Science Innovation
INTERNATIONAL SCIENTIFIC JOURNAL

ISSN: 2181-3337

SCIENCE & INNOVATION

INTERNATIONAL SCIENTIFIC JOURNAL

VOLUME 5 | ISSUE 9 | 2026
Series D: Medical Sciences

Science Innovation
INTERNATIONAL SCIENTIFIC JOURNAL

International Scientific Journal
SCIENCE AND INNOVATION

Series D
Volume 5 Issue 9
September 2026

Tashkent 2026

INTERNATIONAL SCIENTIFIC JOURNAL

SCIENCE & INNOVATION

Series D: Medical Sciences

VOLUME	ISSUE	PUBLICATION DATE	PLACE
5	9	31 SEPTEMBER 2026	TASHKENT

ISSUE IDENTIFICATION

RECOMMENDED ISSUE CITATION

Science and Innovation. Series D: Medical Sciences. Volume 5, Issue 9, 31 August 2026. Tashkent: Science and Innovation LLC. ISSN 2181-3337.

Individual article DOIs are registered through Crossref under prefix 10.67620.

JOURNAL INFORMATION

Volume / issue	Volume 5 · Issue 9	**Publication date**	31 September 2026
ISSN	2181-3337	**Publisher**	Science and Innovation LLC
Established	2022	**Publication language**	English
Frequency	Monthly	**Publication format**	Electronic · Open Access
Peer review	Double-blind peer review	**License**	Creative Commons Attribution 4.0
DOI registration	Crossref · Prefix 10.67620	**Official website**	https://scientists.uz

AIMS AND SCOPE

Series D publishes original research and reviews in clinical and preclinical medicine, public health, pediatrics, dentistry, pharmacy and pharmacology, biomedical sciences, health education, healthcare management, and other interdisciplinary areas relevant to human health and medical practice.

EDITORIAL AND PUBLICATION STANDARDS

PEER REVIEW

Editorial screening, integrity checks, independent double-blind review, and a documented editorial decision.

ETHICS & CORRECTIONS

Conflicts of interest, authorship, misconduct, corrections, retractions, complaints, and appeals are handled under published journal policies.

AI TRANSPARENCY

Authors must disclose substantive use of generative AI. AI tools cannot be credited as authors; responsibility remains with the human authors.

EDITORIAL OFFICE

Bakhtiyor Rustamov	CEO Science and innovation LLC	**Kozim Ergashov**	Academic Editor
Gulira'no Rakhmatullayeva	Responsible Secretary	**Feruzabonu Mannonova**	Language Editor
Feruza Ollomurodova	Manuscript Coordinator	**Jahongir Bekmuradov**	Language Editor
Farangiz Sagdullaeva	Technical Editor	**Anvar Ergashev**	Digital Media Designer
Dilnoza Narzullayeva	Editorial Manager	**Asila Khaydaralieva**	Academic Editor
Sevara O'rinboyeva	Editorial Manager	**Bakhrom Qurbonov**	Digital Media Designer

PUBLISHER AND CONTACT

Science and Innovation LLC · Mass Media License No. 1597 (27 April 2022) Publishing License No. 455168 (21 November 2024)
150 Shota Rustaveli Street, Vega Business Center, 6th floor, Room 2, Tashkent 100121, Uzbekistan
info@scientists.uz · +998 90 125 96 54 · https://scientists.uz · https://science-innovation.org

© 2026 Authors. Published by Science and Innovation LLC under CC BY 4.0.

SCIENTIFIC EDITORIAL BOARD

Series D: Medical Sciences

EDITOR-IN-CHIEF: ABDURAKHMONOVA NILUFAR ZAYNOBIDDIN QIZI - DOCTOR OF PHILOLOGICAL SCIENCES, PROFESSOR

24 BOARD MEMBERS | **INTERNATIONAL REPRESENTATION** Uzbekistan · Russian Federation · Georgia · Tajikistan · Türkiye · India · United States

Members are listed by academic standing and editorial responsibility. Current institutional profiles and contact details are maintained on the journal website.

Sidikov Akmal Abdikakharovich DSc, Medical Sciences, Professor *Fergana Medical Institute of Public Health · Uzbekistan*	**Axmedova Dilorom Ilkhamovna** DSc, Medical Sciences, Professor, First-Degree State Prize Laureate of Uzbekistan *Tashkent State Medical University · Uzbekistan*	**Musayeva Dilfuza Makhmudovna** DSc, Medical Sciences, Professor *Central Asian Association of Pharmacologists and Clinical Pharmacologists · Uzbekistan*
Tursunov Sobir Turdiyevich Candidate of Medical Sciences, DSc, Pedagogical Sciences, Professor *Sergeli Abu Ali ibn Sino Public Health Technical College of Tashkent City · Uzbekistan*	**Khalimova Zamira Yusupovna** DSc, Medical Sciences, Professor *Republican Specialized Scientific and Practical Medical Center of Endocrinology · Uzbekistan*	**Novik Gennadiy Ayzikovich** DSc, Medical Sciences, Professor *Ministry of Health of the Russian Federation · Russia*
Sattarov Jamoliddin Bakhronovich DSc, Medical Sciences, Professor *Tashkent State Medical University · Uzbekistan*	**Rasulova Khurshidakhon Abduboriyevna** DSc, Medical Sciences, Professor *Termez Branch of Tashkent Medical Academy · Uzbekistan*	**Sodiqova Zumrat Shavkatovna** DSc, Medical Sciences, Professor *Tashkent Medical Academy · Uzbekistan*
Urinov Muso Boltayevich DSc, Medical Sciences, Professor *Abu Ali ibn Sino Bukhara State Medical Institute · Uzbekistan*	**Khalimova Khanifa Mukhsinovna** DSc, Medical Sciences, Professor *Tashkent Medical Academy · Uzbekistan*	**Ketevan Barabadze** DSc, Medical Sciences, Professor *Tbilisi State Medical University · Georgia*
Khajimuratov Abduqaxkhor Abdumutalovich DSc, Economic Sciences, Professor *Fergana Medical Institute of Public Health · Uzbekistan*	**Ilolov Ahmadsho Mahmadshoyevich** DSc, Chemical Sciences, Professor *International University of Tourism and Entrepreneurship of Tajikistan · Tajikistan*	**Abidov Hasankhodja Alisherovich** DSc, Medical Sciences, Assoc. Professor *Tashkent State Medical University · Uzbekistan*
Ibrohim Alatas DSc, Medical Sciences, Assoc. Professor *Beykent University · Türkiye*	**Javed Khon** DSc, Medical Sciences *Max Hospital · India*	**Nigmatova Iroda Maratovna** Candidate of Medical Sciences, Assoc. Professor *Tashkent State Dental Institute · Uzbekistan*
Abzalova Shahnoza Rustamovna Candidate of Medical Sciences, Assoc. Professor *Tashkent State Medical University · Uzbekistan*	**Jalolova Dilfuza Zukhridinovna** Candidate of Medical Sciences, Assoc. Professor *Samarkand State Medical University · Uzbekistan*	**Muqimov Odiljon Ahmadjonovich** PhD in Medical Sciences, Assoc. Professor *Tashkent State Dental Institute · Uzbekistan*
Pirlepesov Fakhriddin PhD in Radiation Oncology *St. Jude Children's Research Hospital (USA) · USA*	**Kalugina Vera Gennadyevna** Candidate of Medical Sciences *Research Institute of Pediatrics at the Russian National Surgical Center · Russia*	**Khasanova Guzaliya Marsovna** PhD in Medicine *Moscow Region State Budgetary Healthcare Institution (Russia) · Russia*

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

THE ROLE OF MRI-DETECTED EXTRAMURAL VASCULAR INVASION AS A PREDICTOR OF REGIONAL AND DISTANT METASTASIS IN LOW RECTAL CANCER

Ismailova Munojat[1], Akhmatov Bekzod[2]
Department of Medical Radiology, Tashkent State Medical University, Tashkent, Uzbekistan

DOI: 10.67620/sai.59d0001

ABSTRACT
Extramural vascular invasion (EMVI) is an adverse feature of rectal cancer that can be identified on high-resolution magnetic resonance imaging (MRI) before treatment. This study examined associations between EMVI and metastatic disease, tumor stage, nodal status, and histologic differentiation in patients with low rectal cancer. Seventy-eight patients underwent pelvic MRI and computed tomography of the chest and abdomen; 32 subsequently underwent surgery. EMVI was assessed independently by two radiologists using vascular caliber, contour, intraluminal tumor signal, and extension beyond the vessel wall. Associations were tested with Pearson's chi-square test with Yates' correction. In the full cohort, EMVI was present in 24 patients. Distant metastases occurred in 11 of 24 EMVI-positive patients and 12 of 54 EMVI-negative patients, producing a significant association between EMVI and M stage, $\chi^2(1) = 4.22$, $p = .040$. No significant association was identified between EMVI and tumor differentiation, T stage, or regional nodal metastasis. These findings support MRI-detected EMVI as a clinically relevant marker of distant metastatic risk in low rectal cancer, while the small surgical subgroup limits inference regarding local stage and histologic grade.

ACCEPTED

26.09.26

Keywords: *low rectal cancer, magnetic resonance imaging, extramural vascular invasion, distant metastasis, regional lymph nodes, tumor staging.*

CC BY

Introduction

Rectal cancer remains a major oncologic problem because local anatomy, patterns of spread, and treatment-related morbidity make accurate pretreatment staging essential. Tumors arising in the lower rectum are particularly demanding. The distal mesorectum narrows as it approaches the pelvic floor, and the tumor may lie close to the mesorectal fascia, levator ani muscles, sphincter complex, or intersphincteric plane. These relationships influence both the feasibility of sphincter preservation and the risk of an involved resection margin. Consequently, imaging must provide more than a conventional TNM category; it should depict the anatomical and biological features that may alter treatment planning.

High-resolution pelvic magnetic resonance imaging (MRI) is central to local staging because it offers strong soft-tissue contrast and multiplanar assessment without ionizing radiation. MRI can delineate the depth of extramural tumor extension, the relationship of the tumor to the mesorectal fascia, involvement of the pelvic floor and sphincters, regional nodal disease, tumor deposits, and vascular invasion. Contemporary European guidance treats MRI as a structured risk-assessment examination rather than a simple method of assigning T and N categories (Beets-Tan et al., 2018; ESGAR Rectal Imaging Guideline

Group, 2026). This approach is especially relevant in low rectal cancer, where small differences in the extent and direction of spread may affect surgical strategy.

Extramural vascular invasion (EMVI) refers to tumor extension into veins beyond the muscularis propria. On MRI, EMVI is recognized when tumor signal expands or distorts an extramural vessel, produces an irregular vascular contour, or extends along a venous channel. The MRI appearance has been formalized through a five-point grading approach in which higher scores reflect increasing confidence and severity of vascular involvement. Earlier work established that high-resolution MRI can identify prognostically important features of rectal cancer before surgery (Brown et al., 2003; Smith et al., 2008). Unlike histopathologic EMVI, which becomes available only after resection, MRI-detected EMVI (mrEMVI) can contribute to risk stratification at the time treatment decisions are being made.

The prognostic relevance of mrEMVI has been repeatedly associated with metastatic spread and survival. A meta-analysis of 1,262 patients reported substantially higher rates of synchronous and subsequent metastases in mrEMVI-positive tumors than in mrEMVI-negative tumors (Siddiqui et al., 2017). A later systematic review and meta-analysis likewise found poorer overall and disease-free survival among patients with baseline mrEMVI, and persistent mrEMVI after neoadjuvant treatment was associated with worse disease-free survival than radiologic regression (Tan et al., 2021). Cohort studies have also identified mrEMVI as an independent predictor of metachronous metastasis and disease-free survival (van den Broek et al., 2020; Di Fabio et al., 2024). These findings support the view that venous invasion captures an aspect of tumor behavior not fully represented by T or N stage alone.

Even so, the relationship between EMVI and other clinicopathologic characteristics is not uniform across patient groups. Vascular invasion is more often encountered in tumors extending beyond the muscularis propria, but small samples, differences in MRI technique, treatment exposure, and pathologic verification can weaken observed associations. Histologic differentiation may also relate to metastatic behavior, although evidence specific to low rectal tumors and mrEMVI is limited. A focused evaluation of low rectal cancer is therefore useful because anatomical constraints and treatment choices differ from those for mid- and upper-rectal tumors.

The present study examined whether EMVI was associated with distant metastasis, regional nodal metastasis, T stage, and histologic differentiation in patients with low rectal cancer. A further objective was to assess the clinical value of EMVI identified during the initial MRI examination as a marker that could complement conventional staging. The analysis was based on the original cohort and contingency tables reported in the study; no attempt was made to infer unreported outcomes or to replace the observed data with estimates from external literature.

Materials and Methods

The study included 78 patients with low rectal cancer at different stages of disease. The mean age was 62.2 years (SD = 9.3); 47 patients (60.3%) were men and 31 (39.7%) were women. Histologic diagnosis was established from biopsy material obtained during colonoscopy or rectosigmoidoscopy. Moderately differentiated adenocarcinoma was identified in 57 patients, poorly differentiated adenocarcinoma in 13, and well-differentiated adenocarcinoma in 8. Thirty-two patients subsequently underwent surgical treatment and constituted the subgroup used for analyses requiring postoperative or surgical-pathologic information.

All patients underwent pelvic MRI and computed tomography (CT) of the chest and abdomen as part of comprehensive staging. Pelvic MRI was performed on a GE Optima MR450w GEM system using surface and integrated table-mounted coils. The protocol included T2-weighted sequences in the axial, sagittal, and coronal planes with 3-mm section thickness, an axial T1-weighted sequence, and axial diffusion-weighted imaging with b values of 500 and 1,000 s/mm². CT examinations were performed on a Siemens SOMATOM Emotion 6 scanner with bolus administration of nonionic iodinated contrast material.

ISSN: 2181-3337 | SCIENTISTS.UZ

The combined examinations were used to assess local tumor extent, regional nodes, and distant metastatic disease.

Two radiologists independently evaluated the imaging findings. The study retained findings when both readers agreed on the relevant diagnostic feature. MRI criteria for EMVI included tumor-equivalent signal within the lumen of an extramural venous structure, venous dilatation, wall thickening or irregularity, intravascular tumor deposits, and tumor extension through the vascular wall into surrounding pararectal tissue. These criteria are consistent with the morphologic concept underlying established mrEMVI assessment, in which expansion, irregularity, and replacement of a vessel by tumor signal increase confidence that venous invasion is present (Smith et al., 2008).

For the surgical subgroup, the distribution by histologic differentiation was 24 moderately differentiated, 4 poorly differentiated, and 4 well-differentiated adenocarcinomas. The T-stage distribution was T1 in 1 patient, T2 in 2, T3 in 19, and T4 in 10. Histopathologic examination of surgical specimens was used to verify vascular invasion where such confirmation was available, while biopsy specimens established tumor morphology. The source dataset reports several EMVI counts across different analytic subsets; therefore, the statistical analyses below follow the denominators and cell counts specified in each original contingency table rather than treating those subsets as interchangeable.

Associations were examined with Pearson's chi-square test using Yates' continuity correction for 2 × 2 tables. For the analysis of differentiation, well-differentiated tumors were excluded because no EMVI-positive cases occurred in that category, leaving 28 moderately or poorly differentiated tumors. For the T-stage analysis, T1 and T2 tumors were excluded because no EMVI-positive cases occurred in those groups. Statistical significance was interpreted at $p < .05$. Because the available dataset did not provide confidence intervals, multivariable models, or time-to-event outcomes, the analysis was limited to the reported cross-sectional associations.

Results

Among the 32 surgically treated patients, moderately differentiated adenocarcinoma accounted for 75.0% of tumors, whereas well- and poorly differentiated adenocarcinomas each accounted for 12.5% (Table 1). Most surgically treated tumors were locally advanced: 19 patients (59.4%) had T3 disease and 10 (31.2%) had T4 disease; only 3 patients had T1 or T2 tumors (Table 2).

The differentiation analysis included 28 patients with moderately or poorly differentiated adenocarcinoma. EMVI was present in 6 of 24 moderately differentiated tumors and 3 of 4 poorly differentiated tumors (Table 3). Pearson's chi-square test with Yates' correction yielded $\chi^2(1) = 1.97$, $p = .160$. Thus, the observed distribution did not provide evidence of an association between EMVI and histologic differentiation in this surgical subset. The marked numerical difference in proportions should be interpreted cautiously because the poorly differentiated group contained only four patients.

For T stage, the contingency analysis included 19 T3 and 10 T4 tumors. EMVI was recorded in 5 T3 and 4 T4 cases, while EMVI was absent in 14 and 6 cases, respectively (Table 4). The association was not statistically significant, $\chi^2(1) = 0.11$, $p = .740$. The exclusion of the three T1–T2 cases and the modest number of EMVI-positive observations restricted the ability to detect differences between T3 and T4 disease.

Regional nodal status was also not significantly associated with EMVI in the surgical group. Regional lymph node metastases were present in 4 of 9 EMVI-positive patients and in 8 of 23 EMVI-negative patients (Table 5). The corrected chi-square statistic was $\chi^2(1) = 0.21$, $p = .647$. These data do not show that EMVI status and regional nodal metastasis were statistically dependent within the available sample.

A different pattern was observed for distant metastasis in the full cohort of 78 patients. M1 disease was present in 11 of 24 patients with EMVI and 12 of 54 patients without EMVI; M0 disease was present in 13 and 42 patients, respectively (Table 6). The association between EMVI and M stage reached statistical

ISSN: 2181-3337 | SCIENTISTS.UZ

significance, $\chi^2(1) = 4.22$, $p = .040$. Descriptively, distant metastatic disease was therefore more frequent among patients classified as EMVI-positive on the study's imaging assessment.

The detailed metastatic distribution further showed liver and pelvic nodal metastases in four EMVI-positive and three EMVI-negative patients, pulmonary metastases in two EMVI-positive patients, combined liver and lung metastases in two EMVI-positive patients, and prostatic metastases in three EMVI-positive patients. Five EMVI-negative patients had pelvic nodal metastases without the distant patterns listed in the table. No distant metastases were recorded in 13 of 24 EMVI-positive patients and 46 of 54 EMVI-negative patients (Table 7). These category counts are descriptive and were not subjected to separate inferential tests in the source analysis.

Discussion

The principal finding was the significant association between EMVI and distant metastatic disease. In contrast, EMVI was not significantly associated with histologic differentiation, T3 versus T4 stage, or regional nodal metastasis in the analyzed subsets. This pattern is clinically plausible because EMVI represents direct access of tumor to extramural venous channels, a route that can facilitate hematogenous dissemination. The result also aligns with published evidence in which mrEMVI has shown a strong relationship with synchronous and metachronous metastasis (Siddiqui et al., 2017; Sohn et al., 2015). The present data should not be taken to show that EMVI causes metastasis, but they support its use as a marker of a phenotype associated with systemic spread.

The magnitude and consistency of prior findings strengthen the relevance of the observed M-stage association. Siddiqui et al. (2017) reported that mrEMVI-positive rectal cancers were more likely to present with metastatic disease and to develop metastases during follow-up. In a Dutch cohort, van den Broek et al. (2020) found that mrEMVI remained a significant predictor of metachronous metastasis after consideration of several other MRI features. More recent work has similarly linked MRI-predicted tumor deposits and EMVI with disease-free survival after resection (Di Fabio et al., 2024). The current study is smaller and focused on low rectal cancer, yet its direction of association is consistent with this broader literature.

The absence of a significant relationship between EMVI and nodal metastasis deserves separate consideration. Nodal spread and venous invasion are distinct routes of tumor dissemination, and MRI assessment of lymph nodes is itself imperfect because size alone does not reliably distinguish benign from malignant nodes. Contemporary MRI guidance therefore uses morphology, location, and patient-level patterns rather than a single size criterion for mesorectal nodal staging (ESGAR Rectal Imaging Guideline Group, 2026). In this study, 4 of 9 EMVI-positive patients and 8 of 23 EMVI-negative patients had regional nodal metastases. With these small cell counts, a nonsignificant result cannot establish equivalence between groups; it indicates only that the available sample did not demonstrate a statistically reliable association.

A similar limitation applies to T stage. EMVI generally requires tumor extension beyond the muscularis propria and is consequently most relevant in T3–T4 disease. However, once analysis is restricted to advanced T categories, a simple comparison of T3 with T4 may not capture the biologic variation that determines venous invasion. Extramural depth, vessel caliber, tumor deposits, mesorectal fascia involvement, and treatment exposure may all add information that is lost in a two-category table. MRI studies have long emphasized the prognostic importance of features beyond categorical T stage, including circumferential resection margin status and depth of extramural extension (MERCURY Study Group, 2007; Taylor et al., 2014).

Histologic differentiation showed a pronounced descriptive imbalance—EMVI in 3 of 4 poorly differentiated tumors compared with 6 of 24 moderately differentiated tumors—but the corrected chi-square test was not significant. The small poorly differentiated subgroup makes the estimate unstable, and exclusion of well-differentiated tumors further narrows inference. A larger cohort would be needed to

ISSN: 2181-3337 | SCIENTISTS.UZ

determine whether grade contributes independently to EMVI risk in low rectal cancer. Future analyses could retain all differentiation categories and use exact or regression-based methods when sparse cells are present.

From an imaging perspective, the findings reinforce the value of deliberately reporting EMVI at baseline MRI. A structured report should document EMVI status alongside tumor height, T category, mesorectal fascia relationship, sphincter and pelvic-floor involvement in low tumors, nodal disease, and relevant tumor deposits. Current ESGAR recommendations explicitly include EMVI within primary staging and restaging frameworks (ESGAR Rectal Imaging Guideline Group, 2026). Consistent reporting is important because EMVI can be visible before treatment and may change after neoadjuvant therapy. Meta-analytic evidence suggests that persistent mrEMVI after treatment carries an adverse prognosis compared with radiologic regression (Tan et al., 2021).

Several limitations constrain interpretation. First, the full cohort comprised 78 patients, but only 32 underwent surgery, leaving small analytic groups for morphology, T stage, and nodal comparisons. Second, the study used univariable chi-square analyses; potential confounding by tumor size, extramural depth, mesorectal fascia status, treatment, or other risk features could not be addressed. Third, the source dataset reports EMVI counts for different subsets that are not numerically identical. The present revision therefore preserves the denominators of the original contingency tables and avoids combining them into a single derived estimate. Fourth, interobserver agreement was handled by requiring concordance between two radiologists, but a kappa statistic or other reproducibility measure was not reported. Finally, the cross-sectional M-stage analysis does not distinguish synchronous disease from metastases arising during longitudinal follow-up.

These limitations also indicate practical directions for further research. A prospective design with a prespecified MRI protocol, structured EMVI scoring, blinded readers, histopathologic correlation, and longitudinal surveillance would permit stronger evaluation of diagnostic and prognostic performance. Multivariable models could test whether mrEMVI adds information beyond T category, nodal status, mesorectal fascia involvement, tumor deposits, and histologic grade. Reporting effect sizes with confidence intervals would also be more informative than significance testing alone. In low rectal cancer specifically, analyses should consider the anatomical relationship to the sphincter complex and pelvic floor, because these features influence local management even when the principal prognostic question concerns systemic dissemination.

Conclusion

In this cohort of patients with low rectal cancer, EMVI was significantly associated with distant metastatic disease but not with histologic differentiation, T3 versus T4 stage, or regional nodal metastasis. The result supports the inclusion of EMVI in baseline MRI assessment as a marker that may identify patients with a greater burden of systemic risk. The finding should be interpreted within the limits of the small surgical subgroup, univariable analysis, and inconsistent EMVI denominators across source subsets. Larger prospective studies with standardized MRI scoring, reproducibility analysis, and longitudinal outcomes are needed to establish the independent prognostic contribution of mrEMVI and to clarify how it should be integrated with other MRI risk features in treatment planning.

Tables

Table 1

Distribution of Surgically Treated Patients by Histologic Differentiation

Histologic differentiation	n	%
Well differentiated	4	12.5
Moderately differentiated	24	75.0
Poorly differentiated	4	12.5
Total	32	100.0

ISSN: 2181-3337 | SCIENTISTS.UZ

Table 2

Distribution of Surgically Treated Patients by T Stage

T stage	n	%
T1	1	3.1
T2	2	6.3
T3	19	59.4
T4	10	31.2
Total	32	100.0

Table 3

Association Between EMVI and Histologic Differentiation in the Surgical Subgroup

EMVI status	Moderately differentiated	Poorly differentiated	Total
Present	6	3	9
Absent	18	1	19
Total	24	4	28

Note. $\chi^2(1) = 1.97$, $p = .160$.

Table 4

Association Between EMVI and T Stage in the Surgical Subgroup

EMVI status	T3	T4	Total
Present	5	4	9
Absent	14	6	20
Total	19	10	29

Note. $\chi^2(1) = 0.11$, $p = .740$.

Table 5

Association Between EMVI and Regional Lymph Node Metastasis

EMVI status	Nodes present	Nodes absent	Total
Present	4	5	9
Absent	8	15	23
Total	12	20	32

Note. $\chi^2(1) = 0.21$, $p = .647$.

Table 6

Association Between EMVI and Distant Metastasis in the Full Cohort

EMVI status	M0	M1	Total
Present	13	11	24
Absent	42	12	54
Total	55	23	78

Note. $\chi^2(1) = 4.22$, $p = .040$.

Table 7

Distribution of Metastatic Findings by EMVI Status

Characteristic	EMVI present (n = 24)	EMVI absent (n = 54)
Liver and pelvic lymph node metastases	4	3
Pulmonary metastases	2	0
Liver and lung metastases	2	0
Prostatic metastases	3	0
Pelvic lymph node metastases	0	5
No distant metastases	13	46
Total	24	54

ISSN: 2181-3337 | SCIENTISTS.UZ

REFERENCES

1. Beets-Tan, R. G. H., Lambregts, D. M. J., Maas, M., Bipat, S., Barbaro, B., Curvo-Semedo, L., Fenlon, H. M., Gollub, M. J., Gourtsoyianni, S., Halligan, S., Hoeffel, C., Kim, S. H., Laghi, A., Maier, A., Rafaelsen, S. R., Stoker, J., Taylor, S. A., Torkzad, M. R., & Blomqvist, L. (2018). Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. European Radiology, 28, 1465–1475.
2. Brown, G., Radcliffe, A. G., Newcombe, R. G., Dallimore, N. S., Bourne, M. W., & Williams, G. T. (2003). Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. British Journal of Surgery, 90, 355–364.
3. Chand, M., Siddiqui, M. R. S., Swift, I., & Brown, G. (2016). Systematic review of prognostic importance of extramural venous invasion in rectal cancer. World Journal of Gastroenterology, 22(4), 1721–1726.
4. Chand, M., Swift, R. I., Chau, I., Heald, R. J., Tekkis, P. P., & Brown, G. (2014). Adjuvant therapy decisions based on magnetic resonance imaging of extramural venous invasion and other prognostic factors in colorectal cancer. Annals of the Royal College of Surgeons of England, 96, 543–546.
5. Di Fabio, F., Allievi, N., Lord, A., Bhagwanani, A., Venkatasubramaniam, A., Arnold, S., & Moran, B. (2024). MRI-predicted extramural vascular invasion and tumour deposit are main predictors of disease-free survival in patients undergoing surgical resection for rectal cancer. BJS Open, 8(1), zrad139. https://doi.org/10.1093/bjsopen/zrad139
6. ESGAR Rectal Imaging Guideline Group. (2026). MRI to guide clinical management of rectal cancer: Updated consensus recommendations from the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)—Part I: Primary staging. European Radiology, 36(6), 4592–4607. https://doi.org/10.1007/s00330-025-12274-w
7. Tan, J. J., Carten, R. V., Babiker, A., Abulafi, M., Lord, A. C., & Brown, G. (2021). Prognostic importance of MRI-detected extramural venous invasion in rectal cancer: A literature review and systematic meta-analysis. International Journal of Radiation Oncology, Biology, Physics, 111(2), 385–394. https://doi.org/10.1016/j.ijrobp.2021.05.136
8. MERCURY Study Group. (2007). Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: Results of the MERCURY Study. Radiology, 243, 132–139.
9. Nougaret, S., Reinhold, C., Mikhael, H. W., Rouanet, P., Bibeau, F., & Brown, G. (2013). The use of MR imaging in treatment planning for patients with rectal carcinoma: Have you checked the "DISTANCE"? Radiology, 268, 330–344.
10. Siddiqui, M. R. S., Simillis, C., Hunter, C., Chand, M., Bhoday, J., Garant, A., Vuong, T., Artho, G., Rasheed, S., Tekkis, P., Abulafi, A. M., & Brown, G. (2017). A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) versus mrEMVI-negative cases. British Journal of Cancer, 116, 1513–1519. https://doi.org/10.1038/bjc.2017.99
11. Smith, N. J., Barbachano, Y., Norman, A. R., Swift, R. I., Abulafi, A. M., & Brown, G. (2008). Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. British Journal of Surgery, 95(2), 229–236. https://doi.org/10.1002/bjs.5917
12. Smith, N. J., Shihab, O., Arnaout, A., Swift, R. I., & Brown, G. (2008). MRI for detection of extramural vascular invasion in rectal cancer. AJR American Journal of Roentgenology, 191(5), 1517–1522. https://doi.org/10.2214/AJR.08.1298
13. Sohn, B., Lim, J. S., Kim, H., Myoung, S., Choi, J., Kim, N. K., Kim, M. J., & Kim, K. W. (2015). MRI-detected extramural vascular invasion is an independent prognostic factor for synchronous

ISSN: 2181-3337 | SCIENTISTS.UZ

metastasis in patients with rectal cancer. European Radiology, 25, 1347–1355. https://doi.org/10.1007/s00330-014-3527-9

14. Taylor, F. G. M., Quirke, P., Heald, R. J., Moran, B. J., Blomqvist, L., Swift, I. R., Sebag-Montefiore, D., Tekkis, P., & Brown, G. (2014). Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. Journal of Clinical Oncology, 32(1), 34–43. https://doi.org/10.1200/JCO.2012.45.3258
15. van den Broek, J. J., van der Wolf, F. S. W., Heijnen, L. A., & Schreurs, W. H. (2020). The prognostic importance of MRI detected extramural vascular invasion (mrEMVI) in locally advanced rectal cancer. International Journal of Colorectal Disease, 35(10), 1849–1854. https://doi.org/10.1007/s00384-020-03632-9

ISSN: 2181-3337 | SCIENTISTS.UZ

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

METAPHYLAXIS OF URATE NEPHROLITHIASIS IN THE NAMANGAN REGION: A CLINICAL EXPERIENCE

Mazhikhanov Baxodir
Department of Urology-Endourology, Namangan Regional Multidisciplinary Medical Center, Namangan, Uzbekistan

DOI: 10.67620/sai.59d0002

ABSTRACT
Urate nephrolithiasis is an important urological problem in the Namangan region, where climatic and dietary factors may contribute to stone formation and recurrence. This study summarized clinical experience with personalized metaphylaxis for urate nephrolithiasis. A total of 120 patients with urolithiasis who underwent surgical treatment at the Department of Urology-Endourology of the Namangan Regional Multidisciplinary Medical Center during 2024–2025 were evaluated. Spectrometric stone analysis confirmed urate calculi in 60 patients, who formed the metaphylaxis group. These patients underwent metabolic assessment, correction of fluid intake and diet, urine pH monitoring, and citrate alkalizing therapy when indicated. The approach was tailored according to metabolic evaluation, renal function, comorbidities, and individual clinical characteristics. The metaphylaxis protocol included fluid intake of at least 2 L/day, restriction of animal protein, and maintenance of urine pH within 5.2–6.8 using citrate therapy. Febuxostat at 80 mg/day for 1 month was prescribed episodically when urine pH rose above the target range. During 12 months of follow-up, no recurrent stone formation was observed among the 60 patients (0/60). These findings suggest that individualized metaphylaxis combining adequate hydration, dietary modification, and urine pH correction may be effective for short-term prevention of recurrent urate nephrolithiasis in the Namangan region.

ACCEPTED

30.09.26

Keywords: *urate nephrolithiasis, metaphylaxis, urolithiasis, citrate therapy, stone recurrence, Namangan region.*

CC BY

Introduction

Urate nephrolithiasis remains one of the pressing problems of contemporary urology in the Namangan region, demonstrating a steady upward trend in incidence (Chaban et al., 2017). Despite the widespread introduction of modern surgical methods for stone removal, the absence of a comprehensive approach to metaphylaxis leads to a high recurrence rate, which reduces patients' quality of life and increases the economic burden on regional healthcare (Banov & Ceban, 2018; Borisov & Shilov, 2016).

The prevalence of urolithiasis in the region is estimated at 4–8%, while the hot climate of the Fergana Valley and insufficient fluid intake substantially increase the risk of urate stone formation (Otakulov & Yakubov, 2026). Epidemiological monitoring also indicates a predisposition to salt stone formation attributable to the specific features of the local diet and climatic factors (Fathi, 2022; Nakipova et al., 2026).

The rate of recurrent stone formation in patients with urate nephrolithiasis reaches 50% within five years after the initial episode (Kaprin et al., 2022), and the systematic combination of pharmacological

therapy with lifestyle correction is recognized as critical for reducing this risk (Tiselius, 2003). At the same time, current clinical practice in the region is characterized by insufficient involvement of outpatient urologists in conducting in-depth metabolic evaluation, which limits the effectiveness of primary litholytic therapy (Malkhasyan et al., 2022).

The aim of the present study is to summarize our own clinical experience in implementing personalized metaphylaxis protocols aimed at correcting metabolic disorders and preventing recurrent stone formation in patients with urate nephrolithiasis in the Namangan region (Alghamdi et al., 2025; Krasiuk et al., 2025; Tagayeva, 2025).

Materials and Methods

Study Design and Organization

A retrospective analysis was performed of data from patients observed at the Department of Urology-Endourology of the Namangan Regional Multidisciplinary Medical Center (Namangan, Uzbekistan) between 2024 and 2025. The study included 120 patients with urolithiasis (80 men, 40 women) who underwent surgical treatment for renal and ureteral calculi: percutaneous nephrolithotripsy (PCNL) - 30 patients; transurethral ureterolithotripsy with ureteral stenting - 60 patients; open surgery - 30 patients (nephrolithotomy - 10, ureterolithotomy with ureteral stenting - 20).

All removed calculi were sent for chemical (stone) analysis to the Central Research Laboratory (CRL) of Namangan State Technical University, where stone composition was determined by spectrometry. According to the results of stone analysis, urate composition of the calculus was confirmed in 60 of 120 patients, calcium-oxalate composition in 40, and phosphate composition in 20 (Table 1). The present work focuses on the subgroup of 60 patients with confirmed urate nephrolithiasis who underwent the metaphylaxis protocol described below for 12 months after surgery.

After surgical treatment, patients underwent metabolic evaluation, correction of fluid intake and diet, and, where indicated, citrate alkalizing therapy with urine pH monitoring. Preventive management tactics were determined individually, taking into account disease history, presence of recurrences, size and location of calculi, results of laboratory and instrumental examination, comorbidities, and patient adherence to recommendations. At each follow-up visit, clinical status, adherence to therapeutic and preventive recommendations, dynamics of urine parameters, and signs of recurrent stone formation were assessed.

Inclusion and Exclusion Criteria

The analysis included adult patients with an established diagnosis of urate nephrolithiasis, confirmed by a combination of clinical, laboratory, and instrumental data, who could be followed up longitudinally. The diagnosis was established based on the chemical composition of the removed or spontaneously passed calculus, imaging findings, and urine acidity values. Patients with both a primary episode and recurrent disease were included. Patients were excluded if urate composition of the calculus was not confirmed, if the necessary examination could not be performed, if follow-up data were insufficient, or in cases where infectious, cystine, or other non-urate calculi predominated. Patients with concomitant obesity, diabetes mellitus, and gout were also excluded from the study.

Diagnostic Methods

The initial examination included history-taking and assessment of complaints, evaluation of stone-formation risk factors, analysis of dietary pattern and fluid intake, family history of urolithiasis, and documentation of comorbidities and prior treatment. Laboratory diagnostics included urinalysis, determination of urine acidity, assessment of uric acid levels and purine metabolism parameters where clinically indicated, and 24-hour urine testing.

The chemical composition of removed calculi was determined by spectrometry at the Central Research Laboratory of Namangan State Technical University. Instrumental examination included

ISSN: 2181-3337 | SCIENTISTS.UZ

ultrasonography of the kidneys and urinary tract; plain radiography and CT imaging were performed when necessary.

Metaphylactic Measures

Metaphylaxis included abundant fluid intake (≥2 L/day), restriction of dietary animal protein, and maintenance of urine pH within 5.2–6.8 using citrate alkalizing therapy under laboratory monitoring. When urine pH rose above the target range, febuxostat 80 mg once daily for a 1-month course was episodically prescribed. Drug therapy tactics were selected individually based on the results of metabolic evaluation, renal function, and comorbidities. Effectiveness was assessed by clinical symptoms, dynamics of laboratory parameters, changes in stone size and number, frequency of spontaneous stone passage, need for repeat surgical treatment, recurrence rate, and patient adherence to recommendations.

Statistical Analysis

Statistical processing was performed using SPSS, R, and Excel. Quantitative variables are presented as mean ± standard deviation ($M \pm SD$); qualitative variables as absolute values and proportions (n, %). For the stone-recurrence rate (0/60), an exact 95% confidence interval was calculated (Clopper–Pearson method): 0.0–6.0%. Differences were considered statistically significant at $p < .05$.

Ethical Approval

This work is a retrospective analysis of data accumulated in the course of the author's routine clinical practice. A formal ethics committee/IRB was not engaged for this work; diagnosis and treatment of patients were carried out according to the clinical practice standards of the Department of Urology-Endourology. Informed consent for participation in the study and data processing was obtained from all patients.

Results

Clinical and Demographic Characteristics of Patients

The study included 120 patients with urolithiasis: 80 men (66.7%) and 40 women (33.3%). All patients underwent surgical treatment for renal and ureteral calculi (Table 1).

Table 1

Types of Surgical Treatment, Location, and Size of Calculi ($N = 120$)

Intervention type	Location	n	Size, mm
Percutaneous nephrolithotripsy (PCNL)	kidney	30	15–35
Open nephrolithotomy	kidney	10	15–35
Transurethral ureterolithotripsy with ureteral stenting	ureter	60	8–15
Open ureterolithotomy with ureteral stenting	ureter	20	8–15
Total	**-**	**120**	**-**

Renal calculi ($n = 40$: PCNL and open nephrolithotomy) ranged in size from 15 to 35 mm, while ureteral calculi ($n = 80$: transurethral ureterolithotripsy and open ureterolithotomy) ranged from 8 to 15 mm.

According to spectrometric stone analysis of the removed calculi (CRL of Namangan State Technical University), the following chemical composition of stones was established (Table 2).

Table 2

Chemical Composition of Calculi According to Stone Analysis ($N = 120$)

Stone composition	n (%)
Urate	60 (50.0%)
Calcium-oxalate	40 (33.3%)

ISSN: 2181-3337 | SCIENTISTS.UZ

Stone composition	n (%)
Phosphate	20 (16.7%)
Total	**120 (100%)**

Further analysis of clinical and demographic characteristics, risk factors, and metaphylaxis effectiveness (see Stone-Formation Risk Factors and Effectiveness of Metaphylactic Measures) refers to the subgroup of 60 patients with confirmed urate stone composition, which constitutes the subject of the present work. Of these, 40 were men and 20 were women, with a mean age of 44.5 ± 9.2 years (range 21–68 years). All 60 patients (100%) had a primary episode of stone formation; there were no cases of recurrent disease at the time of inclusion. Patients with concomitant obesity, diabetes mellitus, and gout were not included in the study (see Inclusion and Exclusion Criteria).

Table 3

Types of Surgical Treatment in the Urate Nephrolithiasis Subgroup (*N* = 60)

Intervention type	Location	n
Percutaneous nephrolithotripsy (PCNL)	kidney	16
Open nephrolithotomy	kidney	8
Transurethral ureterolithotripsy with ureteral stenting	ureter	26
Open ureterolithotomy with ureteral stenting	ureter	10
Total	**-**	**60**

Thus, in the urate nephrolithiasis subgroup, calculi of renal location were identified in 24 patients (16 + 8), and calculi of ureteral location in 36 patients (26 + 10).

Stone-Formation Risk Factors

Table 4

Stone-Formation Risk Factors in the Urate Nephrolithiasis Subgroup (*N* = 60)

Risk factor	n (%)
Insufficient fluid intake before treatment (no prior recommendations on fluid regimen)	60 (100%)
Excessive intake of purine-rich foods (dietary traditions, regional climatic features)	60 (100%)
Family history of urolithiasis	0 (0%)
Acidic urine reaction (mean pH at initial examination)	pH 5.4

All patients in the subgroup (60/60, 100%) consumed an insufficient amount of fluid before starting metaphylaxis, without having previously received corresponding recommendations, and also had dietary habits with excessive intake of purine-rich foods, which was regarded as a reflection of regional dietary traditions and climatic features of the Namangan region. No family history of urolithiasis was identified in any patient.

All patients in the subgroup had an acidic urine reaction at initial examination, with a mean pH of 5.4, which is consistent with the expected pathophysiology of urate stone formation and justified alkalizing therapy (see Metaphylactic Measures).

Effectiveness of Metaphylactic Measures

All patients in the subgroup (*n* = 60) underwent metaphylaxis, which included abundant fluid intake (≥2 L/day), restriction of dietary animal protein, and maintenance of urine pH within 5.2–6.8 using citrate therapy - versus a baseline mean pH of 5.4 at initial examination (see Stone-Formation Risk Factors). When urine pH rose above the target range, febuxostat 80 mg once daily for a 1-month course was episodically prescribed; over the follow-up period, the need for febuxostat was noted in all 60 patients

ISSN: 2181-3337 | SCIENTISTS.UZ

(100%). No adverse therapy events were recorded. Over the 12-month follow-up period, no recurrence of stone formation was recorded in any of the 60 patients (0/60).

Patient adherence to recommendations was not separately assessed.

Discussion

The clinical results obtained confirm the need to regard urate nephrolithiasis not only as a disease requiring stone removal, but also as a manifestation of metabolic disorders requiring long-term correction. Incorporating assessment of stone composition, uric acid metabolism parameters, daily diuresis, and urine acidity into the treatment program allows a shift from a predominantly surgical approach toward personalized metaphylaxis.

This approach is consistent with the literature, according to which low urine pH, hyperuricosuria, and insufficient urine volume are the main factors in urate stone formation, while alkalizing therapy promotes their dissolution and prevents recurrence (Zisman, 2017).

In the context of the Namangan region, correction of fluid intake is of particular importance: the hot climate and insufficient fluid intake can reduce urine volume and increase uric acid concentration, creating conditions for stone formation. A region-specific approach to prevention is especially important for areas of the Fergana Valley, where climatic, dietary, and social factors may jointly increase the risk of urolithiasis (Nakipova et al., 2026; Otakulov & Yakubov, 2026).

Comparison of our own experience with published data shows that the most well-founded component of treatment is individually selected urine alkalinization: pH monitoring with titration of citrate preparation doses allows assessment of treatment effectiveness and timely correction of the regimen (Borisov & Shilov, 2016; Fathi, 2022). At the same time, excessive alkalinization should be avoided, as it may promote the formation of phosphate salts (Coe et al., 2005). The question of prescribing urate-lowering therapy (allopurinol, febuxostat) should be decided based on the results of metabolic evaluation rather than applied uniformly to all patients (Zisman, 2017).

An important result of the analysis is the identification of organizational limitations of metaphylaxis. Insufficient involvement of outpatient care in conducting extended metabolic evaluation and long-term follow-up reduces the effectiveness of preventive measures (Malkhasyan et al., 2022). Personalized counseling and feedback can improve adherence to long-term prevention, since lack of knowledge about risk factors and urine parameters is one of the reasons for poor adherence to recommendations.

The practical significance of metaphylaxis for the Namangan region lies in the potential to reduce the number of repeat episodes of stone formation, repeat hospitalizations, and surgical interventions. The frequency of follow-up examinations should be determined by individual risk, stone composition, presence of metabolic disorders, and comorbidities (Krasiuk et al., 2025).

Study Limitations

This work has a number of limitations. It is a single-center retrospective observation without a control group (comparison with patients who did not receive metaphylaxis or received a different treatment regimen), which does not allow a causal relationship to be established between specific components of the protocol and the absence of recurrences.

The sample size (n = 60) is moderate, and the follow-up period (12 months) is relatively short: the risk of urate nephrolithiasis recurrence persists for 5–10 years or more, so the absence of recurrence at 1 year does not exclude later recurrences. Patient adherence to recommendations was not formally assessed, which could have affected the outcome. Formal approval by an ethics committee/IRB was not obtained (see Ethical Approval), which may also be noted by reviewers.

Conclusion

Urate nephrolithiasis is a multifactorial disease whose development and recurrence are determined by a combination of metabolic, dietary, behavioral, and climatic factors. For patients in the Namangan

ISSN: 2181-3337 | SCIENTISTS.UZ

region, insufficient fluid intake, a hot climate, dietary characteristics, excess body weight, and acidic urine are of particular importance (Fathi, 2022; Otakulov & Yakubov, 2026).

Metaphylaxis should be based on a comprehensive patient evaluation, including assessment of stone composition, uric acid metabolism parameters, urine acidity and daily volume, renal function, and comorbidities. An individualized approach allows dietary, behavioral, and pharmacological measures to be selected on a sound basis, taking into account risk factors and the clinical course of the disease (Borisov & Shilov, 2016; Krasiuk et al., 2025).

In the present case series, personalized metaphylaxis (abundant fluid intake, restriction of animal protein, maintenance of urine pH within 5.2–6.8, febuxostat when necessary) ensured the absence of stone-formation recurrence in all 60 patients with urate nephrolithiasis over 12 months of follow-up (0/60), which confirms the effectiveness of the proposed protocol under the conditions of the Namangan region.

REFERENCES

1. Alghamdi, A., Alqurashi, E. A., Alsubaie, A. T., et al. (2025). Management of recurrent urolithiasis: Advances in preventive strategies.
2. Banov, P., & Ceban, E. (2018). The efficacy of metaphylaxis in treatment of recurrent urolithiasis.
3. Borisov, V. V., & Shilov, E. M. (2016). Litholytic therapy for urate nephrolithiasis (clinical lecture).
4. Chaban, N. G., Putin, A. Yu., Rapoport, L. M., et al. (2017). Phytopreparations in the prevention and treatment of urate nephrolithiasis.
5. Coe, F. L., Evan, A., & Worcester, E. (2005). Kidney stone disease. *Journal of Clinical Investigation*, *115*(10), 2598–2608.
6. Fathi, R. (2022). Optimization of urolithiasis treatment and diagnosis in the Turkestan region.
7. Kaprin, A. D., Apolikhin, O. I., et al. (2022). The incidence of urolithiasis in the Russian Federation from 2005 to 2020.
8. Krasiuk, I. V., Hrydniev, A. A., & Pylypenko, Y. (2025). A modern view on the prevention and metaphylaxis of urolithiasis.
9. Malkhasyan, V., Gazimiev, M. A., Martov, A. G., et al. (2022). Current state of metaphylaxis of urinary stones in Russian Federation.
10. Nakipova, Z., Oshibayeva, A., & Babayeva, G. A. (2026). Epidemiology and risk factors of urolithiasis in the Turkestan region: A case-control study.
11. Otakulov, G., & Yakubov, A. (2026). Causes of urolithiasis and its prevention.
12. Tagayeva, Z. (2025). Modern aspects of the metaphylaxis management for recurrent urolithiasis.
13. Tiselius, H.-G. (2003). Epidemiology and medical management of stone disease.
14. Zisman, A. L. (2017). Effectiveness of treatment modalities on kidney stone recurrence. *Clinical Journal of the American Society of Nephrology*, *12*(10), 1699–1708.

ISSN: 2181-3337 | SCIENTISTS.UZ

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

CONFRONTING HYPERVIRULENT KLEBSIELLA PNEUMONIAE: INSIGHTS INTO PATHOGENICITY, RESISTANCE, AND INTERVENTION STRATEGIES

Khujaeva Shakhnoz
Associate professor of Alfraganus University
E-mail: shaxnoz-7273@mail.ru

DOI: 10.67620/sai.59d0003

ABSTRACT

Community-acquired infections caused by Klebsiella pneumoniae (K. pneumoniae) have emerged as a major global health concern, particularly with the rise of hypervirulent strains (hvKP). These strains are capable of causing severe infections-such as pyogenic liver abscesses-even in otherwise healthy individuals. First identified in Taiwan in the 1980s, hvKP has since achieved worldwide distribution. Its heightened pathogenicity is driven by a diverse repertoire of virulence factors that facilitate host colonization and enable evasion of immune defenses. The recent convergence of hypervirulence with antimicrobial resistance has further complicated clinical management. As a member of the ESKAPE group of pathogens, K. pneumoniae demonstrates high-level resistance to multiple antibiotics, posing significant therapeutic challenges in healthcare settings.

This review presents an in-depth analysis of hvKP, examining its structural and pathogenic distinctions from classical K. pneumoniae strains, major virulence determinants, and mechanisms underlying antimicrobial resistance. We also address the escalating threat of multidrug-resistant hvKP and evaluate both current treatment recommendations and emerging therapeutic approaches aimed at mitigating the impact of this formidable pathogen.

ACCEPTED

30.09.26

Keywords: *hypervirulent Klebsiella pneumoniae; antibiotic resistance; multidrug resistance; pathogenesis; treatment strategies.*

CC BY

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative, encapsulated, non-motile bacterium from the *Enterobacteriaceae* family. It is a well-known opportunistic pathogen and a major cause of nosocomial infections, particularly in immunocompromised patients. This organism is implicated in a broad range of diseases, including pneumonia, urinary tract infections, bacteremia, and liver abscesses (Magill et al., 2014; Makharita et al., 2020; Paczosa & Mecsas, 2016).

In recent years, the emergence of hypervirulent *K. pneumoniae* (hvKP) has significantly increased the threat of severe invasive infections, affecting not only immunocompromised patients but also healthy individuals. While classical *K. pneumoniae* (cKP) primarily targets hospitalized or immunocompromised patients-especially those with underlying conditions such as diabetes, malignancy, or recent surgical procedures-hvKP demonstrates a distinct ability to cause aggressive, community-acquired infections in individuals without known risk factors. This remarkable pathogenicity is linked to its enhanced virulence arsenal, which includes a hypermucoviscous capsule, overproduction of siderophores, and resistance to phagocytosis, enabling it to penetrate host barriers and evade immune responses more effectively than cKP

(Al Ismail et al., 2024; Fazili et al., 2016; Kareem et al., 2021; Lin, Siu, et al., 2012; Nadasy et al., 2007; Shon et al., 2013).

Unlike cKP, which is largely associated with hospital-acquired infections, hvKP is more frequently linked to community-acquired disease and is capable of causing a broader spectrum of systemic illnesses, such as pneumonia, hepatic abscesses, meningitis, and necrotizing fasciitis.

One of hvKP's hallmark traits is the hypermucoviscous phenotype, traditionally identified via the "string test" (>5 mm viscous string formation) (Fang et al., 2004). However, this phenotypic marker is not entirely reliable-some hvKP strains do not display hypermucoviscosity, while certain cKP strains do (Mai et al., 2023; Nannini et al., 2025; Pu et al., 2023; Russo & Marr, 2019). Consequently, molecular biomarkers such as *iucA*, *rmpA*, *rmpA2*, and *peg-344* have become essential for accurate identification (Chen et al., 2024; García-Cobos et al., 2025).

The recent rise of antibiotic-resistant hvKP strains has further intensified the clinical challenge. As part of the ESKAPE group, *K. pneumoniae* exhibits resistance to multiple antibiotic classes, including carbapenems and colistin, making treatment increasingly difficult (Algammal et al., 2023). The convergence of hypervirulence and multidrug resistance in hvKP represents a major public health concern, underscoring the urgent need for novel therapeutic approaches (García-Cobos et al., 2025).

This review provides an in-depth examination of hvKP, focusing on its structural and pathogenic differences from cKP, mechanisms of antimicrobial resistance, and the growing concern over multidrug-resistant hvKP. Additionally, we discuss current and emerging treatment strategies to counter this highly virulent and drug-resistant pathogen.

2. Differences Between Classical and Hypervirulent *K. pneumoniae*

K. pneumoniae exists in two major pathotypes: classical (cKP) and hypervirulent (hvKP), which differ significantly in epidemiology, host susceptibility, molecular characteristics, and virulence mechanisms. Understanding these distinctions is crucial for accurate diagnosis, infection control, and tailored therapy.

cKP is predominantly a healthcare-associated pathogen, infecting immunocompromised or hospitalized patients, and is a frequent cause of hospital-acquired pneumonia, urinary tract infections, and bloodstream infections (Chew et al., 2017). In contrast, hvKP has emerged as a more aggressive variant capable of causing severe, community-acquired infections in otherwise healthy individuals. It is linked to a wider range of invasive diseases, including pyogenic liver abscess, meningitis, endophthalmitis, and necrotizing fasciitis (Catalán-Nájera et al., 2017; Russo & Marr, 2019; Zhu et al., 2021).

Hypermucoviscosity was historically used to distinguish hvKP from cKP via the string test (>5 mm viscous string) (Fang et al., 2004; Russo et al., 2018). However, its limited specificity-due to overlap between strains-has diminished its diagnostic reliability (Catalán-Nájera et al., 2017; Russo et al., 2018), prompting a shift toward molecular markers.

hvKP harbors additional virulence genes, often plasmid-encoded, including *rmpA* and *rmpA2* (capsule overproduction), *iucA* (aerobactin siderophore synthesis), and *peg-344* (linked to enhanced in vivo virulence) (Russo et al., 2018). These genes are absent in most cKP strains and have high predictive accuracy (>95%) for hvKP. A chromosomal *rmpA* (*crmpA*) variant can also drive capsule overexpression and immune evasion.

Capsular types K1, K2, K5, K20, K54, and K57 are strongly associated with hvKP (Shon et al., 2013; Yu et al., 2008). The K1 serotype, often linked to sequence type ST23, is especially associated with liver abscesses, while K2 occurs in multiple sequence types such as ST65 and ST86. These serotypes enhance resistance to phagocytosis and complement-mediated killing, aiding hvKP survival in the bloodstream and deep tissues. A notable virulence feature of hvKP is its superior iron uptake, particularly via elevated production of aerobactin - a siderophore crucial for bacterial growth in iron-limited environments like the human host (Russo et al., 2015).

ISSN: 2181-3337 | SCIENTISTS.UZ

hvKP strains exhibit heightened resistance to neutrophil phagocytosis and complement activation compared to cKP (L. Wang et al., 2017), promoting rapid systemic spread and a higher risk of metastatic infection.

Beyond the string test, functional assays such as centrifugation-based mucoviscosity tests have been proposed, where hvKP typically resists sedimentation, leaving a turbid supernatant (Walker et al., 2020). Nevertheless, molecular genotyping remains the gold standard for definitive differentiation. While cKP remains a significant cause of nosocomial infections, hvKP poses a growing global health threat due to its ability to cause severe, often metastatic, community-acquired infections in healthy individuals. Accurate differentiation requires integrating clinical, phenotypic, and molecular diagnostic approaches to guide timely and effective management.

3. Diseases Caused by Hypervirulent *Klebsiella pneumoniae* (hvKP)

The first recognized syndrome linked to hvKP was cryptogenic hepatic abscess, reported in 1980 (J.-H. Wang et al., 1998; Liu et al., 1986, 1991). Clinically, hvKP infections typically present with fever, abdominal pain, leukocytosis, and chills (Kong et al., 2017). Hepatic abscess caused by hypervirulent strains is regarded as a distinct clinical entity due to its unique features (Liu et al., 1991; Oikonomou & Aye, 2017). Unlike other hepatic abscesses-commonly associated with biliary tract disease or prior invasive procedures-those caused by hvKP often occur in individuals with normal liver function and intact biliary systems (Zhang et al., 2016).

The most common route of hvKP entry is via the oropharynx through inhalation, leading to pneumonia. In the 1990s, community-acquired *K. pneumoniae* pneumonia accounted for less than 1% of pneumonia cases requiring hospitalization in Argentina, Australia, Europe, and North America (Carpenter, 1990; Ko et al., 2002; Marrie et al., 1989; Vergis et al., 2000).

Endophthalmitis is a severe complication of hvKP infection and one of the earliest distinguishing features between classical *K. pneumoniae* (cKP) and hvKP (Liu et al., 1986). Endogenous endophthalmitis caused by Gram-negative bacilli was rare in healthy individuals prior to the emergence of hvKP, but it is now recognized as a relatively frequent complication, affecting approximately 5% of hvKP-infected patients (Lee et al., 2006). Exogenous endophthalmitis-arising from trauma or surgery-remains rare in hvKP cases. Symptoms of endogenous hvKP endophthalmitis typically include sudden-onset blurred vision, ocular redness, and periocular swelling (Kishibe et al., 2016).

In Asia, *K. pneumoniae* has been identified as a leading cause of community-acquired meningitis in patients without prior head injury or neurosurgical intervention (Chang et al., 2012; Fang, Chang, et al., 2000; Jang et al., 1993; Tang et al., 1997). With the global spread of hvKP, such cases are now reported worldwide (Durand et al., 1993). hvKP meningitis can occur as a primary infection or as a metastatic complication (Fang, Chen, et al., 2000; Lin, Liu, et al., 2012), and some cases present with multiple, diffuse brain abscesses (Hentzien et al., 2017; Yoon, 2013). The infection may also involve ventriculitis (Yoon, 2013), epidural abscess, or subdural empyema (Doud et al., 2009; Hentzien et al., 2017; Hsieh et al., 2009; Kuramochi et al., 2005; Liu et al., 1986; Russo & Marr, 2019).

In Taiwan, hvKP is among the principal causes of necrotizing fasciitis, which carries a high mortality rate (Cheng et al., 2012). Although initially concentrated in Southeast Asia, cases have now been reported globally (Gunnarsson et al., 2009; Ng & Frazee, 2015; Ye et al., 2016). Presentations may include intramuscular abscesses-either alone or in combination with necrotizing fasciitis (Liu et al., 1991; Mgbemena et al., 2017)-as well as pyomyositis (commonly affecting the lower extremities), sometimes accompanied by septic arthritis (Kishibe et al., 2016). Osteomyelitis may also occur and, when multifocal, can mimic malignancy until progressing to necrotizing fasciitis (Prokesch et al., 2016).

Deep neck infections may be primary or secondary to metastatic spread (Frazee et al., 2009; Nadasy et al., 2007), and can lead to septic thrombophlebitis as a complication (McCabe et al., 2010). hvKP can

ISSN: 2181-3337 | SCIENTISTS.UZ

also cause superficial skin and soft tissue infections through systemic dissemination (Paraschiv et al., 2018).

Although rare, urinary tract involvement can occur following ascending colonization (Shon et al., 2013). In some patients, hvKP infection is found concurrently with both hepatic abscess and colon cancer (Qu et al., 2012).

Bacteremia is a frequent complication of hvKP infection, most often originating from pyogenic hepatic abscess (Lee et al., 2006). In many cases, bacteremia has no identifiable primary focus. While hvKP-associated endocarditis is rare, purulent endocarditis is the most common form linked to this pathogen (Rivero et al., 2010), with hepatic abscess or hematogenous spread (Hentzien et al., 2017) being possible sources (Figure 1).

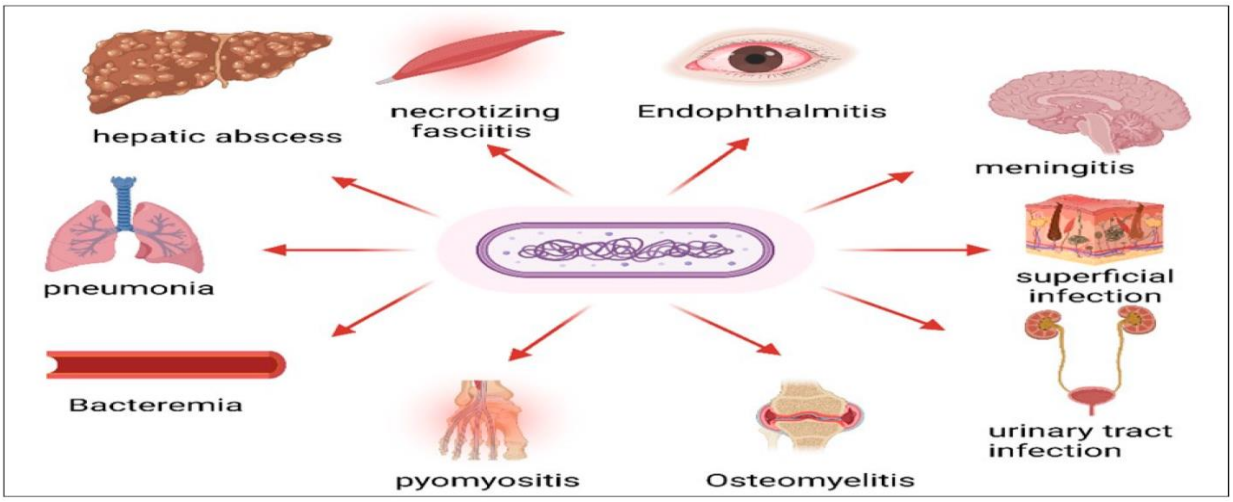


Figure 1. Diseases caused by hvKP. It affects almost all systems and causes endophthalmitis, meningitis, necrotizing fasciitis, pyomylitis, osteomyelitis, pneumonia, bacteremia, hepatic abscess, urinary tract infection, and superficial infection.

4. Discovery and Epidemiology of hvKP

The hypervirulent *Klebsiella pneumoniae* (hvKP) strain was first described in 1986 by Liu et al. in Taiwan. They reported seven cases of community-acquired *K. pneumoniae* infections presenting with liver abscesses and severe extrahepatic complications, including prostate abscess, endophthalmitis, and purulent meningitis. Despite receiving aggressive antimicrobial therapy, several patients experienced permanent vision loss, underscoring the high pathogenic potential of hvKP (Liu et al., 1986).

Since its initial identification, hvKP infections have been increasingly reported across the globe, including in Europe, Australia, and North America. Epidemiologically, East and Southeast Asia remain the primary epicenters, with Taiwan, South Korea, Iran, and China accounting for a large proportion of documented cases (Al Ismail et al., 2024). In a multicenter study conducted in China, 22.8% of invasive *K. pneumoniae* infections were attributed to hvKP. Another regional study revealed that hvKP was responsible for 90.9% of pyogenic liver abscess cases (Ye et al., 2016).

While prevalence in Western countries is lower, it is steadily increasing. In the United States, hvKP has been detected in approximately 6–8% of clinical *K. pneumoniae* isolates, often linked to severe disease and cases involving recent international travel (Russo & Marr, 2019).

The emergence of novel sequence types (STs)-notably ST23, ST65, and ST86-demonstrates the ongoing evolution and adaptation of hvKP. In China, multidrug-resistant hvKP (MDR-hvKP) strains are increasingly observed, with ST11 being the predominant lineage associated with carbapenem resistance. This convergence of hypervirulence and multidrug resistance poses a dual threat to public health, emphasizing the need for comprehensive epidemiological surveillance and genomic monitoring.

ISSN: 2181-3337 | SCIENTISTS.UZ

In early 2024, the World Health Organization (WHO) reported the global emergence of hvKP ST23 strains carrying carbapenemase genes, conferring resistance to last-line antibiotics. These strains have been detected in at least one country within each of the six WHO regions, including Algeria, Argentina, Australia, Canada, India, Iran, Japan, Oman, the Philippines, Switzerland, Thailand, the United Kingdom, and the United States. The co-occurrence of hypervirulence and extensive drug resistance in these strains presents major challenges for both treatment and infection control. The WHO has stressed the urgent need to strengthen laboratory diagnostic capabilities, expand molecular testing, and implement robust surveillance systems to track and mitigate the spread of these high-risk pathogens.

5. Bacterial Structure

Similar to other members of the *Enterobacteriaceae* family, hvKP possesses a lipid bilayer outer membrane composed of lipopolysaccharides, lipoproteins, and proteins. Surrounding this outer membrane is a polysaccharide capsule (Figure 2). While both hvKP and classical *K. pneumoniae* (cKP) possess capsules, certain serotypes-K1, K2, K5, K20, K54, and K57-are more prevalent in hvKP, with K1 and K2 together accounting for approximately 70% of hvKP isolates (Russo et al., 2018; Shon et al., 2013; Yu et al., 2008).

However, other capsular types, such as K47 or K64, may emerge in hypervirulent strains if classical variants acquire plasmids carrying virulence-associated genes, a phenomenon observed in recent years. The O-antigen (O-Ag) of the lipopolysaccharide is also an important structural feature, with K1 and K2 capsule types most frequently occurring alongside the O1 O-Ag, making it the most common combination in hvKP.

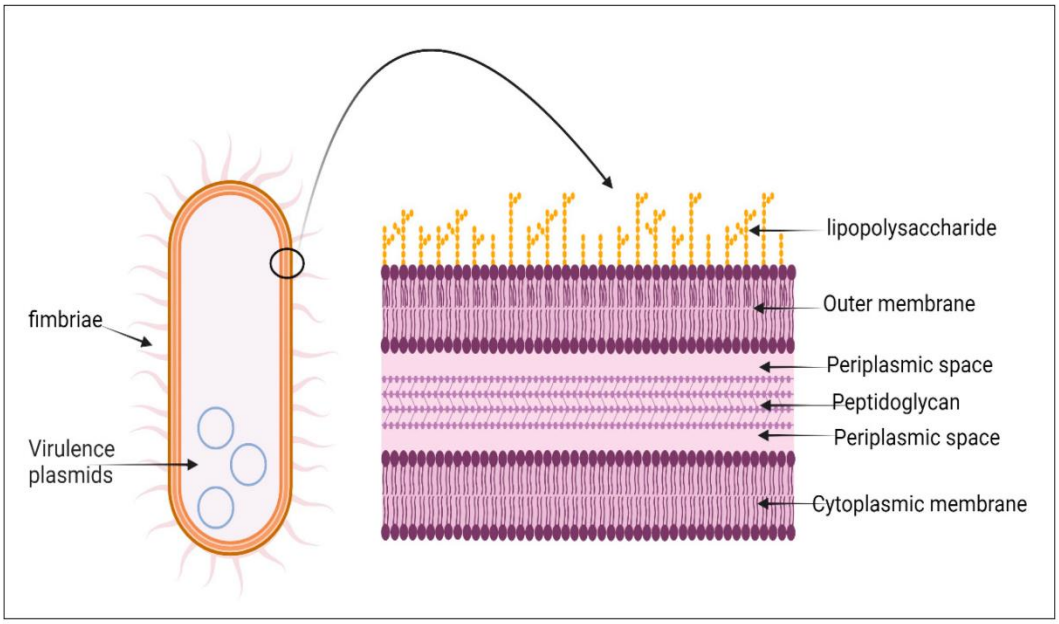


Figure 2. The cell wall structure of *K. pneumoniae*. Like most other gram-negative bacteria, it is composed of an outer membrane that contains lipopolysaccharide, periplasmic spaces, a thin layer of peptidoglycan, and a cytoplasmic membrane.

Both the outer membrane and the capsule play critical roles in pathogen–host and pathogen–environment interactions. These structures contribute to antimicrobial resistance-via permeability barriers and efflux pump mechanisms-and to pathogenesis, particularly through immune evasion mediated by the capsule. A notable feature of hvKP is the rmpA- and/or rmpA2-mediated overproduction of capsular polysaccharides, which significantly enhances systemic virulence (Fang et al., 2004).

Additionally, hvKP produces specialized components that aid in environmental survival, colonization, and host infection. These include the type VI secretion system, which facilitates bacterial

ISSN: 2181-3337 | SCIENTISTS.UZ

competition and persistence, and iron-acquisition systems such as siderophores, which are essential for bacterial growth in iron-limited host environments.

6. Pathogenesis of hvKP

Klebsiella pneumoniae readily colonizes human skin and mucosal surfaces, including the oropharynx and gastrointestinal (GI) tract, where colonization is typically benign. However, under certain conditions, it can breach these barriers and cause severe invasive infections. In hospital-acquired cases, the most common routes of invasion are through disrupted epithelial or mucosal integrity-such as surgical wounds, indwelling catheters, or endotracheal tubes. In community-acquired infections, including those affecting otherwise healthy individuals, alternative mechanisms of tissue invasion are likely involved. The frequent occurrence of pyogenic liver abscesses in hvKP infections suggests that these strains can penetrate the intestinal mucosa and disseminate to the liver via the portal circulation.

In hvKP, genes encoding colibactin are located on the integrative and conjugative element ICEKp10, which also harbors genes for microcin E492 and yersiniabactin production. Colibactin is most commonly found in capsule type K1, particularly within clonal group CG23, but occurs less frequently in other hypervirulent strains. Notably, CG23-I sublineages that acquired ICEKp10 in 1928 have since achieved global dissemination, indicating a significant role of colibactin in hvKP evolutionary success.

Microcin E492 is an 8-kDa bacteriocin with potent activity against members of the *Enterobacteriaceae* family. Its function requires salmochelin attachment, enabling uptake by target bacteria. The combined production of salmochelin, microcin E492, and colibactin enhances hvKP's competitive colonization capacity within the intestinal environment.

Additional structural modifications-such as glucuronic acid pyruvation and fucose acetylation-further protect hvKP from phagocytosis. Even after engulfment by neutrophils, hvKP strains, particularly those with the K1 capsule type, can evade intracellular killing, facilitating systemic spread to distant sites like the liver, where they induce abscess formation.

Iron acquisition is another key factor in hvKP pathogenesis. Bacterial growth in vivo and in vitro is highly dependent on iron availability. Hypervirulent strains possess approximately 12 distinct iron uptake systems, including three siderophore-based pathways-iroA, the *Yersinia* high-pathogenicity island, and iuc -as well as two ATP-binding cassette (ABC) transporters, Sit and Kfu. These systems play a crucial role in the pathogen's ability to thrive in iron-restricted host environments.

7. Virulence Factors and Genes

7.1. Capsule

The polysaccharide capsule is a central virulence determinant present in all *K. pneumoniae* strains. Forming a dense, sugar-rich layer around the bacterial cell, it contributes to the organism's mucoid phenotype and provides robust protection against host immune defenses. The capsule inhibits phagocytosis, neutralizes the antimicrobial activity of host peptides, and suppresses inflammatory signaling by downregulating key cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Figure 3).

ISSN: 2181-3337 | SCIENTISTS.UZ

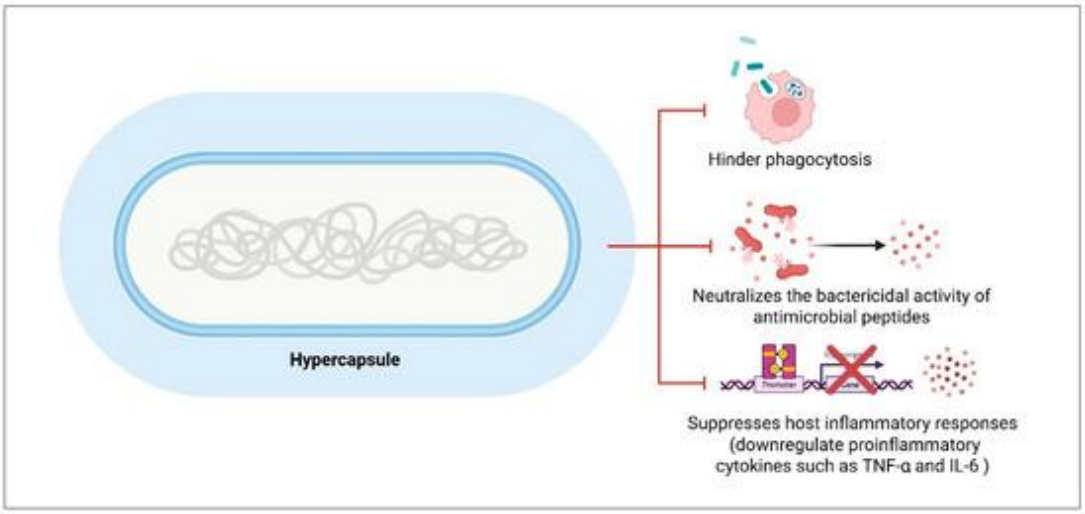


Figure 3. Protective functions of the hypercapsule in hypervirulent *K. pneumoniae* (hvKP). The hypercapsule in hvKP serves as a multifunctional defense structure, contributing to immune evasion and enhanced survival. It impairs phagocytic clearance, reduces susceptibility to host-derived antimicrobial peptides and therapeutic agents, and attenuates inflammatory responses by modulating cytokine production.

Recent research has shown that the hypercapsule of hvKP strains promotes immunosuppression not only by physically masking bacterial antigens but also by disrupting host pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs). This disruption dampens the activation of the nuclear factor-kappa B (NF-κB) signaling pathway, reducing the transcription of key proinflammatory mediators. The dense polysaccharide layer also inhibits complement activation and impairs immune cell recruitment, further weakening local inflammatory responses. Together, these mechanisms contribute to the subdued innate immune activation observed in hvKP infections, allowing systemic dissemination with minimal early detection.

Compared to classical *K. pneumoniae* (cKP), hvKP strains typically possess larger, more robust capsules that provide enhanced protection and survival. However, this enlarged capsule may also act as a physical barrier to horizontal gene transfer, limiting DNA uptake and possibly explaining the lower prevalence of antimicrobial resistance genes in hvKP relative to cKP.

Capsule biosynthesis is chromosomally encoded, with at least 79 distinct K-antigen types identified based on polysaccharide composition and antigenic structure. Among hvKP isolates, eight capsule types predominate-K1, K2, K5, K16, K20, K54, K57, and KN1-with K1 and K2 collectively accounting for about 70% of strains (Russo et al., 2018; Shon et al., 2013). Multiple studies have shown that these two serotypes exhibit significantly higher virulence than other capsule types (L. Wang et al., 2017).

Multilocus sequence typing (MLST) reveals that K1 is strongly associated with sequence type (ST) 23, while K2 displays greater genetic diversity, being linked to ST25, ST86, ST375, and ST380. Notably, K1 and K2 lack mannose and rhamnose residues-sugars recognized by macrophage lectin receptors-which may reduce phagocytic uptake.

Additional virulence-enhancing mechanisms have been identified. In K1 strains, the surface protein fructose-1,6-bisphosphate aldolase (FBA) can protect neutrophils from cell death under hyperglycemic conditions by upregulating its expression. Moreover, sialic acid residues in K1 and K2 capsular polysaccharides contribute to the hypermucoviscous phenotype and play a role in their antiphagocytic properties.

7.2 Siderophores

For *K. pneumoniae* to thrive during infection, it must acquire iron-a scarce nutrient tightly sequestered by host iron-binding proteins as part of nutritional immunity. To overcome this restriction, the

ISSN: 2181-3337 | SCIENTISTS.UZ

bacterium produces siderophores-low-molecular-weight, high-affinity iron chelators that extract iron from host proteins.

Siderophores outcompete host proteins for iron binding and are subsequently internalized by the bacterial cell via specific receptors such as YbtQ, IutA, FepA, and IroN (Figure 4). hvKP produces four major siderophores: yersiniabactin (Ybt), enterobactin (Ent), salmochelin (Iro), and aerobactin (Iuc). The latter two are considered more characteristic of hvKP, with aerobactin being the most critical for systemic infection, accounting for nearly 90% of siderophore activity in laboratory studies (Russo et al., 2015).

While yersiniabactin is a key virulence factor in cKP, its role in hvKP pathogenesis remains less clear (Russo et al., 2018). The host innate immune system can partially neutralize siderophore activity-e.g., aerobactin can be bound by the antimicrobial peptide LL-37, and lipocalin-2 can sequester enterobactin, preventing its uptake. To counteract this, hvKP produces multiple siderophores simultaneously, ensuring iron acquisition across diverse tissue niches and reducing the risk of neutralization by host defenses.

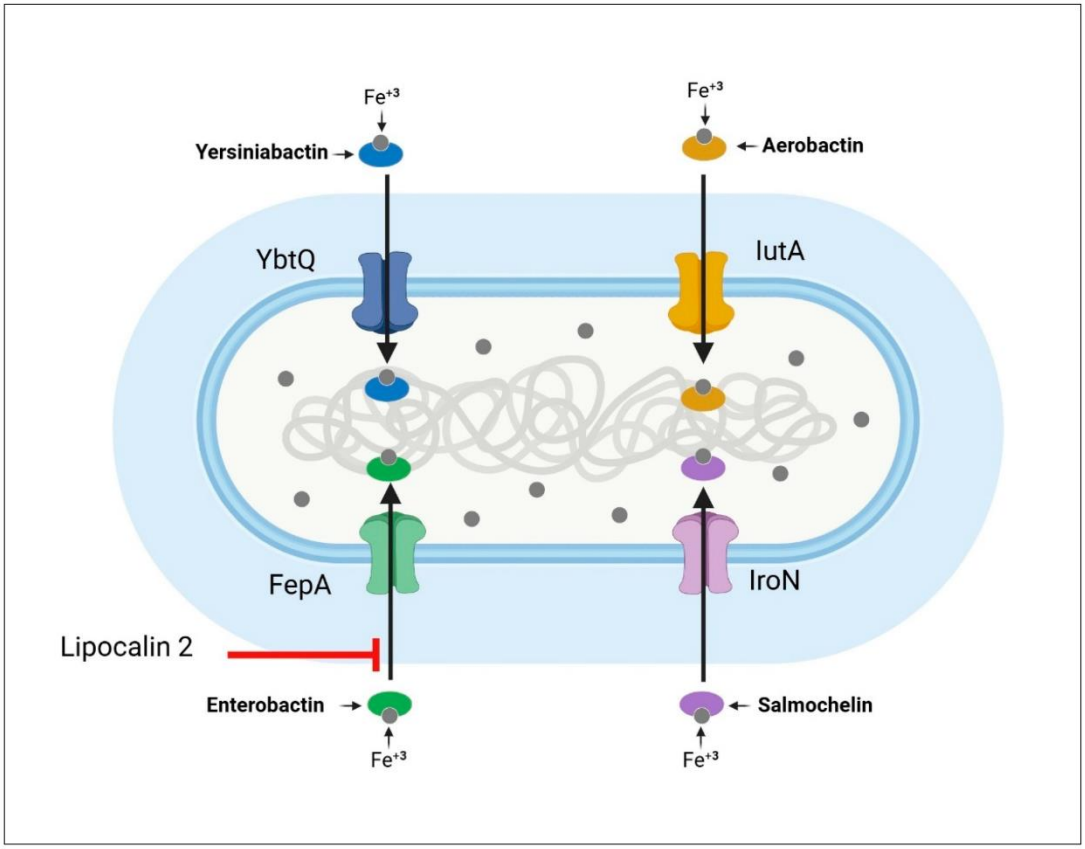


Figure 4. Iron acquisition by siderophores in hypervirulent Klebsiella pneumoniae (hvKP). Siderophores enable hvKP to overcome host nutritional immunity by sequestering iron from host iron-binding proteins. With superior iron-binding affinity, these molecules outcompete host proteins and facilitate iron uptake through dedicated bacterial receptors, supporting growth and virulence within the iron-limited environment of the host.

7.3. Lipopolysaccharide (LPS)

Lipopolysaccharide (LPS) is a fundamental structural element of the outer membrane in all Gram-negative bacteria, including both classical *K. pneumoniae* (cKP) and hypervirulent (hvKP) strains. It plays a pivotal role in virulence and immune evasion. LPS is composed of three distinct regions: lipid A, which anchors the molecule to the bacterial membrane and is responsible for its endotoxic activity; the core oligosaccharide; and the O-antigen, the most exposed portion on the bacterial surface.

The O-antigen acts as a defensive barrier against host immunity by binding complement component C3b, thereby blocking complement-mediated killing, preventing membrane attack complex (MAC)

ISSN: 2181-3337 | SCIENTISTS.UZ

formation, and reducing phagocytosis. Of the eight recognized O-antigen serotypes, O1 is the most common among clinical *K. pneumoniae* isolates and is frequently linked to enhanced virulence.

Experimental studies have shown that O1-negative strains exhibit reduced pathogenicity compared to their O1-positive counterparts. However, in K1 hvKP strains, the role of the O1 antigen is less defined, as it is likely masked by the prominent hypercapsule, limiting its interaction with host immune components. This concealment raises questions about the true contribution of the O1 antigen in hvKP pathogenesis.

7.4. Fimbriae

Fimbriae are hair-like appendages on the bacterial surface that mediate adhesion to host cells and abiotic surfaces, facilitating colonization and biofilm development. In *K. pneumoniae*, two main fimbrial types are well characterized: type 1 fimbriae, which are mannose-sensitive and promote attachment to epithelial cells, and type 3 fimbriae, which are mannose-resistant and primarily support biofilm formation on non-living surfaces. While type 3 fimbriae are established contributors to biofilm development in cKP, their exact significance in hvKP remains uncertain.

Comparative genomics has revealed at least seven fimbrial gene clusters in *K. pneumoniae*-kpa, kpb, kpc, kpd, kpe, kpf, and kfg-with kpc being the most prevalent in hvKP, especially in K1 serotype strains. Functional analysis of strain CG43 demonstrated that type 3 fimbrial expression and biofilm formation are regulated by the ferric uptake regulator (Fur) and influenced by environmental iron availability. This suggests that under the iron-limited conditions encountered in vivo, type 3 fimbriae may have a reduced role in hvKP virulence (Shon et al., 2013).

7.5. Allantoin Metabolism

While most bacterial species utilize allantoin as a nitrogen source, *K. pneumoniae* can exploit it as both a nitrogen and carbon source. In hvKP, allantoin metabolism is mediated by the allantoinase (allB) enzyme, the negative regulator (allR), the transcriptional activator (allS), and allantoin permease (ybbW).

Deletion of *allS*, a key activator of the allantoin operon, has been shown to significantly reduce hvKP pathogenicity in in vivo models. Moreover, previous studies have reported that the allantoin operon occurs at higher frequencies in liver abscess-associated hvKP strains than in cKP, suggesting a role in tissue-specific adaptation and virulence.

7.6. Colibactin

Colibactin is a genotoxic secondary metabolite synthesized by *K. pneumoniae* strains harboring the pks genomic island. Its biosynthesis involves the coordinated function of non-ribosomal peptide synthetases (NRPSs), polyketide synthases (PKSs), and accessory enzymes encoded within the pks cluster.

The *pks* locus is particularly prevalent among hypervirulent K1 serotype strains, with detection rates reported between 66% and 100% in various studies. Although the exact contribution of colibactin to hvKP pathogenesis is not yet fully defined, its DNA-damaging activity is believed to facilitate tissue invasion, disrupt host cellular defenses, and enhance bacterial persistence. This genotoxic effect may provide hvKP with a competitive advantage during systemic infection.

7.7. Peg-344

Peg-344 is a genetic marker strongly linked to hypervirulent *K. pneumoniae* (hvKP) and is believed to play a role in the enhanced pathogenic potential of these strains. Although its precise biochemical function remains uncertain, it is predicted to encode an inner membrane transporter. In vivo studies have demonstrated that peg-344 is essential for full hvKP virulence, particularly in lung and liver infections. Interestingly, deletion of this gene does not significantly impair the bacterium's ability to cause systemic infections, suggesting that peg-344 may be more critical for organ-specific pathogenesis rather than for widespread dissemination (Russo et al., 2018).

7.8. Type VI Secretion System (T6SS)

The type VI secretion system (T6SS) is a recently identified virulence mechanism in hvKP. Structurally resembling a contractile nanosyringe, the T6SS delivers toxic effector proteins directly into

ISSN: 2181-3337 | SCIENTISTS.UZ

neighboring bacterial competitors or host eukaryotic cells. This contact-dependent system contributes to interbacterial competition, host cell damage, and enhanced colonization under hostile environmental conditions. While still under investigation, the presence of a functional T6SS in hvKP is increasingly recognized as an important factor in its pathogenic arsenal.

8. Convergence of Hypervirulence and Multidrug Resistance (MDR) in *K. pneumoniae*

Reports of multidrug-resistant hypervirulent *K. pneumoniae* (MDR-hvKP) are increasing. MDR-hvKP can emerge via two primary pathways:

1. **Type I MDR-hvKP** – hvKP strains acquire antimicrobial resistance genes or plasmids via horizontal gene transfer. For example, a K2 ST86 MDR-hvKP strain was found to carry two carbapenemase plasmids simultaneously: a *bla_{NDM-1}*-bearing IncN plasmid and a *bla_{KPC-2}*-bearing IncFIIK plasmid.
2. **Type II MDR-hvKP** – classical MDR *K. pneumoniae* strains acquire pLVPK-like virulence plasmids. A notable example is a fatal outbreak in China caused by a KPC-producing ST11 strain that had gained such a virulence plasmid.

Peg-344, present on the virulence plasmid, serves as a valuable diagnostic marker for both Type I and Type II MDR-hvKP. A peg-344 loop-mediated isothermal amplification assay has been developed to enable rapid detection.

9. The Escalating Threat of Antibiotic Resistance in hvKP

K. pneumoniae has developed an extraordinary ability to acquire antibiotic resistance, prompting the World Health Organization (WHO) to classify it as a **"critical" priority pathogen** and list it among the ESKAPE group of bacteria (including *Enterococcus faecium, Staphylococcus aureus, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp.*) that are responsible for most hospital-acquired drug-resistant infections.

The bacterium commonly acquires antimicrobial resistance (AMR) genes via **horizontal gene transfer,** facilitated by plasmids, integrons, and transposons. Many *K. pneumoniae* strains harbor three or more stable AMR plasmids-often more stable than those in *E. coli*. Mobile genetic elements such as **integrons (**e.g., integron 1), **insertion sequences** (e.g., IS26), and **transposons** (e.g., Tn4401a) further promote the spread of resistance genes between plasmids and the chromosome.

Mechanisms of Resistance

1. **Plasmid-mediated resistance** – hvKP can acquire AMR genes through conjugative plasmids.
2. **Integration of AMR determinants into virulence elements** – integrative and conjugative elements (ICEs) carrying resistance genes may insert into virulence plasmids or the chromosome.
3. **Chromosomal mutations** – particularly in outer membrane proteins (OMPs), which can alter permeability and reduce drug uptake.
4. **Convergence events** – MDR or extensively drug-resistant (XDR) cKP strains acquiring hvKP virulence plasmids.

A proposed mechanism suggests that conjugative plasmids carrying *bla_{KPC}* carbapenemase genes share an 11.2-kb homologous region with certain hvKP virulence plasmids, facilitating recombination and gene exchange-though this requires further experimental confirmation.

Intrinsic and Acquired Resistance Profiles

- **Intrinsic resistance** – All *K. pneumoniae* strains, including hvKP, are naturally resistant to ticarcillin and ampicillin, and display variable susceptibility to nitrofurantoin.
- **β-lactam and carbapenem resistance** – Carbapenemase- or ESBL-producing strains carry plasmids conferring resistance to tetracyclines, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole.
- **ESBLs** such as TEM, CTX-M, and SHV hydrolyze 3rd/4th-generation cephalosporins and aztreonam, reducing the efficacy of β-lactam/β-lactamase inhibitor combinations (Kong et al., 2017).

ISSN: 2181-3337 | SCIENTISTS.UZ

- Some hvKP strains also produce **AmpC β-lactamases**, extending resistance to cephamycins like cefotetan and cefoxitin.
- **Carbapenemases** – The main classes are KPC (Class A), NDM and IMP (Class B metallo-β-lactamases), and OXA (Class D). Among these, **KPC-type** enzymes are the most common.
- **Polymyxin resistance** – Often plasmid-mediated via *mcr-1*, or through lipid A modification by the PhoP–PhoQ–Arn pathway. Inactivation of *mgrB*, a negative regulator of this pathway, has been linked to colistin resistance.
- **Tigecycline resistance** – Associated with overexpression of the efflux pump regulator *ramA* and its repressor *acrR*. cKP strains that acquire hvKP virulence plasmids may also gain tigecycline resistance.

10. Clinical and Epidemiological Risk Factors

The presence of K1 or K2 capsular serotypes and other virulence determinants does not appear to directly influence patient mortality. Instead, several **clinical parameters** have been identified as significant predictors of increased mortality, including:

- Bacteremia
- Respiratory distress (respiratory rate > 30 breaths/min)
- Altered mental status
- Septic shock
- Arterial pH < 7.35
- Tachycardia (heart rate > 125 beats/min)
- Hematocrit < 30%
- Elevated blood urea nitrogen (>10.71 mmol/L).

Mortality risk is generally comparable between infections caused by hvKP and those caused by cKP. However, **cKP infections** are more frequently observed in hospitalized cancer patients, likely reflecting the higher prevalence of immunosuppression in this population.

In bloodstream infections (BSIs), patients with hvKP-BSI are **more likely** to have diabetes mellitus (DM) and **less likely** to be immunocompromised compared to those with cKP-BSI. Pyogenic liver abscesses represent a more frequent source of hvKP-BSIs than cKP-BSIs. Established risk factors for hvKP infection include DM, community-acquired infection, solid malignancies, and hypertension, whereas immunosuppression appears to be paradoxically protective against hvKP-BSI.

Although hvKP infections can occur across all ethnic groups, they are reported more frequently in **Asian**, **Hispanic**, and **Pacific Island** populations-possibly due to higher colonization rates and environmental exposure (Fazili et al., 2016; McCabe et al., 2010; Nadasy et al., 2007). Regarding gender differences, some studies suggest a higher infection rate among males, while others report no significant sex-based variation (Ye et al., 2016).

11. Association with Malignancy

Multiple studies have demonstrated a **higher incidence of colorectal cancer** in patients with *K. pneumoniae* liver abscess compared to those without liver abscess or with abscesses caused by other pathogens. This association is thought to be linked to **colibactin**, a genotoxic metabolite produced by certain *Klebsiella* strains. Colibactin-induced DNA damage may contribute to tumorigenesis, supporting the hypothesis that liver abscess caused by hvKP could represent a **precancerous condition**.

Given this association, **colonoscopy screening** should be considered for all patients with hvKP-related liver abscess-particularly those with additional risk factors such as family history of colorectal cancer or older age.

12. Clinical Challenges in hvKP Infection

12.1. Diagnostic Challenges

ISSN: 2181-3337 | SCIENTISTS.UZ

A major hurdle in hvKP management is **accurate strain identification**. In China, hvKP was detected in 22.8% (84/369) of *K. pneumoniae* isolates linked to invasive infections. Compared to cKP, hvKP is more prone to causing **multifocal, invasive disease**, often leading to higher mortality. However, there is **no standardized clinical definition** for hvKP, and classification criteria vary widely between studies.

Traditional phenotypic tests-such as the **string test** and **aerobactin detection**-have shown limited reliability, often resulting in inconsistent clinical interpretations (Zhang et al., 2016). In practice, diagnosis often relies on **clinical suspicion**, especially in cases of metastatic infection in otherwise healthy individuals. While hvKP was initially considered a disease of young adults, recent findings-such as the 45.7% prevalence reported by Liu et al. in older patients-highlight its wider demographic impact.

Molecular diagnostics offer a more precise approach, distinguishing hvKP from cKP through genotypic and phenotypic markers. Key hypervirulence-associated markers include **mobile genetic element-associated genes** and **virulence plasmid genes** such as *iroB*, *peg-344*, *iucA*, *prmpA2*, and *rmpA*. Certain combinations-particularly *iuc* plus total siderophore production, along with *rmpA*/*rmpA2*-are considered among the most sensitive and specific for hvKP identification (Russo et al., 2018). Despite their diagnostic potential, the **routine clinical use** of such molecular tools remains limited by cost and logistical challenges, maintaining a gap in hvKP–cKP differentiation in many healthcare settings.

12.2. Antibiotic Resistance and Treatment Challenges

One of the most pressing obstacles in hvKP management is the **escalating problem of antimicrobial resistance**. Many hvKP strains now exhibit **multidrug resistance (MDR)**, severely restricting therapeutic options. The prevalence of resistant hvKP isolates has risen markedly in recent years, especially in endemic regions such as China (Zhang et al., 2016). In a study by Zhang et al. (2016), 37% of clinical *K. pneumoniae* isolates were classified as hvKP based on the presence of *rmpA*, and 13% of these also produced extended-spectrum β-lactamases (ESBLs).

Resistance acquisition in hvKP occurs via **multiple mechanisms**, including horizontal gene transfer and the acquisition of resistance-encoding plasmids (Khujaeva, 2024a, 2024b; Russo & Marr, 2019). The convergence of hypervirulence and MDR creates significant clinical challenges, as standard antibiotic regimens often fail. These limitations underscore the need for **alternative therapeutic strategies** such as bacteriophage therapy, combination antibiotic regimens, and the development of novel antimicrobial compounds.

Given these trends, **rigorous infection control and active surveillance** are crucial to preventing hvKP spread within healthcare environments. Strong antimicrobial stewardship programs must also be implemented to curb inappropriate antibiotic use, which accelerates resistance development. An effective hvKP management strategy should integrate **rapid diagnostics**, optimized antimicrobial therapy, and strict infection prevention protocols.

13. Strategies for Controlling hvKP Infections

A comprehensive control plan for hvKP should combine **traditional measures** with **innovative interventions**. Key components include infection monitoring, targeted antibiotic therapy, phage therapy, biofilm disruption strategies, monoclonal antibodies, and vaccine development.

Prompt **radiological assessment** and **abscess drainage** are central to treatment, given the high incidence of abscess formation in hvKP infections. The hypermucoviscous (HMV) phenotype produces **highly viscous pus**, which complicates drainage procedures. Antimicrobial therapy alone may suffice for abscesses < 5 cm, but larger abscesses typically require intervention. Long-term follow-up is essential, as reinfections have been reported months or years after initial treatment (Shon et al., 2013).

Empirical antibiotic selection should reflect **local resistance profiles**. While *K. pneumoniae* is inherently resistant to ampicillin, there is no universally accepted regimen for hvKP. For central nervous system (CNS) infections, **meropenem plus ceftriaxone** has been suggested, whereas ocular infections

ISSN: 2181-3337 | SCIENTISTS.UZ

may require systemic and local administration of cefazolin, ceftazidime, aminoglycosides, or imipenem Treatment duration often extends to six weeks, depending on infection site and severity (Shon et al., 2013).

- **Phage therapy:** Promising results have been achieved when bacteriophages are combined with antibiotics, particularly for treating carbapenem-resistant hvKP. Phages active against MDR *K. pneumoniae* have been identified, highlighting their potential as adjunctive therapy.
- **Vaccines:** A bivalent bioconjugate vaccine targeting K1/K2 serotypes has been developed using genetically engineered *E. coli*. Vaccines incorporating B-cell epitopes from type 1 fimbrial antigens have also shown protective effects.
- **Monoclonal antibodies:** Experimental models indicate that monoclonal antibodies can reduce intestinal hvKP colonization, preventing systemic spread.

Biofilm formation enhances hvKP persistence and **reduces antibiotic penetration**. Potential biofilm-disruption strategies include:

- **Quorum-sensing (QS) inhibitors** (furans, pyridines, phenyl acyl alkaloids, fatty acids) to block bacterial signaling and biofilm maturation.
- **Enzymatic degradation** of extracellular polymeric substances using dispersin B or DNase, improving antibiotic efficacy.
- **Synthetic polymers and antimicrobial peptides** (e.g., polymyxin, polyalanine) to prevent or dismantle biofilms.
- **Metal-based nanotherapies** with copper or gold nanoparticles, which disrupt bacterial membranes and interfere with metabolism .
- **Combination therapies** integrating multiple anti-biofilm agents, producing synergistic eradication effects.

Priorities include the development of **rapid molecular diagnostics** for hvKP detection and resistance profiling, potentially integrating whole-genome sequencing with AI-based predictive models. Preventive measures-such as vaccines and monoclonal antibodies-require further refinement for durable protection. Enhancing anti-biofilm strategies will also be essential for managing persistent infections.

Ultimately, a **global, multidisciplinary approach**-integrating antimicrobial stewardship, infection prevention, rapid diagnostics, and novel therapeutics-will be key to mitigating the expanding threat posed by hvKP.

14. Conclusions

Klebsiella pneumoniae remains one of the leading causes of **nosocomial infections**, particularly among immunocompromised patients. The emergence of **hypervirulent subtypes (hvKP)** has elevated this pathogen to a critical public health concern, as it now affects not only vulnerable hospital populations but also otherwise healthy individuals. hvKP can cause severe, often life-threatening infections involving multiple organ systems, with **hepatic abscesses** being among the earliest and most characteristic presentations.

Accurate differentiation between **classical K. pneumoniae (cKP)** and hvKP is essential, relying on the detection of specific **molecular and phenotypic biomarkers** to ensure precise diagnosis. The pathogen's capacity to acquire a wide range of **antimicrobial resistance (AMR) genes**-facilitated by its presence in diverse environmental and host reservoirs-further compounds the challenge. In recognition of its escalating drug resistance, the **World Health Organization (WHO)** has designated *K. pneumoniae* as a "critical priority pathogen." The rapid dissemination of resistance determinants has resulted in the alarming emergence of **multidrug-resistant (MDR)** and **extensively drug-resistant (XDR)** hvKP strains, which are refractory to most conventional antibiotics.

In response to these challenges, research has increasingly focused on **innovative therapeutic strategies**, including bacteriophage therapy, biofilm-disrupting agents, monoclonal antibodies, and vaccine development. The integration of **nanotechnology-based approaches** holds additional promise for

ISSN: 2181-3337 | SCIENTISTS.UZ

improving prevention and treatment outcomes. Moving forward, sustained **global collaboration** will be indispensable to advancing these novel interventions, enhancing early diagnostic capabilities, and implementing effective infection control measures to curb the growing threat posed by this highly virulent and drug-resistant pathogen.

REFERENCES

1. Al Ismail, D., Campos-Madueno, E. I., Donà, V., & Endimiani, A. (2024). Hypervirulent *Klebsiella pneumoniae* (hvKp): Overview, epidemiology, and laboratory detection. *Pathogens and Immunity*, *10*, 80–119. https://doi.org/10.20411/pai.v10i1.777
2. Algammal, A., Hetta, H. F., Mabrok, M., & Behzadi, P. (2023). Editorial: Emerging multidrug-resistant bacterial pathogens "superbugs": A rising public health threat. *Frontiers in Microbiology*, *14*, 1135614. https://doi.org/10.3389/fmicb.2023.1135614
3. Carpenter, J. L. (1990). Klebsiella pulmonary infections: Occurrence at one medical center and review. *Reviews of Infectious Diseases*, *12*, 672–682. https://doi.org/10.1093/clinids/12.4.672
4. Catalán-Nájera, J. C., Garza-Ramos, U., & Barrios-Camacho, H. (2017). Hypervirulence and hypermucoviscosity: Two different but complementary *Klebsiella spp.* phenotypes? *Virulence*, *8*, 1111–1123. https://doi.org/10.1080/21505594.2017.1317412
5. Chang, W.-N., Huang, C.-R., Lu, C.-H., & Chien, C.-C. (2012). Adult *Klebsiella pneumoniae* meningitis in Taiwan: An overview. *Acta Neurologica Taiwanica*, *21*, 87–96.
6. Chen, T., Ying, L., Xiong, L., Wang, X., Lu, P., Wang, Y., Shen, P., & Xiao, Y. (2024). Understanding carbapenem-resistant hypervirulent *Klebsiella pneumoniae*: Key virulence factors and evolutionary convergence. *hLife*, *2*, 611–624. https://doi.org/10.1016/j.hlife.2024.06.005
7. Cheng, N.-C., Yu, Y.-C., Tai, H.-C., Hsueh, P.-R., Chang, S.-C., Lai, S.-Y., Yi, W.-C., & Fang, C.-T. (2012). Recent trend of necrotizing fasciitis in Taiwan: Focus on monomicrobial *Klebsiella pneumoniae* necrotizing fasciitis. *Clinical Infectious Diseases*, *55*, 930–939. https://doi.org/10.1093/cid/cis565
8. Chew, K. L., Lin, R. T., & Teo, J. W. (2017). *Klebsiella pneumoniae* in Singapore: Hypervirulent infections and the carbapenemase threat. *Frontiers in Cellular and Infection Microbiology*, *7*, 515. https://doi.org/10.3389/fcimb.2017.00515
9. Doud, M. S., Grimes-Zeppegno, R., Molina, E., Miller, N., Balachandar, D., Schneper, L., Poppiti, R., & Mathee, K. (2009). A k2A-positive *Klebsiella pneumoniae* causes liver and brain abscess in a Saint Kitt's man. *International Journal of Medical Sciences*, *6*, 301. https://doi.org/10.7150/ijms.6.301
10. Durand, M. L., Calderwood, S. B., Weber, D. J., Miller, S. I., Southwick, F. S., Caviness, V. S., Jr., & Swartz, M. N. (1993). Acute bacterial meningitis in adults: A review of 493 episodes. *The New England Journal of Medicine*, *328*(1), 21–28. https://doi.org/10.1056/NEJM199301073280104
11. Fang, C.-T., Chang, S.-C., Hsueh, P.-R., Chen, Y.-C., Sau, W.-Y., & Luh, K.-T. (2000). Microbiologic features of adult community-acquired bacterial meningitis in Taiwan. *Journal of the Formosan Medical Association*, *99*(4), 300–304.
12. Fang, C.-T., Chen, Y.-C., Chang, S.-C., Sau, W.-Y., & Luh, K.-T. (2000). *Klebsiella pneumoniae* meningitis: Timing of antimicrobial therapy and prognosis. *QJM: An International Journal of Medicine*, *93*(1), 45–53. https://doi.org/10.1093/qjmed/93.1.45
13. Fang, C.-T., Chuang, Y.-P., Shun, C.-T., Chang, S.-C., & Wang, J.-T. (2004). A novel virulence gene in *Klebsiella pneumoniae* strains causing primary liver abscess and septic metastatic complications. *Journal of Experimental Medicine*, *199*, 697–705. https://doi.org/10.1084/jem.20030857
14. Fazili, T., Sharngoe, C., Endy, T., Kiska, D., Javaid, W., & Polhemus, M. (2016). *Klebsiella pneumoniae* liver abscess: An emerging disease. *The American Journal of the Medical Sciences*, *351*, 297–304. https://doi.org/10.1016/j.amjms.2015.12.018

ISSN: 2181-3337 | SCIENTISTS.UZ

15. Frazee, B. W., Hansen, S., & Lambert, L. (2009). Invasive infection with hypermucoviscous *Klebsiella pneumoniae*: Multiple cases presenting to a single emergency department in the United States. *Annals of Emergency Medicine*, *53*, 639–642. https://doi.org/10.1016/j.annemergmed.2008.11.007
16. García-Cobos, S., Oteo-Iglesias, J., & Pérez-Vázquez, M. (2025). Hypervirulent *Klebsiella pneumoniae*: Epidemiology outside Asian countries, antibiotic resistance association, methods of detection and clinical management. *Enfermedades Infecciosas y Microbiología Clínica*, *43*, 102–109. https://doi.org/10.1016/j.eimc.2024.12.008
17. Gunnarsson, G. L., Brandt, P. B., Gad, D., Struve, C., & Justesen, U. S. (2009). Monomicrobial necrotizing fasciitis in a white male caused by hypermucoviscous *Klebsiella pneumoniae*. *Journal of Medical Microbiology*, *58*, 1519–1521. https://doi.org/10.1099/jmm.0.011064-0
18. Hentzien, M., Rosman, J., Decré, D., Brenkle, K., Mendes-Martins, L., & Mateu, P. (2017). Seven hypervirulent ST380 *Klebsiella pneumoniae* septic localizations. *Médecine et Maladies Infectieuses*, *47*, 171–173. https://doi.org/10.1016/j.medmal.2016.10.002
19. Hsieh, M.-J., Lu, T.-C., Ma, M. H.-M., Wang, H.-P., & Chen, S.-C. (2009). Unrecognized cervical spinal epidural abscess associated with metastatic *Klebsiella pneumoniae* bacteremia and liver abscess in nondiabetic patients. *Diagnostic Microbiology and Infectious Disease*, *65*, 65–68. https://doi.org/10.1016/j.diagmicrobio.2009.05.013
20. Jang, T., Wang, F., Wang, L., Yu, K., & Liu, C. (1993). Gram-negative bacillary meningitis in adults: A recent six-year experience. *Journal of the Formosan Medical Association*, *92*, 540–546.
21. Kareem, S. M., Al-Kadmy, I. M., Kazaal, S. S., Mohammed Ali, A. N., Aziz, S. N., Makharita, R. R., Algammal, A. M., Al-Rejaie, S., Behl, T., & Batiha, G. E.-S. (2021). Detection of gyrA and parC mutations and prevalence of plasmid-mediated quinolone resistance genes in *Klebsiella pneumoniae*. *Infection and Drug Resistance*, *14*, 555–563. https://doi.org/10.2147/IDR.S275852
22. Khujaeva, S. A. (2024a). Advances in the human skin microbiota and its roles in cutaneous diseases. *Eurasian Journal of Medical and Natural Sciences*, *4*(3), 240–256.
23. Khujaeva, S. A. (2024b). Antibiotic resistance in bacteria: The most dangerous pathogens. *Eurasian Journal of Medical and Natural Sciences*, *4*(10), 65–67.
24. Kishibe, S., Okubo, Y., Morino, S., Hirotaki, S., Tame, T., Aoki, K., Ishii, Y., Ota, N., Shimomura, S., & Sakakibara, H. (2016). Pediatric hypervirulent *Klebsiella pneumoniae* septic arthritis. *Pediatrics International*, *58*, 382–385. https://doi.org/10.1111/ped.12806
25. Ko, W.-C., Paterson, D. L., Sagnimeni, A. J., Hansen, D. S., Von Gottberg, A., Mohapatra, S., Casellas, J. M., Goossens, H., Mulazimoglu, L., & Trenholme, G. (2002). Community-acquired *Klebsiella pneumoniae* bacteremia: Global differences in clinical patterns. *Emerging Infectious Diseases*, *8*, 160. https://doi.org/10.3201/eid0802.010025
26. Kong, H., Yu, F., Zhang, W., & Li, X. (2017). Clinical and microbiological characteristics of pyogenic liver abscess in a tertiary hospital in East China. *Medicine*, *96*, e8050. https://doi.org/10.1097/MD.0000000000008050
27. Kuramochi, G., Takei, S.-I., Sato, M., Isokawa, O., Takemae, T., & Takahashi, A. (2005). *Klebsiella pneumoniae* liver abscess associated with septic spinal epidural abscess. *Hepatology Research*, *31*, 48–52. https://doi.org/10.1016/j.hepres.2004.09.006
28. Lee, H. C., Chuang, Y. C., Yu, W. L., Lee, N. Y., Chang, C. M., Ko, N. Y., Wang, L. R., & Ko, W. C. (2006). Clinical implications of hypermucoviscosity phenotype in *Klebsiella pneumoniae* isolates: Association with invasive syndrome in patients with community-acquired bacteraemia. *Journal of Internal Medicine*, *259*, 606–614. https://doi.org/10.1111/j.1365-2796.2006.01641.x
29. Lin, Y.-T., Liu, C.-J., Chen, T.-J., & Fung, C.-P. (2012). Long-term mortality of patients with septic ocular or central nervous system complications from pyogenic liver abscess: A population-based study. *PLOS ONE*, *7*, e33978. https://doi.org/10.1371/journal.pone.0033978

30. Lin, Y.-T., Siu, L. K., Lin, J.-C., Chen, T.-L., Tseng, C.-P., Yeh, K.-M., Chang, F.-Y., & Fung, C.-P. (2012). Seroepidemiology of *Klebsiella pneumoniae* colonizing the intestinal tract of healthy Chinese and overseas Chinese adults in Asian countries. *BMC Microbiology*, *12*, 13. https://doi.org/10.1186/1471-2180-12-13
31. Liu, Y.-C., Cheng, D.-L., & Lin, C.-L. (1986). *Klebsiella pneumoniae* liver abscess associated with septic endophthalmitis. *Archives of Internal Medicine*, *146*, 1913–1916. https://doi.org/10.1001/archinte.1986.00360220057011
32. Liu, Y.-C., Yen, M.-Y., & Wang, R.-S. (1991). Septic metastatic lesions of pyogenic liver abscess: Their association with *Klebsiella pneumoniae* bacteremia in diabetic patients. *Archives of Internal Medicine*, *151*, 1557–1559.
33. Magill, S. S., Edwards, J. R., Bamberg, W., Beldavs, Z. G., Dumyati, G., Kainer, M. A., Lynfield, R., Maloney, M., McAllister-Hollod, L., & Nadle, J. (2014). Multistate point-prevalence survey of health care–associated infections. *The New England Journal of Medicine*, *370*, 1198–1208. https://doi.org/10.1056/NEJMoa1306801
34. Mai, D., Wu, A., Li, R., Cai, D., Tong, H., Wang, N., & Tan, J. (2023). Identification of hypervirulent *Klebsiella pneumoniae* based on biomarkers and *Galleria mellonella* infection model. *BMC Microbiology*, *23*, 369. https://doi.org/10.1186/s12866-023-03124-0
35. Makharita, R. R., El-Kholy, I., Hetta, H. F., Abdelaziz, M. H., Hagagy, F. I., Ahmed, A. A., & Algammal, A. M. (2020). Antibiogram and genetic characterization of carbapenem-resistant gram-negative pathogens incriminated in healthcare-associated infections. *Infection and Drug Resistance*, *13*, 3991–4002. https://doi.org/10.2147/IDR.S276975
36. Marrie, T. J., Durant, H., & Yates, L. (1989). Community-acquired pneumonia requiring hospitalization: 5-year prospective study. *Reviews of Infectious Diseases*, *11*, 586–599. https://doi.org/10.1093/clinids/11.4.586
37. McCabe, R., Lambert, L., & Frazee, B. (2010). Invasive *Klebsiella pneumoniae* infections, California, USA. *Emerging Infectious Diseases*, *16*, 1490. https://doi.org/10.3201/eid1609.100386
38. Mgbemena, O., Serota, D. P., Kumar, S., Wozniak, J. E., Weiss, D. S., & Kempker, R. R. (2017). Peculiar purulence: Hypervirulent *Klebsiella pneumoniae* causing pyomyositis. *International Journal of Infectious Diseases*, *65*, 90–92. https://doi.org/10.1016/j.ijid.2017.09.030
39. Nadasy, K. A., Domiati-Saad, R., & Tribble, M. A. (2007). Invasive *Klebsiella pneumoniae* syndrome in North America. *Clinical Infectious Diseases*, *45*, e25–e28. https://doi.org/10.1086/519424
40. Nannini, E. C., Lahitte, M., Scapellato, P., Nemirosvky, C., Zylberman, M., Vila, A., Rodríguez, V., Zucchi, R., Mykietiuk, A., David, V., Limansky, A., Marchiaro, P., & Rinaudo, M. (2025). Diversity of hypervirulent *Klebsiella pneumoniae* clones causing cryptogenic liver abscesses and metastatic complications in Argentina. *Revista Argentina de Microbiología*, *57*(4), 356–363. https://doi.org/10.1016/j.ram.2024.11.006
41. Ng, D., & Frazee, B. (2015). Necrotizing fasciitis caused by hypermucoviscous *Klebsiella pneumoniae* in a Filipino female in North America. *Western Journal of Emergency Medicine*, *16*, 165. https://doi.org/10.5811/westjem.2014.11.23599
42. Oikonomou, K. G., & Aye, M. (2017). *Klebsiella pneumoniae* liver abscess: A case series of six Asian patients. *The American Journal of Case Reports*, *18*, 1028. https://doi.org/10.12659/AJCR.905191
43. Paczosa, M. K., & Mecsas, J. (2016). *Klebsiella pneumoniae*: Going on the offense with a strong defense. *Microbiology and Molecular Biology Reviews*, *80*, 629–661. https://doi.org/10.1128/MMBR.00078-15
44. Paraschiv, F., Popescu, G. A., & Borcan, A. M. (2018). Septic cutaneous emboli revealing a severe case of *Klebsiella pneumoniae* liver abscess syndrome. *JMM Case Reports*, *5*, e005148. https://doi.org/10.1099/jmmcr.0.005148

ISSN: 2181-3337 | SCIENTISTS.UZ

45. Prokesch, B. C., TeKippe, M., Kim, J., Raj, P., TeKippe, E. M., & Greenberg, D. E. (2016). Primary osteomyelitis caused by hypervirulent *Klebsiella pneumoniae*. *The Lancet Infectious Diseases*, *16*, e190–e195. https://doi.org/10.1016/S1473-3099(16)30021-4
46. Pu, D., Zhao, J., Chang, K., Zhuo, X., & Cao, B. (2023). "Superbugs" with hypervirulence and carbapenem resistance in *Klebsiella pneumoniae*: The rise of such emerging nosocomial pathogens in China. *Science Bulletin*, *68*, 2658–2670. https://doi.org/10.1016/j.scib.2023.09.040
47. Qu, K., Liu, C., Wang, Z.-X., Tian, F., Wei, J.-C., Tai, M.-H., Zhou, L., Meng, F.-D., Wang, R.-T., & Xu, X.-S. (2012). Pyogenic liver abscesses associated with nonmetastatic colorectal cancers: An increasing problem in Eastern Asia. *World Journal of Gastroenterology*, *18*, 2948. https://doi.org/10.3748/wjg.v18.i23.2948
48. Rivero, A., Gomez, E., Alland, D., Huang, D. B., & Chiang, T. (2010). K2 serotype *Klebsiella pneumoniae* causing a liver abscess associated with infective endocarditis. *Journal of Clinical Microbiology*, *48*, 639–641. https://doi.org/10.1128/JCM.01779-09
49. Russo, T. A., & Marr, C. M. (2019). Hypervirulent *Klebsiella pneumoniae*. *Clinical Microbiology Reviews*, *32*, e00001–e00019. https://doi.org/10.1128/CMR.00001-19
50. Russo, T. A., Olson, R., Fang, C.-T., Stoesser, N., Miller, M., MacDonald, U., Hutson, A., Barker, J. H., La Hoz, R. M., & Johnson, J. R. (2018). Identification of biomarkers for differentiation of hypervirulent *Klebsiella pneumoniae* from classical *K. pneumoniae*. *Journal of Clinical Microbiology*, *56*, e00776-18. https://doi.org/10.1128/JCM.00776-18
51. Russo, T. A., Olson, R., MacDonald, U., Beanan, J., & Davidson, B. A. (2015). Aerobactin, but not yersiniabactin, salmochelin, or enterobactin, enables the growth/survival of hypervirulent (hypermucoviscous) *Klebsiella pneumoniae* ex vivo and in vivo. *Infection and Immunity*, *83*, 3325–3333. https://doi.org/10.1128/IAI.00430-15
52. Shon, A. S., Bajwa, R. P., & Russo, T. A. (2013). Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*: A new and dangerous breed. *Virulence*, *4*, 107–118. https://doi.org/10.4161/viru.22718
53. Tang, L.-M., Chen, S.-T., Hsu, W.-C., & Chen, C.-M. (1997). Klebsiella meningitis in Taiwan: An overview. *Epidemiology and Infection*, *119*, 135–142. https://doi.org/10.1017/S0950268897007930
54. Vergis, E. N., Indorf, A., File, T. M., Phillips, J., Bates, J., Tan, J., Sarosi, G. A., Grayston, J. T., Summersgill, J., & Victor, L. Y. (2000). Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients: A prospective, randomized, multicenter trial. *Archives of Internal Medicine*, *160*, 1294–1300. https://doi.org/10.1001/archinte.160.9.1294
55. Walker, K. A., Treat, L. P., Sepúlveda, V. E., & Miller, V. L. (2020). The small protein RmpD drives hypermucoviscosity in *Klebsiella pneumoniae*. *mBio*, *11*, e01750-20. https://doi.org/10.1128/mBio.01750-20
56. Wang, J.-H., Liu, Y.-C., Lee, S. S.-J., Yen, M.-Y., Chen, Y.-S., Wang, J.-H., Wann, S.-R., & Lin, H.-H. (1998). Primary liver abscess due to *Klebsiella pneumoniae* in Taiwan. *Clinical Infectious Diseases*, *26*, 1434–1438. https://doi.org/10.1086/516369
57. Wang, L., Shen, D., Wu, H., & Ma, Y. (2017). Resistance of hypervirulent *Klebsiella pneumoniae* to both intracellular and extracellular killing of neutrophils. *PLOS ONE*, *12*, e0173638. https://doi.org/10.1371/journal.pone.0173638
58. Ye, M., Tu, J., Jiang, J., Bi, Y., You, W., Zhang, Y., Ren, J., Zhu, T., Cao, Z., & Yu, Z. (2016). Clinical and genomic analysis of liver abscess-causing *Klebsiella pneumoniae* identifies new liver abscess-associated virulence genes. *Frontiers in Cellular and Infection Microbiology*, *6*, 165. https://doi.org/10.3389/fcimb.2016.00165

59. Yoon, W. (2013). A rare presentation of brain abscess and ventriculitis/INS; caused by Klebsiella pneumonia. *Journal of the Neurological Sciences*, *333*, e286. https://doi.org/10.1016/j.jns.2013.07.1082
60. Yu, W.-L., Ko, W.-C., Cheng, K.-C., Lee, C.-C., Lai, C.-C., & Chuang, Y.-C. (2008). Comparison of prevalence of virulence factors for *Klebsiella pneumoniae* liver abscesses between isolates with capsular K1/K2 and non-K1/K2 serotypes. *Diagnostic Microbiology and Infectious Disease*, *62*, 1–6. https://doi.org/10.1016/j.diagmicrobio.2008.04.007
61. Zhang, Y., Zhao, C., Wang, Q., Wang, X., Chen, H., Li, H., Zhang, F., Li, S., Wang, R., & Wang, H. (2016). High prevalence of hypervirulent *Klebsiella pneumoniae* infection in China: Geographic distribution, clinical characteristics, and antimicrobial resistance. *Antimicrobial Agents and Chemotherapy*, *60*, 6115–6120. https://doi.org/10.1128/AAC.01127-16
62. Zhu, J., Wang, T., Chen, L., & Du, H. (2021). Virulence factors in hypervirulent *Klebsiella pneumoniae*. *Frontiers in Microbiology*, *12*, 734. https://doi.org/10.3389/fmicb.2021.642484

ISSN: 2181-3337 | SCIENTISTS.UZ

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

THE INFLUENCE OF METABOLIC SYNDROME COMPONENTS ON THE DEVELOPMENT OF FETAL MACROSOMIA

Karimova Bonu
2nd-year Master's student in Obstetrics and Gynecology
Tashkent State Medical University

DOI: 10.67620/sai.59d0004

ABSTRACT

Fetal macrosomia, commonly defined as a birth weight of ≥4000 g or above the 90th percentile for gestational age, remains a frequent and clinically significant complication of pregnancy worldwide. Maternal metabolic syndrome (MetS), characterized by central obesity, insulin resistance or hyperglycemia, dyslipidemia, and arterial hypertension, is increasingly recognized as an important risk factor for excessive fetal growth. This review synthesizes current evidence on the pathophysiological mechanisms and clinical associations linking individual components of maternal MetS with fetal macrosomia and examines their combined predictive value. A narrative review of PubMed/MEDLINE and Scopus-indexed literature was conducted, focusing on cohort and case-control studies, systematic reviews, and meta-analyses published over the past two decades. The evidence indicates that maternal hyperglycemia and compensatory fetal hyperinsulinemia constitute the central pathogenic pathway of macrosomia, consistent with the Pedersen hypothesis. Maternal obesity independently and synergistically increases this risk through chronic low-grade inflammation, dysregulation of leptin and adiponectin, and enhanced placental nutrient transport. Elevated maternal triglycerides and altered lipid indices may further contribute to fetal overgrowth through glucose-independent mechanisms. In contrast, the relationship between hypertensive disorders and macrosomia is more heterogeneous and may be influenced by placental insufficiency, which can attenuate fetal growth. The coexistence of multiple metabolic syndrome components is associated with a substantially greater risk of macrosomia than the presence of individual risk factors alone. Overall, maternal metabolic syndrome components contribute to fetal overgrowth through overlapping but distinct mechanisms, with hyperglycemia, insulin resistance, and dyslipidemia demonstrating the most consistent associations. Early identification and integrated metabolic risk stratification during the first and second trimesters may improve the prediction and prevention of macrosomia-related perinatal complications.

ACCEPTED

04.10.26

Keywords: *metabolic syndrome, fetal macrosomia, gestational diabetes mellitus, insulin resistance, maternal obesity, dyslipidemia, large for gestational age.*

CC BY

Introduction

Fetal macrosomia, which is defined as a birth weight of 4000 g or more regardless of gestational age, or an estimated fetal weight above the 90th percentile for gestational age, complicates approximately 5-20% of pregnancies in published studies and is increasingly important in the setting of rising maternal

obesity and gestational diabetes mellitus (GDM) (Gaudet et al., 2014; Sourinejad et al., 2019). Macrosomic infants are more likely to experience shoulder dystocia, birth trauma, perinatal asphyxia, neonatal hypoglycemia, and cesarean delivery, and they are also more likely to develop childhood obesity, insulin resistance, and type 2 diabetes later in life, perpetuating an intergenerational cycle of metabolic disease (Gaudet et al., 2014; Mou et al., 2023). Metabolic syndrome (MetS) in pregnancy is defined by the presence of central obesity, poor glucose tolerance or insulin resistance, dyslipidemia (high triglycerides and low high-density lipoprotein cholesterol), and raised blood pressure. Each of these components has been linked to fetal growth abnormalities, while their combined and interacting effects have increasingly been studied as a clustered metabolic phenotype (Sourinejad et al., 2019). Understanding how individual and clustered metabolic disorders affect fetal growth trajectories is critical for establishing effective early detection tools and tailored preventive interventions during prenatal care. The purpose of this review is to summarize and critically analyze the current evidence regarding the role of individual metabolic syndrome components - obesity/adiposity, hyperglycemia and insulin resistance, dyslipidemia, and hypertensive disorders - in the pathogenesis of fetal macrosomia, as well as to discuss their combined predictive and clinical significance.

Materials and methods.

A narrative literature review covering papers from 2005 to 2025 was undertaken using the PubMed/MEDLINE, Scopus, and Google Scholar databases. The search phrases included “metabolic syndrome,” “fetal macrosomia,” “large for gestational age,” “gestational diabetes,” “insulin resistance,” “maternal obesity,” “dyslipidemia,” and “pregnancy.” Original cohort and case-control studies, peer-reviewed reviews, systematic reviews, and meta-analyses that investigated the link between at least one metabolic syndrome component and fetal birth-weight outcomes were included. For Uzbekistan-specific epidemiologic context, relevant conference and institutional publications were also consulted when national peer-reviewed data were unavailable. Case reports and studies not relevant to human pregnancy were excluded. Data were summarized narratively based on the primary pathophysiological route addressed by each component.

Normal pregnancy is associated with progressive physiological insulin resistance in the second and third trimesters, which is triggered by placental hormones such as human placental lactogen, progesterone, cortisol, and prolactin, which divert maternal energy sources to the developing baby (Hernández-Baraza et al., 2025). In women with underlying metabolic syndrome, this physiological adaptation is exacerbated, resulting in persistent maternal hyperglycemia, hyperlipidemia, and a chronic low-grade pro-inflammatory state. The Pedersen hypothesis proposes that excess glucose, free fatty acids, and amino acids enter the placenta and induce fetal pancreatic β-cell hyperplasia, resulting in fetal hyperinsulinemia. This mechanism explains faster fetal adipose and somatic growth (Desoye & Carter, 2022; Hernández-Baraza et al., 2025). Hyperinsulinemia raises fetal oxygen consumption and basal metabolic rate and can be followed by relative fetal hypoxemia, erythropoietin overproduction, and polycythemia, linking metabolic and hematological issues in macrosomic pregnancies (Desoye & Carter, 2022). Pre-pregnancy body mass index (BMI) is one of the most reliable predictors of fetal macrosomia. Maternal obesity is associated with approximately a twofold increase in the odds of fetal macrosomia compared with normal-weight pregnancy, with insulin resistance providing an important mechanistic link even in the absence of overt GDM (Gaudet et al., 2014). A prospective study of women meeting metabolic syndrome criteria in the first trimester found significantly higher BMI, waist-to-hip ratio, and neonatal birth weight compared with healthy controls. Maternal BMI above 24.5 kg/m² was identified as the strongest independent predictor of fetal macrosomia (Migda et al., 2016). Obesity-related adiponectin deficiency is accompanied by higher levels of leptin, E-selectin, and inflammatory cytokines (Migda et al., 2016). Gestational diabetes mellitus is widely regarded as a major metabolic syndrome-related driver of macrosomia, with the risk of large-for-gestational-age (LGA) birth reported to increase approximately five-fold in GDM and up to ten-fold in pregestational diabetes despite good glycemic control (Eslamian et al., 2013). A systematic review and meta-analysis of 17,711 women with GDM found that elevated glycated hemoglobin (HbA1c) at 24-28 weeks of gestation was associated with an increased risk of macrosomia and LGA, indicating potential value as a predictive biomarker (Mou et al., 2023). Elevated fasting glucose, together with reduced insulin

ISSN: 2181-3337 | SCIENTISTS.UZ

sensitivity, has also been associated with adverse perinatal outcomes from early pregnancy (Migda et al., 2016).

Maternal dyslipidemia, particularly hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels, has been identified as a significant and partially glucose-independent factor contributing to fetal overgrowth. Placental lipases hydrolyze elevated maternal triglycerides into free fatty acids and glycerol, which can support fetal nutrient supply and growth (Firatligil et al., 2025). Large prospective cohort studies in China involving tens of thousands of pregnancies found that high maternal triglyceride levels mediate a measurable proportion of the association between pre-pregnancy overweight/obesity and macrosomia, including in non-diabetic women (Song, Chen, Zhang, Liu, Wei, Sun, et al., 2022; Song, Chen, Zhang, Liu, Wei, Wang, et al., 2022; Wan et al., 2023). Composite lipid indices, such as the triglyceride-to-HDL cholesterol ratio and the triglyceride-glucose (TyG) index, have been linked to neonatal macrosomia and are being studied as accessible, low-cost prognostic markers in non-diabetic pregnancies (Firatligil et al., 2025). Preconceptional obesity has also been linked to different trajectories of maternal lipid profiles during gestation, including greater triglycerides, reduced HDL-C, and elevated inflammatory markers such as high-sensitivity C-reactive protein, regardless of GDM status (Bozkurt et al., 2016). The link between the hypertensive component of metabolic syndrome and fetal growth is more complicated and, at times, contradictory. Hypertensive disorders of pregnancy, particularly when severe or complicated by placental insufficiency, are more commonly associated with fetal growth restriction than overgrowth. When hypertension coexists with obesity and hyperglycemia as part of a broader metabolic syndrome phenotype, neonatal size may reflect the combined metabolic profile rather than blood pressure alone (Sourinejad et al., 2019). This heterogeneity emphasizes the need to analyze metabolic syndrome as a constellation of interacting factors rather than simply screening hypertension.

Several studies have found that the presence of multiple metabolic syndrome components is more strongly and consistently associated with macrosomia than any single component alone. Women who met metabolic syndrome criteria in early pregnancy had significantly higher neonatal birth weights and a higher frequency of macrosomic neonates (>4000 g) than metabolically healthy controls, as well as elevated inflammatory and reduced anti-inflammatory adipokine profiles (Migda et al., 2016). Biomarker panels that combine clinical characteristics (pre-pregnancy BMI, gestational weight gain, parity), glycemic parameters, and lipid fractions have achieved high predictive accuracy (area under the receiver operating characteristic curve approaching 0.97) for GDM-related macrosomia, highlighting the importance of a multi-component metabolic risk assessment rather than relying solely on a single marker such as fasting glucose (Yuan et al., 2023). The cumulative evidence suggests that antenatal screening protocols should include a broader metabolic risk profile, including early-pregnancy BMI, waist-to-hip ratio, fasting glucose, HbA1c, triglycerides, and HDL cholesterol, rather than relying solely on the standard oral glucose tolerance test for GDM. Early detection of clustered metabolic abnormalities may allow for timely lifestyle and nutritional interventions, more frequent glycemic and lipid monitoring, and individualized decisions about delivery timing and mode, potentially lowering the incidence of macrosomia-associated birth trauma and long-term metabolic sequelae in offspring (Eslamian et al., 2013; Mou et al., 2023). Given the high and modifiable contribution of maternal adiposity to this pathway, preconception counselling and weight management before pregnancy remain important preventive measures (Gaudet et al., 2014).

ISSN: 2181-3337 | SCIENTISTS.UZ

Table 1

Metabolic Syndrome Components and Their Associations With Fetal Macrosomia

MetS component	Common diagnostic threshold in pregnancy	Principal mechanism linking to fetal overgrowth	Direction/strength of association with macrosomia
Central obesity/adiposity	Pre-pregnancy BMI >24.5-25 kg/m²; increased waist-to-hip ratio	Chronic low-grade inflammation, hyperleptinemia, hypoadiponectinemia, enhanced placental nutrient transfer, and insulin resistance independent of GDM	Strong and consistent; obesity is associated with about twofold higher odds of macrosomia (Gaudet et al., 2014; Migda et al., 2016).
Hyperglycemia /insulin resistance (GDM)	Elevated fasting glucose; abnormal OGTT; HbA1c measured at 24-28 weeks	Pedersen pathway: maternal hyperglycemia → fetal hyperinsulinemia → accelerated adipogenesis and somatic growth	Strong association; LGA risk has been reported to rise about five-fold in GDM and ten-fold in pregestational diabetes (Eslamian et al., 2013; Mou et al., 2023).
Dyslipidemia	Elevated fasting triglycerides (e.g., ≥90th percentile); reduced HDL-C; elevated TyG index or TG:HDL-C ratio	Placental lipid handling increases fetal exposure to free fatty acids and glycerol, providing a partly glucose-independent nutrient pathway	Moderate and partly mediating; high maternal triglycerides explained about 3.8-11.1% of the obesity-macrosomia association in one large non-diabetic cohort (Song, Chen, Zhang, Liu, Wei, Sun, et al., 2022).
Hypertension/vascular dysfunction	Blood pressure ≥130/85 mmHg or gestational hypertensive disorder	Endothelial dysfunction may alter placental transfer, but hypertensive placental insufficiency can favor growth restriction	Heterogeneous; effects depend on severity and co-occurring metabolic components (Sourinejad et al., 2019).

Note. BMI = body mass index; GDM = gestational diabetes mellitus; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LGA = large for gestational age; MetS = metabolic syndrome; OGTT = oral glucose tolerance test; TG:HDL-C = triglyceride-to-high-density lipoprotein cholesterol ratio; TyG = triglyceride-glucose index.

The link between maternal metabolic disorders and excessive fetal growth is especially noteworthy in Uzbekistan, where gestational diabetes mellitus (GDM), overweight, obesity, and other metabolic risk factors are increasingly recognized as important issues in antenatal care. Although complete nationwide data on fetal macrosomia related to maternal metabolic syndrome are scarce, available regional evidence indicates that the metabolic risk profile of pregnant women in Uzbekistan warrants further clinical attention. The prevalence of GDM is a key local indicator. Between 2017 and 2020, a screening project in the Samarkand, Khorezm, and Ferghana regions examined 1,211 pregnant women aged 18 to 40 years who were 16 to 30 weeks' gestation. Anthropometric evaluation, specialist examination, fetal ultrasound, fasting

ISSN: 2181-3337 | SCIENTISTS.UZ

venous glucose measurement, and a 75-g oral glucose tolerance test (OGTT) were used, with results interpreted according to IADPSG criteria. A total of 108 women were diagnosed with GDM, giving a reported prevalence of 8.9%; the regional distribution was 22 cases in Samarkand, 54 in Khorezm, and 32 in Ferghana (Ibragimova & Tojieva, 2020). The OGTT was completed in 898 of the 1,211 women screened, highlighting both the feasibility of systematic screening and the importance of consistent implementation. The same Uzbekistan report identified several clinically important risk factors among pregnant women with GDM: maternal age above 33 years in 23.1%, a previous macrosomic child (>4,000 g) in 12.8%, a family history of type 2 diabetes in 19.4%, overweight in 26.8%, obesity in 26.8%, excessive gestational weight gain of more than 15-20 kg in 10.1%, and arterial hypertension or pre-eclampsia in 2.7% (Ibragimova & Tojieva, 2020). These findings are relevant to the metabolic-syndrome concept because they show that hyperglycemia commonly coexists with other metabolic and obstetric risk factors rather than occurring as an isolated abnormality. The Uzbek findings therefore reinforce the central premise of this review: fetal overgrowth should not be seen solely as a result of hyperglycemia. Maternal overweight and obesity, excessive gestational weight gain, past macrosomia, family history of diabetes, and hypertension may occur in the same patient and may interact to increase the likelihood of excessive fetal growth. This is consistent with the broader evidence reviewed here, which suggests that clustered metabolic abnormalities may pose a higher risk than any one component alone. For pregnant women in Uzbekistan, a central clinical challenge is to identify high-risk women early. GDM can develop without obvious symptoms, allowing clinically significant abnormalities in glucose metabolism to remain unrecognized. If hyperglycemia is identified only after excessive fetal growth has occurred, opportunities for preventive intervention may be limited. This is especially relevant because the Pedersen pathway links maternal hyperglycemia with increased fetal glucose exposure, fetal pancreatic hyperinsulinemia, and accelerated fetal growth (Hernández-Baraza et al., 2025).

The clinical significance of macrosomia goes beyond birth weight alone. Excessive fetal growth increases the risk of difficult labour, shoulder dystocia, birth trauma, surgical delivery, and neonatal metabolic problems (Gaudet et al., 2014; Mou et al., 2023). These complications are especially important when a large fetus is not identified accurately before delivery. Local clinical evidence shows that fetal macrosomia is an important issue in Uzbek obstetric practice. A study conducted at Samarkand State Medical University included 200 women in labour with fetal macrosomia, with 78 managed actively and 122 managed expectantly (Zakirova et al., 2022). Although this study does not provide a nationwide prevalence estimate, it demonstrates that macrosomia is sufficiently common in regional obstetric practice to require specific pregnancy and labour management considerations. It is critical, however, to differentiate between the prevalence of macrosomia and GDM. Uzbekistan currently has far less robust nationwide epidemiological data on macrosomia specifically connected with metabolic syndrome than some other countries. The existing Uzbek evidence is primarily regional or institution-based. As a result, it would be incorrect to assert that 8.9% is the national prevalence of macrosomia; rather, 8.9% is the reported prevalence of GDM in the three-region screening initiative (Ibragimova & Tojieva, 2020). This distinction is critical to ensuring the article's scientific accuracy.

Conclusion. Fetal macrosomia should not be viewed as a single obstetric result, but rather as a complex syndrome heavily influenced by maternal metabolic health. The evidence reviewed in this study shows that hyperglycemia, insulin resistance, maternal obesity, and dyslipidemia are the most consistent metabolic determinants of excessive fetal growth, acting through interconnected pathways such as fetal hyperinsulinemia, altered placental nutrient transport, chronic inflammation, and abnormal lipid metabolism. The presence of many metabolic syndrome components appears to enhance the risk of macrosomia more significantly than any individual factor alone, underlining the significance of an integrated rather than single-marker approach to risk assessment. Preventive interventions should start before conception and last throughout pregnancy and the postpartum period. Preconception counselling, appropriate weight management, balanced nutrition, safe physical activity, timely gestational diabetes screening, adequate glycemic control, and individualized fetal growth monitoring can all help to reduce the risk of excessive fetal growth and its associated maternal and neonatal complications. For women with

ISSN: 2181-3337 | SCIENTISTS.UZ

various metabolic risk factors, multidisciplinary care from obstetricians, endocrinologists, nutritionists, and other healthcare providers may give extra benefits. At the same time, additional multicenter prospective studies in Uzbekistan are required to produce nationally representative estimates, explain the combined impact of metabolic syndrome components on fetal macrosomia, and construct population-specific predictive models. This integrated strategy could lead to earlier intervention, more personalized antenatal care, and better maternal outcomes.

REFERENCES

1. Bozkurt, L., Göbl, C. S., Hörmayer, A.-T., Luger, A., Pacini, G., & Kautzky-Willer, A. (2016). The impact of preconceptional obesity on trajectories of maternal lipids during gestation. *Scientific Reports, 6*, 29971. https://doi.org/10.1038/srep29971
2. Desoye, G., & Carter, A. M. (2022). Fetoplacental oxygen homeostasis in pregnancies with maternal diabetes mellitus and obesity. *Nature Reviews Endocrinology, 18*(10), 593-607. https://doi.org/10.1038/s41574-022-00717-z
3. Eslamian, L., Akbari, S., Marsoosi, V., & Jamal, A. (2013). Effect of different maternal metabolic characteristics on fetal growth in women with gestational diabetes mellitus. *Iranian Journal of Reproductive Medicine, 11*(4), 325-334. https://pmc.ncbi.nlm.nih.gov/articles/PMC3941422/
4. Firatligil, F. B., Tuncdemir, S., Sucu, S., Reis, Y. A., Ozkan, S., Dereli, M. L., Sucu, S. T., & Engin-Ustun, Y. (2025). Association of the triglyceride-glucose index and the ratio of triglyceride to high-density lipoprotein cholesterol with fetal macrosomia in nulliparous pregnant women: A prospective case-control study. *BMC Pregnancy and Childbirth, 25*, 175. https://doi.org/10.1186/s12884-025-07317-5
5. Gaudet, L., Ferraro, Z. M., Wen, S. W., & Walker, M. (2014). Maternal obesity and occurrence of fetal macrosomia: A systematic review and meta-analysis. *BioMed Research International, 2014*, 640291. https://doi.org/10.1155/2014/640291
6. Hernández-Baraza, L., Brito-Casillas, Y., Valverde-Tercedor, C., Recio, C., Fernández-Pérez, L., Guerra, B., & Wägner, A. M. (2025). Mechanisms of fetal overgrowth in gestational diabetes: The potential role of SOCS2. *Nutrients, 17*(9), 1519. https://doi.org/10.3390/nu17091519
7. Ibragimova, N., & Tojieva, I. (2020). The prevalence of gestational diabetes in Uzbekistan [Conference abstract]. *Gynecological and Reproductive Endocrinology and Metabolism, 1*(Suppl. 1), 515. https://gremjournal.com/wp-content/uploads/2020/11/Abstract-Book-GREM.pdf
8. Migda, M., Migda, M. S., Migda, B., Krzyżanowska, P., & Wender-Ożegowska, E. (2016). Components of metabolic syndrome in the first trimester of pregnancy as predictors of adverse perinatal outcome. *Ginekologia Polska, 87*(9), 644-650. https://doi.org/10.5603/GP.2016.0060
9. Mou, S. S., Gillies, C., Hu, J., Danielli, M., Al Wattar, B. H., Khunti, K., & Tan, B. K. (2023). Association between HbA1c levels and fetal macrosomia and large for gestational age babies in women with gestational diabetes mellitus: A systematic review and meta-analysis of 17,711 women. *Journal of Clinical Medicine, 12*(11), 3852. https://doi.org/10.3390/jcm12113852
10. Song, X., Chen, L., Zhang, S., Liu, Y., Wei, J., Sun, M., Shu, J., Wang, T., & Qin, J. (2022). High maternal triglyceride levels mediate the association between pre-pregnancy overweight/obesity and macrosomia among singleton term non-diabetic pregnancies: A prospective cohort study in Central China. *Nutrients, 14*(10), 2075. https://doi.org/10.3390/nu14102075
11. Song, X., Chen, L., Zhang, S., Liu, Y., Wei, J., Wang, T., & Qin, J. (2022). Gestational diabetes mellitus and high triglyceride levels mediate the association between pre-pregnancy overweight/obesity and macrosomia: A prospective cohort study in Central China. *Nutrients, 14*(16), 3347. https://doi.org/10.3390/nu14163347

ISSN: 2181-3337 | SCIENTISTS.UZ

12. Sourinejad, H., Shayan, A., Niyati, S., & Moghaddam-Banaem, L. (2019). The effect of metabolic syndrome and its components in midpregnancy on neonatal outcomes. *Medical Journal of the Islamic Republic of Iran, 33*, 147. https://doi.org/10.34171/mjiri.33.147
13. Wan, Y., Chen, Y., Wu, X., Yin, A., Tian, F., Zhang, H., Huang, X., Wu, L., & Niu, J. (2023). Mediation effect of maternal triglyceride and fasting glucose level on the relationship between maternal overweight/obesity and fetal growth: A prospective cohort study. *BMC Pregnancy and Childbirth, 23*, 449. https://doi.org/10.1186/s12884-023-05716-0
14. Yuan, Y., Zhu, Q., Yao, X., Shi, Z., & Wen, J. (2023). Maternal circulating metabolic biomarkers and their prediction performance for gestational diabetes mellitus related macrosomia. *BMC Pregnancy and Childbirth, 23*, 113. https://doi.org/10.1186/s12884-023-05440-9
15. Zakirova, N. I., Zakirova, F. I., & Abdullaeva, N. E. (2022). Features of pregnancy management and birth outcomes in women with fetal macrosomia with active and expectant tactics. *Journal of Reproductive Health and Uro-Nephrology Research, 3*(4), 77-79. https://www.sammu.uz/en/article/2184

ISSN: 2181-3337 | SCIENTISTS.UZ

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

PREGNANCY AFTER KIDNEY TRANSPLANTATION: CURRENT APPROACHES TO ALLOGRAFT MONITORING AND MATERNAL OUTCOMES

Matkarimov Zohidjon[1], Azimova Marguba[2], Abdurahmonova Nigora[3], Elmurodova Nigina[4], Komilova Dildora[5]

State Institution "Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V.Vakhidov"

DOI: 10.67620/sai.59d0005

ABSTRACT

Pregnancy after kidney transplantation is increasingly achievable, but it remains a high-risk condition requiring coordinated nephrological, transplant, and obstetric care. This review summarizes current evidence on maternal outcomes and approaches to kidney allograft monitoring before conception, during pregnancy, and in the postpartum period. Available meta-analyses show high live-birth rates among kidney transplant recipients, while preeclampsia, hypertensive disorders, preterm birth, infection, and acute allograft rejection remain important complications. Favorable outcomes are most strongly associated with stable baseline allograft function, minimal proteinuria, controlled blood pressure, absence of recent rejection, and pregnancy-compatible immunosuppression. Monitoring should include serial assessment of serum creatinine, proteinuria, blood pressure, urinary infection, and calcineurin-inhibitor concentrations, with particular attention to pregnancy-related pharmacokinetic changes in tacrolimus. Because conventional eGFR equations are not well validated in pregnancy, creatinine trends should be interpreted against individual baseline values and the overall clinical context. Deterioration in allograft function requires careful differentiation among preeclampsia, infection, obstruction, drug toxicity, volume depletion, and acute rejection. Postpartum surveillance is also essential because hemodynamic and pharmacokinetic changes may alter allograft function and immunosuppressive exposure. Current evidence suggests that pregnancy does not necessarily worsen long-term allograft survival in appropriately selected women, although standardized monitoring strategies and better validated biomarkers of early allograft injury are still needed.

ACCEPTED

04.10.26

Keywords: *kidney transplantation; pregnancy; kidney allograft function; preeclampsia; immunosuppression; tacrolimus.*

CC BY

Introduction

Kidney transplantation is the most effective form of renal replacement therapy for patients with end-stage kidney disease and is associated with substantial improvements in overall health, quality of life, and reproductive function. Restoration of kidney function following transplantation generally leads to normalization of the hypothalamic–pituitary–gonadal axis and recovery of fertility, making pregnancy feasible for a considerable proportion of women of reproductive age. However, pregnancy in kidney

transplant recipients remains a high-risk condition and requires multidisciplinary care involving transplant physicians, nephrologists, and obstetricians. Over the past several decades, accumulating evidence has demonstrated that pregnancy after kidney transplantation can result in a live birth in the majority of cases, although the incidence of complications remains higher than in the general population. A systematic review and meta-analysis including 50 studies, 4,706 pregnancies, and 3,570 kidney transplant recipients reported a live-birth rate of 73.5%, a preeclampsia rate of 27.0%, gestational diabetes mellitus in 8.0% of pregnancies, cesarean delivery in 56.9%, and preterm birth in 45.6%. The authors emphasized that more favorable outcomes were observed among patients with a lower-risk profile and better baseline allograft function (Deshpande et al., 2011).

More recent evidence confirms the persistently high incidence of obstetric complications in this population. A 2024 meta-analysis including 109 studies, 7,708 pregnancies, and 5,107 kidney transplant recipients reported a live-birth rate of 78.48%, preeclampsia in 20.87%, hypertensive disorders of pregnancy in 24.30%, preterm birth in 45.30%, and acute allograft rejection in 8.06% of cases. Allograft loss following pregnancy was reported in 123 of 853 patients for whom relevant outcome data were available (Mustafa et al., 2024).

Thus, although the number of successful pregnancies after kidney transplantation has increased, substantial maternal, obstetric, and nephrological risks remain. Interpretation of complication rates requires consideration of baseline allograft function, the presence of proteinuria and arterial hypertension, the time elapsed since transplantation, and the type of immunosuppressive therapy.

One of the most important determinants of pregnancy outcomes is the functional status of the kidney allograft before conception. The most favorable clinical profile is generally characterized by stable allograft function, absent or minimal proteinuria, well-controlled blood pressure, and no recent episodes of acute rejection.

According to a position statement from the Italian Society of Nephrology, a relatively favorable preconception profile includes an estimated glomerular filtration rate (eGFR) of ≥60 mL/min, absent or minimal proteinuria, well-controlled blood pressure, no recent rejection episodes, stable immunosuppressive therapy, and the absence of potentially teratogenic medications. Reduced allograft function, proteinuria, and hypertension are associated with an increased risk of deterioration in kidney function and adverse pregnancy outcomes (Cabiddu et al., 2018).

Proteinuria deserves particular attention because it may represent either a manifestation of pre-existing chronic allograft injury or an early marker of preeclampsia. Therefore, assessment of 24-hour urinary protein excretion or the urinary protein-to-creatinine ratio before conception and throughout pregnancy is essential for differentiating obstetric complications from transplant-related pathology.

Physiological pregnancy is accompanied by increases in circulating blood volume and renal blood flow, as well as an increase in glomerular filtration. In kidney transplant recipients, these physiological changes occur in the setting of a limited functional reserve of the transplanted kidney.

Some patients experience increases in serum creatinine, urea, and proteinuria during pregnancy. However, transient changes in allograft function do not necessarily indicate acute rejection. In a study evaluating kidney allograft function during pregnancy, allograft dysfunction was observed in a proportion of patients and was primarily associated with preeclampsia and, less frequently, with rejection, urinary tract obstruction, or infection. In most patients, these changes were transient (Aivazoglou et al., 2011).

This finding has important clinical implications because an increase in serum creatinine during pregnancy requires careful assessment of its underlying cause. The differential diagnosis should include preeclampsia, urinary tract infection and graft pyelonephritis, obstructive complications, calcineurin inhibitor nephrotoxicity, volume depletion, and acute allograft rejection.

Recent evidence also highlights the importance of specifically evaluating allograft function during the postpartum period. A systematic review and meta-analysis of 38 studies reported an approximately

ISSN: 2181-3337 | SCIENTISTS.UZ

9.4% risk of allograft loss within the first two years following pregnancy, although allograft function generally remained stable thereafter in patients with a functioning graft. Baseline proteinuria, arterial hypertension, and higher serum creatinine levels before pregnancy were identified as important risk factors for adverse outcomes (van Buren et al., 2020).

A more recent 2025 meta-analysis comparing pregnant and non-pregnant kidney transplant recipients likewise found no statistically significant increase in the risk of allograft loss among women who had experienced pregnancy compared with controls. Nevertheless, a modest increase in serum creatinine was observed after delivery, emphasizing the need for continued and structured postpartum monitoring (Kanbay et al., 2025).

Arterial hypertension is one of the most common complications of pregnancy in kidney transplant recipients. Pre-existing hypertension, particularly when accompanied by proteinuria and impaired allograft function, is associated with an increased risk of preeclampsia and deterioration of kidney function. According to a recent meta-analysis, hypertensive disorders of pregnancy occur in approximately one-quarter of kidney transplant recipients, while preeclampsia affects approximately one in five patients (Mustafa et al., 2024).

The diagnosis of preeclampsia in kidney transplant recipients can be challenging. Chronic hypertension, pre-existing proteinuria, and abnormalities in kidney function may be present before conception and can mimic manifestations of preeclampsia. Therefore, diagnosis should not rely on a single laboratory parameter but should be based on the dynamics of clinical and laboratory findings and their overall clinical context.

Maintaining adequate immunosuppression is essential for preserving kidney allograft function during pregnancy. At the same time, potential fetal exposure to medications with teratogenic effects must be minimized. Immunosuppressive agents that are generally considered compatible with pregnancy after kidney transplantation include tacrolimus, cyclosporine, azathioprine, and corticosteroids. In contrast, mycophenolic acid preparations and mammalian target of rapamycin (mTOR) inhibitors should not be used during pregnancy planning and require substitution before conception. KDIGO recommends discontinuation or replacement of mycophenolate before attempts at conception and recommends replacement of mTOR inhibitors. Particular attention has been devoted to tacrolimus. Pregnancy is associated with substantial pharmacokinetic changes that may result in a decrease in whole-blood tacrolimus concentrations despite preservation or even an increase in the unbound fraction of the drug. These changes are partly related to reduced serum albumin concentrations and alterations in hematological parameters. Consequently, interpretation of tacrolimus exposure based solely on whole-blood trough concentrations may be challenging (Hebert et al., 2013).

Clinical studies have shown that maintaining therapeutic tacrolimus concentrations during pregnancy often requires an increase in the daily dose. In one observational series, the mean tacrolimus dose increased from 3.2 mg/day to 7.3 mg/day during the third trimester and subsequently decreased after delivery (Aktürk et al., 2015).

Therefore, a decline in tacrolimus blood concentration during pregnancy should not automatically be interpreted as poor adherence to treatment. It may reflect physiological pharmacokinetic changes associated with pregnancy. Regular therapeutic drug monitoring, together with serial assessment of allograft function, is therefore essential.

Pregnancy in the setting of immunosuppressive therapy is associated with an increased clinical significance of infectious complications. Urinary tract infections and graft pyelonephritis are of particular concern.

European recommendations for the management of kidney transplant recipients have emphasized the importance of regular urinalysis and urine cultures during pregnancy because urinary tract infections

ISSN: 2181-3337 | SCIENTISTS.UZ

may be asymptomatic and may pose a risk to both maternal health and allograft function (EBPG Expert Group on Renal Transplantation, 2002).

Infectious inflammation of the transplanted kidney may result in increased serum creatinine and proteinuria and can therefore mimic acute allograft rejection. Consequently, when allograft function deteriorates during pregnancy, infectious, immunological, and obstetric causes should be evaluated concurrently.

Despite concerns regarding immunological changes during pregnancy, acute allograft rejection is relatively uncommon in patients with stable baseline allograft function and adequate immunosuppression. Nevertheless, its clinical significance remains substantial because rejection may result in irreversible allograft injury and loss.

In the 2024 meta-analysis, acute rejection was reported in approximately 8% of pregnancies, although the incidence varied considerably across individual studies (Mustafa et al., 2024).

The postpartum period should also be taken into consideration. Historical studies have documented episodes of acute rejection after delivery, supporting the need for continued close monitoring of allograft function and immunosuppressive drug concentrations during the postpartum period (Marushak et al., 1986).

Current approaches consider pregnancy after kidney transplantation a multidisciplinary process that should begin before conception and continue throughout pregnancy and the postpartum period. Preconception assessment should include evaluation of kidney allograft function, serum creatinine, proteinuria, blood pressure, potential infectious foci, stability of immunosuppressive therapy, and the absence of recent rejection episodes.

During pregnancy, regular monitoring should include complete blood count, urinalysis, proteinuria, serum creatinine, urea, electrolytes, liver function tests, blood pressure, and concentrations of calcineurin inhibitors. An Italian expert group recommends nephrological follow-up with laboratory assessment at least every 2–4 weeks in patients with good allograft function and without proteinuria or hypertension, with more frequent monitoring in patients with additional risk factors (Cabiddu et al., 2018).

Assessment of estimated glomerular filtration rate represents a particular challenge. Equations developed for non-pregnant populations have not been adequately validated for reliable estimation of GFR during pregnancy in kidney transplant recipients. Therefore, changes in serum creatinine should be interpreted in relation to the patient's baseline values and the overall clinical context. The postpartum period represents an important stage of follow-up because the cessation of pregnancy-related physiological changes is accompanied by alterations in the pharmacokinetics of immunosuppressive drugs, hemodynamics, and fluid and electrolyte balance.

Following delivery, monitoring of serum creatinine, proteinuria, blood pressure, and tacrolimus or cyclosporine concentrations should be continued. Particular attention should be paid to changes in tacrolimus exposure because doses increased during pregnancy may become excessive after delivery. Pharmacokinetic studies have demonstrated substantial changes in tacrolimus disposition during pregnancy, followed by restoration of the pre-pregnancy pharmacokinetic profile after delivery (Versluis et al., 2024).

Overall, current evidence suggests that pregnancy itself does not necessarily compromise long-term allograft survival in women with stable kidney allograft function. A systematic review and meta-analysis of long-term outcomes found no significant difference in allograft survival between women who became pregnant and matched non-pregnant kidney transplant recipients.

Despite the substantial increase in published evidence, most studies of pregnancy after kidney transplantation remain retrospective, single-center, or registry-based. The relatively small number of patients in individual studies limits the ability to establish precise threshold values for serum creatinine, proteinuria, and eGFR that reliably define pregnancy-related risk (van Buren et al., 2020).

ISSN: 2181-3337 | SCIENTISTS.UZ

In addition, early biomarkers of allograft injury that could identify dysfunction before a clinically significant increase in serum creatinine remain insufficiently studied. In this context, emerging biomarkers of renal injury, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and urinary microalbumin, represent potentially valuable tools, particularly in pregnant kidney transplant recipients in whom conventional assessment of allograft function is complicated by the physiological changes of pregnancy.

Conclusion. Current evidence indicates that pregnancy after kidney transplantation is feasible and can result in favorable outcomes in most appropriately selected patients receiving careful multidisciplinary monitoring. The principal factors associated with adverse outcomes include baseline allograft function, proteinuria, arterial hypertension, previous episodes of rejection, infection, and the characteristics of immunosuppressive therapy. The most frequently reported complications include preeclampsia, hypertensive disorders of pregnancy, urinary tract infections, anemia, preterm birth, and fetal growth restriction.

A major challenge in transplant medicine is the timely differentiation of physiological changes associated with pregnancy from obstetric complications and true kidney allograft dysfunction. Regular assessment of serum creatinine, proteinuria, blood pressure, infectious markers, and immunosuppressive drug concentrations, complemented by emerging biomarkers of allograft injury, may improve the early detection of clinically significant complications.

Therefore, the development of a standardized monitoring algorithm for kidney transplant recipients during pregnancy and the postpartum period remains an important clinical and research priority.

REFERENCES

1. Aivazoglou, L., Sass, N., Silva, H. T., Jr., Sato, J. L., Medina-Pestana, J. O., & De Oliveira, L. G. (2011). Pregnancy after renal transplantation: An evaluation of the graft function. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 155*(2), 129–131. https://doi.org/10.1016/j.ejogrb.2010.11.020
2. Aktürk, S., Çelebi, Z. K., Erdoğmuş, Ş., Kanmaz, A. G., Yüce, T., Şengül, Ş., & Keven, K. (2015). Pregnancy after kidney transplantation: Outcomes, tacrolimus doses, and trough levels. *Transplantation Proceedings, 47*(5), 1442–1444. https://doi.org/10.1016/j.transproceed.2015.04.041
3. Cabiddu, G., Spotti, D., Gernone, G., Santoro, D., Moroni, G., Gregorini, G., Giacchino, F., Attini, R., Limardo, M., Gammaro, L., Todros, T., Piccoli, G. B., & Kidney and Pregnancy Study Group of the Italian Society of Nephrology. (2018). A best-practice position statement on pregnancy after kidney transplantation: Focusing on the unsolved questions. *Journal of Nephrology, 31*(5), 665–681. https://doi.org/10.1007/s40620-018-0499-x
4. Deshpande, N. A., James, N. T., Kucirka, L. M., Boyarsky, B. J., Garonzik-Wang, J. M., Montgomery, R. A., & Segev, D. L. (2011). Pregnancy outcomes in kidney transplant recipients: A systematic review and meta-analysis. *American Journal of Transplantation, 11*(11), 2388–2404. https://doi.org/10.1111/j.1600-6143.2011.03656.x
5. EBPG Expert Group on Renal Transplantation. (2002). European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrology Dialysis Transplantation, 17*(Suppl. 4), 50–55.
6. Hebert, M. F., Zheng, S., Hays, K., Shen, D. D., Davis, C. L., Umans, J. G., Miodovnik, M., Thummel, K. E., & Easterling, T. R. (2013). Interpreting tacrolimus concentrations during pregnancy and postpartum. *Transplantation, 95*(7), 908–915. https://doi.org/10.1097/TP.0b013e318278d367
7. Kanbay, M., Brinza, C., Ozbek, L., Unlu, S., Abdel-Rahman, S. M., Guldan, M., Aktas, O., Covic, A., Burlacu, A., & Covic, A. (2025). Long-term impact of pregnancy on mortality and graft outcomes in

ISSN: 2181-3337 | SCIENTISTS.UZ

kidney transplant recipients: A systematic review and meta-analysis. *International Urology and Nephrology, 57*(11), 3773–3786. https://doi.org/10.1007/s11255-025-04572-5

8. Marushak, A., Weber, T., Bock, J., Birkeland, S. A., Hansen, H. E., Klebe, J., Kristoffersen, K., Rasmussen, K., & Olgaard, K. (1986). Pregnancy following kidney transplantation. *Acta Obstetricia et Gynecologica Scandinavica, 65*(6), 557–559. https://doi.org/10.3109/00016348609158386
9. Mustafa, M. S., Noorani, A., Abdul Rasool, A., Tashrifwala, F. A. A., Jayaram, S., Raja, S., Jawed, F., Siddiq, M. U., Shivappa, S. G., Hameed, I., & Dadana, S. (2024). Pregnancy outcomes in renal transplant recipients: A systematic review and meta-analysis. *Women's Health, 20*, 17455057241277520. https://doi.org/10.1177/17455057241277520
10. van Buren, M. C., Schellekens, A., Groenhof, T. K. J., van Reekum, F., van de Wetering, J., Paauw, N. D., & Lely, A. T. (2020). Long-term graft survival and graft function following pregnancy in kidney transplant recipients: A systematic review and meta-analysis. *Transplantation, 104*(8), 1675–1685. https://doi.org/10.1097/TP.0000000000003026
11. Versluis, J., Bourgonje, A. R., Touw, D. J., Meinderts, J. R., Prins, J. R., de Jong, M. F. C., & Mian, P. (2024). Pharmacokinetics of tacrolimus in pregnant solid-organ transplant recipients: A retrospective study. *Journal of Clinical Pharmacology, 64*(4), 428–436. https://doi.org/10.1002/jcph.2393

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

INTEGRATED ASSESSMENT OF DENTAL RISK AND QUALITY OF LIFE IN PATIENTS UNDERGOING DIFFERENTIATED PROSTHODONTIC TREATMENT FOR ACID-RELATED GASTRIC DISEASES

Akbarov Avzal[1], Ziyadullaeva Nigora[2], Tulyaganov Jamshid[3]
Doctor of Medical Sciences, Professor[1]
Doctor of Medical Sciences, Associate Professor[2]
PhD, Associate Professor[3]
Tashkent State Medical University, Tashkent, Uzbekistan

DOI: 10.67620/sai.59d0006

ABSTRACT

This study developed an integrated dental risk index for patients with acid-related gastric diseases and evaluated its clinical relevance in relation to oral-health-related quality of life after personalized versus standard prosthodontic care. The study included 150 patients with hyperacid gastric disease, hypoacid gastric disease, or a history of bariatric surgery (50 per group) and 30 healthy controls. Each clinical group was randomized to personalized or standard dental management (n = 25 each). The Integrated Acid-Related Dental Risk Index (IADRI) combined 17 clinical, laboratory, functional, and radiological criteria spanning dental, periodontal, salivary, immunologic, mucosal, microcirculatory, and bone parameters, with a total score of 0–34. OHI-S, BOP, PD, CAL, ICDAS II, BEWE, salivary flow, pH, buffering capacity, and OHIP-14 scores were monitored for 12 months. Personalized management produced greater and more sustained improvements in dental indices and salivary function than standard care. OHIP-14 scores decreased by 50%–55% across the three clinical groups, compared with 27%–34% under standard management, while correlations between quality of life and residual local symptoms were attenuated. IADRI therefore provides a clinically useful framework for stratifying dental risk in patients with acid-related gastric diseases, and risk-guided personalized prosthodontic care may improve oral health outcomes and quality of life.

ACCEPTED

05.10.26

Keywords: *acid-related gastric diseases, dental risk assessment, oral health-related quality of life, personalized dental care, prosthodontic treatment, salivary function.*

CC BY

Introduction

The problem of acid-related gastric diseases is becoming increasingly important because of the high prevalence of this pathology, low detection rates, and the frequent inadequacy of treatment (Pavlenko et al., 2021; Richter & Rubenstein, 2018).

It is well established that diseases of the gastrointestinal tract are accompanied by diverse changes in the oral cavity involving combined damage to the hard dental tissues, periodontium, and salivary glands; the mechanisms of these changes differ substantially depending on the direction of the disturbance in gastric secretion (Eremin, 2013; Hatipoğlu et al., 2025; Madariaga et al., 2023).

Depending on gastric juice secretion, gastritis is classified as hyperacid gastritis, hypoacid gastritis, or gastritis with normal gastric acidity. Hyperacid gastritis is the most common form of acid-related gastric

disease and includes gastric and duodenal peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and other conditions. Hypoacid gastritis is less common and may develop under the influence of external and internal factors, including stress, dietary disturbances, long-term medication use, endocrine disorders, and Helicobacter pylori infection (Cavalcoli et al., 2017; Livzan et al., 2024; Pavlenko et al., 2021).

In accordance with the objective of our research, we included a group of patients after bariatric surgery. Because these patients lose a substantial amount of body weight over 12–18 months, they experience changes in hormonal status, impaired absorption of macro- and microelements (Ca, Fe, Zn), vitamin D and vitamin B12 deficiency, and pronounced restructuring of protein-energy metabolism, all of which contribute to a high level of dental risk. These patients develop systemic changes affecting the musculoskeletal system, vascular regulation, and the structural parameters of the alveolar bone. In combination with more frequent episodes of gastroesophageal reflux, vomiting, and developing xerostomia, these changes lead to a sharp increase in the incidence of dental caries, erosive lesions, and inflammatory periodontal diseases, which in turn complicates prosthodontic treatment in this patient population (Castilho et al., 2019; Marschner et al., 2024; Patel et al., 2017; Rizaev & Elnazarov, 2023).

Analysis of the available data showed that there is still no consensus among specialists regarding the need to take acid-related gastrointestinal diseases into account when preparing the oral cavity for prosthodontic dental treatment. Accordingly, methods for predicting dental risks and complications of dental treatment in patients with acid-related gastric diseases are lacking.

The aim of this study was to develop an integrated dental risk index for patients with acid-related gastric diseases and to evaluate its clinical significance by comparing it with changes in oral-health-related quality of life during personalized and standard prosthodontic treatment.

Materials and Methods

A total of 180 participants aged 25–65 years with partial acquired edentulism were examined and distributed into three clinical-pathogenetic groups of 50 patients each: Group I - hyperacid gastric diseases (chronic hyperacid gastritis, gastric and duodenal peptic ulcer disease); Group II - hypoacid gastric diseases (chronic atrophic gastritis with hypochlorhydria); and Group III - patients after bariatric surgery. Each group was divided by simple randomization into two subgroups of 25 patients: subgroup 1 (personalized treatment algorithm) and subgroup 2 (standard management protocol). The control group consisted of 30 apparently healthy individuals comparable in age and sex.

Based on the results of a comprehensive clinical, laboratory, functional, and radiological examination, the Integrated Acid-Related Dental Risk Index (IADRI) was developed. Clinical data were collected using a standardized case-record form that ensured a unified approach to documenting gastroenterological history, dental status, and longitudinal follow-up findings. On the basis of the obtained data, patients with a high dental risk index received a personalized therapeutic and preventive program addressing dental indices and the functional status of oral fluid. Examinations were performed at admission and repeated after 1 month (30 days), 3 months, 6 months, and 12 months. The OHI-S oral hygiene index, gingival bleeding index (BOP), periodontal pocket depth (PD), clinical attachment loss (CAL), ICDAS II and BEWE indices, unstimulated and stimulated salivary flow rates, oral-fluid pH and buffering capacity, secretory immunoglobulin A (sIgA) concentration, and lysozyme activity were evaluated. Statistical analysis was performed using parametric and nonparametric tests; differences were considered statistically significant at $p < .05$.

Patients in the personalized-treatment subgroup were additionally prescribed a set of local therapeutic and preventive measures differentiated according to the clinical-pathogenetic group. In patients with hyperacid gastric diseases, SensiKIN toothpaste was used twice daily for 8–12 weeks to reduce dentinal hypersensitivity and promote remineralization; KIN Hydrat was used continuously to moisturize the oral mucosa; KIN Care was administered for 10–14 days to improve mucosal repair; professional oral

ISSN: 2181-3337 | SCIENTISTS.UZ

hygiene (Air Flow plus ultrasonic scaling) was performed every 3 months; and topical fluoride varnish was applied every 6 months.

Quality of life was assessed using the OHIP-14 (Oral Health Impact Profile) questionnaire at admission and after 3, 6, and 12 months, followed by correlation analysis between the total score and clinical parameters characterizing the condition of the denture-bearing tissues (Slade, 1997).

Results

The developed IADRI includes 17 diagnostic criteria combined into seven domains: hard dental tissues (ICDAS II, BEWE), periodontium (OHI-S, BOP, PD, CAL), oral fluid (unstimulated salivary flow rate, pH, buffering capacity, xerostomia index XI), local immunity (sIgA, lysozyme), mucosa (thickness of the mucosa of the denture-bearing area), microcirculation (perfusion index according to laser Doppler flowmetry), and bone tissue (height, thickness, and density of the alveolar ridge according to cone-beam computed tomography). Each criterion is scored on a three-level scale (0, 1, or 2 points) depending on the degree of deviation from the physiological norm, and the final IADRI value is the sum of scores for all 17 criteria, ranging from 0 (absence of clinically significant abnormalities) to a maximum of 34 points (a combination of pronounced abnormalities in all parameters).

All criteria included in the index have equal weight. The analysis demonstrated the absence of a single universal diagnostic indicator capable of determining the outcome of prosthodontic treatment; the effectiveness of rehabilitation depends on the combined influence of changes in hard dental tissues, the periodontium, functional status of oral fluid, local immunity, mucosa, microcirculation, and bone tissue. According to the total score, patients are stratified into three risk categories, making it possible to determine the required extent of pre-prosthodontic preparation and to substantiate the choice of prosthetic material in conjunction with the clinical-pathogenetic model of the disease.

A personalized therapeutic and preventive program was applied to patients with a high dental risk index.

At the initial examination of patients with gastric disease associated with excessive gastric juice production, the mean duration of gastroenterological disease exceeded 6 years, and the mean GERD-Q score was more than twice the control value (10.3±2.2 and 10.5±2.3 versus 5.2±1.5; $p < .001$), confirming chronic acid exposure of the oral mucosa. The most characteristic findings were generalized dentinal hypersensitivity, erosive enamel changes on the palatal surfaces of maxillary teeth and occlusal surfaces of molars, and reduced oral-fluid pH and buffering capacity.

In the personalized-treatment subgroup, the OHI-S index decreased from 2.01±0.43 at admission to 1.74±0.40 after 30 days, 1.51±0.37 after 90 days, 1.32±0.34 after 180 days, and 1.18±0.29 points after 12 months; in the standard-treatment subgroup, the decrease was noticeably slower, reaching 1.46±0.35 points at 12 months. A similar pattern was observed for BOP, which decreased from 27.4±8.6% to 10.9±5.4% in the personalized-treatment subgroup, compared with a decrease to only 17.4±6.1% in the standard-treatment subgroup.

After 12 months, PD in subgroup 1 decreased to 2.31±0.38 mm versus 2.55±0.42 mm in subgroup 2 (control, 1.50±0.04 mm; $p < .001$ between subgroups), while CAL decreased to 2.63±0.49 mm versus 2.87±0.58 mm. The BEWE index decreased from a baseline value of 13.6±0.3 to 6.9±0.6 points in subgroup 1 versus 8.5±0.3 points in subgroup 2, whereas ICDAS II in subgroup 1 stabilized at 2.01–2.04 points and in subgroup 2 continued to increase, reaching 2.82±0.5 points by 12 months.

Comprehensive assessment of the functional status of oral fluid in the personalized-treatment subgroup demonstrated consistent restoration of all investigated parameters (Table 1). The most pronounced increases were observed in unstimulated salivary flow (+72.4%) and salivary buffering capacity (+65.3%), whereas local immune parameters - sIgA and lysozyme - increased by 46.1% and 55.4%, respectively. In parallel, against the background of comprehensive treatment, the total GERD-Q

ISSN: 2181-3337 | SCIENTISTS.UZ

score decreased by 36.3% and the xerostomia index by 33.7%, reflecting concomitant improvement in gastroenterological status and subjective oral condition.

Table 1

Changes in Oral-Fluid Parameters and Standardized Questionnaire Scores in Patients With Hyperacid Gastric Diseases, Personalized-Treatment Subgroup (M ± SD)

Oral-fluid parameter (hyperacid group, personalized-treatment subgroup)	At admission	After 12 months	Increase/decrease
Unstimulated salivary flow, mL/min	0.29 ± 0.08	0.50 ± 0.07	+72.4%
Stimulated salivary flow, mL/min	1.23 ± 0.17	1.46 ± 0.15	+18.7%
Oral-fluid pH	5.80 ± 0.21	6.82 ± 0.15	+17.6%
Buffering capacity, points	4.9 ± 1.1	8.1 ± 0.8	+65.3%
sIgA, mg/L	112.4 ± 18.6	164.2 ± 18.5	+46.1%
Lysozyme, µg/mL	8.3 ± 1.5	12.9 ± 1.2	+55.4%
GERD-Q, points	9.1 ± 2.6	5.8 ± 2.0	−36.3%
Xerostomia Index (XI), points	24.6 ± 7.3	16.3 ± 5.7	−33.7%

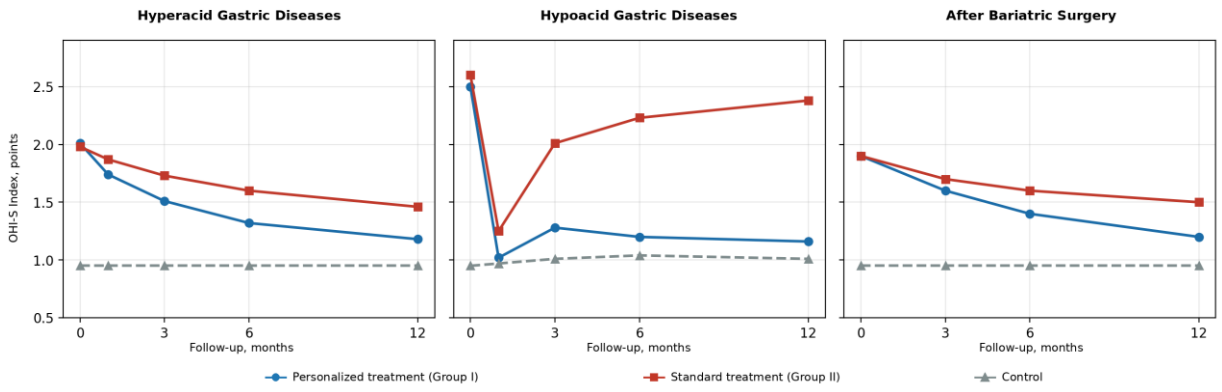
Note. All changes were statistically significant compared with baseline ($p < .05$ to $p < .001$).

In patients with hypoacid gastric pathology, the dynamics of the indices were fundamentally different. In subgroup 2 (standard treatment), a return of the parameters toward baseline was observed after a short-term improvement by day 30: OHI-S decreased to 1.25 points by day 30 but increased to 2.38 points by day 360 (baseline, 2.60 points), and BOP similarly returned from 15.2% to 28.7% (baseline, 32.0%). In subgroup 1, analogous parameters, once improved, remained stable throughout the entire follow-up period. The unstimulated salivary flow rate, which was initially the lowest among the three groups (0.15–0.16 mL/min versus 0.50 mL/min in the control group), recovered to 0.47 mL/min in subgroup 1 compared with only 0.27 mL/min in subgroup 2.

In patients after bariatric surgery, baseline index values were formed under the combined influence of residual gastroesophageal reflux and nutritional deficiency. By 12 months, subgroup 1 achieved stabilization of the ICDAS index (total number of lesions) and BEWE; salivary buffering capacity increased to 7.7 points versus 7.0 points in subgroup 2, and secretory immunoglobulin A concentration increased to 159.2 mg/L versus 134.7 mg/L.

Figure 1

Dynamics of the OHI-S Oral Hygiene Index in the Three Clinical-Pathogenetic Groups



Note. Solid lines show changes in the personalized- and standard-treatment subgroups; the dashed line represents the control group. Of particular note is the divergent pattern in the standard-treatment subgroup of the hypoacid group: after improvement by day 30, the parameter returns toward its baseline level.

In all three groups, differences between the personalized- and standard-treatment subgroups reached statistical significance ($p < .05$ to $p < .001$) for most of the investigated parameters as early as 6 months of follow-up. The most pronounced contrast between the subgroups was recorded in the hypoacid group, in which the standard strategy was accompanied not merely by slower improvement but by reversal of the positive dynamics, with loss of the achieved improvement by the end of follow-up. This reflects the instability of the effect of standard treatment in the presence of secretory insufficiency underlying this clinical-pathogenetic model.

ISSN: 2181-3337 | SCIENTISTS.UZ

Analysis of patient quality of life showed that in patients with hyperacid gastric diseases, the total OHIP-14 score decreased from 29.6–30.1 at admission to 13.5 points after 12 months in the personalized-treatment subgroup (a level close to the control value of 10.8 points), compared with 19.8 points in the standard-treatment subgroup - a reduction of 54% versus 34%. In patients with hypoacid diseases, the score decreased from 30.4–31.0 to 15.1 points versus 22.6 points (a reduction of 50% versus 27%), representing the least complete recovery among the three groups and reflecting the more inert nature of compensation for secretory insufficiency. In post-bariatric patients, in whom the OHIP-14 score increased by almost 1.7-fold immediately after surgery (from baseline values of 18.4–18.8 to 31.8–32.4 points), the personalized strategy reduced the score to 14.2 points compared with 21.9 points under standard management (a reduction of 55% versus 32%).

Table 2

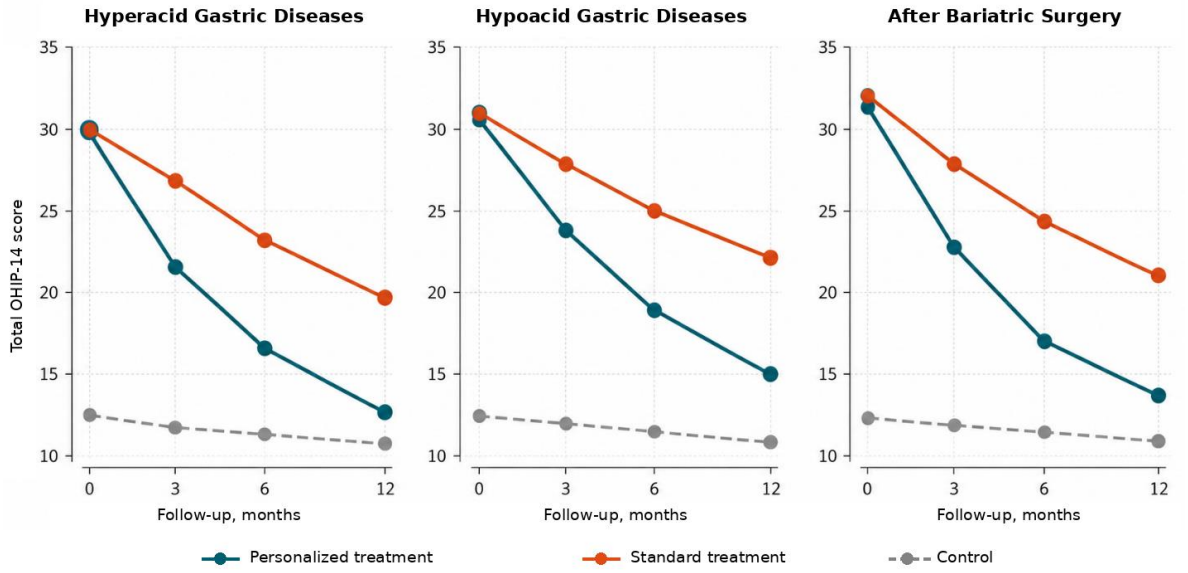
Final Reduction in OHIP-14 Score and Attenuation of the Correlation With Local Symptoms After 12 Months

Group	OHIP-14 reduction, personalized (%)	OHIP-14 reduction, standard (%)	r with local symptoms, personalized	r with local symptoms, standard
Hyperacid diseases	54%	34%	.25–.34	.55–.62
Hypoacid diseases	50%	27%	.28–.36	.57–.65
After bariatric surgery	55%	32%	.29–.34	.61–.67

Note. *r* is the correlation coefficient between the total OHIP-14 score and the leading local symptoms in each group (hypersensitivity/BEWE for hyperacid diseases; xerostomia/mucosal inflammation for hypoacid diseases; hyperemia/pain/pressure areas for post-bariatric patients).

Figure 2

Dynamics of the Total OHIP-14 Score in the Three Clinical-Pathogenetic Groups



In all three groups, personalized treatment statistically significantly attenuated the correlation between OHIP-14 and residual local manifestations of disease. In hyperacid patients, the association with hypersensitivity and the BEWE erosive index decreased from *r* = .55–.62 (standard treatment) to *r* = .25–.34 (personalized treatment). In hypoacid patients, the association with xerostomia and mucosal inflammation decreased from *r* = .57–.65 to *r* = .28–.36. In post-bariatric patients, the association with mucosal hyperemia, the number of areas of increased pressure, and pain intensity according to the VAS decreased from *r* = .61–.67 ($p < .001$) to *r* = .29–.34 ($p > .05$), whereas the negative correlation between OHIP-14 and the degree of functional adaptation to the prosthesis, conversely, persisted and remained statistically significant in both subgroups (*r* = −.52 in the personalized-treatment subgroup versus *r* = −.69 in the standard-treatment subgroup).

The observed pattern—attenuation of the dependence of quality of life on residual local pathology specifically in the personalized-treatment subgroups, with persistence and even strengthening of this

ISSN: 2181-3337 | SCIENTISTS.UZ

dependence in the standard-treatment subgroups—indicates that the personalized approach does not merely accelerate the resolution of individual symptoms but alters the pathogenetic mechanism underlying dental discomfort itself, shifting it away from dependence on residual local pathology toward overall functional adaptation to the prosthodontic construction.

Conclusion

The developed Integrated Acid-Related Dental Risk Index (IADRI), which combines 17 clinical, laboratory, functional, and radiological criteria into a unified three-level scoring system, provides objective stratification of patients with acid-related gastric diseases regardless of the predominant pathogenetic mechanism.

Personalized dental care provides a more pronounced and, importantly, more sustained normalization of clinical indices and functional parameters of oral fluid than the standard strategy in all three studied clinical-pathogenetic groups of patients with acid-related gastric diseases. The most important clinical advantage of the personalized approach—prevention of recurrence of pathological changes observed under standard management in hypoacid patients—emphasizes the need to consider the specific pathogenetic variant of the disease when planning the scope and content of dental care.

Comparison of the dynamics of IADRI with oral-health-related quality of life confirms the clinical significance of the developed system. In all three studied groups, personalized treatment aimed at reducing dental risk not only provides more complete restoration of quality of life but also qualitatively changes the mechanism determining it—from dependence on residual local symptoms to the predominant role of functional adaptation to the prosthodontic construction.

REFERENCES

1. Castilho, A. V. S. S., Foratori-Junior, G. A., & Sales-Peres, S. H. C. (2019). Bariatric surgery impact on gastroesophageal reflux and dental wear: A systematic review. *ABCD. Arquivos Brasileiros de Cirurgia Digestiva, 32*(4), e1466. https://doi.org/10.1590/0102-672020190001e1466
2. Cavalcoli, F., Zilli, A., Conte, D., & Massironi, S. (2017). Micronutrient deficiencies in patients with chronic atrophic autoimmune gastritis: A review. *World Journal of Gastroenterology, 23*(4), 563–572. https://doi.org/10.3748/wjg.v23.i4.563
3. Eremin, O. V. (2013). *Ortopedicheskoe lechenie defektov zubnykh ryadov u patsientov s khronicheskimi zabolevaniyami zheludochno-kishechnogo trakta* [Prosthodontic treatment of dentition defects in patients with chronic diseases of the gastrointestinal tract] [Abstract of doctoral dissertation, V. I. Razumovsky Saratov State Medical University].
4. Hatipoğlu, Ö., Yıldırım, Ö., & Hatipoğlu, F. P. (2025). Impact of gastroesophageal reflux disease on salivary flow rate, pH and buffer capacity: A systematic review and meta-analysis. *Journal of Oral Rehabilitation, 52*(10), 1682–1698. https://doi.org/10.1111/joor.14025
5. Livzan, M. A., Bordin, D. S., Gaus, O. V., Lisovskiy, M. A., Mozgovoi, S. I., & Kononov, A. V. (2024). Classification of chronic gastritis: Historical digression and current state of the issue. A review. *Terapevticheskii Arkhiv, 96*(2), 153–158. https://doi.org/10.26442/00403660.2024.02.202578
6. Madariaga, V. I., Pereira-Cenci, T., Walboomers, X. F., & Loomans, B. A. C. (2023). Association between salivary characteristics and tooth wear: A systematic review and meta-analysis. *Journal of Dentistry, 138*, 104692. https://doi.org/10.1016/j.jdent.2023.104692
7. Marschner, F., Kanzow, P., & Wiegand, A. (2024). Anamnestic risk factors for erosive tooth wear: Systematic review, mapping, and meta-analysis. *Journal of Dentistry, 144*, 104962. https://doi.org/10.1016/j.jdent.2024.104962
8. Patel, J. J., Mundi, M. S., Hurt, R. T., Wolfe, B., & Martindale, R. G. (2017). Micronutrient deficiencies after bariatric surgery: An emphasis on vitamins and trace minerals. *Nutrition in Clinical Practice, 32*(4), 471–480. https://doi.org/10.1177/0884533617712226

ISSN: 2181-3337 | SCIENTISTS.UZ

9. Pavlenko, V. I., Goncharova, O. M., & Soluyanova, I. P. (2021). *Kislotozavisimye i assotsiirovannye s Helicobacter pylori zabolevaniya v praktike uchastkovogo vracha-terapevta* [Acid-related and Helicobacter pylori-associated diseases in primary care practice]. Amur State Medical Academy.
10. Richter, J. E., & Rubenstein, J. H. (2018). Presentation and epidemiology of gastroesophageal reflux disease. *Gastroenterology, 154*(2), 267–276. https://doi.org/10.1053/j.gastro.2017.07.045
11. Rizaev, J. A., & Elnazarov, A. T. (2023). Dental health after bariatric surgery. *Problems of Biology and Medicine, 6*(150), 218–223.
12. Slade, G. D. (1997). Derivation and validation of a short-form oral health impact profile. *Community Dentistry and Oral Epidemiology, 25*(4), 284–290. https://doi.org/10.1111/j.1600-0528.1997.tb00941.x

ISSN: 2181-3337 | SCIENTISTS.UZ

ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 9 | SEPTEMBER 2026

HEMODYNAMIC CHANGES IN KIDNEY TRANSPLANT RECIPIENTS DURING LATE PREGNANCY AND AFTER DELIVERY

Matkarimov Zohidjon[1], Azimova Marguba[2], Abdurahmonova Nigora[3], Elmurodova Nigina[4], Komilova Dildora[5]

State Institution "Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V.Vakhidov"

DOI: 10.67620/sai.59d0007

ABSTRACT

Pregnancy after kidney transplantation is a high-risk condition in which cardiovascular adaptation may be influenced by renal and vascular factors. This comparative observational study assessed systolic and diastolic blood pressure dynamics in kidney transplant recipients during late pregnancy and after delivery and compared pre-delivery values with those of healthy pregnant women. The study included 23 women with a functioning kidney allograft and 23 healthy pregnant women. In transplant recipients, systolic blood pressure decreased from 125 ± 3.06 mmHg before delivery to 116.7 ± 2.34 mmHg after delivery, representing a statistically significant reduction ($p = 0.0368$). Diastolic blood pressure decreased from 81.96 ± 2.17 mmHg to 77.2 ± 1.57 mmHg, but this change was not statistically significant ($p = 0.0826$). Before delivery, transplant recipients had significantly higher systolic blood pressure than healthy pregnant women (125 ± 3.06 vs 110 ± 2.27 mmHg; $p = 0.000297$) and markedly higher diastolic blood pressure (81.96 ± 2.17 vs 60 ± 1.62 mmHg; $p < 0.000001$). These findings demonstrate elevated blood pressure in kidney transplant recipients during late pregnancy, with significant postpartum improvement in the systolic component, and support continued individualized blood pressure monitoring throughout pregnancy and the postpartum period.

ACCEPTED

05.10.26

Keywords: *kidney transplantation; pregnancy; arterial hypertension; systolic blood pressure; diastolic blood pressure; postpartum period.*

CC BY

Introduction

Pregnancy after kidney transplantation is considered a high-risk clinical condition requiring close multidisciplinary monitoring because of the complex interaction between physiological changes associated with pregnancy and the underlying characteristics of the kidney transplant recipient (Mallett et al., 2024; Wiles et al., 2019). Pregnancy is accompanied by substantial hemodynamic adaptations, including changes in circulating blood volume, cardiac output, vascular resistance, and blood pressure (Meah et al., 2016; Troiano, 2018). In kidney transplant recipients, these physiological changes may be modified by pre-existing renal dysfunction, vascular abnormalities, and long-term immunosuppressive therapy (Wiles et al., 2019).

Arterial hypertension is common among kidney transplant recipients and represents an important factor associated with cardiovascular complications and deterioration of kidney allograft function (Loutradis et al., 2021). During pregnancy, elevated blood pressure may additionally increase the risk of pregnancy-related complications, including preeclampsia and preterm delivery (Shah et al., 2019; Wiles et

al., 2019). Therefore, assessment of blood pressure dynamics during late pregnancy and the postpartum period is an important component of monitoring women with a transplanted kidney (Mallett et al., 2024; Wiles et al., 2019).

The postpartum period is characterized by rapid hemodynamic changes associated with delivery and the transition from pregnancy to the non-pregnant state (Meah et al., 2016; Troiano, 2018). Evaluation of blood pressure before and after delivery may provide clinically relevant information regarding the cardiovascular response to these changes and may contribute to the optimization of post-transplant monitoring.

The aim of this analysis was to assess the dynamics of systolic and diastolic blood pressure in kidney transplant recipients during the last months of pregnancy and after delivery, and to compare blood pressure values before delivery with those observed in healthy pregnant women.

Materials and methods. A comparative observational study was conducted to assess arterial blood pressure dynamics in pregnant kidney transplant recipients during late pregnancy and the postpartum period. The study included 23 women with a functioning kidney allograft who subsequently delivered, as well as 23 healthy pregnant women who constituted the comparison group.

Results. Systolic blood pressure (SBP) before delivery was 125 ± 3.06 mmHg, compared with 116.7 ± 2.34 mmHg after delivery; the difference was statistically significant ($p < 0.05$). Pregnancy is associated with physiological changes in hemodynamic load, which may be reflected in higher SBP during the late gestational period. Following delivery, the cardiovascular system undergoes hemodynamic unloading, accompanied by changes in circulating blood volume and a return toward a more stable blood pressure level (Meah et al., 2016; Troiano, 2018).

Diastolic blood pressure (DBP) was 81.96 ± 2.17 mmHg before delivery and 77.2 ± 1.57 mmHg after delivery. Although a downward trend was observed, the difference did not reach statistical significance ($p > 0.05$). This may be explained by individual variability in vascular tone and the effects of immunosuppressive therapy (Loutradis et al., 2021).

Table 1.

Blood Pressure in Kidney Transplant Recipients During the Last Months of Pregnancy and After Delivery

Blood pressure, mmHg	Systolic	Diastolic
Before delivery (N=23)	125 ± 3.06	81.96 ± 2.17
After delivery (N=23)	116.7 ± 2.34	77.2 ± 1.57
p-value	Statistically significant difference (p=0.036836)	Not statistically significant (p=0.082612)

The reduction in blood pressure after delivery may be clinically relevant in kidney transplant recipients, as hypertension is an important risk factor for deterioration of allograft function (Loutradis et al., 2021). The statistically significant reduction in SBP suggests that this parameter may be more sensitive to the hemodynamic changes occurring after delivery. The absence of a statistically significant difference in DBP indicates that a larger sample size may be required to clarify this trend.

Table 1. Dynamics of blood pressure in kidney transplant recipients before and after delivery presents the mean systolic and diastolic blood pressure values with 95% confidence intervals. A statistically significant reduction in SBP was observed after delivery ($p = 0.037$), whereas the difference in DBP did not reach statistical significance ($p = 0.083$). Thus, kidney transplant recipients in the last

ISSN: 2181-3337 | SCIENTISTS.UZ

months of pregnancy demonstrated relatively higher blood pressure, predominantly due to the systolic component. After delivery, a statistically significant decrease in SBP was observed ($p < 0.05$), consistent with postpartum hemodynamic changes and cardiovascular unloading (Meah et al., 2016; Troiano, 2018). DBP also showed a downward trend; however, the difference did not reach statistical significance ($p > 0.05$). These findings emphasize the importance of continuous blood pressure monitoring in kidney transplant recipients during pregnancy and the postpartum period, as hypertension remains an important risk factor for maternal complications and impaired kidney allograft function (Loutradis et al., 2021; Mallett et al., 2024; Wiles et al., 2019).

Table 2.

Blood Pressure in Kidney Transplant Recipients and Healthy Pregnant Women Before Delivery

Blood pressure, mmHg	**Systolic**	**Diastolic**
Kidney transplant recipients (N=23)	125 ± 3.06	81.96 ± 2.17
Healthy pregnant women (N=23)	110 ± 2.27	60 ± 1.62
p-value	Statistically significant difference (p=0.000297)	Statistically significant difference (p<0.000001)

Systolic blood pressure in kidney transplant recipients was 125 ± 3.06 mmHg, compared with 110 ± 2.27 mmHg in healthy pregnant women. The difference was statistically significant ($p = 0.000297$), indicating higher SBP among kidney transplant recipients during late pregnancy.

Diastolic blood pressure was 81.96 ± 2.17 mmHg in kidney transplant recipients and 60 ± 1.62 mmHg in healthy pregnant women, with a highly statistically significant difference ($p < 0.000001$). This finding indicates substantially higher DBP in the transplant recipient group.

Overall, both systolic and diastolic blood pressure were higher in pregnant kidney transplant recipients than in healthy pregnant women. The mean difference was approximately 15 mmHg for SBP and 22 mmHg for DBP, which is clinically relevant in the context of pregnancy after kidney transplantation.

These findings are consistent with recognized mechanisms contributing to elevated blood pressure in kidney transplant recipients, including long-term exposure to calcineurin inhibitors, vascular remodeling, reduced arterial compliance, and renal-related mechanisms (Loutradis et al., 2021). Hypertension in this population is an important risk factor for pregnancy-related complications, including preeclampsia, placental dysfunction, and preterm delivery, as well as for deterioration of kidney allograft function (Loutradis et al., 2021; Shah et al., 2019; Wiles et al., 2019).

Thus, blood pressure values in kidney transplant recipients were significantly higher than those observed in healthy pregnant women. The significant differences in both systolic and diastolic blood pressure highlight the increased cardiovascular and obstetric risk profile of this population and underscore the importance of careful blood pressure monitoring and timely management throughout pregnancy (Mallett et al., 2024; Wiles et al., 2019).

Conclusion.

1. Kidney transplant recipients demonstrated higher arterial blood pressure during the last months of pregnancy compared with healthy pregnant women. Mean systolic blood pressure was **125.0 ± 3.06 mmHg** versus **110.0 ± 2.27 mmHg**, respectively (**p = 0.000297**), while mean diastolic blood pressure was **81.96 ± 2.17 mmHg** versus **60.0 ± 1.62 mmHg (p < 0.000001).**

2. After delivery, a statistically significant reduction in systolic blood pressure was observed, from **125.0 ± 3.06 mmHg** to **116.7 ± 2.34 mmHg (p = 0.0368**). This finding reflects the hemodynamic changes accompanying the transition from pregnancy to the postpartum period.

ISSN: 2181-3337 | SCIENTISTS.UZ

3. Diastolic blood pressure also decreased after delivery, from **81.96 ± 2.17 mmHg** to **77.2 ± 1.57 mmHg**; however, the difference did not reach statistical significance (**p = 0.0826**).

4. The observed differences in blood pressure indicate that kidney transplant recipients require careful and continued blood pressure monitoring during late pregnancy and after delivery. Particular attention should be given to systolic blood pressure, which demonstrated a statistically significant postpartum decrease in the present cohort.

5. The higher blood pressure values observed in kidney transplant recipients compared with healthy pregnant women emphasize the importance of individualized cardiovascular and renal monitoring throughout pregnancy and the postpartum period to support maternal health and preservation of kidney allograft function.

REFERENCES

1. Loutradis, C., Sarafidis, P., Marinaki, S., Berry, M., Borrows, R., Sharif, A., & Ferro, C. J. (2021). Role of hypertension in kidney transplant recipients. *Journal of Human Hypertension*, *35*(11), 958–969. https://doi.org/10.1038/s41371-021-00540-5
2. Mallett, C., Scale, R., Metodiev, Y., Ali, A., Thomas, H., Khalid, U., & Griffin, S. (2024). Late pregnancy in women with renal transplants: A multidisciplinary guide. *Obstetric Medicine*, *17*(2), 71–76. https://doi.org/10.1177/1753495X231209647
3. Meah, V. L., Cockcroft, J. R., Backx, K., Shave, R., & Stöhr, E. J. (2016). Cardiac output and related haemodynamics during pregnancy: A series of meta-analyses. *Heart*, *102*(7), 518–526. https://doi.org/10.1136/heartjnl-2015-308476
4. Shah, S., Venkatesan, R. L., Gupta, A., Sanghavi, M. K., Welge, J., Johansen, R., Kean, E. B., Kaur, T., Gupta, A., Grant, T. J., & Verma, P. (2019). Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review. *BMC Nephrology*, *20*(1), 24. https://doi.org/10.1186/s12882-019-1213-5
5. Troiano, N. H. (2018). Physiologic and hemodynamic changes during pregnancy. *AACN Advanced Critical Care*, *29*(3), 273–283. https://doi.org/10.4037/aacnacc2018911
6. Wiles, K., Chappell, L., Clark, K., Elman, L., Hall, M., Lightstone, L., Mohamed, G., Mukherjee, D., Nelson-Piercy, C., Webster, P., Whybrow, R., & Bramham, K. (2019). Clinical practice guideline on pregnancy and renal disease. *BMC Nephrology*, *20*(1), 401. https://doi.org/10.1186/s12882-019-1560-2

ISSN: 2181-3337 | SCIENTISTS.UZ

CONTENTS

Ismailova Munojat Mazhikhanov Baxodir, Akhmatov Bekzod
THE ROLE OF MRI-DETECTED EXTRAMURAL VASCULAR INVASION AS A PREDICTOR OF REGIONAL AND DISTANT METASTASIS IN LOW RECTAL CANCER 4

Mazhikhanov Baxodir
METAPHYLAXIS OF URATE NEPHROLITHIASIS IN THE NAMANGAN REGION: A CLINICAL EXPERIENCE 12

Khujaeva Shakhnoz
CONFRONTING HYPERVIRULENT KLEBSIELLA PNEUMONIAE: INSIGHTS INTO PATHOGENICITY, RESISTANCE, AND INTERVENTION STRATEGIES 18

Karimova Bonu
THE INFLUENCE OF METABOLIC SYNDROME COMPONENTS ON THE DEVELOPMENT OF FETAL MACROSOMIA 36

Matkarimov Zohidjon, Azimova Marguba, Abdurahmonova Nigora, Elmurodova Nigina, Komilova Dildora
PREGNANCY AFTER KIDNEY TRANSPLANTATION: CURRENT APPROACHES TO ALLOGRAFT MONITORING AND MATERNAL OUTCOMES 43

Akbarov Avzal, Ziyadullaeva Nigora, Tulyaganov Jamshid
INTEGRATED ASSESSMENT OF DENTAL RISK AND QUALITY OF LIFE IN PATIENTS UNDERGOING DIFFERENTIATED PROSTHODONTIC TREATMENT FOR ACID-RELATED GASTRIC DISEASES 49

Matkarimov Zohidjon, Azimova Marguba, Abdurahmonova Nigora, Elmurodova Nigina, Komilova Dildora
HEMODYNAMIC CHANGES IN KIDNEY TRANSPLANT RECIPIENTS DURING LATE PREGNANCY AND AFTER DELIVERY 56

ISSN: 2181-3337 | SCIENTISTS.UZ

International Scientific Journal
Science and Innovation Series D
Volume 5 Issue 9

ISSN: 2181-3337

Published: 31.09.2026. Font: “Times New Roman”.

LLC “Science and innovation”
License Mass Media №:1597 27.04.2022
License Publisher №:455168 21.11.2024
Address: 100121, Uzbekistan, Tashkent city, Yakkasaroy district,
Shota Rustaveli Street 150, Vega Business Center, 6th floor, Room 2.
www.scientists.uz, info@scientists.uz, +998901259654

ISSN: 2181-3337