgical teams sometimes oversee multiple aspects of patient care simultaneously during extended procedures. The presence of AI systems that consistently evaluate and highlight significant changes enables therapists to concentrate on high-priority tasks instead of being burdened by routine oversight. The ability of AI to provide concise, actionable insights improves decision-making, hence increasing the overall efficiency of the surgical team (54).

The reduction of alert fatigue is a notable benefit of AI-driven monitoring systems. Traditional alarms can be onerous, especially when they trigger repeatedly during complex processes. Therapists may get desensitized to the constant stream of signals over time, leading to delayed responses or, in certain cases, missed opportunities for intervention. AI mitigates this

problem by prioritizing notifications based on clinical significance and providing more context. An AI system may categorize alerts by urgency, ensuring that the most critical events are swiftly brought to the doctor's attention, while minimizing distractions from trivial or non-urgent fluctuations in patient data. This improves clinicians' concentration and promotes the overall safety and responsiveness of the team (55).

AI-enhanced monitoring devices facilitate personalized therapy by adapting to the distinct baseline and characteristics of each patient. Every patient is distinct, and AI systems may continuously adjust their thresholds and monitoring parameters based on particular factors such as age, comorbidities, medications, and previous surgeries. This allows AI to deliver more tailored recommendations, taking into account the patient's specific needs and circumstances, which is particularly vital in high-risk surgeries or for patients with complex medical histories (56).

Personalized Anesthetic Care: A Shift toward Precision

Anesthesiology utilizes established protocols for pharmacological selection, dosage calculation, and monitoring methods. These overarching standards have promoted patient safety and uniformity, however they often overlook patient variation. Indeed, every patient is distinct. Age, weight, metabolic rate, genetics, prior health issues, concurrent medications, psychological state, and surgical environment all affect anesthetic response. Thus, an anesthetic strategy that is successful for one patient may provide hazards for another. Artificial intelligence in anesthesiology is evolving from a standardized protocol methodology to precision anesthetic therapy customized for individual patients (57).

Artificial intelligence may examine extensive datasets of anonymised health records from thousands or millions of individuals with machine learning techniques. These databases often include demographic information, laboratory findings, physiological reactions to anesthesia, intraoperative complications, recovery outcomes, and long-term postoperative data. By recognizing trends in the responses of analogous individuals to diverse anesthetic medications and methodologies, AI can construct predictive models to guide decisions for new patients. These recommendations are based not solely on assumptions or clinical intuition, but on comprehensive, data-driven evaluations grounded in actual clinical outcomes (58).

Artificial intelligence may identify that volatile anesthetics and opioids are more likely to cause respiratory difficulties in elderly individuals with chronic obstructive pulmonary disease and congestive heart failure. This evidence indicates that AI can recommend regional anesthetics, short-acting medicines, or improved respiratory monitoring to reduce risk and improve postoperative recovery (59). A young, healthy adult undergoing a standard outpatient procedure may endure a broader range of anesthetics and advantage from a rapid-onset, rapid-offset protocol that enables same-day discharge. These customized insights are especially advantageous in high-risk or complex scenarios, where little changes in medication choice or dosage could affect patient safety and recovery. Besides preoperative planning, AI enables intraoperative adjustments (30).

AI can recommend dose titration or agent substitution by employing real-time physiological data during surgery, such as heart rate variability, blood pressure trends, oxygen saturation, and BIS index scores. This adaptability ensures sufficient anesthetic depth, reducing intraoperative consciousness and averting excessive sedation or hemodynamic instability. The conduct of each patient throughout surgery can aid AI in delivering enhanced recommendations for analogous circumstances (60). Pharmacogenomics, the study of how genetic variations affect drug metabolism, constitutes a compelling domain in AI-driven personalization. Many anesthetics are metabolized by hepatic enzymes, particularly those in the CYP450 family, which demonstrate considerable diversity (61). Rapid metabolizers necessitate increased or more frequent dosages, while slow metabolizers demonstrate greater susceptibility to drug buildup and toxicity. Pharmacogenomic data can aid AI in developing more precise anesthetic dose protocols. Future anesthetic strategies may integrate preoperative genetic testing, with AI analyzing the data to offer recommendations that reduce problems and improve efficacy (62).

Furthermore, precision anesthesiology surpasses pharmacology. Artificial intelligence can forecast and regulate preoperative anxiety, postoperative nausea and vomiting (PONV), and the onset of delirium. Artificial intelligence can identify at-risk patients and provide non-pharmacological interventions, such as music therapy or cognitive-behavioral support, in conjunction with medical management to improve surgical outcomes and patient satisfaction by analyzing behavioral and psychological indicators. AI-driven tailored anesthetic therapy signifies a substantial advancement in anesthesiology (63). Artificial intelligence empowers physicians to provide personalized care via data analysis, real-time monitoring, and the incorporation of patient-specific information. This modification enhances safety, mitigates issues, accelerates recovery, and facilitates precision medicine. With the advancement and integration of AI technology into clinical workflows, precision anesthesiology will become achievable and vital for providing optimal surgical care (64).

The Future of AI in Anesthesia

The future of anesthesiology is optimistic owing to breakthroughs in artificial intelligence that will transform anesthetic administration, surveillance, and oversight. Once confined to science fiction, robots that aid in decision-making, diagnose issues, and tailor to particular patient needs are rapidly becoming a clinical reality. AI technologies are expected to be progressively integrated into the anesthetic process, acting as a vital, intelligent companion during the perioperative journey (65).

The amalgamation of wearable technologies with remote monitoring systems signifies a potential progression for the future. AI-driven platforms will oversee a patient's physiological data before and after surgery as wearable biosensors progress. To evaluate preoperative risk, AI may examine a patient's heart rate variability, oxygen saturation, sleep quality, physical activity, and stress levels in the days preceding a procedure. These devices can detect delirium, respiratory depression, and pain crises postoperatively, enabling prompt interventions and a more efficient recovery at home. This promotes the progression of perioperative precision medicine, which customizes care during surgical interventions (66).

Voice-activated surgical suites signify a further advancement. Natural language processing and machine learning will empower anesthesiologists to employ voice commands for the management of monitors, drug delivery systems, and medical records during surgical procedures. The clinical emphasis is maintained while improving efficiency, sterility, and cognitive burden. Imagine an anesthesiologist directing the AI, "Increase propofol infusion by 10%," or "Exhibit BIS trend for the last 20 minutes," with the AI responding swiftly. Integrations will enhance workflow and situational awareness in critical environments (67).

Explainable AI will progress markedly. Unlike "black-box" algorithms that provide recommendations without context, XAI systems offer transparent and interpretable explanations. An XAI model may not suggest a lower anesthetic dosage but instead assert, "Given this patient's age, BMI, renal function, and genetic profile, there is a 30% increased risk of delayed drug clearance, indicating a reduced dosage." Effective communication cultivates clinician trust, improves understanding, and ensures that AI supports clinical decision-making (68).

In anesthesiology, immediate judgments can significantly impact lives; therefore, practitioners must have faith in their tools. Artificial intelligence is expected to broaden its impact in the realms of education and training. AI-powered virtual simulators will allow anesthesiology residents and trainees to emulate realistic surgical circumstances, including unusual complications and emergencies, inside an interactive and adaptive learning environment. These devices provide objective performance assessments to improve training quality and standardize education. Artificial intelligence can aid professionals in recognizing their strengths and weaknesses in competency-based assessments, therefore guiding their professional development (69). AI technologies are expected to be integrally incorporated into Clinical Decision Support Systems, Electronic Health Records, and robotic surgical platforms as they advance. AI-driven anesthetic systems may ultimately manage sedative levels, modify drug dosages on a minute-by-minute basis, and coordinate with robotic surgeons to improve timing and precision. These autonomous systems will be supervised; yet, their capacity to do repetitive, data-intensive activities with accuracy will alleviate weariness and improve precision in extended or intricate operations (70).

Artificial intelligence could become as essential to anesthesiology as the stethoscope, monitor, and syringe, augmenting their functionality. Healthcare professionals will utilize AI to improve data analysis, decision-making, and patient management throughout treatment. It will function as a meticulous assistant, adept at continuously analyzing patterns, assimilating insights from prior cases, and producing customized recommendations for unique patient profiles in real-time. This sophisticated support system will improve patient outcomes by addressing difficulties, accelerating recovery times, and enhancing safety, while simultaneously strengthening provider confidence through the use of state-of-the-art technologies (71).

Ultimately, artificial intelligence in anesthesiology will augment human capabilities rather than merely automate procedures. Anesthesiologists will provide more tailored, efficient, and educated care using advanced tools for analyzing, forecasting, and meeting patient demands. Artificial intelligence will provide accuracy, collaboration, and advancement in anesthetic care as it becomes increasingly integrated into clinical practice (72).

CONCLUSION

Artificial Intelligence is transforming the field of anesthesia not by replacing practitioners, but by augmenting their talents. Artificial intelligence improves anesthesia via sophisticated monitoring, tailored drug delivery, predictive analytics, and automated support, leading to enhanced safety, efficiency, and personalization. As with any nascent technology, meticulous deployment, continuous evaluation, and ethical oversight are essential. The trajectory is clear: the future of anesthetic treatment will entail a partnership between human expertise and advanced technologies, presenting considerable advantages for both

practitioners and their patients.

Acknowledgment

The author is grateful to all the experts of the Bart Al-Anan Hospital, Sana, Yemen who have cooperated in this research.

Authors's Contribution

Ezzadeen Hadi Mohammad Al Kaiati: Conceptualization and writing.The author read and confirmed the final manusctipt.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable.

REFERENCES

1.Häggström M, Brodin K. The meaning of being conscious during surgery with local or regional anesthesia–A phenomenological hermeneutic study. International Journal of Nursing Studies Advances. 2024;7:100224.

2.Aagaard N, Aasvang EK, Meyhoff CS. Discrepancies between Promised and Actual AI Capabilities in the Continuous Vital Sign Monitoring of In-Hospital Patients: A Review of the Current Evidence. Sensors (Basel, Switzerland). 2024;24(19).

3.Davoud SC, Kovacheva VP. On the Horizon: Specific Applications of Automation and Artificial Intelligence in Anesthesiology. Current anesthesiology reports. 2023;13(2):31-40.

4.Moran T, Kaye A, Mai A, Bok L. Sedation, Analgesia, and Local Anesthesia: A Review for General and Interventional Radiologists. Radiographics : a review publication of the Radiological Society of North America, Inc. 2013;33:E47-60.

5.Harfaoui W, Alilou M, El Adib AR, Zidouh S, Zentar A, Lekehal B, et al. Patient Safety in Anesthesiology: Progress, Challenges, and Prospects. Cureus. 2024;16(9):e69540.

6.Rashidi HH, Pantanowitz J, Hanna MG, Tafti AP, Sanghani P, Buchinsky A, et al. Introduction to Artificial Intelligence and Machine Learning in Pathology and Medicine: Generative and Nongenerative Artificial Intelligence Basics. Modern Pathology. 2025;38(4):100688.

7.Kambale M, Jadhav S. Applications of artificial intelligence in anesthesia: A systematic review. Saudi journal of anaesthesia. 2024;18(2):249-56.

8.Singhal M, Gupta L, Hirani K. A Comprehensive Analysis and Review of Artificial Intelligence in Anaesthesia. Cureus. 2023;15(9):e45038.

9.Singh M, Nath G. Artificial intelligence and anesthesia: A narrative review. Saudi journal of anaesthesia. 2022;16(1):86-93.

10.Allam H. Prescribing the Future: The Role of Artificial Intelligence in Pharmacy. Information [Internet]. 2025; 16(2).

11.Parihar S, Shah P, Sekhar R, Lagoo J. Model Predictive Control and Its Role in Biomedical Therapeutic Automation: A Brief Review. Applied System Innovation [Internet]. 2022; 5(6).

12.Huang L, Huhulea EN, Abraham E, Bienenstock R, Aifuwa E, Hirani R, et al. The Role of Artificial Intelligence in Obesity Risk Prediction and Management: Approaches, Insights, and Recommendations. Medicina [Internet]. 2025; 61(2).

13.Singam A. Revolutionizing Patient Care: A Comprehensive Review of Artificial Intelligence Applications in Anesthesia. Cureus. 2023;15(12):e49887.

14.Hashimoto DA, Witkowski E, Gao L, Meireles O, Rosman G. Artificial Intelligence in Anesthesiology: Current Techniques, Clinical Applications, and Limitations. Anesthesiology. 2020;132(2):379-94.

15.El-Tallawy SN, Pergolizzi JV, Vasiliu-Feltes I, Ahmed RS, LeQuang JK, El-Tallawy HN, et al. Incorporation of "Artificial Intelligence" for Objective Pain Assessment: A Comprehensive Review. Pain and Therapy. 2024;13(3):293-317.

16.Shukla A, Salma A, Patel D, David John J, Kantamneni R, Patel T, et al. Harnessing Artificial Intelligence (AI) in Anaesthesiology: Enhancing Patient Outcomes and Clinical Efficiency. Cureus. 2024;16(11):e73383.

17.Gaba DM. Anaesthesiology as a model for patient safety in health care. BMJ (Clinical research ed). 2000;320(7237):785-8.

18.Novita D, Adikusuma FW, Rohadi N, Wibawa BM, Trisanto A, Defi IR, et al. Development of contactless human vital signs monitoring device with remote-photoplethysmography using adaptive region-of-interest and hybrid processing methods. Intelligence-Based Medicine. 2024;10:100160.

19.Al Kuwaiti A, Nazer K, Al-Reedy A, Al-Shehri S, Al-Muhanna A, Subbarayalu AV, et al. A Review of the Role of Artificial Intelligence in Healthcare. Journal of personalized medicine. 2023;13(6).

20.Michard F, Futier E. Predicting intraoperative hypotension: from hope to hype and back to reality. British Journal of Anaesthesia. 2023;131(2):199-201.

21.Al-Anazi S, Al-Omari A, Alanazi S, Marar A, Asad M, Alawaji F, et al. Artificial intelligence in respiratory care: Current scenario and future perspective. Annals of

thoracic medicine. 2024;19(2):117-30.
22.Rehouma H, Noumeir R, Essouri S, Jouvet P. Advancements in Methods and Camera-Based Sensors for the Quantification of Respiration. Sensors [Internet]. 2020; 20(24).
23.Michard F, Mulder MP, Gonzalez F, Sanfilippo F. AI for the hemodynamic assessment of critically ill and surgical patients: focus on clinical applications. Annals of intensive care. 2025;15(1):26.
24.Lopes S, Rocha G, Guimarães-Pereira L. Artificial intelligence and its clinical application in Anesthesiology: a systematic review. Journal of clinical monitoring and computing. 2024;38(2):247-59.
25.Cascella M, Tracey MC, Petrucci E, Bignami EG. Exploring Artificial Intelligence in Anesthesia: A Primer on Ethics, and Clinical Applications. Surgeries [Internet]. 2023; 4(2):[264-74 pp.].
26.DiMaria S, Mangano N, Bruzzese A, Bartula B, Parikh S, Costa A. Genetic Variation and Sex-Based Differences: Current Considerations for Anesthetic Management. Current issues in molecular biology. 2025;47(3).
27.Cai X, Wang X, Zhu Y, Yao Y, Chen J. Advances in automated anesthesia: a comprehensive review. Anesthesiology and Perioperative Science. 2025;3(1):3.
28.Wang X, Zhu Y, Yao Y, Chen J. Advances in automated anesthesia: a comprehensive review. Anesthesiology and Perioperative Science. 2025;3.
29.Zeng S, Qing Q, Xu W, Yu S, Zheng M, Tan H, et al. Personalized anesthesia and precision medicine: a comprehensive review of genetic factors, artificial intelligence, and patient-specific factors. Frontiers in medicine. 2024;11:1365524.
30.Zeng S, Qing Q, Xu W, Yu S, Zheng M, Tan H, et al. Personalized anesthesia and precision medicine: a comprehensive review of genetic factors, artificial intelligence, and patient-specific factors. 2024;Volume 11 - 2024.
31.Li S, Liu X, Chen X, Xu H, Zhang Y, Qian W. Development and Validation of an Artificial Intelligence Preoperative Planning and Patient-Specific Instrumentation System for Total Knee Arthroplasty. Bioengineering [Internet]. 2023; 10(12).
32.Zhang Z, Duan Y, Lin J, Luo W, Lin L, Gao Z. Artificial intelligence in anesthesia: insights from the 2024 Nobel Prize in Physics. Anesthesiology and Perioperative Science. 2025;3(1):5.
33.Chellam Singh B, Arulappan J. Operating Room Nurses' Understanding of Their Roles and Responsibilities for Patient Care and Safety Measures in Intraoperative Practice. SAGE open nursing. 2023;9:23779608231186247.
34.Bekbolatova M, Mayer J, Ong CW, Toma M. Transformative Potential of AI in Healthcare: Definitions, Applications, and Navigating the Ethical Landscape and Public Perspectives. Healthcare (Basel, Switzerland). 2024;12(2).
35.Yoon SB, Lee J, Lee H-C, Jung C-W, Lee H. Comparison of NLP machine learning models with human physicians for ASA Physical Status classification. npj Digital Medicine. 2024;7(1):259.
36.Chang JL, Goldberg AN, Alt JA, Mohammed A, Ashbrook L, Auckley D, et al. International Consensus Statement on Obstructive Sleep Apnea. International forum of allergy & rhinology. 2023;13(7):1061-482.
37.Maleki Varnosfaderani S, Forouzanfar M. The Role of AI in Hospitals and Clinics: Transforming Healthcare in the 21st Century. Bioengineering (Basel, Switzerland). 2024;11(4).
38.Ueda D, Kakinuma T, Fujita S, Kamagata K, Fushimi Y, Ito R, et al. Fairness of artificial intelligence in healthcare: review and recommendations. Japanese journal of radiology. 2024;42(1):3-15.
39.Solanki SL, Pandrowala S, Nayak A, Bhandare M, Ambulkar RP, Shrikhande SV. Artificial intelligence in perioperative management of major gastrointestinal surgeries. World journal of gastroenterology. 2021;27(21):2758-70.
40.Gala D, Behl H, Shah M, Makaryus AN. The Role of Artificial Intelligence in Improving Patient Outcomes and Future of Healthcare Delivery in Cardiology: A Narrative Review of the Literature. Healthcare (Basel, Switzerland). 2024;12(4).
41.Li P, Wang Y, Zhao R, Hao L, Chai W, Jiying C, et al. The Application of artificial intelligence in periprosthetic joint infection. Journal of Advanced Research. 2025.
42.Harrison M, Pellechi J, DuBois S. Updates to Thoracic Procedures: Perioperative Care and Anesthetic Considerations. In: Ng Pellegrino A, Stawicki SP, editors. Updates in Anesthesia - The Operating Room and Beyond. Rijeka: IntechOpen; 2022.
43.Bajwa J, Munir U, Nori A, Williams B. Artificial intelligence in healthcare: transforming the practice of medicine. Future healthcare journal. 2021;8(2):e188-e94.
44.Bekbolatova M, Mayer J, Ong CW, Toma M. Transformative Potential of AI in Healthcare: Definitions, Applications, and Navigating the Ethical Landscape and Public Perspectives. Healthcare [Internet]. 2024; 12(2).
45.Melesse DY, Mekonnen ZA, Kassahun HG, Chekol WB. Evidence based perioperative optimization of patients with obstructive sleep apnea in resource limited areas: A systematic review. International Journal of Surgery Open. 2020;23:23-34.
46.Harris J, Matthews J. Artificial Intelligence: Predicting Perioperative Problems. British journal of hospital medicine (London, England : 2005). 2024;85(8):1-4.
47.Bellini V, Russo M, Domenichetti T, Panizzi M, Allai S, Bignami EG. Artificial Intelligence in Operating Room Management. Journal of medical systems.

2024;48(1):19.
48.Tsai F-F, Chang Y-C, Chiu Y-W, Sheu B-C, Hsu M-H, Yeh H-M. Machine Learning Model for Anesthetic Risk Stratification for Gynecologic and Obstetric Patients: Cross-Sectional Study Outlining a Novel Approach for Early Detection. JMIR Form Res. 2024;8:e54097.
49.Myatra SN, Jagiasi BG, Singh NP, Divatia JV. Role of artificial intelligence in haemodynamic monitoring. Indian journal of anaesthesia. 2024;68(1):93-9.
50.Soori M, Arezoo B, Dastres R. Artificial intelligence, machine learning and deep learning in advanced robotics, a review. Cognitive Robotics. 2023;3:54-70.
51.LaBoone PA, Marques O. Overview of the future impact of wearables and artificial intelligence in healthcare workflows and technology. International Journal of Information Management Data Insights. 2024;4(2):100294.
52.Zahradka N, Geoghan S, Watson H, Goldberg E, Wolfberg A, Wilkes M. Assessment of Remote Vital Sign Monitoring and Alarms in a Real-World Healthcare at Home Dataset. Bioengineering [Internet]. 2023; 10(1).
53.Tsvetanov F. Integrating AI Technologies into Remote Monitoring Patient Systems. Engineering Proceedings [Internet]. 2024; 70(1).
54.Montomoli J, Hilty MP, Ince C. Artificial intelligence in intensive care: moving towards clinical decision support systems. Minerva anestesiologica. 2022;88(12):1066-72.
55.Fernandes CO, Miles S, Lucena CJP, Cowan D. Artificial Intelligence Technologies for Coping with Alarm Fatigue in Hospital Environments Because of Sensory Overload: Algorithm Development and Validation. Journal of medical Internet research. 2019;21(11):e15406.
56.Visco V, Izzo C, Mancusi C, Rispoli A, Tedeschi M, Virtuoso N, et al. Artificial Intelligence in Hypertension Management: An Ace up Your Sleeve. Journal of cardiovascular development and disease. 2023;10(2).
57.Chen J, Ren W, Liu J, Fu Z, Yao Y, Chen X, et al. Feasibility of intelligent drug control in the maintenance phase of general anesthesia based on convolutional neural network. Heliyon. 2023;9(1):e12481.
58.Collins C, Dennehy D, Conboy K, Mikalef P. Artificial intelligence in information systems research: A systematic literature review and research agenda. International Journal of Information Management. 2021;60:102383.
59.Ivascu R, Torsin LI, Hostiuc L, Nitipir C, Corneci D, Dutu M. The Surgical Stress Response and Anesthesia: A Narrative Review. Journal of Clinical Medicine [Internet]. 2024; 13(10).
60.Chalasani SH, Syed J, Ramesh M, Patil V, Pramod Kumar TM. Artificial intelligence in the field of pharmacy practice: A literature review. Exploratory research in clinical and social pharmacy. 2023;12:100346.
61.Qahwaji R, Ashankyty I, Sannan NS, Hazzazi MS, Basabrain AA, Mobashir M. Pharmacogenomics: A Genetic Approach to Drug Development and Therapy. Pharmaceuticals [Internet]. 2024; 17(7).
62.Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. Genomics, proteomics & bioinformatics. 2016;14(5):298-313.
63.Hoshijima H, Miyazaki T, Mitsui Y, Omachi S, Yamauchi M, Mizuta K. Machine learning-based identification of the risk factors for postoperative nausea and vomiting in adults. PloS one. 2024;19(8):e0308755.
64.Sahu M, Gupta R, Ambasta RK, Kumar P. Chapter Three - Artificial intelligence and machine learning in precision medicine: A paradigm shift in big data analysis. In: Teplow DB, editor. Progress in Molecular Biology and Translational Science. 190: Academic Press; 2022. p. 57-100.
65.Xie BH, Li TT, Ma FT, Li QJ, Xiao QX, Xiong LL, et al. Artificial intelligence in anesthesiology: a bibliometric analysis. Perioperative medicine (London, England). 2024;13(1):121.
66.Liao Y, Thompson C, Peterson S, Mandrola J, Beg MS. The Future of Wearable Technologies and Remote Monitoring in Health Care. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting. 2019;39:115-21.
67.Le KDR, Tay SBP, Choy KT, Verjans J, Sasanelli N, Kong JCH. Applications of natural language processing tools in the surgical journey. Frontiers in surgery. 2024;11:1403540.
68.Antoniadi AM, Du Y, Guendouz Y, Wei L, Mazo C, Becker BA, et al. Current Challenges and Future Opportunities for XAI in Machine Learning-Based Clinical Decision Support Systems: A Systematic Review. Applied Sciences [Internet]. 2021; 11(11).
69.Komasawa N. Transformative Landscape of Anesthesia Education: Simulation, AI Integration, and Learner-Centric Reforms: A Narrative Review. Anesthesia Research [Internet]. 2024; 1(1):[34-43 pp.].
70.Ouanes K, Farhah N. Effectiveness of Artificial Intelligence (AI) in Clinical Decision Support Systems and Care Delivery. Journal of medical systems. 2024;48(1):74.
71.Li Y, Wang M, Wang L, Cao Y, Liu Y, Zhao Y, et al. Advances in the Application of AI Robots in Critical Care: Scoping Review. Journal of medical Internet research. 2024;26.
72.Meyer LM, Stead S, Salge TO, Antons D. Artificial intelligence in acute care: A systematic review, conceptual synthesis, and research agenda. Technological Forecasting and Social Change. 2024;206:123568.

Spring 2025, Volume 10, Issue 37 (20- 30) DOI: 10.22034/pmj.2025.2058093.1057

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Emerging Threats: Multidrug Resistance and Clinical Challenges of Acinetobacter spp. in Modern Healthcare

Azadeh Taftian[1,*], Neda Abedi[2], Ali Zolfi Gol[3]

[1]Department of Obstetrics and Gynecology, Kamali Hospital, Alborz University of Medical Sciences, Karaj, Iran.
[2]Department of Microbiology, North Branch of Azad University, Tehran, Iran.
[3]Department of Pediatrics, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran.

ARTICLE INFO

Paper Type: Review Article

Submitted: 2025-02-11
Accepted: 2025-05-25

Keywords:
MDR Acinetobacter baumannii
Multidrug resistance
Middle East
Carbapenem resistance
Novel therapeutics

Corresponding author:
Azadeh Taftian, Department of Obstetrics and Gynecology, Kamali Hospital, Alborz University of Medical Sciences, Karaj, Iran. Email: Azadehtaftian64@gmail.com.

ABSTRACT

Multidrug-resistant (MDR) bacteria, including *Acinetobacter baumannii*, have increased in healthcare systems, particularly in the Middle East. This bacterium is notoriously resistant to various medications, complicating disease therapy. The proliferation of XDR bacteria and the decline of effective antibiotics threaten patient safety and healthcare efficiency.

This study addresses the issues associated with MDR *Acinetobacter baumannii* in hospitals, especially in the Middle East. It examines the bacterium's epidemiology, molecular resistance mechanisms, clinical problems, and innovative treatment approaches.

We conducted a comprehensive study by searching PubMed, Scopus, and Web of Science for research published from 2010 to 2024. The investigation identified Middle Eastern research regarding the prevalence, resistance mechanisms, clinical care, and patient outcomes of MDR Acinetobacter baumannii. This study offers a comprehensive perspective on the escalating threat posed by this disease and its ramifications for regional healthcare professionals through the integration of qualitative and quantitative data.

Carbapenem-resistant *Acinetobacter baumannii* is common in 60–70% of Middle Eastern intensive care units and kills 40–50%. OXA-type carbapenemases, ESBLs, MBLs, efflux pump overexpression, target site changes, and biofilm formation make the bacterium resistant. We also found novel resistance determinants including bla_OXA-235 and regulatory gene alterations like adeRS. Overcrowded hospitals, long stays, antibiotic overuse, and poor infection control aggravate this issue. However, these issues are being fixed. Modern molecular diagnosis, ultraviolet disinfection, and genetic surveillance reduce these diseases. Increasing MDR *Acinetobacter baumannii* prevalence in the Middle East presents a difficult challenge that requires a coordinated, multidisciplinary approach. This pathogen's hazards can be reduced by improved antimicrobial stewardship, infection control, regional surveillance, and therapeutic development.

How to Cite this Article:
A. Taftian, N. Abedi, A. Zolfi Gol. "EEmerging Threats: Multidrug Resistance and Clinical Challenges of Acinetobacter spp. in Modern Healthcare" Personalized & Precision Medicine Journal, Vol. 10, no. 37, pp. 20- 30.

INTRODUCTION

Background and Clinical Significance

Acinetobacter species are a diverse group of Gram-negative bacteria that thrive in oxygen-rich environments and do not ferment sugars. These bacteria are found almost everywhere in nature soils, water, and even on plant surfaces. Their ability to survive in both natural and man-made environments makes them incredibly resilient and adaptable. Among this group, *Acinetobacter baumannii* stands out as particularly important in the medical field (1).

What makes *A. baumannii* so concerning is its ability to survive on a wide range of surfaces, including those found in hospitals. It can withstand drying out and resist many disinfectants, which allow it to form colonies that are difficult to eliminate (2). This makes it a serious threat in healthcare settings, as the bacteria can contaminate various objects, such

as hospital equipment, ventilators, and even the hands and clothing of healthcare workers. As a result, *A. baumannii* can spread easily and become a dangerous hospital-acquired infection (3).

A. baumannii is associated with several serious illnesses. It is one of the leading causes of ventilator-associated pneumonia (VAP), and it is also frequently found in bloodstream infections (BSIs), urinary tract infections (UTIs), meningitis, and wound infections (4). This bacterium is especially dangerous for critically ill patients, particularly those who have undergone invasive procedures or have weakened immune systems. The growing number of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of A. baumannii over the past few decades has made treatment more complicated, and the outcomes less predictable (2).

The World Health Organization (WHO) has recognized *A. baumannii* as a priority pathogen due to the rising threat posed by these resistant strains. This designation highlights the urgent need for new treatments and more effective infection control strategies in hospitals to combat the increasing prevalence of this dangerous bacterium (5).

Focus on the Middle East

The genus Acinetobacter includes a diverse range of Gram-negative bacteria that are strictly aerobic and do not ferment sugars. These bacteria can be found all around us, in places like soil, water, and on plant surfaces. Thanks to their impressive resilience, they can thrive in both natural and man-made environments, making them highly adaptable to various conditions. Among the Acinetobacter species, Acinetobacter baumannii is particularly concerning in the medical field (6).

What makes *A. baumannii* so problematic is its ability to survive on a wide range of surfaces, including those commonly found in hospitals. It has an extraordinary ability to resist drying out and can withstand many disinfectants, which allows it to form colonies that are tough to eliminate. This makes it easy for the bacterium to spread through contaminated hospital equipment, ventilators, and even the hands and clothing of healthcare workers, turning it into a dangerous hospital-acquired infection (7).

Clinically, *A. baumannii* is linked to a variety of serious health conditions. It's often found in bloodstream infections (BSIs), urinary tract infections (UTIs), meningitis, and wound infections. One of its most concerning roles is as a major cause of ventilator-associated pneumonia (VAP), especially in critically ill patients who are intubated in intensive care units (ICUs). People in these vulnerable states especially those who've had invasive surgeries or have weakened immune systems are at high risk of infection, making *A. baumannii* a significant public health threat (4, 8).

Over the past few decades, the rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *A. baumannii* has made treatment options more limited and clinical outcomes more unpredictable. The World Health Organization (WHO) has designated *A. baumannii* as a priority pathogen due to the growing danger posed by these resistant strains. This classification highlights the urgent need for new treatment strategies and stronger infection control practices in healthcare settings to prevent the spread of this dangerous bacterium (9).

Epidemiology of MDR *A. baumannii* in the Middle East

Overview and Regional Trends

Recent studies across several countries in the Middle East namely Iran, Saudi Arabia, Egypt, and Lebanon have consistently shown that multidrug-resistant (MDR) Acinetobacter baumannii is a growing concern in hospitals. In intensive care units (ICUs), carbapenem resistance in *A. baumannii* strains has been found in 60% to 70% of cases, limiting treatment options and leading to poorer outcomes for patients. A study published in 2023 revealed that the overall hospital death rate for patients infected with MDR A. baumannii is around 45%, which is notably higher than for patients infected with strains that are susceptible to antibiotics (10).

In Iran, hospitals, especially tertiary care centers, have reported that up to 40% of ICU samples show resistance to multiple drugs. These outbreaks not only highlight the bacteria's ability to rapidly develop resistance but also point to gaps in infection control and antibiotic use. The situation in Iran makes it clear that there is an urgent need for faster diagnostic tools and targeted treatments to help prevent the continued spread of these resistant strains (11).

In Saudi Arabia, the problem is equally concerning, with some hospitals reporting resistance rates exceeding 70% in their ICUs. The situation is worsened by high mortality rates sometimes above 50%. Overcrowding, the overuse of broad-spectrum antibiotics and weaknesses in infection control practices are all contributing factors to the rise in resistance and the grim outlook for patients (12).

Egypt faces particular challenges, especially when it comes to ventilator-associated pneumonia (VAP). Many studies have shown that VAP, which is common in critically ill patients requiring mechanical ventilation, is often caused by MDR *A. baumannii* (13). This not only increases the risk of serious complications for patients but also puts additional strain on the healthcare system due to longer hospital stays and higher resource demands. The data from Egypt underscores the need for stronger infection control measures—such as improved

hand hygiene, better sterilization practices, and more effective antibiotic management.

Together, these findings paint a worrying picture of a public health crisis in the Middle East. The widespread presence of MDR *A. baumannii* in intensive care units, along with the growing number of patient deaths, calls for immediate action. It's clear that improving infection control, optimizing antibiotic use, and strengthening surveillance systems must be a priority to curb the spread of this dangerous pathogen and improve patient outcomes in the region. Only through collective, coordinated efforts can healthcare systems hope to control *A. baumannii* and protect public health (14).

Contributing Factors

Several interconnected factors contribute to the rise and rapid spread of MDR *Acinetobacter baumannii* in the Middle East, creating complex challenges for healthcare systems in the region. Here's a closer look at the key issues:

Overcrowded Hospitals and Limited Resources: In many Middle Eastern hospitals, especially those in densely populated urban areas, overcrowding is a major issue. Intensive care units (ICUs), in particular, struggle with a high patient-to-bed ratio. This congestion makes it difficult for healthcare workers to provide the necessary time and attention for effective infection control. Research from hospitals in Egypt, for example, shows that up to 75% of ventilator-associated pneumonia (VAP) cases are linked to MDR *A. baumannii*, a situation that's worsened by overcrowding and understaffing. On top of that, limited funding means that essential equipment like sterilization machines and rapid diagnostic tools are often outdated or unavailable, making it even harder to control infections effectively (15).

Prolonged Hospital Stays and Invasive Procedures: Patients with severe illnesses frequently endure prolonged hospital stays, during which they may require invasive interventions, such as mechanical ventilation or urine catheterization (16). Regrettably, these medical gadgets may serve as conduits for bacteria, such as A. baumannii, to infiltrate the body. The duration of a patient's hospital stay correlates positively with the likelihood of acquiring a nosocomial infection. Epidemiological data highlight the prevalence of infectious and febrile diseases, leading to frequent healthcare visits (17). Inadequate infection control methods during invasive procedures might undermine natural defenses, facilitating bacterial colonization and infection in patients (18, 19).

Unrestricted Use of Antibiotics: The extensive and frequently improper utilization of antibiotics significantly contributes to the emergence of antibiotic-resistant microorganisms. Numerous hospitals in the Middle East provide antibiotics without sufficient testing or microbiological investigation, hence fostering optimal circumstances for the proliferation of resistant bacteria. The situation is exacerbated by the accessibility of over-the-counter antibiotics and the prevalent habit of self-medication. The excessive or extended administration of antibiotics in patients elevates the risk of acquiring and disseminating *MDR A. baumannii* (20).

Inefficient Infection Control Measures: Efficient infection management is essential for averting the dissemination of resistant germs; yet, numerous hospitals in the region have difficulties in this domain. Factors contributing to the issue include substandard hand hygiene, irregular cleaning of hospital settings, and insufficient sterilization of medical instruments. Although several hospitals have commenced the utilization of advanced technology such as UV light disinfection, which has demonstrated a 30% reduction in environmental contamination, these practices remain inadequately adopted. The disparity between existing procedures and optimal criteria for infection control facilitates the ongoing proliferation of resistant pathogens (21).

Vulnerable Patient Populations: The Middle East exhibits a significant prevalence of chronic health disorders such as diabetes, cancer, and chronic kidney disease. Individuals with these conditions frequently possess compromised immune systems, rendering them more vulnerable to infections. In hospital environments, these susceptible patients face an elevated risk of acquiring MDR *A. baumannii*, potentially resulting in severe consequences and heightened mortality rates. The interplay of preexisting health conditions and exposure to intrusive interventions establishes a perilous loop, wherein infection and resistance perpetually escalate.

Collectively, these characteristics establish an environment conducive to the proliferation and persistence of MDR *A. baumannii*. A comprehensive approach is required to tackle this escalating issue, encompassing enhancements to hospital infrastructure, fortification of infection control protocols, enforcement of rigorous antibiotic stewardship programs, and prioritization of targeted treatments to safeguard the most at-risk patients (22).

Outbreaks and Surveillance

Multidrug-resistant *A. baumannii* has significantly affected the region, as evidenced by numerous epidemiological investigations. A recent epidemic in a prominent hospital in Tehran revealed that around 40% of ICU isolates exhibited resistance to various drugs. Subsequent analysis verified that these strains proliferated through clonal expansion, with certain strains harboring OXA-23 and OXA-51-like enzymes, which enhance their resistance. Comparable epidemics have been noted in Saudi Arabia, where patients frequently endure extended

hospitalizations—occasionally an extra 10 to 15 days attributable to infections induced by MDR *A. baumannii*. Regrettably, these prolonged durations are associated with elevated mortality rates, exacerbating the overall burden. Notwithstanding these concerning tendencies, a deficiency in cooperation persists regarding regional surveillance. Despite advancements in real-time genetic surveillance, the lack of defined standards throughout the region complicates consistent and effective problem resolution (23) (Table 1) .

Mechanisms Underpinning Multidrug Resistance

Acquisition of Resistance Genes

MDR Acinetobacter baumannii exhibits remarkable adaptability and can rapidly acquire antibiotic resistance due to its capacity for horizontal gene transfer with other bacteria. This mechanism, termed horizontal gene transfer (HGT), enables bacteria to exchange DNA, encompassing genes that confer antibiotic resistance. This exchange occurs through three primary methods:

Conjugation: This resembles a bacterial "handshake" between two bacteria. One bacteria can transfer a tiny segment of DNA, known as a plasmid, to another using a specialized structure called a conjugative pilus. These plasmids frequently possess antibiotic resistance genes. The bla_OXA-235 gene, which confers resistance to Carbapenem drugs in *A. baumannii*, can be transferred between bacteria via conjugation. The capacity to disseminate resistance genes enables *A. baumannii* to endure in antibiotic-laden environments, such as hospitals (29).

Transformation: In this process, *A. baumannii* acquires free DNA fragments from its environment, typically originating from deceased bacteria. By integrating these DNA fragments, the bacteria acquire novel resistance characteristics, complicating treatment efforts. *A. baumannii's* inherent capacity to assimilate exogenous DNA is crucial to the development of resistance to many antibiotics (30).

•**Transduction**: This technique resembles a virus functioning as a genetic delivery system. During transduction, a bacteriophage may inadvertently acquire DNA from its bacterial host, encompassing genes associated with antibiotic resistance. The virus subsequently introduces this DNA into a novel bacterium, disseminating resistance. Although less prevalent in *A. baumannii* compared to certain other bacteria, transduction remains a viable mechanism for the dissemination of resistance genes among bacterial populations (31). Collectively, these pathways render MDR A. baumannii a formidable pathogen in healthcare settings. Comprehending the mechanisms by which it disseminates its resistance genes is essential for devising strategies to halt the proliferation of antibiotic resistance and effectively address this escalating issue (32).

Together, these mechanisms make MDR *A. baumannii* a dangerous pathogen in hospitals. Understanding how it shares and spreads its resistance genes is crucial in finding ways to stop the spread of antibiotic resistance and better tackle this growing problem (33).

Intrinsic Resistance Mechanisms

β-Lactamase Production

Multidrug-resistant (MDR) Acinetobacter baumannii can evade many antibiotics, especially β-lactam antibiotics, by producing β-lactamases. These are special enzymes that break down and deactivate the antibiotics, such as penicillins, cephalosporins, and Carbapenems, which are usually essential for treating bacterial infections. By producing these enzymes, *A. baumannii* can survive even in the presence of antibiotics that would normally kill it (34). The main types of β-lactamases that help A. baumannii resist treatment are:

OXA-Type Carbapenemases: OXA-type carbapenemases are some of the most important β-lactamases in A. baumannii, especially because they make the bacteria resistant to Carbapenems antibiotics that are often used as a last line of defense against serious infections. There are a few main types of these enzymes, including:

Table 1. Summary of Epidemiology and Resistance Characteristics of MDR A. *baumannii* in the Middle East

Country	Carbapenem Resistance Rate	Mortality Rate (%)	Notable Resistance Mechanisms	Key Contributing Factors	Ref
Iran	~65%	~45%	OXA-23, OXA-51-like enzymes, ESBLs, MBLs	Overcrowded ICUs, prolonged hospital stays, invasive procedures	(21,22)
Saudi Arabia	~70%	>50%	OXA-23, overexpressed efflux pumps, mutations (e.g., adeRS)	High ICU occupancy, indiscriminate antibiotic use, suboptimal infection control	(23)
Egypt	~60%	~40–50%	OXA-type carbapenemases, robust biofilm formation	Overcrowded facilities, limited healthcare resources, high VAP rates	(24)
Lebanon	~55%	~45%	Emerging determinants (e.g., bla_OXA-235), OXA-23, genomic variants	Variable surveillance, suboptimal infection control, inconsistent antibiotic stewardship	(25)

•OXA-23, OXA-24/40, and OXA-58: These acquired carbapenemases are found in many multidrug-resistant *A. baumannii* strains and are primarily responsible for resistance to imipenem, meropenem, and doripenem, which are all powerful Carbapenems antibiotics.
•OXA-51-like Variants: These enzymes are a bit different because they are part of *A. baumannii*'s natural DNA, not something it has acquired. Although they don't have strong Carbapenems resistance on their own, they can become much more active when certain genetic elements, like ISAba1, are added. These elements act like "boosters," making the enzymes more powerful and helping the bacteria resist treatment (35).

The widespread spread of OXA-type carbapenemases has seriously limited the effectiveness of carbapenem drugs against *A. baumannii* infections, making these enzymes a significant contributor to the growing problem of antimicrobial resistance (36).

Extended-Spectrum β-Lactamases (ESBLs)

Extended-spectrum β-lactamases (ESBLs) are another major class of β-lactamases found in MDR *A. baumannii*. These enzymes provide resistance to third- and fourth-generation Cephalosporins, hence diminishing the efficacy of medications such as cefotaxime, ceftazidime, and Cefepime (37). The predominant ESBL families found in *A. baumannii* encompass:
• TEM-type (Temoneira) β-lactamases
• SHV-type (Sulfhydryl Variable) β-lactamases
•CTX-M-type (Cefotaximase) β-lactamases
β-lactamases
In contrast to carbapenemases, ESBL-producing *A. baumannii* strains may retain susceptibility to Carbapenems; nonetheless, their capacity to hydrolyze Cephalosporins considerably restricts treatment alternatives. The introduction of ESBLs, in conjunction with additional resistance mechanisms such as porin loss or efflux pump overexpression, complicates treatment further (37).

Metallo-β-Lactamases (MBLs)

Metallo-β-lactamases (MBLs) represent a significant threat among carbapenemases due to their ability to hydrolyze practically all β-lactam antibiotics, encompassing carbapenems, cephalosporins, and penicillins, except for monobactams such as aztreonam. These enzymes contrast with OXA-type carbapenemases as they necessitate divalent metal ions, such as zinc (Zn^{2+}), for their enzymatic function (38). The most clinically relevant MBLs in *A. baumannii* comprise:

•**NDM (New Delhi Metallo-β-lactamase)**: A formidable Carbapenemase that has been extensively spread in healthcare settings.

•**VIM (Verona Integron-encoded Metallo-β-lactamase)**: Commonly linked to integrons that enable the horizontal transmission of resistance genes.

•**IMP (Imipenemase-type Metallo-β-lactamase)**:

One of the first identified metallo-β-lactamases, responsible for imipenem resistance. Given that MBLs are not susceptible to inhibition by clavulanic acid or Sulbactam, conventional β-lactamase inhibitors are ineffectual against them. Nevertheless, they are vulnerable to zinc chelators (such as EDTA), which inhibit enzyme activity by removing vital metal ions (39).

CLINICAL IMPLICATIONS

The presence of many β-lactamase enzymes in a single strain of *A. baumannii* complicates treatment significantly, as these bacteria may demonstrate resistance to almost all β-lactam medicines. The extensive prevalence of OXA-type carbapenemases, ESBLs, and MBLs has resulted in the recurrent ineffectiveness of empirical antibiotic therapy, requiring the implementation of alternative or combination treatments such as:
• Polymyxins (Colistin and Polymyxin B)
•Tigecycline
•Combinations based on Sulbactam
Comprehending the function of β-lactamases in *A. baumannii* resistance is essential for informing antibiotic choice and formulating new β-lactamase inhibitors that can reinstate the efficacy of current β-lactam antibiotics (40).

Efflux Pump Overexpression

Efflux pumps actively expel antibiotics, reducing intracellular concentrations. The key systems are:

•**AdeABC System:** Composed of AdeA, AdeB, and AdeC, and is regulated by the AdeRS two-component system. Mutations in regulatory genes can lead to up to a fivefold increase in pump expression (41).

•**AdeIJK System:**Although constitutively expressed, this system is inducible under antibiotic stress and is crucial for intrinsic resistance (42).

Target Site Modifications

Mutations in target proteins decrease antibiotic binding:
•**Penicillin-Binding Proteins (PBPs):** Alterations reduce susceptibility to β-lactams (43).
•**DNA Gyrase and Topoisomerase IV:** Mutations in gyrA and parC confer resistance to fluoroquinolones (44).
•**Ribosomal Alterations:** Structural changes diminish aminoglycoside binding (45).

Reduced Membrane Permeability

Downregulation or modification of outer membrane proteins (e.g., CarO and OmpA) limits drug uptake, working in tandem with efflux mechanisms (46).

Biofilm Formation

Biofilms act as a physical and metabolic barrier, protecting bacterial communities from antibiotics and immune responses. Advanced imaging studies have detailed the structure of *A. baumannii* biofilms and the role of extracellular polymeric substances (EPS) in impeding drug penetration (47).

Detailed Analysis of Resistance Mechanisms

β-Lactamase Production

Recent research employing genomic and proteomic studies has found new variants of OXA-type carbapenemases, including OXA-235. These changes, together with insertion sequences such as ISAba1, markedly augment resistance. The simultaneous occurrence of ESBLs and MBLs restricts therapeutic options by inactivating a wide range of β-lactams (48).

Mechanisms of Efflux Pumps

The overexpression of efflux pumps is a crucial element in the emergence of multidrug resistance. A quantitative study showed that mutations in the AdeRS regulation system lead to substantial enhancements in efflux pump activity, hence decreasing the intracellular concentration of pharmaceuticals. Recent studies on efflux pump inhibitors (EPIs) indicate that preclinical results may show possible reductions in minimum inhibitory concentrations (MICs) when these inhibitors are used in conjunction with traditional therapies (49).

Amendments Concerning the Membrane and the Designated Location

A correlation exists between mutations in penicillin-binding proteins (PBPs), DNA gyrase, and topoisomerase IV, and elevated minimum inhibitory concentrations (MICs) for certain pharmaceuticals. Moreover, proteomic analyses have demonstrated that resistant strains often have diminished levels of outer membrane proteins, such as CarO and OmpA, thereby limiting the quantity of medication that can be assimilated by the organism (50).

The Mechanisms of Biofilm Development

The formation of biofilm complicates treatment by establishing antibiotic gradients and promoting bacterial persistence. Recent studies employing confocal microscopy have elucidated the three-dimensional structure of *A. baumannii* biofilms, underscoring the significance of extracellular polymeric substances (EPS) in conferring antibiotic resistance to bacteria. In clinical environments, infections linked to biofilms are associated with extended treatment periods and increased chances of relapse (51).

Clinical Implications and Therapeutic Challenges

Colistin: Efficacy and Limitations

Colistin (polymyxin E) is among the limited therapeutic alternatives available for the treatment of extensively drug-resistant (XDR) *Acinetobacter baumannii* infections. This cationic polypeptide antibiotic destabilizes the bacterial outer membrane by engaging with lipopolysaccharides (LPS), resulting in cell lysis (52). Although colistin is effective against multidrug-resistant bacteria, its usage is considerably limited by certain clinical challenges:

• Narrow Therapeutic Window: Colistin demonstrates a precarious equilibrium between efficacy and toxicity, necessitating meticulous dosing to prevent inadequate treatment or significant adverse effects (53).

• Nephrotoxicity and Neurotoxicity: A significant issue associated with colistin therapy is dose-dependent renal impairment, with documented acute kidney injury (AKI) rates above 50% in critically ill patients. Neurological side effects, including dizziness, paresthesia, and neuromuscular blocking, have also been noted (54).

• Emerging Resistance: The rising resistance to colistin significantly jeopardizes its therapeutic efficacy. Resistance mechanisms encompass alterations in lipid A of LPS (regulated by genes such as pmrAB and lpxACD) and plasmid-mediated resistance genes (e.g., mcr-1 to mcr-10). Documented resistance rates of 20–30% in critical care units (ICUs) further diminish its efficacy as a monotherapy (55). Considering these constraints, combination therapy and alternative treatment options are being rigorously investigated to enhance outcomes and reduce the development of resistance.

Combination Therapies

To enhance the efficacy of colistin and minimize resistance emergence, combination therapy with other antimicrobial agents has been extensively studied. These combinations work through synergistic mechanisms, often targeting different bacterial pathways to enhance bactericidal effects (56).

Promising Combination Regimens:With the increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Acinetobacter baumannii, monotherapy with colistin has shown limited efficacy due to high nephrotoxicity, poor tissue penetration, and the rapid emergence of resistance. To overcome these limitations, combination therapy has been proposed as an effective strategy to enhance bacterial clearance, delay resistance development, and improve patient outcomes (57).

Mechanism of Synergy in Combination Therapy:

Combination therapies work through synergistic mechanisms, where different antimicrobial agents target distinct bacterial pathways to increase bactericidal effects (58). This approach not only improves drug efficacy but also reduces the likelihood of resistance emergence. Key mechanisms include:

•**Membrane Disruption & Protein Synthesis Inhibition:** Colistin disrupts the bacterial outer membrane, allowing better penetration of intracellularly acting antibiotics (59).

•**Inhibition of Bacterial RNA Polymerase:** Some antibiotics enhance the susceptibility of A. baumannii by interfering with RNA transcription and gene expression (60).

•**β-Lactamase Inhibition:** Novel β-lactamase inhibitors restore the activity of β-lactam antibiotics against resistant strains (61).

Emerging Therapeutic Strategies

With the rising prevalence of pan-drug-resistant (PDR) A. baumannii strains, novel therapeutic approaches are being developed to overcome resistance mechanisms and provide alternative treatment options beyond conventional antibiotics (62).

Novel β-Lactamase Inhibitors

Next-generation β-lactamase inhibitors are under development to target both serine β-lactamases (OXA-type, ESBLs) and metallo-β-lactamases (MBLs). These inhibitors, when used in combination with existing β-lactam antibiotics, have shown promising reductions in minimum inhibitory concentrations (MICs) for resistant A. baumannii strains (63).

Key β-Lactamase Inhibitors in Development:

•**Vaborbactam**: Primarily targets class A carbapenemases, but is less effective against OXA-type enzymes (64).

•**Relebactam**: Demonstrates synergy with imipenem against MDR *A. baumannii* (65).

Taniborbactam: Exhibits efficacy against both serine β-lactamases and metallo-β-lactamases, positioning it as a formidable option for combating resistance (36).

•As these inhibitors progress through clinical trials, they may offer viable treatment alternatives for carbapenem-resistant infections.

Infection Control and Antimicrobial Stewardship

Enhanced Monitoring and Swift Diagnostics

The use of whole-genome sequencing (WGS) and fast PCR diagnostics into standard surveillance have markedly enhanced outbreak detection and management. Hospitals utilizing these technologies have documented a 30–40% decrease in outbreak durations (66).

Enhancing Environmental and Clinical Controls

Improved infection control protocols—such as ultraviolet light disinfection and antimicrobial surface treatments—have been linked to a reduction in environmental contamination of up to 30%. These techniques are essential for preventing the dissemination of MDR infections when used alongside rigorous hand hygiene and patient isolation policies (67).

Antimicrobial Stewardship Initiatives

Effective stewardship systems are crucial for mitigating the misuse of broad-spectrum antibiotics. Numerous hospitals in the Middle East have seen a 20–25% reduction in antibiotic prescriptions after the introduction of stewardship initiatives (68).

Case Analyses and Regional Insights

Investigation of the Tehran Outbreak

An exhaustive outbreak investigation at a tertiary care hospital in Tehran indicated that approximately 40% of ICU isolates were multidrug-resistant, with molecular typing verifying clonal proliferation of bacteria harboring OXA-23 and OXA-51-like enzymes. The outbreak led to elevated mortality rates, prolonged hospitalizations (averaging 10–15 days), and increased healthcare expenditures. These findings highlight the necessity for immediate intervention and comprehensive genetic surveillance (69).

Multicenter Investigation in Saudi Arabia

A multicenter study done in various Saudi Arabian hospitals found that MDR *A. baumannii* infections were associated with extended hospital stays and fatality rates of over 50% in severe instances. The adoption of combination medicines and improved surveillance techniques resulted in better clinical results, underscoring the efficacy of integrated infection control strategies (70).

National Surveillance Programs in Lebanon

Lebanese hospitals have recently established a statewide surveillance program that integrates whole genome sequencing and quick diagnostic techniques. This endeavor has disclosed elevated resistance rates to Carbapenems, Cephalosporins, and Colistin, along with the emergence of resistance determinants. The statistics have guided policy modifications and emphasized the necessity for coordinated regional efforts to address MDR *A. baumannii* (71).

Prospective Directions and Research Priorities

Progressing Molecular Research

Continued research utilizing next-generation sequencing (21) and proteomics is crucial for elucidating emerging resistance mechanisms and pinpointing new treatment targets. Research on new plasmids and point mutations will enhance tailored treatment techniques (72).

Advancement of Innovative Therapeutics

Expedited investigation into innovative antimicrobials such as next-generation β-lactamase inhibitors, bacteriophage therapy, immunomodulators, and nanoparticle-based therapies is essential. Cooperative initiatives involving academic institutions, industry, and global health organizations are essential to translate these advances into clinical practice (73).

Enhancing Regional Surveillance

Standardizing laboratory techniques and creating real-time genomic surveillance networks throughout the Middle East will enhance the identification of developing resistance trends and inform targeted public health responses (74).

Improving Infection Control Protocols

Future infection control should utilize both conventional approaches and advanced technologies (e.g., automated UV disinfection systems, and antimicrobial coatings) to mitigate nosocomial spread. Training and continuous oversight of healthcare staff are critical elements (75).

Policy and Regulatory Measures

Enhanced limits on antibiotic prescriptions and over-the-counter sales, along with comprehensive antimicrobial stewardship programs, are essential for mitigating the selective pressure that fosters resistance. Policymakers must endorse these programs through sufficient funding and incorporation into national public health plans (76).

Interdisciplinary Collaborations

A collaborative, interdisciplinary strategy involving clinicians, microbiologists, public health specialists, and policymakers is essential. Forming regional consortia for research and data sharing would expedite the dissemination of best practices and the execution of innovative solutions (77).

CONCLUSION

Acquired resistance genes and intrinsic mechanisms contribute to the rapid proliferation of multidrug-resistant *Acinetobacter baumannii* in healthcare environments in the Middle East. These methods encompass the synthesis of β-lactamase, the overexpression of efflux pumps, modifications to target sites, and the development of biofilms. The treatment efforts are further complicated by recently identified determinants such as bla_OXA-235. The threat presented by MDR *A. baumannii* is undeniable, as its prevalence in intensive care units (ICUs) exceeds 70 percent, with fatality rates surpassing 50 percent in specific nations. An urgent need exists for a comprehensive and multidisciplinary strategy. This plan must encompass enhanced antibiotic stewardship, stringent infection control, advanced molecular diagnostics, and the creation of novel therapeutics. To safeguard patient care in the Middle East, forthcoming studies must enhance our comprehension of resistance mechanisms and translate these findings into effective clinical therapies.

Author's Contribution

Azadeh Taftian, Neda Abedi and Ali Zolfi Gol were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable

REFERENCES

1.Howard A, O'Donoghue M, Feeney A, Sleator RD. Acinetobacter baumannii: an emerging opportunistic pathogen. Virulence. 2012;3(3):243-50.
2.Ayoub Moubareck C, Hammoudi Halat D. Insights into Acinetobacter baumannii: A Review of Microbiological, Virulence, and Resistance Traits in a Threatening Nosocomial Pathogen. Antibiotics (Basel). 2020;9(3).
3.Gedefie A, Demsis W, Ashagrie M, Kassa Y, Tesfaye M, Tilahun M, et al. Acinetobacter baumannii Biofilm Formation and Its Role in Disease Pathogenesis: A Review. Infect Drug Resist. 2021;14:3711-9.
4.Mukhopadhyay H, Bairagi A, Mukherjee A, Prasad AK, Roy AD, Nayak A. Multidrug resistant Acinetobacter baumannii: A study on its pathogenesis and therapeutics. Current Research in Microbial Sciences. 2025;8:100331.
5.Męcik M, Stefaniak K, Harnisz M, Korzeniewska E. Hospital and municipal wastewater as a source of carbapenem-resistant Acinetobacter baumannii and Pseudomonas aeruginosa in the environment: a review. Environmental Science and Pollution Research. 2024;31(36):48813-38.
6.Nguyen M, Joshi SG. Carbapenem resistance in Acinetobacter baumannii, and their importance in hospital-acquired infections: a scientific review. Journal of Applied Microbiology. 2021;131(6):2715-

38.
7.Ibrahim S, Al-Saryi N, Al-Kadmy IMS, Aziz SN. Multidrug-resistant Acinetobacter baumannii as an emerging concern in hospitals. Mol Biol Rep. 2021;48(10):6987-98.
8.Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant Acinetobacter baumannii: in pursuit of an effective treatment. Clinical Microbiology and Infection. 2019;25(8):951-7.
9.Tamburro M, Lombardi A, Sammarco ML, Ripabelli G. Molecular Epidemiology Revealed Distinct Patterns Among Multidrug Resistant Clinical Acinetobacter baumannii Strains in Different Periods in the Main Hospital in Molise Region, Central Italy. 2025;5(1):9.
10.Elbehiry A, Marzouk E, Moussa I, Mushayt Y, Algarni AA, Alrashed OA, et al. The Prevalence of Multidrug-Resistant Acinetobacter baumannii and Its Vaccination Status among Healthcare Providers. Vaccines (Basel). 2023;11(7).
11.Salarvan S, Abdollahi A, Afarinesh Khaki P, Norouzi Shadehi M, Beigh Mohammadi MT, Miratashi Yazdi SA, et al. Antibiotic Resistance Pattern in Intensive Care Units in a Large Referral Hospital in Iran. Iran J Pathol. 2023;18(4):433-8.
12.Almakrami M, Salmen M, Aldashel YA, Alyami MH, Alquraishah N, AlZureea M, et al. Prevalence of multidrug-, extensively drug-, and pandrug-resistant bacteria in clinical isolates from King Khaled Hospital, Najran, Saudi Arabia. Discover Medicine. 2024;1(1):108.
13.Elsheikh M, Kuriyama A, Goto Y, Takahashi Y, Toyama M, Nishikawa Y, et al. Incidence and predictors of ventilator-associated pneumonia using a competing risk analysis: a single-center prospective cohort study in Egypt. BMC Infect Dis. 2024;24(1):1007.
14.Kruk ME, Gage AD, Arsenault C, Jordan K, Leslie HH, Roder-DeWan S, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. Lancet Glob Health. 2018;6(11):e1196-e252.
15.Du X, Du Y, Zhang Y, Zhu Y, Yang Y. Urban and rural disparities in general hospital accessibility within a Chinese metropolis. Scientific Reports. 2024;14(1):23359.
16.Jafari N, Shahabi Rabori V, Zolfi Gol A, Saberiyan M. Crosstalk of NLRP3 inflammasome and noncoding RNAs in cardiomyopathies. Cell biochemistry and function. 2023;41(8):1060-75.
17.Roosta Y, Abedi N. The Evolving Landscape of Drug Resistance: From Mechanisms to Therapeutic Strategies %J Personalized Medicine Journal. 2025;10(36):1-11.
18.Zhang T, Xu X, Xu C-F, Bilya SR, Xu W. Mechanical ventilation-associated pneumonia caused by Acinetobacter baumannii in Northeast China region: analysis of genotype and drug resistance of bacteria and patients' clinical features over 7 years. Antimicrobial Resistance & Infection Control. 2021;10(1):135.
19.Zolfigol A, Pirhadi M. Phytotherapy in Children's Colds %J Plant Biotechnology Persa. 2025;7(1):96-100.
20.Endale H, Mathewos M, Abdeta D. Potential Causes of Spread of Antimicrobial Resistance and Preventive Measures in One Health Perspective-A Review. Infect Drug Resist. 2023;16:7515-45.
21.Tartari E, Weterings V, Gastmeier P, Rodríguez Baño J, Widmer A, Kluytmans J, et al. Patient engagement with surgical site infection prevention: an expert panel perspective. Antimicrob Resist Infect Control. 2017;6:45.
22.Gupta A, Marzook H, Ahmad F. Comorbidities and clinical complications associated with SARS-CoV-2 infection: an overview. Clinical and Experimental Medicine. 2023;23(2):313-31.
23.Azimzadeh M, Bahador A, Shiralizadeh S, Mahshouri P, Akbari L, Makari S, et al. A single-center analysis of clonal transmission of carbapenem-resistant Acinetobacter baumannii among intensive care unit patients during the COVID-19 pandemic. Scientific Reports. 2024;14(1):25897.
24.Bialvaei AZ, Kouhsari E, Salehi-Abargouei A, Amirmozafari N, Ramazanzadeh R, Ghadimi-Daresajini A, et al. Epidemiology of multidrug-resistant Acinetobacter baumannii strains in Iran: a systematic review and meta-analysis. J Chemother. 2017;29(6):327-37.
25.Jasemi S, Douraghi M, Adibhesami H, Zeraati H, Rahbar M, Boroumand MA, et al. Trend of extensively drug-resistant Acinetobacter baumannii and the remaining therapeutic options: a multicenter study in Tehran, Iran over a 3-year period. Lett Appl Microbiol. 2016;63(6):466-72.
26.Ibrahim ME. Prevalence of Acinetobacter baumannii in Saudi Arabia: risk factors, antimicrobial resistance patterns and mechanisms of carbapenem resistance. Ann Clin Microbiol Antimicrob. 2019;18(1):1.
27.Thomsen J, Abdulrazzaq NM, AlRand H, Everett DB, Senok A, Menezes GA, et al. Epidemiology and antimicrobial resistance trends of Acinetobacter species in the United Arab Emirates: a retrospective analysis of 12 years of national AMR surveillance data. Front Public Health. 2023;11:1245131.
28.Al-Orphaly M, Hadi HA, Eltayeb FK, Al-Hail H, Samuel BG, Sultan AA, et al. Epidemiology of Multidrug-Resistant Pseudomonas aeruginosa in the Middle East and North Africa Region. mSphere. 2021;6(3).
29.Zong G, Zhong C, Fu J, Zhang Y, Zhang P, Zhang W,

et al. The carbapenem resistance gene bla(OXA-23) is disseminated by a conjugative plasmid containing the novel transposon Tn6681 in Acinetobacter johnsonii M19. Antimicrob Resist Infect Control. 2020;9(1):182.
30.Traglia GM, Pasteran F, Moheb S, Akhtar U, Gonzalez S, Maldonado C, et al. Insights into Acinetobacter baumannii AMA205's Unprecedented Antibiotic Resistance. International Journal of Molecular Sciences [Internet]. 2024; 25(21).
31.Pfeifer E, Bonnin RA, Rocha EPC. Phage-Plasmids Spread Antibiotic Resistance Genes through Infection and Lysogenic Conversion. mBio. 2022;13(5):e0185122.
32.Teng J, Imani S, Zhou A, Zhao Y, Du L, Deng S, et al. Combatting resistance: Understanding multi-drug resistant pathogens in intensive care units. Biomedicine & Pharmacotherapy. 2023;167:115564.
33.Gauba A, Rahman KM. Evaluation of Antibiotic Resistance Mechanisms in Gram-Negative Bacteria. Antibiotics [Internet]. 2023; 12(11).
34.Kyriakidis I, Vasileiou E, Pana ZD, Tragiannidis A. Acinetobacter baumannii Antibiotic Resistance Mechanisms. Pathogens. 2021;10(3).
35.Chan K-W, Liu C-Y, Wong H-Y, Chan W-C, Wong K-Y, Chen S. Specific Amino Acid Substitutions in OXA-51-Type β-Lactamase Enhance Catalytic Activity to a Level Comparable to Carbapenemase OXA-23 and OXA-24/40. International Journal of Molecular Sciences [Internet]. 2022; 23(9).
36.Liu B, Trout REL, Chu GH, McGarry D, Jackson RW, Hamrick JC, et al. Discovery of Taniborbactam (VNRX-5133): A Broad-Spectrum Serine- and Metallo-β-lactamase Inhibitor for Carbapenem-Resistant Bacterial Infections. J Med Chem. 2020;63(6):2789-801.
37.Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. JAC Antimicrob Resist. 2021;3(3):dlab092.
38.Sakalauskienė GV, Malcienė L, Stankevičius E, Radzevičienė A. Unseen Enemy: Mechanisms of Multidrug Antimicrobial Resistance in Gram-Negative ESKAPE Pathogens. Antibiotics (Basel). 2025;14(1).
39.Huang Y-S, Zhou H. Breakthrough Advances in Beta-Lactamase Inhibitors: New Synthesized Compounds and Mechanisms of Action Against Drug-Resistant Bacteria. Pharmaceuticals [Internet]. 2025; 18(2).
40.Tooke CL, Hinchliffe P, Bragginton EC, Colenso CK, Hirvonen VHA, Takebayashi Y, et al. β-Lactamases and β-Lactamase Inhibitors in the 21st Century. J Mol Biol. 2019;431(18):3472-500.
41.Ranjbar R, Zayeri S, Afshar D. High Frequency of AdeA, AdeB and AdeC Genes among Acinetobacter baumannii Isolates. Iran J Public Health. 2020;49(8):1539-45.
42.Brand C, Newton-Foot M, Grobbelaar M, Whitelaw A. Antibiotic-induced stress responses in Gram-negative bacteria and their role in antibiotic resistance. Journal of Antimicrobial Chemotherapy. 2025.
43.Lunha K, Chumpol W, Jiemsup S, Samngamnim S, Assavacheep P, Yongkiettrakul S. Relationship between Penicillin-Binding Proteins Alterations and β-Lactams Non-Susceptibility of Diseased Pig-Isolated Streptococcus suis. Antibiotics (Basel). 2023;12(1).
44.Rezaei S, Tajbakhsh S, Naeimi B, Yousefi F. Investigation of gyrA and parC mutations and the prevalence of plasmid-mediated quinolone resistance genes in Klebsiella pneumoniae clinical isolates. BMC Microbiology. 2024;24(1):265.
45.O'Sullivan ME, Poitevin F, Sierra RG, Gati C, Dao EH, Rao Y, et al. Aminoglycoside ribosome interactions reveal novel conformational states at ambient temperature. Nucleic Acids Res. 2018;46(18):9793-804.
46.Uppalapati SR, Sett A, Pathania R. The Outer Membrane Proteins OmpA, CarO, and OprD of Acinetobacter baumannii Confer a Two-Pronged Defense in Facilitating Its Success as a Potent Human Pathogen. Front Microbiol. 2020;11:589234.
47.Shree P, Singh CK, Sodhi KK, Surya JN, Singh DK. Biofilms: Understanding the structure and contribution towards bacterial resistance in antibiotics. Medicine in Microecology. 2023;16:100084.
48.Hammoudi Halat D, Ayoub Moubareck C. The Current Burden of Carbapenemases: Review of Significant Properties and Dissemination among Gram-Negative Bacteria. Antibiotics [Internet]. 2020; 9(4).
49.Zhang S, Wang J, Ahn J. Advances in the Discovery of Efflux Pump Inhibitors as Novel Potentiators to Control Antimicrobial-Resistant Pathogens. Antibiotics [Internet]. 2023; 12(9).
50.Gauba A, Rahman KM. Evaluation of Antibiotic Resistance Mechanisms in Gram-Negative Bacteria. Antibiotics (Basel). 2023;12(11).
51.Roy S, Chowdhury G, Mukhopadhyay AK, Dutta S, Basu S. Convergence of Biofilm Formation and Antibiotic Resistance in Acinetobacter baumannii Infection. Front Med (Lausanne). 2022;9:793615.
52.El-Sayed Ahmed MAE, Zhong LL, Shen C, Yang Y, Doi Y, Tian GB. Colistin and its role in the Era of antibiotic resistance: an extended review (2000-2019). Emerg Microbes Infect. 2020;9(1):868-85.
53.Gontijo AVL, Cavalieri AVG. Optimal control for colistin dosage selection. J Pharmacokinet Pharmacodyn. 2021;48(6):803-13.
54. Kilic I, Ayar Y, Ceylan İ, Kaya PK, Caliskan G.

Nephrotoxicity caused by colistin use in ICU: a single centre experience. BMC Nephrology. 2023;24(1):302.
55.Schumann A, Gaballa A, Yang H, Yu D, Ernst RK, Wiedmann M. Site-selective modifications by lipid A phosphoethanolamine transferases linked to colistin resistance and bacterial fitness. mSphere. 2024;9(12):e0073124.
56.Jalil AT, Alrawe RTA, Al-Saffar MA, Shaghnab ML, Merza MS, Abosaooda M, et al. The use of combination therapy for the improvement of colistin activity against bacterial biofilm. Braz J Microbiol. 2024;55(1):411-27.
57.Scoffone VC, Trespidi G, Barbieri G, Arshad A, Israyilova A, Buroni S. The Evolution of Antimicrobial Resistance in Acinetobacter baumannii and New Strategies to Fight It. Antibiotics [Internet]. 2025; 14(1).
58.Basavegowda N, Baek KH. Combination Strategies of Different Antimicrobials: An Efficient and Alternative Tool for Pathogen Inactivation. Biomedicines. 2022;10(9).
59.Sabnis A, Hagart KL, Klöckner A, Becce M, Evans LE, Furniss RCD, et al. Colistin kills bacteria by targeting lipopolysaccharide in the cytoplasmic membrane. Elife. 2021;10.
60.Norton MD, Spilkia AJ, Godoy VG. Antibiotic resistance acquired through a DNA damage-inducible response in Acinetobacter baumannii. J Bacteriol. 2013;195(6):1335-45.
61.Kang S-J, Kim D-H, Lee B-J. Metallo-β-lactamase inhibitors: A continuing challenge for combating antibiotic resistance. Biophysical Chemistry. 2024;309:107228.
62.Thacharodi A, Vithlani A, Hassan S, Alqahtani A, Pugazhendhi A. Carbapenem-resistant Acinetobacter baumannii raises global alarm for new antibiotic regimens. iScience. 2024;27(12):111367.
63.Sargianou M, Stathopoulos P, Vrysis C, Tzvetanova ID, Falagas ME. New β-Lactam/β-Lactamase Inhibitor Combination Antibiotics. Pathogens [Internet]. 2025; 14(4).
64.Langley GW, Cain R, Tyrrell JM, Hinchliffe P, Calvopiña K, Tooke CL, et al. Profiling interactions of vaborbactam with metallo-β-lactamases. Bioorg Med Chem Lett. 2019;29(15):1981-4.
65.Xu C, Chen T, Zhang S, Zhou C, Liao W, Fang R, et al. In vitro activity of imipenem-relebactam alone and in combination with fosfomycin against carbapenem-resistant gram-negative pathogens. Diagnostic Microbiology and Infectious Disease. 2022;103(3):115712.
66. Sundermann AJ, Kumar P, Griffith MP, Waggle KD, Srinivasa VR, Raabe N, et al. Genomic Surveillance for Enhanced Healthcare Outbreak Detection and Control. medRxiv. 2024.
67.Resendiz M, Blanchard D, West GF. A systematic review of the germicidal effectiveness of ultraviolet disinfection across high-touch surfaces in the immediate patient environment. J Infect Prev. 2023;24(4):166-77.
68.Chukwu EE, Oshun PO, Osuolale KA, Chuka-Ebene VO, Salako A, Idigbe IE, et al. Antimicrobial stewardship programmes in healthcare facilities in Lagos State, Nigeria: a needs assessment. Journal of Global Antimicrobial Resistance. 2021;25:162-70.
69.Gupta N, Angadi K, Jadhav S. Molecular Characterization of Carbapenem-Resistant Acinetobacter baumannii with Special Reference to Carbapenemases: A Systematic Review. Infect Drug Resist. 2022;15:7631-50.
70.Aldali JA. Acinetobacter baumannii: A multidrug-resistant pathogen, has emerged in Saudi Arabia. Saudi Med J. 2023;44(8):732-44.
71.Iskandar K, Molinier L, Hallit S, Sartelli M, Hardcastle TC, Haque M, et al. Surveillance of antimicrobial resistance in low- and middle-income countries: a scattered picture. Antimicrob Resist Infect Control. 2021;10(1):63.
72.Bianconi I, Aschbacher R, Pagani E. Current Uses and Future Perspectives of Genomic Technologies in Clinical Microbiology. Antibiotics (Basel). 2023;12(11).
73.Murugaiyan J, Kumar PA, Rao GS, Iskandar K, Hawser S, Hays JP, et al. Progress in Alternative Strategies to Combat Antimicrobial Resistance: Focus on Antibiotics. Antibiotics (Basel). 2022;11(2).
74.Struelens MJ, Ludden C, Werner G, Sintchenko V, Jokelainen P, Ip M. Real-time genomic surveillance for enhanced control of infectious diseases and antimicrobial resistance. 2024;Volume 2 - 2024.
75.Garcia R, Barnes S, Boukidjian R, Goss LK, Spencer M, Septimus EJ, et al. Recommendations for change in infection prevention programs and practice. Am J Infect Control. 2022;50(12):1281-95.
76.Aslam B, Asghar R, Muzammil S, Shafique M, Siddique AB, Khurshid M, et al. AMR and Sustainable Development Goals: at a crossroads. Globalization and Health. 2024;20(1):73.
77.Lane HG, Allgood SD, Schexnayder J, Bosworth HB, Baumann AA, Lewinski AA. Recommendations for interdisciplinary research collaboration for early career dissemination and implementation researchers: A multi-phase study. J Clin Transl Sci. 2025;9(1):e39.

Spring 2025, Volume 10, Issue 37 (31- 38) DOI: 10.22034/pmj.2025.2058727.1060

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Microplastic Neurotoxicity: Pathways, Mechanisms, and Implications for Neurodegenerative Diseases

Shabnam Radbakhsh[1*], **Rezvan Norouzzadeh**[2]

[1]Department of Medicine, McGill University, Montréal, Québec, Canada.
[2]Department of Neurology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran.

ARTICLE INFO

Paper Type: Review Article

Submitted: 2025-01-30
Accepted: 2025-05-27

Keywords:
Microplastics
Neurodegenerative diseases
Alzheimer›s disease
Nanoplastics
Neurotoxicity

Corresponding author:
Shabnam Radbakhsh, Department of Medicine, McGill University, Montréal, Québec, Canada.
Email: Shabnam.radbakhsh@umontreal.ca.

ABSTRACT

This review synthesizes and elaborates on current studies examining the neurotoxic effects of microplastics, emphasizing their mechanisms of entry into the central nervous system and their possible involvement in the development of neurodegenerative disorders. The pervasive presence of microplastics in the environment has heightened concerns about their accumulation in biological systems, particularly their capacity to traverse biological boundaries and engage with neuronal tissues. This article seeks to synthesize and critically evaluate the existing scientific literature on microplastic neuroinvasion, concentrating on the mechanisms through which these particles penetrate the blood-brain barrier (BBB) specifically via transcellular, paracellular, or Trojan horse pathways—and their ensuing effects on neuronal homeostasis.

We investigate the physiological and molecular reactions triggered by microplastics, encompassing oxidative stress induction, mitochondrial failure, neuroinflammation, and synaptic disruption. These pathogenic processes may facilitate the onset and advancement of several neurodegenerative disorders, including Alzheimer's disease, by intensifying amyloid-beta aggregation, tau phosphorylation, and neuroimmune activation. Additionally, we examine the burgeoning epidemiological and experimental evidence associating microplastic exposure with cognitive deterioration and neuronal impairment.

This review offers a thorough analysis of microplastic neurotoxicity by evaluating both in vitro and in vivo studies, with the objective of elucidating the potential neurological hazards associated with these environmental contaminants. We emphasize significant deficiencies in existing research and propose future avenues, encompassing enhanced detection techniques, public health initiatives, and efforts to reduce human exposure to microplastics.

How to Cite this Article:
SH. Radbakhsh, R. Norouzzadeh. "Microplastic Neurotoxicity: Pathways, Mechanisms, and Implications for Neurodegenerative Diseases" Personalized & Precision Medicine Journal, Vol. 10, no. 37, pp. 31- 38.

INTRODUCTION

Microplastics, defined as plastic particles less than 5 millimetres in diameter, originate from diverse sources. Primary microplastics are intentionally manufactured, such as microbeads in personal care products or plastic pellets used in industrial processes (1). Secondary microplastics, however, result from the breakdown of larger plastic debris through environmental weathering, including UV radiation, wave action, and abrasion. These fragmentation processes yield progressively smaller particles, contributing significantly to environmental contamination. Additionally, the washing of synthetic textiles releases microfibers, a prevalent form of secondary microplastic (2).

Quantifying annual microplastic production is complex due to the varied sources and ongoing fragmentation. Nevertheless, it is known that the global production of plastics is massive, and a portion of that plastic ends up breaking down into microplastics (3). Recent studies indicate that millions of tons of plastic waste enter aquatic environments annually, with a significant portion degrading into microplastics (4).

Factors contributing to the amount of microplastics produced yearly include the amount of plastic produced globally, the amount of plastic waste that is mismanaged, and the rate which plastic degrades in the environment. Therefore, the estimated amounts of microplastics entering the environment vary, but all evidence points to a massive and growing problem (5).

The pervasive nature of microplastics raises significant concerns about their potential harm to human health. Entry into the human body occurs through various pathways, including ingestion via contaminated food and water, inhalation of airborne particles, and dermal absorption (6). Once inside, these minute plastic fragments can trigger inflammatory responses and oxidative stress, potentially damaging tissues and organs. Furthermore, microplastics can act as vectors, carrying harmful chemicals and pathogens that can leach into the body, further exacerbating health risks. Research is actively investigating the long-term effects of microplastic accumulation, with studies exploring links to disruptions in the endocrine system, immune responses, and potential carcinogenic effects (7).

The distribution of microplastics throughout the human body is becoming increasingly understood. They have been detected in various tissues and organs, including the lungs, liver, kidneys, and even the brain, indicating their ability to traverse biological barriers. Nanoplastics, even smaller particles, pose a heightened risk due to their capacity to penetrate cells and potentially interact with cellular components (8). The implications of this widespread presence are still being explored, but the potential for chronic exposure to lead to a range of adverse health outcomes is a growing concern. The ability of micro and nano plastics to carry other harmful chemicals also increases the likelihood of negative health impacts (9).

The nervous system, a complex network of neurons and supporting cells orchestrates communication throughout the body, including the brain and spinal cord (10). Nerve fibers of this system originate in the fascia, muscles, joints, and skin and include heat, mechanical, chemical, itching, and pain Receptors (11). Its delicate structure is protected by the blood-brain barrier (BBB), a highly selective membrane that restricts the passage of many substances (12). However, recent research suggests that microplastics, particularly nanoplastics, can breach this barrier (13). Several mechanisms facilitate this entry: direct translocation through the BBB via endocytosis, a process where cells engulf particles; indirect transport by acting as carriers for other neurotoxic substances; and inflammatory responses triggered by microplastic presence, which can compromise BBB integrity (14). Once inside, these particles can accumulate in neural tissues, potentially disrupting synaptic function and triggering neuroinflammation. The potential link between microplastic exposure and neurodegenerative diseases is an emerging area of concern (15). Neuroinflammation, a hallmark of many neurodegenerative conditions like Alzheimer's and Parkinson's disease, can be exacerbated by the presence of microplastics. These particles can activate microglia, the brain's resident immune cells, leading to the release of inflammatory cytokines and oxidative stress, which can damage neurons (16, 17). Furthermore, the ability of microplastics to adsorb and transport neurotoxic chemicals, such as heavy metals and persistent organic pollutants, could further contribute to neuronal dysfunction and accelerate the progression of neurodegenerative processes (18). While direct causal links are still being investigated, the potential for microplastics to contribute to neurotoxicity is significant. The small size of nanoplastics allows for intracellular uptake, potentially interfering with cellular processes like protein folding and mitochondrial function, both critical for neuronal health (13, 19). The accumulation of these particles could lead to chronic neuroinflammation and neuronal damage over time. Further research is needed to fully understand the long-term effects of microplastic exposure on the nervous system and to establish definitive links between these particles and the development or progression of neurodegenerative diseases (19). This article aims to review the neurotoxicity of microplastics, detailing how these particles break down into the nervous system and their potential role in neurodegenerative processes. It seeks to integrate the understanding of the mechanisms by which microplastics affect neurological health.

A History of Microplastic Origins and Production

The emergence of microplastics as a pervasive environmental contaminant is intrinsically linked to the rise of synthetic polymers in the mid-20th century. While large plastic debris was recognized as a pollution problem earlier, the insidious nature of microscopic plastic fragments became increasingly apparent in the late 20th and early 21st centuries (20). Initially, primary microplastics were intentionally manufactured for industrial and consumer applications. Examples include microbeads in personal care products, designed for exfoliation, and plastic powders used in cleaning and blasting. These intentionally produced microplastics were released directly into the environment through wastewater systems (21).

However, the vast majority of microplastics originate from the breakdown of larger plastic items. Secondary microplastics are formed through the fragmentation of plastic litter due to environmental weathering. Factors such as ultraviolet radiation, wave action, abrasion, and temperature fluctuations contribute to the gradual degradation of plastic waste into smaller and smaller

particles (22). This process occurs in both terrestrial and aquatic environments, with oceans acting as significant sinks for plastic debris. The widespread use of synthetic textiles, particularly those made from polyester, nylon, and acrylic, has also emerged as a significant source of microfibers (22). These microfibers are released during washing and are transported through wastewater systems into rivers and oceans. The production of plastics has increased exponentially since the 1950s, leading to a corresponding rise in microplastic pollution (23). The sheer volume of plastic waste generated globally, coupled with inadequate waste management practices, has resulted in the widespread dissemination of microplastics throughout the environment. As our understanding of the environmental and health implications of microplastics grows, efforts are being made to reduce plastic production, improve waste management, and develop alternative materials (24).

Microplastic Entry and Mechanisms of Human Health Impact

Microplastics, ubiquitous in modern environments, enter the human body through multiple pathways. Ingestion is a primary route, occurring via contaminated food and beverages, including seafood, drinking water, and even honey. Inhalation of airborne microplastics, particularly fibres released from textiles, also contributes to internal exposure (25). Dermal absorption, while less understood, may also play a role, especially with prolonged contact with contaminated surfaces or personal care products. Once inside the body, these particles can translocate across biological barriers, reaching various tissues and organs. The mechanisms by which microplastics exert adverse health effects are multifaceted (26). Their small size, especially in the nanometer range, allows them to penetrate cell membranes and interact with intracellular components. This can disrupt cellular processes, induce oxidative stress, and trigger inflammatory responses. Furthermore, microplastics can act as vectors for other harmful substances (27). They can adsorb and concentrate toxic chemicals, such as heavy metals and persistent organic pollutants, releasing them into the body upon ingestion or cellular uptake. This co-exposure to microplastics and other contaminants can amplify the overall toxicity (28). The immune system plays a crucial role in responding to microplastic exposure. Macrophages, immune cells that engulf foreign particles, attempt to clear microplastics from tissues. However, chronic exposure can lead to persistent inflammation and tissue damage. The body's inability to fully eliminate these particles can result in their accumulation, potentially leading to long-term health consequences (29). Chronic inflammation can also disrupt normal immune function, which could lead to increased susceptibility to other illnesses. Research is ongoing to fully elucidate the long-term health impacts of microplastic exposure. Studies are investigating potential links to endocrine disruption, respiratory diseases, reproductive disorders, and even cancer (30). The ability of microplastics to cross the blood-brain barrier raises concerns about neurotoxicity and potential contributions to neurodegenerative diseases. The growing body of evidence underscores the need for further research to assess the full scope of microplastic toxicity and to develop strategies to mitigate their impact on human health (31).

Microplastic Neuroinvasion and Neurological Impact

The blood-brain barrier (BBB), a highly selective physiological barrier, meticulously regulates the passage of substances from the bloodstream into the central nervous system (CNS), safeguarding the delicate neural environment. However, increasing evidence suggests that microplastics, particularly nanoplastics, can circumvent this formidable defense (32). Several mechanisms facilitate this neuroinvasion. Firstly, direct translocation across the BBB can occur via endocytosis, a process where cells engulf particles, allowing nanoplastics to be internalized and transported. Secondly, microplastics can serve as Trojan horses, adsorbing and carrying neurotoxic substances like heavy metals or persistent organic pollutants, effectively delivering these harmful agents into the brain parenchyma (33). Thirdly, the presence of microplastics can trigger localized inflammation, disrupting the tight junctions that maintain BBB integrity, thereby increasing permeability and facilitating particle entry. This compromise of the BBB is particularly concerning, as it allows for the potential accumulation of microplastics and associated toxins within the CNS (19).

Once within the nervous system, microplastics can interact with various neural components, disrupting normal neuronal function. They can accumulate in different brain regions, including the hippocampus, cortex, and cerebellum, potentially interfering with synaptic transmission and neuronal signaling (14). Microplastics can induce oxidative stress by generating reactive oxygen species, which can damage cellular components like lipids, proteins, and DNA, leading to neuronal dysfunction and even cell death (34). Furthermore, they can activate microglia, the brain's resident immune cells, triggering the release of pro-inflammatory cytokines, and contributing to chronic neuroinflammation. This neuroinflammation, a hallmark of many neurodegenerative diseases, can exacerbate neuronal damage and accelerate disease progression (35). The ability of nanoplastics to enter cells also means they can potentially disrupt intracellular processes, like protein folding, and mitochondrial function, which are essential for

neuronal viability (36).

The potential link between microplastic exposure and neurodegenerative diseases is a growing area of concern. The chronic neuroinflammation induced by microplastics can contribute to the pathogenesis of diseases like Alzheimer's and Parkinson's. The ability of these particles to carry neurotoxic substances can further exacerbate neuronal damage and accelerate disease progression (33). For example, some studies suggest that microplastics may facilitate the accumulation of amyloid-beta plaques, a hallmark of Alzheimer's disease. Moreover, the disruption of synaptic function and neuronal signaling caused by microplastics can contribute to cognitive decline and behavioral changes (37). The long-term effects of chronic microplastic exposure on brain health are still being investigated, but the potential for these particles to contribute to neurotoxicity and neurodegenerative diseases is significant. The implications of microplastic neuroinvasion extend beyond direct neuronal damage (38). The disruption of the BBB can also compromise the brain's ability to clear metabolic waste and maintain ionic homeostasis, further contributing to neuronal dysfunction. The interaction of microplastics with neurotransmitter systems can also lead to alterations in mood, behavior, and cognitive function (39). Furthermore, the potential for microplastics to interact with neural stem cells raises concerns about developmental neurotoxicity and the potential for long-term neurological consequences (39). Further research is crucial to fully understand the mechanisms by which microplastics affect the nervous system and to assess the long-term health risks associated with chronic exposure.

Mitigating the Microplastic Burden: Detection and Reduction Strategies

Detecting microplastics within the human body, particularly the nervous system, presents significant challenges. Current methods primarily rely on analyzing tissue and fluid samples using techniques like Raman spectroscopy, Fourier-transform infrared spectroscopy (FTIR), and mass spectrometry (40). These techniques allow for the identification and quantification of microplastic particles, but they are often invasive and limited in their ability to provide real-time or in vivo assessments. Developing non-invasive imaging techniques, such as advanced microscopy or nanoparticle-based sensors, is crucial for understanding the distribution and dynamics of microplastics within the body (41). Additionally, improving analytical techniques to detect and quantify nanoplastics, which pose a greater challenge due to their smaller size, is essential for a comprehensive assessment of internal exposure. Research is also being conducted into the use of biological markers to assess exposure and potential harm (42).

Reducing microplastic exposure requires a multi-faceted approach, targeting both environmental and individual behaviors. At the environmental level, reducing plastic production and improving waste management are paramount. Implementing stricter regulations on single-use plastics, promoting the use of biodegradable alternatives, and investing in advanced recycling technologies can significantly decrease the amount of plastic entering the environment (43). Wastewater treatment plants can be upgraded to more effectively filter microplastics. Additionally, addressing microfiber pollution from textiles by promoting the use of natural fibers, developing washing machine filters, and improving textile manufacturing processes is crucial. Individual behavioral changes, such as reducing plastic consumption, choosing products with minimal plastic packaging, and properly disposing of plastic waste, can also contribute to reducing environmental contamination (44). Within the human body, strategies for reducing microplastic burden are still in their early stages. Research is exploring the potential of chelating agents or other compounds that can bind to and remove microplastics from tissues. However, these approaches require careful consideration of potential side effects and the long-term safety of these interventions (45). Lifestyle modifications, such as consuming filtered water and avoiding processed foods with plastic packaging, can minimize further exposure. Supporting research into methods that promote the body's natural clearance mechanisms, such as enhancing macrophage activity or improving lymphatic drainage, may also prove beneficial. Further studies on the human microbiome may also provide insights into how to improve the body's natural ability to degrade or eliminate microplastics (46).

The Role of Microplastics in Causing Alzheimer's Disease

The potential link between microplastic exposure and Alzheimer's disease is an emerging area of scientific inquiry. While direct causation remains to be established, several lines of evidence suggest a plausible connection (47). Alzheimer's disease is characterized by the accumulation of amyloid-beta plaques and tau protein tangles in the brain, leading to neuronal dysfunction and cognitive decline (48). Microplastics, particularly nanoplastics, can potentially contribute to these pathological processes. Firstly, their ability to breach the blood-brain barrier allows them to directly interact with brain tissue (49). Secondly, they can act as vectors for neurotoxic substances, such as heavy metals and persistent organic pollutants, which are known risk factors for Alzheimer's. Thirdly, microplastics can induce chronic

neuroinflammation, a key factor in the progression of the disease (37).

The mechanisms by which microplastics might contribute to Alzheimer's pathology are multifaceted. Chronic neuroinflammation, triggered by the presence of microplastics, can activate microglia, the brain's immune cells, leading to the release of pro-inflammatory cytokines (50). These cytokines can promote the formation of amyloid-beta plaques and tau tangles, exacerbating the pathological hallmarks of Alzheimer's. Furthermore, microplastics can disrupt calcium homeostasis in neurons, a process crucial for synaptic function and neuronal survival. Dysregulation of calcium signaling can contribute to neuronal damage and promote the aggregation of amyloid-beta (51). The oxidative stress induced by microplastics can also damage cellular components, including proteins and lipids, further contributing to neuronal dysfunction and the accumulation of pathological aggregates. The ability of nanoplastics to enter cells means they can also potentially interfere with protein folding, which is relevant to both amyloid beta and tau protein aggregation (52).

The role of microplastics as carriers of neurotoxic substances is particularly concerning. Heavy metals like aluminum, lead, and mercury, which are known neurotoxins, can adsorb onto microplastic particles and be transported into the brain. These metals can contribute to oxidative stress, neuroinflammation, and the formation of amyloid-beta plaques and tau tangles (53). Similarly, persistent organic pollutants, such as pesticides and flame retardants, can also be carried by microplastics and contribute to neurotoxicity. These substances can disrupt neuronal signaling, promote neuroinflammation, and increase the risk of Alzheimer's disease (32). The synergistic effect of microplastics and these neurotoxic substances may amplify the overall neurotoxicity and accelerate the progression of Alzheimer's. Further research is needed to fully elucidate the connection between microplastic exposure and Alzheimer's disease (38). Longitudinal studies that track microplastic exposure and cognitive function over time are essential. In vitro and in vivo studies are also needed to investigate the specific mechanisms by which microplastics contribute to Alzheimer's pathology. Understanding the potential role of microplastics in Alzheimer's disease is crucial for developing strategies to mitigate their impact on brain health and to prevent or delay the onset of this debilitating disease (54).

DISCUSSION AND CONCLUSION

The burgeoning field of microplastic research has illuminated the pervasive nature of these pollutants and their potential to inflict significant harm on human health, particularly within the delicate confines of the nervous system. The ability of microplastics, especially nanoplastics, to breach the blood-brain barrier and induce neuroinflammation, oxidative stress, and neuronal dysfunction raises serious concerns about their contribution to neurodegenerative diseases like Alzheimer's (55). While direct causal links are still under investigation, the accumulating evidence strongly suggests that chronic exposure to microplastics can exacerbate existing neuropathologies and potentially accelerate disease progression. The role of microplastics as vectors for neurotoxic substances further amplifies these concerns, highlighting the complex interplay between environmental pollutants and human health (56).

The challenges associated with detecting and quantifying microplastics within the human body, particularly the nervous system, necessitate the development of advanced analytical and imaging techniques. Current research efforts are focused on refining existing methods and exploring novel approaches to assess internal exposure and track the distribution of microplastics in vivo (57). Simultaneously, mitigating microplastic exposure requires a multi-pronged strategy encompassing environmental remediation, individual behavioral changes, and the development of interventions to reduce the internal microplastic burden (58). Reducing plastic production, improving waste management, and promoting the use of sustainable alternatives are crucial for minimizing environmental contamination. Research into chelating agents and other compounds that can remove microplastics from tissues, as well as strategies to enhance the body's natural clearance mechanisms, holds promise for mitigating internal exposure (59).

The potential connection between microplastics and Alzheimer's disease underscores the urgency of addressing this global health issue. The ability of microplastics to induce neuroinflammation, disrupt calcium homeostasis, and act as carriers for neurotoxic substances suggests a plausible mechanism by which they can contribute to the pathological hallmarks of Alzheimer's (60). Further research is needed to fully elucidate the complex interplay between microplastic exposure and neurodegenerative processes. Longitudinal studies, in vitro and in vivo experiments, and epidemiological analyses are essential for establishing definitive links and identifying potential therapeutic targets (60).

In conclusion, microplastics represent a significant and growing threat to human health, particularly the nervous system. The ability of these particles to penetrate biological barriers and induce a cascade of adverse effects necessitates a concerted effort to mitigate their impact. Addressing this challenge requires a holistic approach, encompassing

environmental protection, technological innovation, and individual responsibility. Continued research is crucial for deepening our understanding of microplastic toxicity and developing effective strategies to protect human health from these ubiquitous pollutants.

Authors's Contribution

Shabnam Radbakhsh and Rezvan Norouzzadeh: Conceptualization and writing. The authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable

Conflict of Interest

No conflict of interest was declared.

Consent for publication

Not Applicable.

REFERENCES

1.Das A. The emerging role of microplastics in systemic toxicity: Involvement of reactive oxygen species (ROS). Science of The Total Environment. 2023;895:165076.
2.Helm PA. Improving microplastics source apportionment: a role for microplastic morphology and taxonomy? Analytical Methods. 2017;9(9):1328-31.
3.Yu Y, Kumar M, Bolan S, Padhye LP, Bolan N, Li S, et al. Various additive release from microplastics and their toxicity in aquatic environments. Environmental Pollution. 2024;343:123219.
4.Wang C, Zhao J, Xing B. Environmental source, fate, and toxicity of microplastics. Journal of hazardous materials. 2021;407:124357.
5.Yin K, Wang Y, Zhao H, Wang D, Guo M, Mu M, et al. A comparative review of microplastics and nanoplastics: Toxicity hazards on digestive, reproductive and nervous system. Science of the total environment. 2021;774:145758.
6.Bouaicha O, Mimmo T, Tiziani R, Praeg N, Polidori C, Lucini L, et al. Microplastics make their way into the soil and rhizosphere: A review of the ecological consequences. Rhizosphere. 2022;22:100542.
7.Bostan N, Ilyas N, Akhtar N, Mehmood S, Saman RU, Sayyed R, et al. Toxicity assessment of microplastic (MPs); a threat to the ecosystem. Environmental Research. 2023;234:116523.
8.Wu P, Lin S, Cao G, Wu J, Jin H, Wang C, et al. Absorption, distribution, metabolism, excretion and toxicity of microplastics in the human body and health implications. Journal of Hazardous Materials. 2022;437:129361.
9.Li Y, Tao L, Wang Q, Wang F, Li G, Song M. Potential health impact of microplastics: a review of environmental distribution, human exposure, and toxic effects. Environment & Health. 2023;1(4):249-57.
10.Noruzzadeh R, Modabbernia A, Aghamollaii V, Ghaffarpour M, Harirchian MH, Salahi S, et al. Memantine for Prophylactic Treatment of Migraine Without Aura: A Randomized Double-Blind Placebo-Controlled Study. Headache. 2016;56(1):95-103.
11.Radbakhsh S, Kesharwani P, Sahebkar A. Therapeutic potential of curcumin in autophagy modulation: Insights into the role of transcription factor EB. Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis. 2024;829:111879.
12.Yong CQY, Valiyaveettil S, Tang BL. Toxicity of microplastics and nanoplastics in mammalian systems. International journal of environmental research and public health. 2020;17(05):1509.
13.Radbakhsh S, Barreto GE, Bland AR, Sahebkar A. Curcumin: A small molecule with big functionality against amyloid aggregation in neurodegenerative diseases and type 2 diabetes. Biofactors. 2021;47(4):570-86.
14.Zheng Y, Xu S, Liu J, Liu Z. The effects of micro- and nanoplastic on the central nervous system: A New Threat to Humanity? Toxicology. 2024:153799.
15.Aslam M, Ali MH, Erum W, Shehzadi S, Khalid Z. Effect of Environmental Pollutants on Neurological Disorders. Markhor (The Journal of Zoology). 2021:09-13.
16.Aleya L, Uddin MS. Environmental pollutants and the risk of neurological disorders. Environmental Science and Pollution Research. 2020;27(36):44657-8.
17.Eghbalpour F, Aghaei M, Ebrahimi M, Tahsili MR, Golalipour M, Mohammadi S, et al. Effect of indole-3-carbinol on transcriptional profiling of wound-healing genes in macrophages of systemic lupus erythematosus patients: an RNA sequencing assay. Lupus. 2020;29(8):954-63.
18.Jin H, Yang C, Jiang C, Li L, Pan M, Li D, et al. Evaluation of neurotoxicity in BALB/c mice following chronic exposure to polystyrene microplastics. Environmental health perspectives. 2022;130(10):107002.
19.Amato-Lourenço LF, Dantas KC, Júnior GR, Paes VR, Ando RA, de Oliveira Freitas R, et al. Microplastics in the olfactory bulb of the human brain. JAMA Network Open. 2024;7(9):e2440018-e.
20.Chen M, Du M, Jin A, Chen S, Dasgupta S, Li J, et al. Forty-year pollution history of microplastics in the largest marginal sea of the western Pacific. Geochem Perspect Lett. 2020;13:42-7.

21.de Ruijter VN, Redondo-Hasselerharm PE, Koelmans AA. A brief history of microplastics effect testing: Guidance and prospect. Environmental Pollution. 2025:125711.
22.Martin J, Lusher AL, Nixon FC. A review of the use of microplastics in reconstructing dated sedimentary archives. Science of the Total Environment. 2022;806:150818.
23.Bancone CE, Turner SD, Ivar do Sul JA, Rose NL. The paleoecology of microplastic contamination. Frontiers in Environmental Science. 2020;8:574008.
24.Leng P, Yu H, Wang X, Li D, Feng J, Liu J, et al. Effects of different concentrations and particle sizes of microplastics on the full life history of freshwater Chlorella. Environmental Pollution. 2024;344:123349.
25.Blackburn K, Green D. The potential effects of microplastics on human health: What is known and what is unknown. Ambio. 2022;51(3):518-30.
26.Vethaak AD, Legler J. Microplastics and human health. Science. 2021;371(6530):672-4.
27.Prata JC, Da Costa JP, Lopes I, Duarte AC, Rocha-Santos T. Environmental exposure to microplastics: An overview on possible human health effects. Science of the total environment. 2020;702:134455.
28.Ghosh S, Sinha JK, Ghosh S, Vashisth K, Han S, Bhaskar R. Microplastics as an emerging threat to the global environment and human health. Sustainability. 2023;15(14):10821.
29.Prata JC. Microplastics and human health: Integrating pharmacokinetics. Critical reviews in environmental science and technology. 2023;53(16):1489-511.
30.Yee MS-L, Hii L-W, Looi CK, Lim W-M, Wong S-F, Kok Y-Y, et al. Impact of microplastics and nanoplastics on human health. Nanomaterials. 2021;11(2):496.
31.De-la-Torre GE. Microplastics: an emerging threat to food security and human health. Journal of food science and technology. 2020;57(5):1601-8.
32.Liu S, He Y, Yin J, Zhu Q, Liao C, Jiang G. Neurotoxicities induced by micro/nanoplastics: A review focusing on the risks of neurological diseases. Journal of Hazardous Materials. 2024:134054.
33.Kim DY, Park MK, Yang HW, Woo SY, Jung HH, Son D-S, et al. Effects of Microplastic Accumulation on Neuronal Death After Global Cerebral Ischemia. Cells. 2025;14(4):241.
34.Carlos RA, editor Microplastics and Autism: A plausible link. ISEE Conference Abstracts; 2023.
35.Solleiro-Villavicencio H, Gomez-De León CT, Del Río-Araiza VH, Morales-Montor J. The detrimental effect of microplastics on critical periods of development in the neuroendocrine system. Birth Defects Research. 2020;112(17):1326-40.
36.Li G, Liu X, Sun X, Huang L, Kuang W, Ou J, et al. Polystyrene microplastics induce anxiety via HRAS derived PERK-NF-κB pathway. Environment international. 2024;185:108543.
37.Sofield CE, Anderton RS, Gorecki AM. Mind over microplastics: exploring microplastic-induced gut disruption and gut-brain-axis consequences. Current issues in molecular biology. 2024;46(5):4186-202.
38.Kaushik A, Singh A, Gupta VK, Mishra YK. Nano/micro-plastic, an invisible threat getting into the brain. Chemosphere. 2024;361:142380.
39.Sun J, Peng S, Yang Q, Yang J, Dai Y, Xing L. Microplastics/nanoplastics and neurological health: An overview of neurological defects and mechanisms. Toxicology. 2024:154030.
40.Onyena AP, Aniche DC, Ogbolu BO, Rakib MRJ, Uddin J, Walker TR. Governance strategies for mitigating microplastic pollution in the marine environment: a review. Microplastics. 2021;1(1):15-46.
41.Schuhen K, Sturm MT. Microplastic pollution and reduction strategies. Handbook of Microplastics in the Environment. 2020:1-33.
42.Usman S, Abdull Razis AF, Shaari K, Azmai MNA, Saad MZ, Mat Isa N, et al. The burden of microplastics pollution and contending policies and regulations. International Journal of Environmental Research and Public Health. 2022;19(11):6773.
43.Schuhen K, Sturm MT. Microplastic pollution and reduction strategies. Handbook of Microplastics in the Environment: Springer; 2022. p. 1097-128.
44.Massahi T, Hossini H, Parnoon K, Nouri M, Naseri S, Massahi D. Mitigation Strategies and Policies for Microplastics Pollution in Biotic Systems. Microplastic Pollutants in Biotic Systems: Environmental Impact and Remediation Techniques: ACS Publications; 2024. p. 279-86.
45.Mishra S, Ren Y, Sun X, Lian Y, Singh AK, Sharma N. Microplastics pollution in the Asian water tower: Source, environmental distribution and proposed mitigation strategy. Environmental Pollution. 2024:124247.
46.Ezeh EM, Agu PC. Environmental Risks and Human Health Impact of Microplastic Pollution. Microplastics in African and Asian Environments: The Influencers, Challenges, and Solutions: Springer; 2024. p. 375-94.
47.Watts GF, Chan DC. Microplastics, cardiometabolic risk, genetics and Alzheimer's disease. Current Opinion in Endocrinology, Diabetes and Obesity. 2022;29(2):85-6.
48.Wang G, Lin Y, Shen H. Exposure to polystyrene microplastics promotes the progression of cognitive impairment in Alzheimer's disease: association with induction of microglial pyroptosis. Molecular Neurobiology. 2024;61(2):900-7.
49.Wang S, Han Q, Wei Z, Wang Y, Xie J, Chen M. Polystyrene microplastics affect learning and

memory in mice by inducing oxidative stress and decreasing the level of acetylcholine. Food and Chemical Toxicology. 2022;162:112904.
50.Abdulrahman A. Investigating the link between microplastic exposure (benzyl butyl phthalate) and neurodegenerative diseases using high-performance computational toxicology. Toxicology Research. 2025;14(1):tfae211.
51.Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. The Lancet. 2021;397(10284):1577-90.
52.Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. New England Journal of Medicine. 2023;388(1):9-21.
53.Gou X, Fu Y, Li J, Xiang J, Yang M, Zhang Y. Impact of nanoplastics on Alzheimer's disease: Enhanced amyloid-β peptide aggregation and augmented neurotoxicity. Journal of Hazardous Materials. 2024;465:133518.
54.Jeong A, Park SJ, Lee EJ, Kim KW. Nanoplastics exacerbate Parkinson's disease symptoms in C. elegans and human cells. Journal of Hazardous Materials. 2024;465:133289.
55.Xu J-L, Lin X, Wang JJ, Gowen AA. A review of potential human health impacts of micro- and nanoplastics exposure. Science of the Total Environment. 2022;851:158111.
56.Allouzi MMA, Tang DYY, Chew KW, Rinklebe J, Bolan N, Allouzi SMA, et al. Micro (nano) plastic pollution: The ecological influence on soil-plant system and human health. Science of the Total Environment. 2021;788:147815.
57.Walker TR, Wang L, Horton A, Xu EG. Micro (nano) plastic toxicity and health effects: Special issue guest editorial. Environment International. 2022.
58.Jayavel S, Govindaraju B, Michael JR, Viswanathan B. Impacts of micro and nanoplastics on human health. Bulletin of the National Research Centre. 2024;48(1):1-19.
59.Sangkham S, Faikhaw O, Munkong N, Sakunkoo P, Arunlertaree C, Chavali M, et al. A review on microplastics and nanoplastics in the environment: Their occurrence, exposure routes, toxic studies, and potential effects on human health. Marine Pollution Bulletin. 2022;181:113832.
60.O'Neill SM, Lawler J. Knowledge gaps on micro and nanoplastics and human health: A critical review. Case Studies in Chemical and Environmental Engineering. 2021;3:100091.

Spring 2025, Volume 10, Issue 37 (39- 47) DOI: 10.22034/pmj.2025.2049550.1050

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Pharmacogenomics: Unlocking the Future of Personalized Medicine and Precision Drug Development

Sanaz Khosravi Ghareh Cheh [1,*]

[1]Assistant doctor, Neurology Department, 93413 Cham, Germany.

ARTICLE INFO

Paper Type: Review Article

Submitted: 2025-01-22
Accepted: 2025-05-18

Keywords:
Pharmacogenomics
Personalized medicine
Drug development
Adverse drug reactions
Genomic profiling

Corresponding author:
Sanaz Khosravi Ghareh Cheh, Assistant doctor, Neurology Department, 93413 Cham, Germany. Email: sanazkhosravigharehcheh@gmail.com.

ABSTRACT

Pharmacogenomics is a relatively new subject that utilizes genomics and pharmacology to investigate how genetic variants influence individual responses to treatment with pharmaceuticals. A departure from the conventional "one-size-fits-all" treatment strategy is marked by the advent of pharmacogenomics, which makes it possible to tailor pharmacological regimens to the specific genetic profile of an individual. This domain can lead to significant improvements in pharmacological efficacy, reductions in adverse drug reactions (ADRs), and assistance in developing drugs that are both safe and effective for a wide range of conditions. The purpose of this study is to investigate the prospective results of pharmacogenomics, with a particular emphasis on its function in the process of drug development and its incorporation into personalized medicine. The purpose of this study is to investigate the genetic characteristics that influence the metabolism, efficacy, and toxicity of drugs, as well as to investigate the regulatory framework that is associated with pharmacogenomics testing. This paper summarizes the key genes related to pharmacogenomic responses and discusses the possible challenges in using them in practice, along with the expected advancements in this field of study.

How to Cite this Article:
S. Khosravi Ghareh Cheh . "Pharmacogenomics: Unlocking the Future of Personalized Medicine and Precision Drug Development" Personalized & Precision Medicine Journal, Vol. 10, no. 37, pp. 39- 47

INTRODUCTION

The field of pharmacogenomics is a relatively new field that combines genomics and pharmacology to shed light on the relationship between genetic variation and drug response (1). The human genome has a large number of genetic variants, each of which has the potential to affect how an individual reacts to drugs. There is a correlation between these genetic polymorphisms and the metabolism of drugs, the efficiency of treatments, and the likelihood of adverse drug reactions (ADRs) (2). Through the incorporation of pharmacogenomics data into clinical decision-making, medical professionals can optimize pharmaceutical therapy for specific patients, thereby tailoring therapies to the genetic profiles of those patients (3).

The conventional approach to the production of medications has generally adhered to a uniform strategy, in which a single medicine or dose regimen is delivered to all patients (4). This technique does not take into account genetic variances, which can have a significant impact on an individual's response to medication and how those medications are metabolized (5). Genetic differences in enzymes that help break down drugs, like cytochrome P450, can lead to either weaker effects of the medication or unwanted side effects in patients (6). The goal of personalized medicine, which is driven by pharmacogenomics, is to address these issues by ensuring that patients receive the most effective pharmaceuticals at the optimal dosages that are matched to their genetic profiles (7). When genetic features that influence medication responsiveness are identified, it has the potential to change both the

process of developing new drugs and clinical practice. Pharmacogenomics testing is the examination of several genetic markers to shed light on the ways in which the genetic profile of an individual can influence the effectiveness of a specific pharmacological treatment (8). Practitioners can give more accurate therapies that reduce risks and boost therapeutic effectiveness when they incorporate this knowledge into common practices in the healthcare industry (9). The purpose of this review article is to provide a comprehensive analysis of pharmacogenomics, with the main objective being to investigate its significance in the process of drug discovery, its incorporation into personalized medicine, and its potential for future developments. During the course of the project, genetic mechanisms that influence pharmaceutical responses will be investigated, critical pharmacogenomics genes will be investigated, and clinical applications in a variety of therapeutic spaces will be evaluated (8).

The Role of Pharmacogenomics in Drug Development

Pharmacogenomics is essential in contemporary drug research, informing the creation of safer and more efficacious drugs (9). Integrating genetic data into medication discovery and development enables pharmaceutical companies to enhance the identification of appropriate therapeutic candidates and diminish the probability of clinical trial failures (10). This section examines the influence of pharmacogenomics on drug development, especially regarding personalized medicine.

The Shift toward Personalized Medicine

Pharmacogenomics is essential in contemporary drug research, informing the creation of safer and more efficacious drugs. Bringing genetic information into the process of finding and developing new medications helps drug companies better identify suitable treatment options and reduce the chances of clinical trial failures (10). This section examines the influence of pharmacogenomics on drug development, especially regarding personalized medicine.

The Shift toward Personalized Medicine

Traditionally, the objective of medication research was to construct therapies that would serve the broader population, frequently neglecting the genetic variability within patients (11). The universal approach has resulted in various issues, such as poor treatments for certain individuals and adverse drug reactions (ADRs) in others. Pharmacogenomics mitigates these constraints by facilitating personalized treatment options, wherein medications and dosages are customized according to an individual's distinct genetic profile (12). The transition to customized medicine signifies a fundamental transformation in the delivery of healthcare. Pharmacogenomics testing offers critical insights into how an individual's genetic composition influences their reaction to specific medications (13). For instance, certain genetic differences can cause a medicine to either digest too quickly, limiting its effectiveness, or too slowly, increasing the risk of toxicity (14). By finding genetic differences early, doctors can make better choices about which drugs to use and how much to give, reducing the chances of bad reactions and improving treatment results. With the increasing prevalence of customized medicine, the emphasis is transitioning from creating pharmaceuticals for the "average" patient to formulating drugs tailored to the "specific" patient, informed by their genetic data (15). This change can significantly improve how well medications work and how safe they are, while also reducing healthcare costs by avoiding the guesswork in prescribing drugs.

Early Integration of Pharmacogenomics in Drug Discovery

Pharmacogenomics is influencing clinical decision-making and is being included in the initial phases of drug research (16). In conventional drug development, researchers frequently perform clinical trials with diverse patient populations, presuming that the majority will exhibit comparable responses to a specific medication (17). This assumption can lead to drug candidates being unsuccessful in later stages of clinical development, particularly when the drugs cause unwanted side effects or do not work well for certain groups of patients (18). Pharmacogenomics addresses this difficulty by facilitating the identification of genetic biomarkers that might forecast a patient's reaction to a certain medication. Genomic profiling of patients participating in clinical trials can identify genetic variants that influence medication metabolism, efficacy, and safety (19). By incorporating pharmacogenomics data early in drug discovery, researchers can predict which patient populations are most likely to benefit from a treatment, helping to influence clinical trial design and lower the likelihood of trial failure (20).

The early incorporation of pharmacogenomics in drug research facilitates the identification of genetic variables that lead to treatment resistance. Certain alterations in cancer cells can render malignancies resistant to chemotherapy agents (21). By detecting these mutations promptly, researchers can create tailored treatments that particularly tackle these genetic modifications, enhancing therapeutic efficacy (22).

Regulatory Approaches to Pharmacogenomics

With the expansion of pharmacogenomics, regulatory bodies such as the U.S. Food and Drug Administration (FDA) have acknowledged its

significance in enhancing drug safety and efficacy (23). The FDA has actively formulated guidelines for integrating pharmacogenomics data into drug labeling, assisting doctors in making educated decisions based on patients' genetic profiles (24).

Pharmacogenomics labeling offers critical insights into the influence of genetic differences on medication metabolism, efficacy, and safety. Pharmacogenomics labels on medications such as warfarin, clopidogrel, and abacavir assist healthcare providers in determining the suitable treatment for patients according to their genetic profiles (25). Patients with certain genetic variations in the CYP2C9 gene might need a lower dose of warfarin because they are more sensitive to it, while those with a variant of the HLA-B gene may be at a higher risk of allergic reactions to abacavir (26). Regulatory agencies are helping to include genetic testing in regular medical practice by supporting pharmacogenomics labels for more and more medications. This regulatory initiative is facilitating the wider implementation of pharmacogenomics, which could substantially enhance patient outcomes (27).

Genetic Variation and Drug Response

Genetic variations are a crucial factor in determining individual responses to drugs. These changes can happen in genes that affect how drugs are processed, moved around, and how they interact with their targets, leading to differences in how well medications work, their safety, and their potential side effects (28). This section will look at the two main parts of pharmacogenomics pharmacokinetics and pharmacodynamics and explore how genetic differences affect how people respond to medications.

Pharmacokinetics: How Genetic Variation Affects Drug Metabolism

Pharmacokinetics refers to the mechanisms via which the body absorbs, distributes, metabolizes, and eliminates medicines (29). Genetic differences that impact how the body handles medications are mostly found in genes responsible for drug-metabolizing enzymes, drug transporters, and drug receptors. Genetic differences can lead to markedly divergent medication reactions among individuals, influencing the efficacy and safety of treatment (30). Pharmacogenomics has facilitated the comprehension of these differences and their implications for personalized medicine, allowing for the customization of medication therapy according to an individual's genetic profile (31). Genetic factors that influence pharmacokinetics can change how quickly a drug is absorbed, how it spreads in the body, how fast the liver breaks it down, and how well the kidneys remove it (32). These processes eventually govern the drug concentration at the site of action, which influences the therapeutic impact and the probability of adverse drug reactions (33).

Cytochrome P450 (CYP450) Enzyme Family

The cytochrome P450 (CYP450) enzyme family is a key component in pharmacokinetics. These enzymes facilitate the oxidative metabolism of several therapeutic pharmaceuticals, encompassing those utilized for pain management, depression, cardiovascular disorders, and cancer treatment. The CYP450 family plays a crucial role in phase I drug metabolism, wherein pharmaceuticals undergo modification via oxidation, reduction, or hydrolysis, typically enhancing their water solubility and facilitating excretion (34). Genetic differences in these enzymes can result in modified drug metabolism, which influences individual drug processing. The CYP450 enzyme family comprises more than 50 members, with CYP2D6, CYP2C19, CYP2C9, and CYP3A4 being the most clinically significant. The functional differences in these enzymes can lead to diverse metabolic phenotypes, from poor metabolizers (PMs) to ultra-rapid metabolizers (UMs) (35).

CYP2D6: A Key Enzyme in Drug Metabolism

CYP2D6 is one of the most extensively researched enzymes in pharmacogenomics, metabolizing a diverse range of medications, such as antidepressants, antipsychotics, opioids, and beta-blockers (36). Genetic variation in the CYP2D6 gene can produce varying amounts of enzyme activity, resulting in diverse metabolic phenotypes:
• Suboptimal Metabolizers (SMs): People with less active or non-working versions of the CYP2D6 gene may have lower enzyme activity, which can make it harder for their bodies to process certain drugs. Individuals with poor metabolisms of CYP2D6 substrates may exhibit elevated plasma drug concentrations, thereby heightening the risk of drug toxicity and adverse consequences (37). A poor metabolizer of codeine may not achieve pain relief since CYP2D6 is essential for turning codeine into its active metabolite, morphine. Antidepressants such as paroxetine and fluoxetine may accumulate in the body, resulting in adverse effects including nausea, dizziness, and serotonin syndrome (38).

•Ultra-Rapid Metabolizers (UMs) are people who have multiple copies of the CYP2D6 gene or specific gene variations that make them process drugs much faster. These individuals demonstrate heightened enzyme activity, resulting in accelerated drug metabolism (39). Consequently, therapeutic medication concentrations may remain unattainable due to rapid metabolism and clearance of the drug. People who metabolize tamoxifen very quickly might not get enough benefits from the treatment because the drug needs to be

changed into its active form (endoxifen) by CYP2D6 to work effectively against cancer (40). Due to the considerable heterogeneity in CYP2D6 activity, pharmacogenomics testing can assist doctors in identifying suitable medication and dosage for each patient. Testing for CYP2D6 can help doctors select the right antidepressant or opioid and adjust the dosages based on a person's metabolism, which can reduce the chances of side effects or not getting enough benefit from the treatment (41).

CYP2C19 and Clopidogrel

A notable instance of genetic diversity in drug metabolism pertains to the CYP2C19 enzyme, essential for the metabolism of clopidogrel, an antiplatelet medication commonly employed to avert blood clots, particularly in individuals at risk of myocardial infarctions and cerebrovascular accidents (42). Clopidogrel requires metabolism by the CYP2C19 enzyme to become active and produce its therapeutict (43).
• Diminished Enzyme Activity: Individuals possessing specific CYP2C19 polymorphisms, notably the CYP2C19*2 allele, demonstrate diminished or nonexistent CYP2C19 activity (44). This leads to a reduced activation rate of clopidogrel, making the medication less efficacious in preventing thrombotic incidents such as myocardial infarctions or cerebrovascular accidents. These individuals may face an elevated risk of cardiovascular events owing to the insufficient antiplatelet efficacy of clopidogrel (45). Conversely, individuals possessing the CYP2C19*17 allele, associated with heightened enzyme activity, may encounter an augmented antiplatelet impact, hence elevating the chance of bleeding problems (46).

To lower these risks, it is recommended to test for CYP2C19 gene variations, particularly for people using clopidogrel after being diagnosed with coronary artery disease or having a stent placed (47). For those with weak metabolism, prasugrel or ticagrelor may be safer and more effective than drugs that depend on CYP2C19 for activation. Pharmacogenomic testing can detect these patients and inform therapy choices to enhance clinical outcomes (48).

CYP2C9 and Warfarin

A key example of how drug processing can vary among individuals involves the enzyme CYP2C9, which is important for breaking down warfarin, a commonly used blood thinner. Warfarin is utilized to avert deep vein thrombosis, pulmonary embolism, and stroke in individuals with atrial fibrillation (49). The dosage of warfarin requires meticulous monitoring due to its narrow therapeutic index; insufficient dosage may result in thrombosis, while excessive dosage may cause hemorrhage. Variations in CYP2C9 markedly influence warfarin metabolism and the necessarye (50).

•CYP2C9 Polymorphisms: Individuals possessing specific polymorphisms in the CYP2C9 gene, such as CYP2C9*2 or CYP2C9*3, exhibit a reduced metabolic rate for warfarin compared to individuals with the wild-type allele. These individuals necessitate reduced doses of warfarin to attain the equivalent therapeutic benefit. Failure to appropriately regulate the dosage increases the risk of bleeding problems resulting from excessive anticoagulation (51).

•VKORC1 and Warfarin Sensitivity: In addition to CYP2C9, the VKORC1 gene, which makes the enzyme vitamin K epoxide reductase (52), also plays a role in how sensitive someone is to warfarin. Genetic differences in VKORC1 can also change how much warfarin a person needs, so testing for both CYP2C9 and VKORC1 can help doctors give the right amount of warfarin for better treatment. Pharmacogenomic-guided dosing helps doctors reduce risks by adjusting warfarin treatment based on each person's genetic makeup (53).

Pharmacodynamics: Genetic Variation in Drug Targets

Pharmacodynamics pertains to the effects of medicine on the body, and genetic differences in drug targets can markedly change drug response. Pharmacological targets include receptors, enzymes, and transporters, and genetic differences in these targets can cause variations in how well medications work and their side effects (54). Variations in the human leukocyte antigen (HLA) gene family are linked to hypersensitivity reactions to specific medications. A prominent example is the correlation between the HLA-B57:01 allele and abacavir hypersensitivity. Individuals possessing this genetic variant face a markedly elevated risk of severe allergic reactions to abacavir, an antiretroviral treatment for HIV. Conducting pharmacogenomic testing for HLA-B57:01 before initiating abacavir medication can avert potentially fatals (55).

Another instance of genetic diversity in pharmacological targets is the occurrence of mutations in the EGFR gene in non-small cell lung carcinoma (NSCLC). These mutations correlate with a heightened probability of responding to EGFR-targeted treatments, such as erlotinib or gefitinib. Genetic testing for EGFR mutations helps doctors identify patients who are most likely to benefit from specific treatments, improving results and reducing side effects (56).

Key Genes in Pharmacogenomics

Numerous essential genes significantly impact pharmacogenomics by affecting medication metabolism, effectiveness, and safety. This section offers a summary of key genes in pharmacogenomics and their influence on drug therapy (57).

Cytochrome P450 Enzymes

The CYP450 enzyme family facilitates the metabolism of numerous frequently prescribed medications. Changes in the CYP450 genes can lead to differences in how drugs are processed in the body, which can affect how well they work and their side effects. CYP2D6, CYP2C19, and CYP2C9 are among the most extensively researched CYP450 enzymes. Variations in the CYP2D6 gene influence the metabolism of medications such as tamoxifen, utilized in breast cancer therapy (58). Certain individuals possess genetic variations that render them inefficient metabolizers of tamoxifen, hence diminishing the drug's efficacy (59). Pharmacogenomics testing for CYP2D6 can help doctors decide how to give tamoxifen and other drugs that are processed by this enzyme.

The CYP2C19 gene has a role in the metabolism of clopidogrel, an anticoagulant drug. Genetic testing for CYP2C19 differences can help determine if a patient will benefit from clopidogrel or if they should consider other treatment options (60).

Human Leukocyte Antigen (HLA) Genes

The HLA genes play a crucial role in the immune system's capacity to identify and react to exogenous stimuli. Polymorphisms in specific HLA alleles correlate with drug-induced hypersensitivity reactions (61). The HLA-B57:01 variant is linked to a higher chance of having a bad reaction to abacavir, while the HLA-B15:02 allele is associated with a greater risk of Stevens-Johnson syndrome in people taking carbamazepine (62). Genetic testing for these alleles can assist doctors in refraining from providing medications that may elicit adverse reactions in vulnerable patients (63).

VKORC1 and TPMT

The VKORC1 gene plays a role in the metabolism of warfarin, a widely utilized anticoagulant. Variations in VKORC1 can influence a patient's susceptibility to warfarin, necessitating modifications to the medicine dosage. The TPMT gene affects how the body processes thiopurines, which are a type of medicine used to suppress the immune system in treating leukemia and autoimmune diseases. Genetic testing for VKORC1 and TPMT helps doctors adjust medicine dosages and avoid problems that can happen from taking too much or too little (64).

Applications of Pharmacogenomics in Therapeutic Areas

Pharmacogenomics has important implications for various therapeutic domains, including cardiology, cancer, and psychiatry. This section examines the application of pharmacogenomics across several medical disciplines to enhance patient outcomes (65).

Cardiovascular Drugs

Cardiovascular disorders rank among the foremost causes of mortality globally, and pharmacogenomics possesses the capacity to revolutionize the treatment of these ailments. Numerous cardiovascular medications, including anticoagulants and antiplatelet medicines, are processed by enzymes belonging to the CYP450 family (66). Genetic testing for CYP2C19 polymorphisms can inform the administration of clopidogrel in people predisposed to cardiovascular events. Similarly, pharmacogenomics testing for warfarin sensitivity can assist in establishing the correct dosage for individual patients, minimizing the risk of bleeding problems (66).

Oncology

In oncology, pharmacogenomics facilitates the creation of targeted medicines tailored to specific genetic abnormalities in malignancies. Targeted therapies, such as trastuzumab for breast cancer with HER2 positivity and erlotinib for non-small cell lung cancer with EGFR mutations, offer more effective treatments with fewer side effects compared to traditional chemotherapy (67). Integrating pharmacogenomics testing into standard cancer care enables physicians to discern patients who are most likely to benefit from these medications, hence enhancing survival rates and minimizing needless treatments (68).

Psychiatry

Pharmacogenomics is increasingly essential in the management of psychiatric diseases. Numerous psychiatric medicines, such as antidepressants and antipsychotics, are processed by CYP450 enzymes. Genetic testing for polymorphisms in these enzymes helps identify the most effective drugs for particular patients, hence enhancing therapeutic success and minimizing adverse effects (69). Moreover, pharmacogenomic testing can forecast drug resistance in psychiatric patients, facilitating more precise treatment methods.

Challenges and Future Directions

Pharmacogenomics holds exciting promise, but its wider application in clinical practice requires the resolution of a few challenges. The problems encompass the expense of genetic testing, the absence of defined protocols for pharmacogenomics testing, and ethical issues about genetic privacy (70).

Ethical Considerations and Access to Pharmacogenomics Testing

The growing accessibility of pharmacogenomics tests prompts significant ethical concerns about genetic privacy and the risk of hereditary discrimination. Securing patients' genetic information and ensuring its

responsible utilization will be key to building public trust and promoting the extensive implementation of pharmacogenomics testing (71).

Cost and Accessibility

Even though the cost of genetic testing has significantly decreased over the past few years, it continues to be a barrier to its widespread adoption. Access to these treatments is made more difficult for a significant number of people because there are no standardized reimbursement regulations in place for pharmacogenomics testing (72).

Future Directions in Pharmacogenomics

The future of pharmacogenomics relies on improving our understanding of how genes influence how people respond to medications, making genetic testing more accessible, and better using pharmacogenomic information in medical decisions. With the advancement of genetic technology, pharmacogenomics will increasingly influence personalized medicine and precision drug development (73).

CONCLUSION

Pharmacogenomics indicates a paradigm change in drug discovery and clinical treatment. By integrating genetic data, pharmacogenomics is revolutionizing pharmaceutical therapy. The process facilitates more precise and effective therapies, hence improving patient outcomes by enhancing efficacy and reducing side effects. Pharmacogenomics possesses the capacity to transform medicine development and patient treatment worldwide, and this capacity is expanding as research in this domain progresses. In summary, pharmacogenomics is revolutionizing healthcare by facilitating more personalized and precise therapies that enhance drug efficacy, minimize adverse effects, and optimize patient outcomes. The continuous advancement of research indicates that pharmacogenomics has significant potential to transform pharmaceutical development and patient care.

Pharmacogenomics has the chance to transform medicine by transcending broad treatments and integrating genetic data into clinical decision-making, fostering a genuinely individualized and precision-oriented practice. As this domain advances, it will unveil new prospects for enhancing the safety, efficacy, and efficiency of healthcare, establishing personalized medicine as a fundamental aspect of contemporary medical practice.

Authors' Contribution

Sanaz Khosravi Ghareh Cheh was involved in the conceptualization, design and writing of the manuscript draft. The author read and confirmed the final manuscript.

Funding

Not applicable.

Availability of data and materials

All data are obtainable after an appeal from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1.Davis BH, Limdi NA. Translational Pharmacogenomics: Discovery, Evidence Synthesis and Delivery of Race-Conscious Medicine. Clinical pharmacology and therapeutics. 2021;110(4):909-25.
2.Gummadi AC, Guddati AK. Genetic Polymorphisms in Pharmaceuticals and Chemotherapy. World journal of oncology. 2021;12(5):149-54.
3.Behdani AM, Lai J, Kim C, Basalelah L, Halsey T, Donohoe KL, et al. Optimizing pharmacogenomic decision-making by data science. PLOS digital health. 2024;3(2):e0000451.
4.Tyson RJ, Park CC, Powell JR, Patterson JH, Weiner D, Watkins PB, et al. Precision Dosing Priority Criteria: Drug, Disease, and Patient Population Variables. Frontiers in pharmacology. 2020;11:420.
5.Su J, Yang L, Sun Z, Zhan X. Personalized Drug Therapy: Innovative Concept Guided With Proteoformics. Molecular & Cellular Proteomics. 2024;23(3):100737.
6.Hossam Abdelmonem B, Abdelaal NM, Anwer EKE, Rashwan AA, Hussein MA, Ahmed YF, et al. Decoding the Role of CYP450 Enzymes in Metabolism and Disease: A Comprehensive Review. Biomedicines [Internet]. 2024; 12(7).
7.Sadee W, Wang D, Hartmann K, Toland AE. Pharmacogenomics: Driving Personalized Medicine. Pharmacological reviews. 2023;75(4):789-814.
8.Qahwaji R, Ashankyty I, Sannan NS, Hazzazi MS, Basabrain AA, Mobashir M. Pharmacogenomics: A Genetic Approach to Drug Development and Therapy. Pharmaceuticals [Internet]. 2024; 17(7).
9.Javaid M, Haleem A, Singh RP. Health informatics to enhance the healthcare industry's culture: An extensive analysis of its features, contributions, applications and limitations. Informatics and Health. 2024;1(2):123-48.
10.Qahwaji R, Ashankyty I, Sannan NS, Hazzazi MS, Basabrain AA, Mobashir M. Pharmacogenomics: A Genetic Approach to Drug Development and

Therapy. Pharmaceuticals (Basel, Switzerland). 2024;17(7).
11.Shea L, Pesa J, Geonnotti G, Powell V, Kahn C, Peters W. Improving diversity in study participation: Patient perspectives on barriers, racial differences and the role of communities. Health expectations : an international journal of public participation in health care and health policy. 2022;25(4):1979-87.
12.Micaglio E, Locati ET, Monasky MM, Romani F, Heilbron F, Pappone C. Role of Pharmacogenetics in Adverse Drug Reactions: An Update towards Personalized Medicine. Frontiers in pharmacology. 2021;12:651720.
13.Su J, Yang L, Sun Z, Zhan X. Personalized Drug Therapy: Innovative Concept Guided With Proteoformics. Molecular & cellular proteomics : MCP. 2024;23(3):100737.
14.Marques L, Costa B, Pereira M, Silva A, Santos J, Saldanha L, et al. Advancing Precision Medicine: A Review of Innovative In Silico Approaches for Drug Development, Clinical Pharmacology and Personalized Healthcare. Pharmaceutics [Internet]. 2024; 16(3).
15.Raijada D, Wac K, Greisen E, Rantanen J, Genina N. Integration of personalized drug delivery systems into digital health. Advanced Drug Delivery Reviews. 2021;176:113857.
16.Ahsani-Estahbanati E, Sergeevich Gordeev V, Doshmangir L. Interventions to reduce the incidence of medical error and its financial burden in health care systems: A systematic review of systematic reviews. 2022;9.
17.Abad-Santos F, Aliño SF, Borobia AM, García-Martín E, Gassó P, Maroñas O, et al. Developments in pharmacogenetics, pharmacogenomics, and personalized medicine. Pharmacological Research. 2024;200:107061.
18.Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? Acta pharmaceutica Sinica B. 2022;12(7):3049-62.
19.Hippman C, Nislow C. Pharmacogenomic Testing: Clinical Evidence and Implementation Challenges. Journal of personalized medicine. 2019;9(3).
20.Duan X-P, Qin B-D, Jiao X-D, Liu K, Wang Z, Zang Y-S. New clinical trial design in precision medicine: discovery, development and direction. Signal Transduction and Targeted Therapy. 2024;9(1):57.
21.Marcu LG, Marcu DC. Pharmacogenomics and Big Data in medical oncology: developments and challenges. Therapeutic advances in medical oncology. 2024;16:17588359241287658.
22.Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging Therapeutic Strategies to Overcome Drug Resistance in Cancer Cells. Cancers [Internet]. 2024; 16(13).
23.Kabbani D, Akika R, Wahid A, Daly AK, Cascorbi I, Zgheib NK. Pharmacogenomics in practice: a review and implementation guide. 2023;14.
24.Kabbani D, Akika R, Wahid A, Daly AK, Cascorbi I, Zgheib NK. Pharmacogenomics in practice: a review and implementation guide. Frontiers in pharmacology. 2023;14:1189976.
25.Omran S, Leong SL, Blebil A, Mohan D, Teoh SL. Effectiveness of pharmacogenomics educational interventions on healthcare professionals and health professions students: A systematic review. Research in Social and Administrative Pharmacy. 2023;19(11):1399-411.
26.Kloypan C, Koomdee N, Satapornpong P, Tempark T, Biswas M, Sukasem C. A Comprehensive Review of HLA and Severe Cutaneous Adverse Drug Reactions: Implication for Clinical Pharmacogenomics and Precision Medicine. Pharmaceuticals [Internet]. 2021; 14(11).
27.Scott SA. Personalizing medicine with clinical pharmacogenetics. Genetics in Medicine. 2011;13(12):987-95.
28.Jmel H, Sarno S, Giuliani C, Boukhalfa W, Abdelhak S, Luiselli D, et al. Genetic diversity of variants involved in drug response among Tunisian and Italian populations toward personalized medicine. Scientific Reports. 2024;14(1):5842.
29.Kaye AD, Koress CM, Novitch MB, Jung JW, Urits I, Viswanath O, et al. Pharmacogenomics, concepts for the future of perioperative medicine and pain management: A review. Best Practice & Research Clinical Anaesthesiology. 2020;34(3):651-62.
30.Li Y, Meng Q, Yang M, Liu D, Hou X, Tang L, et al. Current trends in drug metabolism and pharmacokinetics. Acta pharmaceutica Sinica B. 2019;9(6):1113-44.
31.Amaro-Álvarez L, Cordero-Ramos J, Calleja-Hernández M. Exploring the impact of pharmacogenetics on personalized medicine: A systematic review. Farmacia hospitalaria : organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria. 2024;48(6):299-309.
32.Bansal N, Momin S, Bansal R, Gurram Venkata SKR, Ruser L, Yusuf KJPM. Pharmacokinetics of drugs: newborn perspective. 2023. 2023;7.
33.Galeano D, Li S, Gerstein M, Paccanaro A. Predicting the frequencies of drug side effects. Nature Communications. 2020;11(1):4575.
34.Iacopetta D, Ceramella J, Catalano A, Scali E, Scumaci D, Pellegrino M, et al. Impact of Cytochrome P450 Enzymes on the Phase I Metabolism of Drugs. Applied Sciences [Internet]. 2023; 13(10).
35.Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, et al. Cytochrome P450 Enzymes and Drug Metabolism in Humans. International journal of molecular sciences. 2021;22(23).

36.Gopisankar MG. CYP2D6 pharmacogenomics. Egyptian Journal of Medical Human Genetics. 2017;18(4):309-13.
37.Vaidya F, Chhipa A, Mishra V, Gupta V, Rawat S, Kumar A, et al. Molecular and cellular paradigms of multidrug resistance in cancer. Cancer Reports. 2020;5.
38.Nahid NA, Johnson JA. CYP2D6 pharmacogenetics and phenoconversion in personalized medicine. Expert opinion on drug metabolism & toxicology. 2022;18(11):769-85.
39.Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics. 2013;138(1):103-41.
40.He W, Grassmann F, Eriksson M, Eliasson E, Margolin S, Thorén L, et al. CYP2D6 Genotype Predicts Tamoxifen Discontinuation and Prognosis in Patients With Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(6):548-57.
41.Hines LJ, Wilke RA, Myers R, Mathews CA, Liu M, Baye JF, et al. Rationale and design for a pragmatic randomized trial to assess gene-based prescribing for SSRIs in the treatment of depression. Clinical and Translational Science. 2024;17(6):e13822.
42.Ellithi M, Baye J, Wilke RA. CYP2C19 genotype-guided antiplatelet therapy: promises and pitfalls. Pharmacogenomics. 2020;21(12):889-97.
43.Mirabbasi SA, Khalighi K, Wu Y, Walker S, Khalighi B, Fan W, et al. CYP2C19 genetic variation and individualized clopidogrel prescription in a cardiology clinic. Journal of community hospital internal medicine perspectives. 2017;7(3):151-6.
44.Shubbar Q, Alchakee A, Issa KW, Adi AJ, Shorbagi AI, Saber-Ayad M. From genes to drugs: CYP2C19 and pharmacogenetics in clinical practice. 2024;15.
45.Squizzato A, Bellesini M, Takeda A, Middeldorp S, Donadini MP. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events. The Cochrane database of systematic reviews. 2017;12(12):Cd005158.
46.Lee CR, Thomas CD, Beitelshees AL, Tuteja S, Empey PE, Lee JC, et al. Impact of the CYP2C19*17 Allele on Outcomes in Patients Receiving Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. Clinical pharmacology and therapeutics. 2021;109(3):705-15.
47.Pereira NL, Rihal CS, So DYF, Rosenberg Y, Lennon RJ, Mathew V, et al. Clopidogrel Pharmacogenetics. Circulation Cardiovascular interventions. 2019;12(4):e007811.
48.Shubbar Q, Alchakee A, Issa KW, Adi AJ, Shorbagi AI, Saber-Ayad M. From genes to drugs: CYP2C19 and pharmacogenetics in clinical practice. Frontiers in pharmacology. 2024;15:1326776.
49.Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e44S-e88S.
50.Tatarunas V, Lesauskaite V, Veikutiene A, Grybauskas P, Jakuska P, Jankauskiene L, et al. The effect of CYP2C9, VKORC1 and CYP4F2 polymorphism and of clinical factors on warfarin dosage during initiation and long-term treatment after heart valve surgery. Journal of thrombosis and thrombolysis. 2014;37(2):177-85.
51.Zhou X-Y, Lu X-R, Li Y-H, Ma Y-Q, Zhao S-W, Wang F, et al. Identification and Enzymatic Activity Evaluation of a Novel CYP2C9 Allelic Variant Discovered in a Patient. 2021;12.
52.Shaw K, Amstutz U, Kim R, Lesko L, Turgeon J, Michaud V, et al. Clinical Practice Recommendations on Genetic Testing of CYP2C9 and VKORC1 Variants in Warfarin Therapy. Therapeutic drug monitoring. 2015;37:428-36.
53.Azzam H, Elwakeel H, Awad I, El-farahaty R, El-Gilany A-H, El-Sharawy S. VKORC1 and CYP2C9 genotypes in Egyptian patients with warfarin resistance. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2014;27.
54.Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. Genomics, proteomics & bioinformatics. 2016;14(5):298-313.
55.Kolou M, Poda A, Diallo Z, Konou E, Dokpomiwa T, Zoungrana J, et al. Prevalence of human leukocyte antigen HLA-B*57:01 in individuals with HIV in West and Central Africa. BMC Immunology. 2021;22(1):48.
56.Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Seminars in cancer biology. 2020;61:167-79.
57.Hossam Abdelmonem B, Abdelaal NM, Anwer EKE, Rashwan AA, Hussein MA, Ahmed YF, et al. Decoding the Role of CYP450 Enzymes in Metabolism and Disease: A Comprehensive Review. Biomedicines. 2024;12(7).
58.Khan BA, Robinson R, Fohner AE, Muzquiz LI, Schilling BD, Beans JA, et al. Cytochrome P450 Genetic Variation Associated with Tamoxifen Biotransformation in American Indian and Alaska Native People. Clinical and translational science. 2018;11(3):312-21.
59.Mulder TAM, de With M, Del Re M, Danesi R, Mathijssen RHJ, van Schaik RHN. Clinical CYP2D6 Genotyping to Personalize Adjuvant

Tamoxifen Treatment in ER-Positive Breast Cancer Patients: Current Status of a Controversy. Cancers. 2021;13(4).
60.Lopez J, Mark J, Duarte GJ, Shaban M, Sosa F, Mishra R, et al. Role of genetic polymorphisms in clopidogrel response variability: a systematic review. Open heart. 2023;10(2).
61.Deshpande P, Hertzman RJ, Palubinsky AM, Giles JB, Karnes JH, Gibson A, et al. Immunopharmacogenomics: Mechanisms of HLA-Associated Drug Reactions. Clinical pharmacology and therapeutics. 2021;110(3):607-15.
62.Kazaoka A, Fujimori S, Yamada Y, Shirayanagi T, Gao Y, Kuwahara S, et al. HLA-B*57:01-dependent intracellular stress in keratinocytes triggers dermal hypersensitivity reactions to abacavir. PNAS nexus. 2024;3(4):pgae140.
63.Molatefi R, Talebi S, Samei A, Roshanravan N, Manshouri S, Hashemi B, et al. Clues of HLAs, metabolic SNPs, and epigenetic factors in T cell-mediated drug hypersensitivity reactions. Heliyon. 2024;10(14):e33976.
64. Shalia K, Doshi S, Parikh S, Pawar P, Divekar S, Varma S, et al. Prevalence of VKORC1 and CYP2C9 gene polymorphisms in Indian population and its effect on warfarin response. The Journal of the Association of Physicians of India. 2012;60:34-8.
65.Shugg T, Tillman EM, Breman AM, Hodge JC, McDonald CA, Ly RC, et al. Development of a Multifaceted Program for Pharmacogenetics Adoption at an Academic Medical Center: Practical Considerations and Lessons Learned. Clinical Pharmacology & Therapeutics. 2024;116(4):914-31.
66.Mauriello A, Ascrizzi A, Molinari R, Falco L, Caturano A, D'Andrea A, et al. Pharmacogenomics of Cardiovascular Drugs for Atherothrombotic, Thromboembolic and Atherosclerotic Risk. Genes. 2023;14(11).
67.Sentana-Lledo D, Academia E, Viray H, Rangachari D, Kobayashi SS, VanderLaan PA, et al. EGFR exon 20 insertion mutations and ERBB2 mutations in lung cancer: a narrative review on approved targeted therapies from oral kinase inhibitors to antibody-drug conjugates. 2023. 2023;12(7):1590-610.
68.Weth FR, Hoggarth GB, Weth AF, Paterson E, White MPJ, Tan ST, et al. Unlocking hidden potential: advancements, approaches, and obstacles in repurposing drugs for cancer therapy. British Journal of Cancer. 2024;130(5):703-15.
69.Alchakee A, Ahmed M, Eldohaji L, Alhaj H, Saber-Ayad M. Pharmacogenomics in Psychiatry Practice: The Value and the Challenges. International journal of molecular sciences. 2022;23(21).
70.Floris M, Moschella A, Alcalay M, Montella A, Tirelli M, Fontana L, et al. Pharmacogenetics in Italy: current landscape and future prospects. Human Genomics. 2024;18(1):78.
71.Stratton TP, Olson AW. Personalizing Personalized Medicine: The Confluence of Pharmacogenomics, a Person's Medication Experience and Ethics. Pharmacy [Internet]. 2023; 11(3).
72.Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics. 2013;14(15):1833-47.
73.Oates JT, Lopez D. Pharmacogenetics: An Important Part of Drug Development with A Focus on Its Application. International journal of biomedical investigation. 2018;1(2).

Spring 2025, Volume 10, Issue 37 (48- 57) DOI: 10.22034/pmj.2025.2058666.1059

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Advancements in Hysterectomy for Women›s Cancers: A Comprehensive Review of Emerging Surgical Techniques and Clinical Results

Hananeh Habib[1,*], **Samira Abdollahi**[1]

[1]Department of Obstetrics, Medical Faculty, Iran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Paper Type: Review Article

Submitted: 2025-02-02
Accepted: 2025-05-21

Keywords:
Hysterectomy
Gynecologic cancers
Cervical cancer
Robotic-assisted hysterectomy
Surgical precision

Corresponding author:
Hananeh Habib, Department of Obstetrics, Medical Faculty, Iran University of Medical Sciences, Tehran, Iran. Email: Hana.habib.us@gmail.com.

ABSTRACT

Hysterectomy is a common treatment for endometrial, cervical, and ovarian tumors. Although open abdominal hysterectomy is successful, it can result in major recovery times, psychological and physical stress, and complications. Modern surgical methods and technologies have helped these treatments produce better clinical results, recovery times, and problem solving. This paper covers laparoscopic, robotic-assisted, and vaginal hysterectomy. The smaller incisions and better vision help to lower blood loss, hospital stays, and time to start regular activities. This review highlights the transforming results of some surgical and technological innovations in gynecologic cancer treatment driven by thorough research. By increasing the accuracy and outcomes of hysterectomies, these developments lower the long-term physical and psychological consequences of cancer treatment, and survival rates improve. Treatment for endometrial, cervical, and ovarian cancer mostly consists of hysterectomy—uterine excision. Requiring open abdominal surgery, traditional hysterectomy could lead to more problems, longer recovery times, and psychological and physical stress. Modern surgical techniques speed recovery, lower complications, and improve clinical outcomes. This thorough study reveals how technology and surgery have evolved gynecologic cancer treatment. These developments increase therapeutic results and survival rates, so lowering long-term physical and psychological consequences from cancer operations and improving hysterectomy accuracy and efficacy.

How to Cite this Article:
H. Habib, S. Abdollahi. "Advancements in Hysterectomy for Women›s Cancers: A Comprehensive Review of Emerging Surgical Techniques and Clinical Results" Personalized & Precision Medicine Journal, Vol. 10, no. 37, pp. 48- 57.

INTRODUCTION

Gynecologic cancers including endometrial, cervical, and ovarian cancers—which impact the reproductive organs cause a major health concern for women everywhere (1). The American Cancer Society reports that uterine cancer is the most often occurring gynecologic cancer; followed by cervical and ovarian cancers. The frequency of gynecologic tumors depends on geography, risk factors, and healthcare availability; these tumors are a main cause of disease and death among women (2). Consequently, the treatment for many patients depends on hysterectomy excision of the uterus, thus the care of these tumors usually calls for surgical intervention (3).

Depending on the degree of the cancer, a hysterectomy may involve the excision of the uterus together with surrounding tissues including the cervix, ovaries, fallopian tubes, and lymph nodes. Apart from particular patient criteria including age, general health, and reproductive concerns, the degree of surgical resection is directly related with the type and stage of cancer as well as with general condition (4). Early-stage endometrial cancer may require a total hysterectomy that is, the excision of the uterus and cervix while invasive cervical cancer may call for a radical hysterectomy that is, the removal of adjacent tissues including the upper vagina, parametria, and pelvic lymph nodes (5).

Hysterectomy, sometimes known as an abdominal or laparotomy hysterectomy, has been performed historically with an open abdominal incision. Though historically thought of as the gold standard, this

approach has many drawbacks. Usually involving big abdominal incisions, open surgery can cause major postoperative pain, longer hospital stays, and longer recovery times (6). Moreover, open surgical operations could increase the possibility of issues including infections, thrombosis, damage to nearby organs, and others. These restrictions draw attention to the need of less invasive options that could generate equivalent or better oncological results while relieving patient physical and psychological load (7).

Gynecologic cancer surgery has experienced a significant transformation thanks to the evolution and broad implementation of minimally invasive techniques during the past twenty years. Laparoscopic and robotic-assisted surgeries are great alternatives for conventional open operation. Often referred to as "keyhole" surgery, laparoscopic hysterectomy is the process carried off using small incisions through which a camera (laparoscope) and specific surgical tools are introduced. Even in difficult cases, modern invention robotic-assisted hysterectomy uses robotic technologies such the da Vinci Surgical System to enable surgeons in performing extremely accurate and controlled motions (8). Among the several main benefits linked with minimally invasive operations are less blood loss, less postoperative complications, shorter hospital stays, and faster recovery times. Moreover, less scarring helps patients as well as enhances psychological well-being and general quality of life (8).

Moreover, advances in surgical technologies have considerably increased the accuracy and safety of hysterectomy operations. 3D imaging systems enable surgeons to view the surgical site in three dimensions, so improving depth perception and magnification that raises procedural accuracy. Using fluorescent markers to detect cancerous tumors in real-time, intraoperative molecular imaging has shown promise in guaranteeing total excision of malignant tissues, so possibly lowering the risk of recurrence. More individualized and successful treatment programs for women with gynecologic cancers have been made possible by the growing application of personalized medicine, which customizes treatment approaches depending on genetic and molecular profiling (9).

Emphasizing innovative surgical methods changing the course of gynecologic cancers, this paper aims to give a thorough overview of developments in hysterectomy techniques and technologies. This study will look at the present state of laparoscopic, robotic-assisted, and vaginal hysterectomies together with the effect of cutting-edge technologies including 3D imaging and intraoperative molecular imaging in enhancing the accuracy, safety, and outcomes of cancer operations. This paper will review the clinical outcomes of several operations together with their effects on surgical success rates, patient recovery, quality of life, and long-term survival rates. We want to make clear how these developments are changing the course of gynecologic cancer surgery and improving patient outcomes.

Evolution of Hysterectomy Techniques

The development of hysterectomy approaches in recent years is marked by notable changes meant to improve patient outcomes and lower the physical consequences of operations. While open abdominal surgery is still a good choice, many patients—especially those with early-stage malignancies are advised less invasive procedures more and more. In gynecologic oncology, the main hysterectomy techniques used are laparoscopic, robotic-assisted, and vaginal hysterectomy (10).

Laparoscopic Hysterectomy

Thought of as minimally invasive or "keyhole" surgery, laparoscopic hysterectomy passes specialized surgical tools through small abdominal incisions using a small camera called laparoscope. Real-time images of the pelvic area provided by the laparoscope help the surgeon to perform the operation with remarkable accuracy. Treating early-stage gynecologic malignancies including endometrial and cervical cancers (11) this approach is particularly useful if the neoplasm is limited to the uterus or cervix.

Among the advantages of laparoscopic hysterectomy are smaller incisions, less blood loss, less postoperative pain, and faster recovery than in open surgery. Studies comparing laparoscopic hysterectomy with traditional open abdominal surgery show that minimally invasive techniques produce less complications—including hernias and infections—along with a shorter hospital stay. Moreover, patients often find less scarring and can start their regular activities more quickly (12).

Though with many advantages, laparoscopic hysterectomy is not suitable for every patient. For those with advanced-stage cancer or bigger tumors, for example, it could be useless. The complexity of the surgery may demand specific knowledge, hence restricting its general use to facilities furnished with qualified surgical teams (13).

Robotic-Assisted Hysterectomy

Robotic-assisted hysterectomy is a sophisticated variation of minimally invasive surgery in which the surgeon is assisted all during the operation by robotic devices mostly the da Vinci Surgical System. The robotic system consists in robotic arms, a high-definition 3D camera, and specialized tools run by the surgeon from a console. Particularly in challenging locations like the pelvic sidewalls and lymph nodes,

the robotic arms offer better precision and a greater range of motion than traditional laparoscopic tools, so enabling more complex tissue dissection (14).

The better visibility provided by the high-density 3D camera which offers more magnification and depth awareness than traditional laparoscopy is a main advantage of robotic-assisted surgery. This helps doctors to more accurately identify and protect important tissues throughout treatment, including blood vessels and nerves. Robotic hysterectomy has shown good results in terms of minimizing blood loss, improving surgical accuracy, and lowering of recuperation times (15, 16). Moreover, robotic surgery fits with reduced rates of conversion to open surgery, which is typically required when laparoscopic operations encounter technical problems. Several studies (17) indicate that robotic-assisted hysterectomy is particularly helpful in complicated patients such as those involving large tumors, obesity, or past abdominal operations.

Robotic surgery has certain restrictions even if it offers many advantages. While the significant learning curve for surgeons requires great training and practice, the great cost of robotic systems is a major barrier to more general use. As technology gets more reasonably priced and training programs more reachable, robotic-assisted surgery is expected to become a progressively common approach for gynecologic oncologic surgery (18).

Vaginal Hysterectomy

An other minimally invasive approach for hysterectomy is vaginal hysterectomy, in which the uterus is excuted through the vaginal canal. For those with early-stage cervical or endometrial cancer, especially when the uterus is not enlarged, vaginal hysterectomy is a perfect substitute even if it is not appropriate for every patient. This approach does away with abdominal incisions, so reducing pain, hastening recovery, and lowering risk of wound infections (19).

A more direct access path to the uterus allows a vaginal hysterectomy to reduce the risk of damage to nearby structures including the bladder and rectum. Still, its effectiveness depends mostly on the anatomical structure of the patient and the surgeon's experience. Vaginal hysterectomy may not be feasible when the uterus is larger or cancer has spread outside the uterus; laparoscopic or robotic-assisted procedures may be preferred (20).

Technological Innovations in Hysterectomy

In recent years, numerous technological breakthroughs have significantly enhanced the safety, precision, and efficacy of hysterectomy surgeries. These improvements have facilitated surgeons in executing more precise procedures with minimum disturbance to adjacent tissues, ultimately resulting in improved patient outcomes (21).

3D Imaging and Navigation Systems

In gynecologic oncology, 3D imaging and navigation technologies taken together have greatly increased the accuracy and efficacy of surgical treatments for female cancers (22). Modern technology's real-time, high-resolution, three-dimensional pelvic area imaging helps surgeons to perform challenging operations with less risk and more accuracy. While historically surgeons have relied on 2D imaging or visual inspection during operations; the switch to 3D imaging offers a more complete and thorough view of anatomical structures, which is especially important in oncological operations where accuracy is absolutely vital (23). In gynecologic oncology, combining 3D imaging with navigation technologies has drastically raised the potency and accuracy of surgical treatments for women's cancers (22). Modern technologies enable doctors to do challenging surgical operations with more accuracy and less risk by offering real-time, high-resolution, three-dimensional images of the pelvic area. Although surgeons have always used 2D imaging or visual inspection for operations, the change to 3D imaging provides a more complete and detailed view of anatomical structures, which is especially important in cancer operations where accuracy is vital (23).

Enhanced Visualization and Anatomical Understanding

Great caution is required when moving around in the surgical area during gynecologic oncology procedures, which includes the uterus, ovaries, bladder, rectum, and nearby blood vessels, because there are many tissues close together and we want to avoid harming important organs. Unlike the flat, two-dimensional images generated by earlier imaging technologies, 3D imaging systems allow surgeons to view structures in three-dimensional space (24). 3D imaging helps us to better grasp the anatomical diversity and complexity unique to every patient by offering a more exact representation of the relative locations and connections among significant components (25).

Improved visibility is absolutely vital when working on malignancies in the pelvic cavity or other areas near sensitive or inaccessible organs. Surgeons can more easily identify sensitive areas—such as blood vessels or nerve pathways—that might call for extra attention during surgery using 3D imaging. Moreover, 3D imaging helps one better view tumors partially hidden by surrounding tissues, so facilitating more complete tumor removal (26).

Increased Surgical Precision

Although navigation systems and 3D imaging have several benefits, their accuracy during surgical

operations defines most of them. Particularly in cases of very complex gynecologic oncology, traditional surgical operations often depend on the tactile sense of the surgeon. Not always are visual cues present. Using 3D imaging allows surgeons to plan and execute millimeter-level accuracy, so helping to restrict the margin of error (27) in surgical operations. For operations including hysterectomy or tumor resections, the 3D scans, for instance, enable the surgeon to precisely cut incisions and remove malignant tissue. This is achieved by helping the surgeon ascertain, ahead of time the precise size, location, and margins of the tumor (25). Furthermore, real-time monitoring of surgical tools is made possible by the junction of three-dimensional imaging technologies and navigation systems. Using the three-dimensional screen, the surgeons can check their tools to make sure they are pointed correctly within the operative area. Particularly important when dealing with vital organs like blood vessels or ureters, which are vulnerable to damage during gynecologic operations, this live tracking improves the surgeon's ability to execute motions with the highest possible degree of accuracy (27). This accuracy not only reduces the unintentional damage to the surrounding tissues but also increases the general general safety of the operation (28). Though their accuracy during surgical operations defines most of their advantages, both 3D imaging and navigation systems have several advantages. Particularly in cases of gynecologic oncology that are especially complex, conventional surgery usually depends on the tactile sense of the surgeon and offers only limited visual cues. 3D imaging gives surgeons the ability to plan and execute operations with millimeter-level accuracy (27), so helping to lower the margin for error. For example, when performing hysterectomies or tumor resections, the 3D scans can help the surgeon identify the tumor's exact size, position, and borders, allowing for more precise incisions and better removal of malignant tissue. Moreover, the amalgamation of navigation systems with 3D imaging facilitates real-time monitoring of surgical instruments (26). Surgeons could check their instruments on a 3D screen to make sure they are positioned and pointed correctly inside the surgical area. Particularly important when dealing with vital organs like blood vessels or ureters, which are prone to damage during gynecologic operations, this live tracking improves the surgeon's capacity to execute motions with the highest possible degree of accuracy. This degree of accuracy not only reduces the possibility of inadvertent damage to the nearby tissues but also makes the operation more safe generally (28).

Improved Outcomes in Complex Cases

Three-dimensional imaging and navigation tools have proven quite helpful in difficult gynecologic oncology operations. Usually related to advanced-stage cancer, these circumstances call for extra operations, such as lymph node dissection. Under these conditions, structural distortion may cause the tumor to have penetrated surrounding structures, so impeding surgical access (27, 28). Conventional 2D imaging or blind dissection techniques may not be sufficient in these complex conditions to give enough direction; hence, either partial resections, more complications, or worse surgical results (29).

With a thorough, three-dimensional view of the operating area, 3D imaging enhances the surgeon's ability to painstakingly negotiate complex anatomical features. In cases of advanced cervical or endometrial cancer, 3D imaging guarantees precise identification and dissection of these tissues, allowing the tumor to have spread to adjacent lymph nodes or the pelvic wall (30). By precisely locating affected nodes and analyzing the lymphatic network, 3D imaging assists surgeons with lymph node dissection to lower the risk of residual malignant tissue and raise the possibility of total excision.

Moreover, three-dimensional drawings allow surgeons to view the structures from multiple angles and perspectives, thereby helping them avoid inadvertently damaging surrounding tissues. Reduction of the possibility of consequences relevant in advanced gynecologic cancer treatments depends on this ability: lymphedema, bladder or intestinal damage, and hemorrhage (31).

Real-Time Surgical Planning and Decision-Making

Including 3D imaging into the surgical operation enhances procedural execution, intraoperative decision-making, and preoperative planning. Before operation, doctors can develop comprehensive treatment plans using 3D imaging data. This helps to fully grasp the features of the tumor, including its size, form, and proximity to important tissues, so enabling the prediction of possible outcomes (32).

Moreover, real-time, high-resolution images help dynamic decision-making during the surgical operation. Should unanticipated outcomes, such the tumor's interaction with nearby tissues or the discovery of other masses, the surgeon can quickly change their approach depending on the real-time, three-dimensional visual data. Depending on the changing visual data, ensuring the use of the most efficient and least invasive technique during the operation will help to enable real-time change in the surgical plan, so improving the outcomes (33).

Minimizing Surgical Risk and Complications

Often used in gynecologic oncology surgeries, three-dimensional imaging and navigation technologies help to reduce the risks and challenges related with surgical

operations. Modern technologies, which are marked by enhanced visibility and accuracy, greatly lower the possibility of inadvertently destroying important structures (34). Finding and conserving the ureters the tubes that transport urine from the kidneys to the bladder is absolutely critical during a hysterectomy for cervical or endometrial cancer. Two most often occurring results of urinary tract damage are urinary incontinence and renal failure. By skillful traversing and identification of challenging 3D imaging structures, surgeons can reduce the risk of ureteral complications (35).

Moreover, the precision of tumor removal made possible by 3D imaging guarantees the complete elimination of malignant tissue, so lowering the possibility of the tumor resurfacing. Studies using three-dimensional navigation during surgical operations have shown a rise in the percentage of whole tumor excision. This is especially true in cases when the tumor has a complex form or sits in difficult angles (36).

Future Potential and Integration with Other Technologies

As 3D imaging advances and interacts with other innovative technologies, we anticipate improved outcomes for gynecologic cancer surgeries. Three-dimensional imaging, intraoperative molecular imaging (IMI), and real-time lighting of tumor areas together could help doctors perform surgeries more accurately. Three-dimensional anatomical structure research, tissue differentiation between benign and malignant, and a higher probability of total tumor excision (37) would all be made possible by this convergence of technology.

Furthermore, on the brink of significantly improving navigation and 3D imaging systems are algorithms for artificial intelligence (AI) and machine learning. Important anatomical features could be automatically found or possible problems could be predicted using artificial intelligence and real-time imaging data. These advancements could result in more easily available, quick, and user-friendly 3D imaging and navigation systems, so improving surgical outcomes and patient safety (38).

Intraoperative Molecular Imaging

Modern and quickly developing method that can greatly increase surgical oncology's accuracy is intraoperative molecular imaging (IMI). During surgery, it provides real-time, extremely sensitive imaging that helps doctors find malignant areas invisible using more traditional imaging techniques. This sophisticated approach releases observable signals gathered by specialized cameras or imaging devices by using molecular tracers either fluorescent dyes or radioactive materials that are most preferably absorbed by cancer cells. In the management of gynecologic tumors, where the difficulty of obtaining complete tumor excision is sometimes exacerbated by the threat of residual disease, IMI's ability to identify hidden or microscopic cancer cells during surgery is especially important (37).

Principles and Technology Behind IMI

IMI's efficacy derives from the particular biological features of cancer cells. Tumor cells vary from normal tissue in many respects on the metabolic and molecular levels, including the expression of some proteins, enzymes, and receptors. IMI uses tracers able to specifically link to cancer cells to leverage these differences. Specialized imaging tools can see these tracers, usually attached with a radioactive element or a fluorescent dye. Fluorescent dyes, unlike radioactive tracers, emit light when excited by a specific wavelength (39).

Cancerous cells absorb the tracers once the tracers are injected into the patient either locally at the tumor site or systemically via the veins and arteries. Using specific imaging methods, the surgeon can view the surgical area and spot cancerous tissue depending on tracer signals. This process helps to identify tumor margins at a microscopic level, thereby improving the chances of total resection and reducing the possibility of residual malignant cells (40). When IMI is combined with more conventional imaging techniques such as MRI, CT, or ultrasonic waves, its advantages become most apparent. These methods may overlook small, subclinical cancer cell deposits or differentiate between benign and malignant tissues even if they do a great job of illuminating structures and anatomy. Using functional molecular data, IMI assists the surgeon in real time to ensure the complete removal of cancer cells, thereby preserving healthy tissue (41).

Applications in Gynecologic Oncology

In the field of gynecologic malignancies, I MI has shown great promise in improving surgical outcomes, particularly in cancers including ovarian, endometrial, and cervical ones with increased risk of residual disease. Many cancer types are associated with the microscopic spread of malignant cells that might go unnoticed to the unaided eye even in advanced disease stages (42).

1. Ovarian cancer

Usually resulting from its asymptomatic features in the first phases, ovarian cancer is often found at advanced stages. Small aggregates of cancer cells can be difficult to separate from surrounding healthy tissue once the tumor is found since the disease may have already spread to other areas of the abdomen or pelvis (43). In helping surgeons find peritoneal implants or

minor metastases otherwise missed, IMI has shown great promise. More thorough debulking which is necessary to improve patient outcomes is made possible by the ability to identify microscopic spread. Studies have shown that the use of fluorescent dyes, such indocyanine green (ICG), in ovarian cancer operations can help identify even minute deposits of cancer, so lowering the possibility of partial resection (44).

2. Endometrial Cancer

The most common gynecologic cancer is endometrial cancer, thus even if it is usually found early on, advanced cases may show difficult to detect lymphatic metastases or peritoneal dissemination. Particularly useful in spotting lymph node metastases—a common site for endometrial cancer's spread—is IMI (45). Radiolabeled tracers or fluorescent compounds allow surgeons to identify and remove affected lymph nodes during operation, so improving staging accuracy and lowering the risk of recurrence. Furthermore, IMI helps to confirm that the tumor margins are free of residual cancer cells, so reducing the local recurrence risk (46).

3. Cancer of the Colon

Often times, cervical cancer results in the tumor spreading to lymph nodes and parametrial tissues. Advanced stages may see the tumor permeating nearby tissues, so complicating the surgeon's ability to differentiate between malignant and normal structures. IMI offers a very successful approach for spotting tiny clusters of cancer cells that might have spread outside of the main tumor (47). In particular, IMI applied during a radical hysterectomy in cervical cancer can help to dissection affected lymph nodes and surrounding tissues, so enabling a more complete excision of malignant cells. Additionally under research is IMI's ability to identify pelvic lymph node metastases, a vital factor influencing treatment plan and cervical cancer patient prognosis (48).

Benefits of IMI in Gynecologic Cancer Surgery

Including IMI in gynecologic cancer operations has a number of advantages that would greatly affect patient outcomes:

1. Enhanced Tumor Excision Accuracy:

I MI can identify cancerous tissue unlike more conventional methods. Among its main benefits are these ones. By means of even small or microscopic cancerous cluster identification, the surgeon can remove all malignant tissue. This reduces the possibility of disease continuation, which might cause recurrence and negative effects down the road. In cases of diseases like ovarian and endometrial malignancies, which often spread microscopically, it is especially important to remove the tumor in whole. Improving survival rates depends on removing all malignant tissue during surgery (49).

2. Stopping Next Occurrences

Increasing the degree of tumor excision helps MI reduce the possibility of cancer returning. This is especially crucial for gynecologic tumors because local recurrence or metastases raise serious concerns. In ovarian cancer, for instance, sophisticated imaging might not be able to show the spread of small cancer cells to lymph nodes or the peritoneum. Minimizing the possibility of postoperative recurrence helps me, MI, to guarantee thorough investigations of these areas and, if necessary, biopsies or resections during surgery (50).

3. Drop in the postoperative problem incidence.

By helping doctors avoid needless dissecting of healthy tissues, IMI helps to lower the risk of damage to vital organs, including the bladder, bowel, and blood vessels. By accurately distinguishing cancerous tissue from healthy tissue, IMI lessens the need to remove healthy parts and helps avoid problems like bleeding, organ harm, and infections after surgery. In pelvic region surgeries, where vital organs are nearby (51), such identification is especially crucial.

4. Improved Treatment schedules and Staging

Excellent cancer treatment depends critically on accurate staging. I MI can increase staging accuracy by spotting malignant lymph nodes or metastatic tumors that might escape conventional imaging modalities. This improved capacity to evaluate the spread of disease guides choices on adjuvant treatments, including targeted therapies, radiation, or chemotherapy. More exact staging helps IMI to improve tailored treatment plans and increase general survival rates (52).

Challenges and Limitations of IMI

Though MI has tremendous promise, its general application in clinical practice is hampered. One great restriction is the need for specific tools and knowledge. Integrating IMI into regular surgical operations still requires a major infrastructure, equipment, and training investment even if technology is becoming more user-friendly. Using molecular tracers allows one to thoroughly evaluate the pharmacokinetics and safety aspects of the chosen drugs. A short half-life, poor tissue penetration, or inability to link to cancer cells while avoiding healthy tissue could make some radioactive tracers or fluorescent dyes useless (53).

The need for thorough clinical studies to show the safety and efficacy of new imaging agents and tracers as part of regulatory licensing adds still another level of challenge. Given their great cost, access to molecular imaging agents and specialized equipment

may be difficult when resources are limited.

Clinical Outcomes and Patient-Centered Considerations

Alongside the technical components of surgery, patient outcomes are a vital factor in assessing various hysterectomy methods. These outcomes encompass oncological findings (e.g., survival rates, recurrence rates), postoperative complications, recuperation durations, and the effect on a patient's quality of life (54).

Oncologic Outcomes

Any surgical intervention aimed at cancer has as its main goal improving survival rates. Studies on oncologic results using laparoscopic, robotic, and open hysterectomy methods abound. Especially for patients with early-stage cancers, these studies show that minimally invasive methods like robotic and laparoscopic hysterectomy have similar cancer outcomes to traditional open surgery (55). Equivalent survival results have been shown from robotic-assisted surgery; some studies suggest it may improve accuracy during lymph node dissection, which is essential for staging and prognosis (56).

Patient-Reported Outcomes

Crucially important markers of surgical success are patient-reported outcomes (PRRs), which include psychological well-being, quality of life, and pain levels. Particularly laparoscopic and robotic-assisted hysterectomy, minimally invasive procedures have shown to dramatically lower PROs when compared to open surgery (57). Those undergoing minimally invasive surgeries have less postoperative pain, fewer complications, and a faster return to normal activity. These advantages help patients to recover emotionally and psychologically since they often have less worry about the surgical treatment and recovery (54).

Since minimally invasive hysterectomy usually results in fewer scars, less pain, and a faster return to normal function, studies have also shown that it may result in better long-term quality of life for patients. It is important not to undervalue the psychological effects of surgery, since fewer problems and a shorter recovery time could help reduce the emotional load related to cancer treatment (58).

Personalized Treatment Approaches

Recent interest in the possible benefits of customized medicine in the therapy of diseases afflicting women has been rather active. Individual characteristics of patients age, tumor type, cancer stage, comorbidities, genetic composition, and molecular background—all help to direct the tailoring of hysterectomy treatments. These factors affect choices about the optimal surgical technique and the necessity of adjuvant treatments, such as radiation or chemotherapy (59).

For patients with advanced-stage malignancies, strict open surgical operations combined with chemotherapy or radiation may be necessary; for those with early-stage cancers, minimally invasive treatments may be successful. In addition to estimating the probability of recurrence, molecular markers and genetic profiles guide targeted treatment (60).

Challenges and Future Directions

Modern hysterectomy techniques have resolved many issues, but some still persist. One of the main problems is that, considering its substantial cost, robotic surgery is not offered in all nations or healthcare systems. Furthermore, not every surgeon will possess the required skills to execute robotic-assisted surgery even if, under the direction of qualified professionals, it has shown remarkable success (61).

Future research should focus on developments in robotic systems, cost reductions, and training courses allowing this technology to be more generally available. Furthermore, necessary for evaluation of the long-term effects of minimally invasive operations for advanced-stage cancer are continuous research and clinical trials. Applied in surgical planning and decision-making, artificial intelligence and machine learning can improve surgical results and change treatment strategies.

CONCLUSION

Minimally invasive and robotic-assisted methods for hysterectomy have revolutionized the treatment of tumor- invading women. Faster recovery times, fewer postoperative problems, and improved surgical accuracy are a few advantages of these improvements. Still unaddressed are issues with access, money, and specialized knowledge. Thanks to advancements in molecular profiling and technology, patients can now have customized treatment programs that are highly likely to improve their outcomes. Future hysterectomies for gynecologic cancers will definitely vary depending on continuous clinical research and improvements in surgical equipment, so optimizing patient outcomes and quality of life.

Authors's Contribution

Hananeh Habib: Conceptualization and writing. The authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable

REFERENCES

1. Zhu B, Gu H, Mao Z, Beeraka NM, Zhao X, Anand MP, et al. Global burden of gynaecological cancers in 2022 and projections to 2050. Journal of global health. 2024;14:04155.
2. Bassette E, Ducie JA. Endometrial Cancer in Reproductive-Aged Females: Etiology and Pathogenesis. Biomedicines. 2024;12(4).
3. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. CA: a cancer journal for clinicians. 2019;69(4):258-79.
4. Bianchi T, Grassi T, Bazzurini L, Di Martino G, Negri S, Fruscio R, et al. Radical Hysterectomy in Early-Stage Cervical Cancer: Abandoning the One-Fits-All Concept. Journal of personalized medicine. 2023;13(9).
5. Chou B, Prasad Venkatesulu B, Coleman RL, Harkenrider M, Small Jr W. Management of stage I and II cervical cancer: a review. International Journal of Gynecological Cancer. 2022;32(3):216-24.
6. Amarin ZO. Hysterectomy: Past, Present and Future. In: Amarin ZO, editor. Hysterectomy - Past, Present and Future. Rijeka: IntechOpen; 2022.
7. Zhang W, Jiang H, Wu G, Huang P, Wang H, An H, et al. The pathogenesis and potential therapeutic targets in sepsis. MedComm. 2023;4(6):e418.
8. Boggi U, Vistoli F, Amorese G. Twenty years of robotic surgery: a challenge for human limits. Updates in surgery. 2021;73(3):789-93.
9. Reddy K, Gharde P, Tayade H, Patil M, Reddy LS, Surya D. Advancements in Robotic Surgery: A Comprehensive Overview of Current Utilizations and Upcoming Frontiers. Cureus. 2023;15(12):e50415.
10. Yurtkal A, Canday M. Optimizing Hysterectomy: A Prospective Comparative Analysis of Surgical Techniques and Their Impact on Women's Lives. Journal of personalized medicine [Internet]. 2024; 14(3).
11. 30th International Congress of the European Association for Endoscopic Surgery (EAES) Kraków, Poland, 5–8 July 2022. Surgical Endoscopy. 2023;37(1):1-204.
12. Chakraborty N, Rhodes S, Luchristt D, Bretschneider CE, Sheyn D. Is total laparoscopic hysterectomy with longer operative time associated with a decreased benefit compared with total abdominal hysterectomy? American journal of obstetrics and gynecology. 2023;228(2):205.e1-.e12.
13. Levy L, Tsaltas J. Recent advances in benign gynecological laparoscopic surgery. Faculty reviews. 2021;10:60.
14. Rivero-Moreno Y, Echevarria S, Vidal-Valderrama C, Pianetti L, Cordova-Guilarte J, Navarro-Gonzalez J, et al. Robotic Surgery: A Comprehensive Review of the Literature and Current Trends. Cureus. 2023;15(7):e42370.
15. Ashrafian H, Clancy O, Grover V, Darzi A. The evolution of robotic surgery: surgical and anaesthetic aspects. British Journal of Anaesthesia. 2017;119:i72-i84.
16. Picozzi P, Nocco U, Labate C, Gambini I, Puleo G, Silvi F, et al. Advances in Robotic Surgery: A Review of New Surgical Platforms. Electronics [Internet]. 2024; 13(23).
17. Kalata S, Thumma JR, Norton EC, Dimick JB, Sheetz KH. Comparative Safety of Robotic-Assisted vs Laparoscopic Cholecystectomy. JAMA Surgery. 2023;158(12):1303-10.
18. Łajczak P, Janiec J, Żerdziński K, Jóźwik K, Nowakowski P, Nawrat Z. M.D. meets machine: the symbiotic future of surgical learning. European Surgery. 2024;56(5):131-42.
19. Muppala H, Rafi J, Najia SK. Laparoscopic-assisted vaginal hysterectomy for endometrial cancer in high body mass index (BMI) patients: a report of six cases. Gynecological Surgery. 2009;6(2):119-23.
20. Meriwether KV, Antosh DD, Olivera CK, Kim-Fine S, Balk EM, Murphy M, et al. Uterine preservation vs hysterectomy in pelvic organ prolapse surgery: a systematic review with meta-analysis and clinical practice guidelines. American journal of obstetrics and gynecology. 2018;219(2):129-46.e2.
21. Patel N, Chaudhari K, Jyotsna G, Joshi JS. Surgical Frontiers: A Comparative Review of Robotics Versus Laparoscopy in Gynecological Interventions. Cureus. 2023;15(11):e49752.
22. Cai Z, Zhang K, Li L, Suo Y. Application of 3D reconstruction and 3D printing technology in advanced ovarian cancer surgery: a retrospective study. Frontiers in oncology. 2024;14:1432970.
23. Zhang J, Liu X, Huang Y, Kong L, Su M, Hu Z. 3D reconstructed models based on real cervical cancer cases for undergraduate gynecological oncology education: a pre- and post-test study. 3D Printing in Medicine. 2025;11(1):7.
24. Kanbergs A, Melamed A, Viveros-Carreño D, Wu CF, Wilke RN, Zamorano A, et al. Surgical Deescalation Within Gynecologic Oncology. JAMA network open. 2025;8(1):e2453604.
25. Alaimo L, Marchese A, Vignola D, Roman D, Conci S, De Bellis M, et al. The Role of Three-Dimensional Modeling to Improve Comprehension of Liver Anatomy and Tumor Characteristics for Medical Students and Surgical Residents. Journal of Surgical Education. 2024;81(4):597-606.

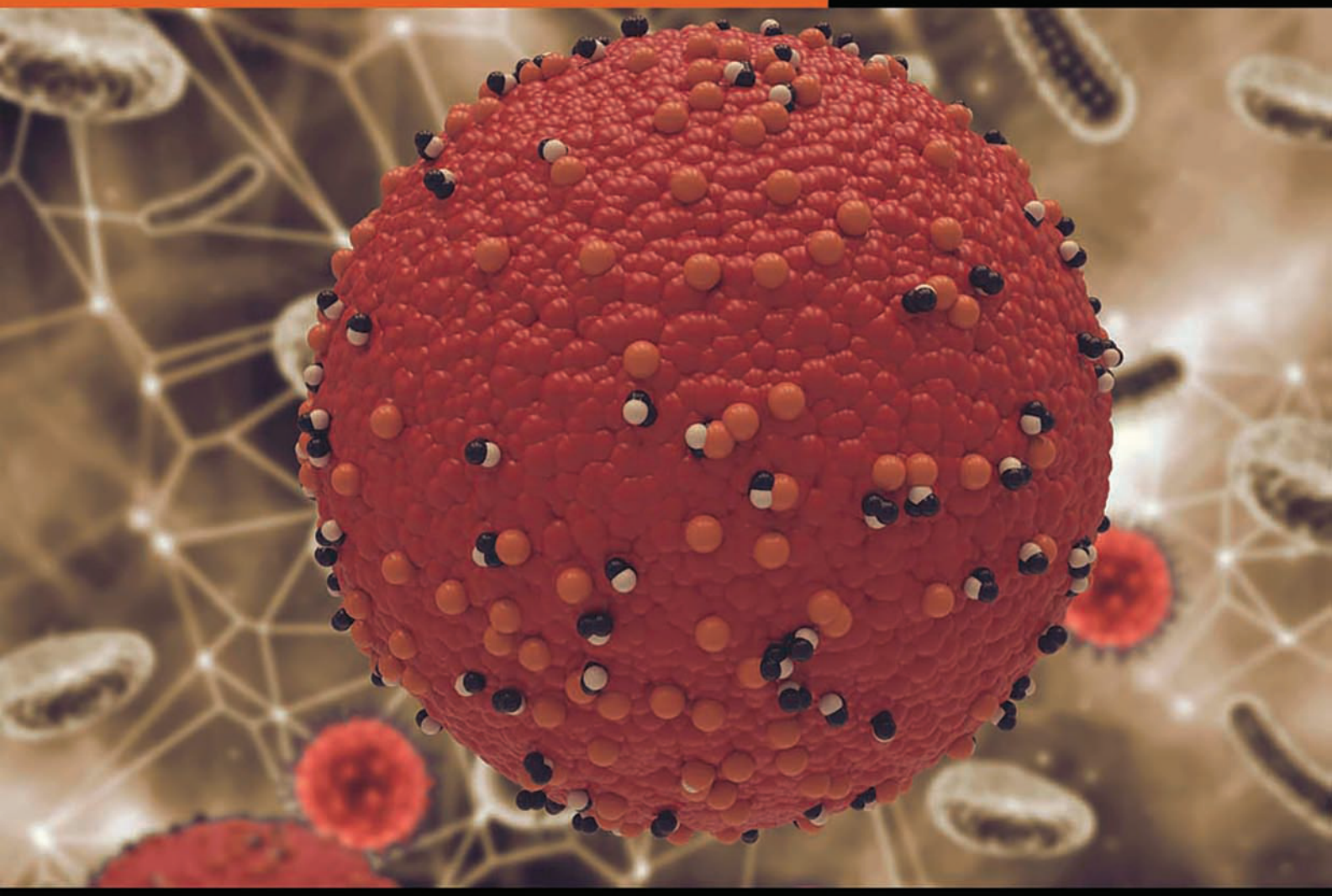
26.Meyer-Szary J, Luis MS, Mikulski S, Patel A, Schulz F, Tretiakow D, et al. The Role of 3D Printing in Planning Complex Medical Procedures and Training of Medical Professionals-Cross-Sectional Multispecialty Review. International journal of environmental research and public health. 2022;19(6).
27.Liu Y, Wu X, Sang Y, Zhao C, Wang Y, Shi B, et al. Evolution of Surgical Robot Systems Enhanced by Artificial Intelligence: A Review. Advanced Intelligent Systems. 2024;6(5):2300268.
28.Hou Y, Tang J. Advantages of Using 3D Intraoperative Ultrasound and Intraoperative MRI in Glioma Surgery. Frontiers in oncology. 2022;12:925371.
29.Pulumati A, Pulumati A, Dwarakanath BS, Verma A, Papineni RVL. Technological advancements in cancer diagnostics: Improvements and limitations. Cancer reports (Hoboken, NJ). 2023;6(2):e1764.
30.Zhang J, Liu X, Huang Y, Kong L, Su M, Hu Z. 3D reconstructed models based on real cervical cancer cases for undergraduate gynecological oncology education: a pre- and post-test study. 3D Print Med. 2025;11(1):7.
31.Alkatout I, O'Sullivan O, Peters G, Maass N. Expanding Robotic-Assisted Surgery in Gynecology Using the Potential of an Advanced Robotic System. Medicina [Internet]. 2024; 60(1).
32.Portnoy Y, Koren J, Khoury A, Factor S, Dadia S, Ran Y, et al. Three-dimensional technologies in presurgical planning of bone surgeries: current evidence and future perspectives. International journal of surgery (London, England). 2023;109(1):3-10.
33.Liu Z, Ali M, Sun Q, Zhang Q, Wei C, Wang Y, et al. Current status and future trends of real-time imaging in gastric cancer surgery: A literature review. Heliyon. 2024;10(16):e36143.
34.Riddle EW, Kewalramani D, Narayan M, Jones DB. Surgical Simulation: Virtual Reality to Artificial Intelligence. Current Problems in Surgery. 2024;61(11):101625.
35.Restaino S, De Giorgio MR, Pellecchia G, Arcieri M, Vasta FM, Fedele C, et al. Artificial Intelligence in Gynecological Oncology from Diagnosis to Surgery. Cancers [Internet]. 2025; 17(7).
36.Privitera L, Paraboschi I, Cross K, Giuliani S. Above and Beyond Robotic Surgery and 3D Modelling in Paediatric Cancer Surgery. Frontiers in pediatrics. 2021;9:777840.
37.Azari F, Zhang K, Kennedy GT, Chang A, Nadeem B, Delikatny EJ, et al. Precision Surgery Guided by Intraoperative Molecular Imaging. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2022;63(11):1620-7.
38.Pinto-Coelho L. How Artificial Intelligence Is Shaping Medical Imaging Technology: A Survey of Innovations and Applications. Bioengineering (Basel, Switzerland). 2023;10(12).
39.Schiliro C, Firestein BL. Mechanisms of Metabolic Reprogramming in Cancer Cells Supporting Enhanced Growth and Proliferation. Cells. 2021;10(5).
40.Wang B, Hu S, Teng Y, Chen J, Wang H, Xu Y, et al. Current advance of nanotechnology in diagnosis and treatment for malignant tumors. Signal Transduction and Targeted Therapy. 2024;9(1):200.
41.Bi WL, Hosny A, Schabath MB, Giger ML, Birkbak NJ, Mehrtash A, et al. Artificial intelligence in cancer imaging: Clinical challenges and applications. CA: a cancer journal for clinicians. 2019;69(2):127-57.
42.Centini G, Schettini G, Pieri E, Giorgi M, Lazzeri L, Martire FG, et al. Endometriosis-Related Ovarian Cancer: Where Are We Now? A Narrative Review towards a Pragmatic Approach. Journal of Clinical Medicine [Internet]. 2024; 13(7).
43.Lengyel E. Ovarian cancer development and metastasis. The American journal of pathology. 2010;177(3):1053-64.
44.Azari F, Kennedy GT, Zhang K, Bernstein E, Maki RG, Gaughan C, et al. Impact of Intraoperative Molecular Imaging after Fluorescent-Guided Pulmonary Metastasectomy for Sarcoma. Journal of the American College of Surgeons. 2022;234(5):748-58.
45.Teng F, Yu H, Wang B, Yan Y, Gao C, Guo F, et al. Patterns of lymph node metastases and their implications in individualized radiotherapeutic clinical target volume delineation of regional lymph nodes in patients with endometrial cancer. Journal of Cancer. 2022;13(14):3575-83.
46.Fumagalli D, De Vitis LA, Caruso G, Occhiali T, Palmieri E, Guillot BE, et al. Low-Volume Metastases in Apparent Early-Stage Endometrial Cancer: Prevalence, Clinical Significance, and Future Perspectives. Cancers (Basel). 2024;16(7).
47.Birge O, Bakir MS, Dogan S, Tuncer HA, Simsek T. The Relationship Between Parametrial Involvement and Parametrial Tissue Removed in Radical Surgery in Early-Stage Cervical Cancer. World journal of oncology. 2022;13(2):59-68.
48.Eissa A, Sighinolfi MC, Elsodany I, Habib G, Puliatti S, Zoeir A, et al. Robotic Pelvic Lymphadenectomy in Gynecological and Urological Malignancies. 2023;50(6).
49.Azari F, Kennedy G, Bernstein E, Hadjipanayis C, Vahrmeijer A, Smith B, et al. Intraoperative molecular imaging clinical trials: a review of 2020 conference proceedings. Journal of biomedical optics. 2021;26(5).
50.Yeung TL, Leung CS, Yip KP, Au Yeung CL, Wong ST, Mok SC. Cellular and molecular processes in

ovarian cancer metastasis. A Review in the Theme: Cell and Molecular Processes in Cancer Metastasis. American journal of physiology Cell physiology. 2015;309(7):C444-56.
51.Vahrmeijer AL, Hutteman M, van der Vorst JR, van de Velde CJH, Frangioni JV. Image-guided cancer surgery using near-infrared fluorescence. Nature Reviews Clinical Oncology. 2013;10(9):507-18.
52.Scheenen TWJ, Zamecnik P. The Role of Magnetic Resonance Imaging in (Future) Cancer Staging: Note the Nodes. Investigative radiology. 2021;56(1):42-9.
53.Rony MKK, Kayesh I, Bala SD, Akter F, Parvin MR. Artificial intelligence in future nursing care: Exploring perspectives of nursing professionals - A descriptive qualitative study. Heliyon. 2024;10(4):e25718.
54.Yurtkal A, Canday M. Optimizing Hysterectomy: A Prospective Comparative Analysis of Surgical Techniques and Their Impact on Women's Lives. Journal of personalized medicine. 2024;14(3).
55.Kim SI, Yoo JG, Lee SJ, Park DC, Yoon JH. Robot-assisted versus conventional laparoscopic radical hysterectomy in cervical cancer stage IB1. International Journal of Medical Sciences. 2023;20(3):287-91.
56.Argenta PA, Mattson J, Rivard CL, Luther E, Schefter A, Vogel RI. Robot-assisted versus laparoscopic minimally invasive surgery for the treatment of stage I endometrial cancer. Gynecologic oncology. 2022;165(2):347-52.
57.Ioana JT, Voiță-Mekereș F, Motofelea AC, Ciprian D, Fulger L, Alexandru I, et al. Surgical Outcomes in Laparoscopic Hysterectomy, Robotic-Assisted, and Laparoscopic-Assisted Vaginal Hysterectomy for Uterine and Cervical Cancers: A Systematic Review. Diagnostics [Internet]. 2024; 14(24).
58.Bartels HC, Rogers AC, Janda M, Obermair A, Brennan DJ. Quality of life following minimally invasive hysterectomy compared to abdominal hysterectomy: A metanalysis. European journal of obstetrics, gynecology, and reproductive biology. 2020;252:206-12.
59.Masucci M, Karlsson C, Blomqvist L, Ernberg I. Bridging the Divide: A Review on the Implementation of Personalized Cancer Medicine. Journal of personalized medicine [Internet]. 2024; 14(6).
60.Khiabani NA, Doustvandi MA, Story D, Nobari SA, Hajizadeh M, Petersen R, et al. Glioblastoma therapy: State of the field and future prospects. Life Sciences. 2024;359:123227.
61.McCarthy A, Samarakoon D, Gray J, Mcmeekin P, McCarthy S, Newton C, et al. Robotic and laparoscopic gynaecological surgery: a prospective multicentre observational cohort study and economic evaluation in England. 2023;13(9):e073990.

Personalized & Precision Medicine JOURNAL

The Future of Medicine is Personalized

10 year / No. 37
Spring 2025
License Holder:
AmitisGen TECH Dev Group
ISSN:3115-7874



www.pmjournal.ir