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# Restoring Purpose to Medical Publishing: Why European Journal of Innovative Medical Research Exists

## OPEN ACCESS

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Mehmet Berksun Tutan

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### *Medical publishing stands at a crossroads.*

That is the polite way of putting it. The truth is far less graceful: the landscape has become crowded with journals that speak of service while serving only themselves. As scientific output accelerates and digital platforms multiply, the gap between what publishing should be and what it has become widens with every passing year. Impact factors have replaced integrity. Budgets overshadow curiosity. And young researchers—bright minds with something meaningful to say—are too often met with paywalls, delays, and indifference.

I've always believed that when an institution forgets its purpose, someone else must remind it. That is why the European Journal of Innovative Medical Research exists.

European Journal of Innovative Medical Research was not created to add another title to an overcrowded shelf. It was created to build a space where authors, patients, and knowledge reclaim their rightful place at the center of the process. We recognize that science does not only flourish in prestigious laboratories with multi-million-euro grants. It grows in quiet clinics, in overburdened hospitals, in operating rooms where decisions are made under pressure and with purpose. It grows wherever a clinician pauses long enough to say, "This is worth sharing."

*Too many journals ask, "Will this be cited?"*

*We ask, "Will this be useful?"*

Our commitment is simple: to evaluate work for its educational merit, its rigor, and its contribution to clinical understanding—not for its ability to decorate citation charts or marketing brochures. The clinician-researcher deserves a publication environment where honesty matters more than novelty, and professionalism is not a luxury but a promise.

This matters now more than ever. We live in an era where data expands exponentially, where machine learning models hunger for diversity, and where large language models grow stronger with every dataset—large or small—that they consume. To dismiss a carefully written case report because it is "not innovative enough" is to misunderstand the architecture of modern science.

*A single observation can sharpen a surgeon's judgment, refine a physician's diagnosis, or expose a pattern that larger datasets have not yet captured.*

At European Journal of Innovative Medical Research,

We value such observations.

We champion them.

Because **innovation**, in its truest form, begins with **attention**.

Our editorial philosophy is not gentle, but it is fair. Peer review must be timely. Feedback must be constructive. Processes must be transparent. A journal earns the trust of authors the same way a politician earns the trust of constituents: through consistency, clarity, and respect. We will not leave authors waiting months without an answer. We will not hide behind bureaucracy. And we will never forget that behind every submission is a human being willing to expose their hard work to scrutiny.

We aim to guide, not to gatekeep.

Of course, professionalism alone is not enough. A modern journal must be a guardian of digital integrity. As a Cross-ref-registered journal, every accepted article receives a DOI—an anchor in the ocean of global scholarship. This ensures permanence, discoverability, and rightful citation. It tells the world, “This work matters, and it will be part of the scientific record long after this issue is printed.”

But beyond technical infrastructure lies something far more important: **community**.

European Journal of Innovative Medical Research’s true ambition is not merely to publish but to gather. To draw clinicians, researchers, and educators from diverse disciplines and nations into a shared conversation about medicine, innovation, and progress. We welcome voices from every corner of the clinical landscape—surgical, medical, behavioral, technological, and interdisciplinary. Science advances not by isolation but by collision, by debate, by the meeting of different minds.

Founding a new journal carries symbolism. It is an act of optimism, certainly—but also an act of defiance. It is a refusal to accept that the current norms of publishing are the best we can offer. It is a commitment to something better: an ecosystem where knowledge is not a commodity but a responsibility.

As we launch this inaugural issue, I extend an invitation—no, a challenge—to the scientific community: join us in restoring purpose to medical publishing. Submit work that is honest, rigorous, and meaningful. Let us reject the notion that value is measured solely in citations. Let us build a home for science that is as ambitious as the minds behind it.

**And if along the way we disrupt a few outdated norms, then so be it. Progress rarely asks permission.**

To our authors, reviewers, and readers: *thank you*. Your dedication to inquiry, to patient care, and to scholarly integrity fuels this endeavor. May this first issue be the beginning of a journal that leads not by shouting but by standing firmly in its convictions.

**Welcome to the European Journal of Innovative Medical Research.**

**We are honored to begin this journey with you.**

# ChatGPT-4 Use During Diabetes Knowledge Testing and AI Readiness Characteristics in Nursing and Midwifery Students

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### ETHICAL APPROVAL

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### INFORMED CONSENT

All students were informed about the study and provided informed consent

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### PEER REVIEW

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## ABSTRACT

**Background:** ChatGPT has gained attention for its role in accessing health information, supporting clinical decisions, and educating patients.

**Materials and Methods:** This study aimed to evaluate nursing and midwifery students' readiness for artificial intelligence (AI) and their diabetes knowledge using ChatGPT-4. A randomized controlled experimental design was used with 105 students (intervention=53, control=52) between April and June 2024. Data were collected using the Information Form, Medical Artificial Intelligence Readiness Scale for Medical Students (MAIRS-MS), and the Diabetes Knowledge Scale for Adults (DKSA). Students in the intervention group used ChatGPT-4 to answer the DKSA, while those in the control group completed it independently without technology.

**Results:** No significant difference was found between groups in MAIRS-MS scores. However, the intervention group had significantly higher DKSA total and sub-dimension scores for risk factors and symptoms (p=0.003; 0.000; 0.002).

**Conclusion:** Using ChatGPT-4 significantly improved diabetes knowledge among nursing and midwifery students.

**Keywords:** artificial intelligence, ChatGPT, diabetes, nursing, midwifery

## Introduction

Chat Generative Pre-trained Transformer (ChatGPT) is one of the large language models developed by OpenAI. OpenAI released the free GPT 3.5 series in 2022, paid GPT-4 on March 14, 2023, and released its first version.<sup>1</sup> Since its launch, ChatGPT 4 has reached more than 180.5 million users in 2024.<sup>2</sup> ChatGPT has built its language capability on a system of various books, articles, and websites.<sup>3</sup> ChatGPT can understand the content of a conversation and generate appropriate responses in different styles and languages.<sup>4</sup> For this reason, ChatGPT has been used in education, healthcare, and many other fields.<sup>2</sup>

Integrating ChatGPT into nursing and midwifery education can offer a personalized and interactive learning environment for students.<sup>2,5</sup> ChatGPT is an advantage in terms of providing students with ready and fast information on the subjects they are

curious about in their courses. In addition, information about the nursing process, treatment guidelines, and clinical approaches can be easily obtained with ChatGPT.<sup>3,4,6,7</sup> Seney et al. suggested that ChatGPT could be used in various teaching strategies to enhance students' clinical judgment skills.<sup>8</sup> They proposed that students could create case studies using ChatGPT, a process that could strengthen their abilities to identify assessment cues, recognize problems, and develop intervention plans. At this point, it is important to ensure that the inevitable and widely used ChatGPT is used consciously and correctly. They need to understand the potential uses, benefits, challenges, disadvantages, and limitations of ChatGPT.<sup>3,4,9</sup>

There are only a limited number of studies that directly investigate how nursing and midwifery students use ChatGPT and how this use affects their learning outcomes.<sup>10</sup> In these existing studies, students were main-

ly asked about their perceptions and attitudes toward artificial intelligence tools, including ChatGPT.<sup>5,11,12</sup> In contrast, the literature contains a larger number of commentaries and review articles discussing the potential role of ChatGPT in nursing education.<sup>2,3,6,7,9</sup> Furthermore, there are also studies focusing on ChatGPT in the context of diabetes, such as those evaluating its role in increasing diabetes awareness<sup>13</sup> and its performance<sup>14</sup> in assessing or supporting diabetes management.<sup>15,16</sup>

To our knowledge, no study has been encountered regarding the application of ChatGPT to nursing and midwifery students in the context of a chronic illness. Based on this gap, the aim of this study is to evaluate the performance of nursing and midwifery students in responding to questions on the Diabetes Knowledge Scale (DKSA) using ChatGPT-4 and to determine their readiness for AI-assisted education.

## Materials and Methods

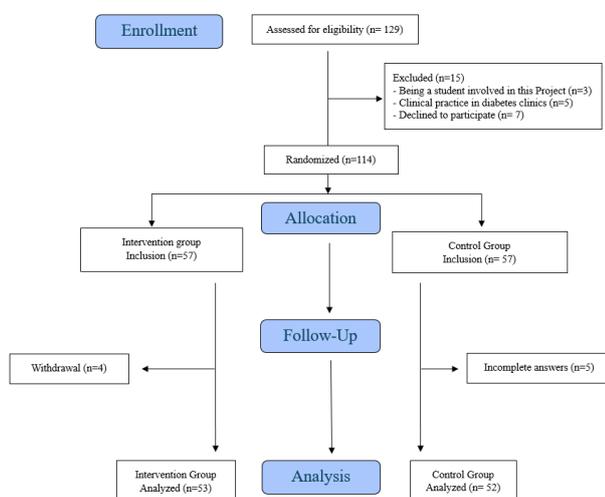
### Study design and participants

This study was a randomized controlled trial. The study was conducted in the nursing and midwifery departments of the Faculty of Health Sciences at a university in Türkiye between April and June 2024. Since the internal medicine nursing course is taken by second-year students in these departments, they constituted the study population. The population consisted of 129 students, including 68 nursing and 61 midwifery students. The study was completed with 105 students (intervention group = 53, control group = 52) (Figure 1).

The inclusion criteria were being a second-year nursing and midwifery student, having the technological equipment to use ChatGPT, and agreeing to participate in the study.

The exclusion criteria were having a diagnosis of diabetes, having prior clinical practice experience in diabetes clinics, providing incomplete responses to the study instruments, being a student who was part of the research team, and being actively involved in the design and implementation of the study. Students who were involved in the research process were excluded

Figure 1. The CONSORT chart of the study



because they were fully aware of the study aims, the content of the DKSA, and the use of ChatGPT-4, which could have introduced bias in their responses.

### Randomization

Students were randomized in a 1:1 allocation ratio, based on a parallel design, into groups either receiving or not receiving ChatGPT-4. Each student's assignment to the intervention or control group was determined using a computer-based randomization table (<https://www.random.org/>). To prevent selection bias, randomization was performed by another lecturer who was not involved in the project. This study was conducted and reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

The study was completed with 105 students. Once data collection was completed, the study's power was recalculated using G\*Power version 3.1. The results showed a statistical power of 85%, based on a 95% confidence interval.

### Instruments

The data were collected using the Information Form, Medical Artificial Intelligence Readiness Scale for Medical Students (MAIRS-MS), and Diabetes Knowledge Scale for Adults (DKSA).

**Information Form:** This form was created by the researchers by reviewing the relevant literature.<sup>5,11,17</sup> It consists of questions about the sociodemographic characteristics of the students, such as age, gender, etc.

**Medical Artificial Intelligence Readiness Scale for Medical Students (MAIRS-MS):** The scale was developed by Karaca et al. to determine the medical artificial intelligence readiness level of medical faculty students. The scale consists of 22 items and four sub-dimensions. The items are rated on a 5-point Likert-type scale (1-strongly disagree to 5-strongly agree). Scale sub-dimensions items and score ranges; Cognition Factor (8 -40 points), Ability Factor (8-40 points), Vision Factor (3-15 points), Ethics Factor (3-15 points). Medical Artificial Intelligence Readiness Factor 22-110 points, so the total score ranges from 22 to 110. A high score means a high level of readiness for medical artificial intelligence. In Karaca et al.'s study, Cronbach's alpha reliability coefficient was 0.87.<sup>17</sup> In our study, the Cronbach's alpha value was found to be 0.85.

**Diabetes Knowledge Scale for Adults (DKSA):** This scale was developed by Yavuz and Erol to determine the knowledge levels of adults. It consists of 28 items and five sub-dimensions.<sup>18</sup> The sub-dimensions in the scale are: general knowledge about diabetes; blood glucose measurement value, diabetes Risk Factors, symptoms of diabetes, and diabetes complications. The items in the scale are marked as yes, no, and don't know. Each correct answer is given 1 point, while 0 points are not given for wrong or 'don't know' answers. The total scores range from 0 to 28. The higher the score, the greater the individual's knowledge about diabetes. Yavuz and Erol Cronbach's alpha reliability coefficient was 0.94.<sup>18</sup> In our study, the Cronbach's alpha value was found to be 0.91.

**Intervention**

The researchers administered all study scales to the students face-to-face in the nursing laboratory. Prior to data collection, both the intervention and control groups had received the same theoretical diabetes-related education as part of their regular semester curriculum, delivered by the same instructor. Topics covered in routine courses included: definition of diabetes, etiology of diabetes, classification, treatment and nursing care, and acute and chronic complications.

The intervention group was allowed to use ChatGPT-4 as an assistive tool while responding to the DKSA. Each student in this group individually accessed ChatGPT-4 on a laboratory computer under the supervision of the researchers. Students were instructed to use ChatGPT-4 freely to help them answer the DKSA questions. Each student completed the questionnaire individually and sequentially, ensuring that responses were not shared among participants.

The control group completed the DKSA independently, without any technological assistance. The use of electronic devices such as mobile phones, computers, or internet-based resources was strictly prohibited during data collection. This procedure allowed for a clear comparison between tool-assisted response performance and non-assisted response performance on the DKSA.

**Data analysis**

Statistical analyses were conducted with SPSS® software version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data, including mean ± standard deviation (SD), percentages, and ranges. The normality of continuous variables was assessed using the Kolmogorov–Smirnov

and Shapiro–Wilk tests. The Chi-square test was used for the analysis of categorical data. The comparison between these two groups was performed using the independent t-test. A p-value below 0.05 within the 95% confidence interval was regarded as indicating statistical significance.

**Ethical considerations**

The study was carried out in accordance with the Declaration of Helsinki 2013 and was approved by the Ethics Committee of Clinical Research of Ankara Medipol University (No:2024-75). All students were informed about the study and provided informed consent.

**Results**

**Sociodemographic**

The two groups had homogenous socio-demographic characteristics (Table 1). 43.81% of the students who participated in the study were between the ages of 18 and 20; 97% were female; 24.8% had someone with diabetes in their family; and none had a diagnosis of diabetes.

**Medical artificial intelligence readiness scale for medical students (MAIRS-MS)**

No statistically significant differences were observed between the intervention and control groups with respect to the Cognitive, Ability, Vision, and Ethics sub-dimensions, nor in the total MAIRS-MS score ( $p > 0.05$ ) (Table 2).

**Diabetes Knowledge Scale for Adults (DKSA)**

The intervention group's scores in the DKSA and sub-dimensions of diabetes risk factors, symptoms of diabetes were higher than those of the control group, and the difference was found to be statistically significant (respectively  $p=0.003$ ,  $p=0.000$ ,  $p=0.002$ ) (Table 3).

**Discussion**

In our study, the intervention and control groups had similar MAIRS-MS scores. The students' MAIRS-MS scores were above the scale averages. However, no statistically significant difference was found between the intervention and control groups. These findings are consistent with previous studies reporting generally positive attitudes of nursing students toward artificial intelligence.<sup>2,5,11,19</sup>

The important finding here is that the intervention group used ChatGPT. And this is how students improved their knowl-

**Table 1.** Sociodemographic characteristics of students

Sociodemographic characteristics	Intervention (n=53)	Control (n=52)	p value
Age	18-20	24 (45.3%)	0.759
	21-25	29 (54.7%)	
Gender	Woman	49 (92.5%)	0.978
	Man	4 (7.5%)	
Family History of Diabetes	Yes	13 (24.5%)	0.955
	No	40 (75.5%)	

**Table 2.** Comparison of MAIRS-MS scale scores of intervention and control groups

Group	MAIRS-MS sub-dimension				Medical Artificial Intelligence Readiness Factor (Total Factor)
	Cognition Factor Mean ± SD	Ability Factor Mean ± SD	Vision Factor Mean ± SD	Ethics Factor Mean ± SD	
Intervention (ChatGPT group)	23.69± 6.01	26.71 ±6.55	9.45 ± 2.46	10.05 ± 2.45	69.96 ±15.02
Control Group	25.21±6.18	29.09±6.69	10.09±2.68	10.80 ±2.77	75.21 ± 16.24
Within-group p-value	0.206	0.069	0.204	0.142	0.090

edge scores about diabetes, including diabetes risk factors and symptoms, using ChatGPT-4. They reflect tool-assisted performance during test completion, as participants were allowed to use ChatGPT-4 while answering the DKSA. Similar to the use of a calculator during a mathematics test, ChatGPT-4 appears to have enhanced response accuracy at the time of assessment, rather than improving conceptual understanding. In parallel with our research, Makhlof et al. found that nurses' knowledge of knowledge-based chatbot systems increased significantly with an artificial intelligence-based robot.<sup>12</sup> The use of ChatGPT in nursing and midwifery education in chronic diseases such as diabetes can be used as an auxiliary tool by providing academic support, answering questions, and promoting learning through interactive conversations. It improves educational outcomes in chronic diseases and care by providing personalized learning experiences based on students' understanding and learning style.<sup>2,5,9</sup> Although artificial intelligence has many applications in nursing and midwifery, the majority of studies have focused on clinical practices, with limited research in the field of education.<sup>10,20</sup> Therefore, we were unable to find studies with which to directly compare our results. However, articles on the clinical use of ChatGPT in diabetes diagnosis, management, and patient guidelines are consistent with our results.<sup>14-16</sup>

In a study evaluating the accuracy of responses to the Diabetes Knowledge Questionnaire (DKQ), the authors suggested that ChatGPT could be a suitable tool for assisting in diabetes education and management.<sup>15</sup> ChatGPT was determined to be able to provide personalized educational content about diabetes management, including dietary recommendations and exercise plans.<sup>16</sup> Jairoun et al. evaluated the benefit-risk scenario of ChatGPT applications in the field of diabetes and metabolic diseases with the participation of 25 endocrinologists and diabetologists.<sup>21</sup> Prominent benefits of ChatGPT include increased diagnostic accuracy, personalized treatment and they found that these elements can improve patient outcomes.<sup>21</sup> In our study, we similarly found that the responses of students using ChatGPT-4 for diabetes symptoms and risk factors were more accurate.

While ChatGPT has these positive aspects, there are also some considerations to be mindful of. ChatGPT may not always provide the most up-to-date or accurate clinical information, which increases the risks of relying solely on artificial intelligence (AI) for health education.<sup>4,15,21</sup> At this point, it is very important for academics to verify the content produced by ChatGPT and AI.<sup>9-11</sup> ChatGPT should not completely replace the

education provided in clinical settings with real patients and experienced instructors when it comes to learning about diabetes and its symptoms. While AI can be a useful supplementary tool for education, the hands-on experience and human interaction in clinical training are irreplaceable for developing a deeper understanding of complex conditions like diabetes.

This research had some limitations. The first limitation of the study is the use of unequal information sources between the intervention and control groups. While the intervention group was allowed to use ChatGPT-4 as an external information support when responding to the DKSA, the control group answered the same scale without access to any technological assistance. Therefore, the results might reflect tool-assisted response performance rather than students' independent acquisition of diabetes knowledge. Second, the study was conducted in a single institution with nursing and midwifery students, which may limit the generalizability of the results to other educational settings or disciplines. Third, students' familiarity with artificial intelligence tools was not measured before the intervention.

### Conclusion

The use of ChatGPT-4 can support nursing and midwifery students in answering diabetes-related questions. Our results revealed a positive effect of integrating ChatGPT-4 into learning processes in chronic diseases such as diabetes, suggesting its potential as an assistive tool for learning about chronic diseases. These results may create an awareness for the conscious use of ChatGPT or large language models in internal medicine courses and other systemic disease courses.

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**Table 3.** Comparison of DKSA scale scores of intervention and control groups

Groups	DKSA sub-dimension					DKSA Total Score
	General Knowledge About Diabetes Mean ± SD	Blood Glucose Measurement Dimension Mean ± SD	Diabetes Risk Factors Mean ± SD	Symptoms of Diabetes Mean ± SD	Diabetes Complications Mean ± SD	
Intervention (ChatGPT group)	3.62 ± 0.62	4.35 ± 0.94	3.37 ± 0.77	7.30 ± 1.08	4.66 ± 0.80	23.32 ± 2.62
Control Group	3.42 ± 0.82	4.07 ± 0.98	2.80 ± 0.86	6.80 ± 1.65	4.31 ± 1.07	21.4 ± 3.08
Within-group p-value	0.165	0.103	0.000*	0.002*	0.006	0.003*

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# Global Research Trends on Sleep Quality in Chronic Kidney Disease: A Comprehensive Bibliometric and SWOT Analysis

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## ABSTRACT

**Background:** Sleep disturbances are increasingly recognized as clinically significant complications across all stages of chronic kidney disease (CKD), yet the global research landscape remains heterogeneous and insufficiently mapped. This study provides a comprehensive bibliometric and SWOT analysis to evaluate worldwide research trends, thematic structures, and strategic gaps in the literature on sleep quality in CKD.

**Materials and Methods:** A bibliometric search of the Web of Science Core Collection (1 January 2020–10 February 2023) identified 149 publications addressing sleep quality in CKD. VOSviewer was used to visualize keyword co-occurrence patterns, authorship and country collaboration networks, and thematic clusters. Temporal publication trends were assessed through linear regression. A SWOT framework was applied to contextualize strengths, weaknesses, opportunities, and threats within the research field.

**Results:** Four major clusters were identified: hemodialysis–psychosocial burden, chronic renal failure–sleep quality, pre-dialysis sleep disorders, and estimated glomerular filtration rate–sleep disturbance. Hemodialysis-centered research formed the densest and most cited cluster, whereas early-stage CKD and objective sleep assessments (e.g., polysomnography, actigraphy) were notably underrepresented. Country-level mapping revealed substantial geographic variability, with China, the United States, and Türkiye leading in output, while Canada, Italy, and Sweden demonstrated high collaboration strength. Forecasting models showed a sustained upward trajectory in global publication volume through 2030. SWOT analysis highlighted a well-established but unevenly distributed research base, methodological variability, and clear opportunities for standardized, longitudinal, and mechanistic studies.

**Conclusion:** Global research activity on sleep quality in CKD is expanding, yet critical gaps persist—particularly in early CKD populations, objective sleep measurement, and multi-national collaboration. Addressing these limitations will be essential for developing robust evidence frameworks and improving clinical management of sleep disturbances across the CKD continuum.

**Keywords:** Chronic kidney disease, sleep quality, hemodialysis, bibliometric analysis, SWOT analysis

## Introduction

Chronic kidney disease (CKD) is defined by a sustained reduction in glomerular filtration rate (GFR) or other markers of kidney damage persisting for at least three months

and represents a major global public health challenge, with prevalence estimates ranging from 8.5% to 9.8% worldwide.<sup>1-3</sup> As renal function declines, patients experience a wide spectrum of systemic complications that contribute to substantial morbidity,

mortality, and healthcare burden.<sup>2,3</sup> Among these complications, sleep disturbances have emerged as highly prevalent yet frequently underrecognized contributors to impaired quality of life and adverse clinical outcomes in the CKD population.<sup>4-7</sup>

Sleep disorders occur across all stages of CKD, including the early phases of kidney dysfunction where objective polysomnographic studies have demonstrated reduced sleep efficiency, increased periodic limb movements, and a higher use of hypnotic agents compared with individuals with normal renal function.<sup>6,8,9</sup> In end-stage renal disease (ESRD), the burden is even greater: between 45% and 80% of hemodialysis patients report clinically significant sleep problems, including insomnia, restless legs syndrome (RLS), sleep-disordered breathing, nocturnal pruritus, and fragmented sleep architecture.<sup>4,10,11</sup> These disturbances are closely interrelated with CKD-specific symptoms such as fatigue, depression, pain, and pruritus—each independently associated with impaired sleep quality and diminished health-related quality of life.<sup>5,11-16</sup> Moreover, sleep abnormalities may influence CKD pathophysiology through mechanisms involving inflammation, sympathetic activation, metabolic dysregulation, and circadian disruption, potentially accelerating disease progression and elevating cardiovascular risk.<sup>7,10,17</sup>

Dialysis modality also plays a significant role in sleep outcomes.<sup>10,18</sup> While conventional hemodialysis is strongly associated with sleep fragmentation, periodic limb movements, and reduced sleep efficiency, peritoneal dialysis may promote better sleep quality in selected populations, and kidney transplantation appears to partially restore sleep parameters, although sleep disorders remain more common than in the general population.<sup>4,10,15,18</sup> Intensive hemodialysis schedules and targeted therapies, including recombinant human erythropoietin and difelikefalin, have demonstrated improvements in sleep-related parameters in randomized and observational studies, yet the overall evidence base for sleep-focused interventions remains limited, heterogeneous, and frequently of low certainty.<sup>19-22</sup> This underscores the need for more rigorous, standardized research aimed at understanding and managing sleep disturbances in CKD.

Despite the clinical importance of sleep disturbances in CKD, research in this area remains fragmented, variably distributed across countries, and lacking in methodological consistency—particularly with respect to objective sleep assessment tools, intervention trials, and longitudinal outcomes.<sup>22</sup> Bibliometric analysis provides a valuable approach for mapping the scientific landscape, identifying research clusters, quantifying

scholarly influence, and highlighting gaps in knowledge.<sup>23,24</sup> When integrated with a SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis, bibliometric mapping enables a strategic evaluation of the field, offering deeper insight into existing evidence, unmet needs, and future directions.

Accordingly, the present study aims to conduct a comprehensive global bibliometric assessment of the literature on sleep quality in chronic kidney disease and to complement these findings with a SWOT analysis. This combined approach seeks to delineate research trends, synthesize thematic patterns, and identify both the opportunities and challenges that shape this evolving domain.

### Materials and Methods

A bibliometric search was conducted in the Web of Science (WoS) Core Collection database on 10 February 2023. The search strategy used the terms “Sleep Quality” AND “Kidney” in the Topics Search, without applying language or document-type restrictions. Publications indexed between 1 January 2020 and 10 February 2023 were included. All retrieved records were exported in full-record and cited-reference format. Quantitative indicators such as annual publication counts, citation numbers, and the distribution of publications across authors, institutions, and countries were examined to characterize the research activity in this field.

Bibliometric maps were generated using VOSviewer software (version 1.6.17; Centre for Science and Technology Studies, Leiden University). VOSviewer was used to visualize keyword co-occurrence patterns, authorship networks, citation relationships, and thematic clusters. The association strength normalization method was applied for all network visualizations. Default thresholds for keyword frequencies and citation counts were used unless otherwise specified.

### Statistical Analysis

Statistical analyses focused on evaluating temporal trends in publication output between 2020 and 2023. Annual publication counts were summarized descriptively and assessed using simple linear regression to examine whether research activity demonstrated a statistically significant upward or downward trend over time. Model assumptions, including linearity and homoscedasticity, were verified using standard diagnostic plots. All statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). A two-sided  $p$ -value  $< 0.05$  was considered statistically significant. No imputation or additional adjustments were required, as bibliometric metadata were complete for the variables analyzed.

**Results**

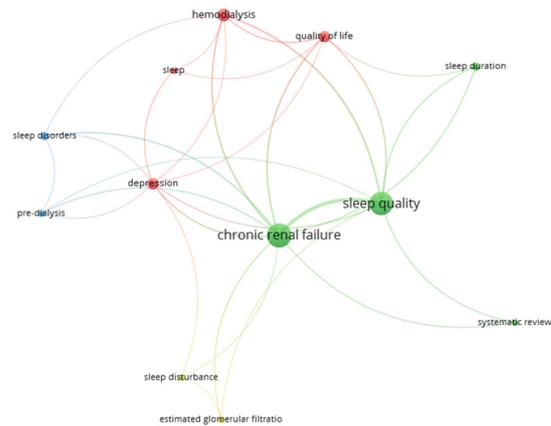
*Keyword and Cluster Analysis*

A total of 149 publications indexed between 2020 and 2023 were analyzed to characterize global research activity on sleep quality in the context of chronic kidney disease. Analysis of the keyword co-occurrence network demonstrated that the most frequently used and highly connected concepts in the literature were “sleep quality” (occurrence: 33; total link strength: 118), “hemodialysis” (23; 102), “chronic kidney disease” (22; 93), “depression” (17; 66), and “quality of life” (16; 71). These keywords formed the structural core of the research field, with “chronic kidney disease” and “sleep quality” emerging as the central nodes of the bibliometric map, reflecting their dominant conceptual influence (Figure 1). In the co-occurrence map, the term chronic renal failure appears as the central node; however, this reflects a controlled vocabulary adjustment applied through the VOSviewer thesaurus file, in which all related expressions (including ‘CKD’ and ‘chronic kidney disease’) were standardized under a single unified label to ensure terminological consistency across the dataset. Additional frequently occurring terms included “sleep” (13; 58), and “sleep disturbance” (6; 20).

The first cluster encompassed terms predominantly related to hemodialysis and psychosocial dimensions of CKD, including hemodialysis, depression, quality of life, and sleep. The relatively high link strengths of hemodialysis (102) and quality of life (71) highlight the density of research addressing sleep-related symptoms among hemodialysis patients, as well as their psychosocial correlates. The second cluster represented the conceptual foundation of CKD–sleep research, linking chronic renal failure with sleep quality, sleep duration, and systematic reviews; this grouping reflects a core research domain centered on the clinical and physiological dimensions of sleep disturbances in CKD. The third cluster included pre-dialysis and sleep disorders, indicating that sleep disturbances have been studied not only in advanced disease but also in earlier stages of renal impairment. The fourth and smallest cluster contained estimated glomerular filtration rate and sleep disturbance, suggesting an emerging line of inquiry examining the relationship between objective renal function markers and specific sleep parameters.

Across the network, frequent co-linkage between hemodialysis and quality of life was apparent through visibly stronger and thicker connecting lines, consistent with their high co-occurrence metrics. Depression exhibited multiple connections with both sleep and sleep disorders, reflecting its recurring presence across clusters. Spatial proximity within the

map corroborated these patterns, illustrating the interconnected nature of psychological, clinical, and treatment-related factors in CKD-related sleep research (Figure 1).



**Figure 1.** Keyword Co-occurrence Network Map of Publications on Sleep Quality and Chronic Kidney Disease

*Country-Level Productivity and Collaboration*

A total of 44 countries contributed to the global literature during the study period, with 18 countries producing four or more publications (Table 1). The collaboration network demonstrated extensive international engagement, with China, Türkiye, and the United States functioning as major hubs exhibiting broad cross-national linkages (Figure 2a). Density visualization further highlighted the United States and Canada as the most concentrated centers of activity, reflecting their combined strength in publication output and citation influence (Figure 2b).

**Table 1.** Productivity and Citation Metrics of the Most Active Countries

Country	Publication Count	Total Citations	Total Link Strength
China	13	45	5
USA	12	265	18
Türkiye	11	70	12
Canada	8	235	10
Italy	7	50	21
Sweden	6	40	21
Brazil	5	82	8
Iran	4	30	3

China ranked first in publication volume (n=13), followed closely by the United States (n=12) and Türkiye (n=11). Canada produced fewer publications (n=8) but displayed a disproportionately high citation count (235 citations), nearly matching that of the United States (265 citations), indicating substantial scientific influence relative to output. Italy and Sweden demonstrated the highest total link strengths (both 21), suggesting robust international collaboration and strong inte-

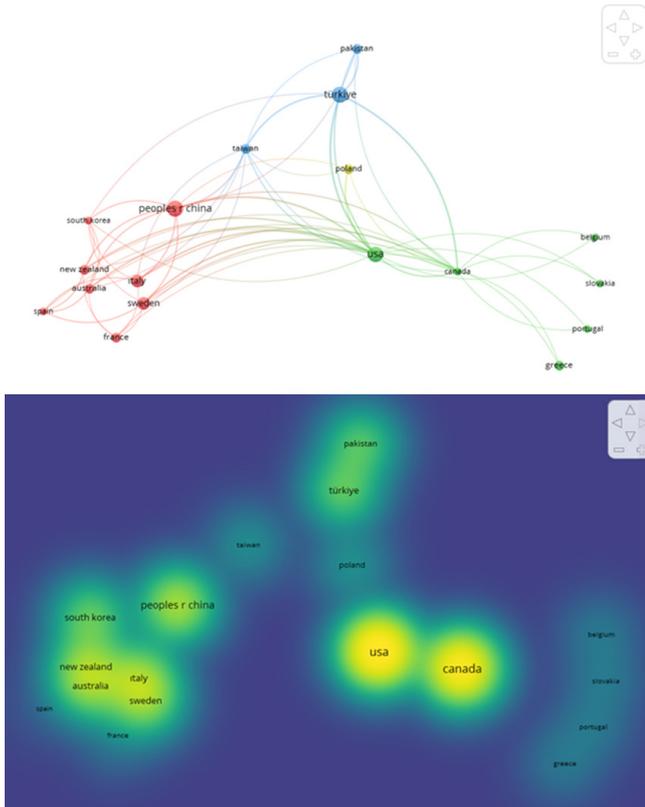


Figure 2. International Collaboration Network and Citation Density Mapping of Countries Contributing to Research on Sleep Quality and Chronic Kidney Disease

gration within the global research network despite producing comparatively fewer publications.

The structural topology of the collaboration map positioned the United States as the primary global connector, with prominent ties to Canada, Türkiye, and several European nations. China formed a dense subnetwork characterized by collaborations with East Asian and Southern European countries, including South Korea, Italy, and Sweden. Türkiye occupied an important intermediary position, acting as a bridge between regions through its linkages with Pakistan, Taiwan, and Poland. This arrangement highlights a globally distributed yet interconnected research environment, characterized by both regional clusters and influential central hubs.

*Global Publication Trends and Future Forecast*

The temporal analysis of global research output demonstrated a consistent upward trajectory in publications addressing sleep quality in the context of chronic kidney disease. Annual publication counts increased steadily from 27–34 articles in 2017–2019 to 38 in 2020, followed by continued growth through 2021 (51), 2022 (46), and 2023 (55). Forecasting based on exponential and cubic models indicated further expansion of scientific activity in the upcoming years, with projected counts of 65 publications in 2024 and 67 in 2025. The model estimated 103 publications for 2026 (95% CI: 42.7–248.9) and

a substantial rise to 202 publications by 2030 (95% CI: 81.4–505.7), suggesting an accelerating research trend with wide confidence bounds reflecting increasing uncertainty over extended forecasting intervals. Collectively, these findings indicate that the scientific attention directed toward CKD-related sleep disturbances is not only sustained but expected to intensify, with a marked expansion in global research productivity over the coming decade (Figure 3).

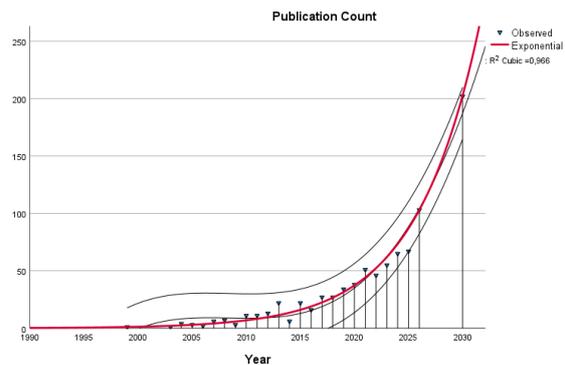


Figure 3. Global publication trends on sleep quality and chronic kidney disease (2010–2030), including observed annual outputs (2010–2023) and model-based forecasts with 95% confidence intervals (2024–2030).

**Discussion**

This bibliometric analysis provides a comprehensive overview of global research trends examining sleep quality in the context of chronic kidney disease. The findings highlight that interest in the interplay between CKD and sleep disturbances has grown steadily in recent years, reflecting increasing recognition of sleep quality as a clinically significant yet frequently overlooked dimension of CKD care. The predominance of the keywords “chronic renal failure” and “sleep quality” at the center of the co-occurrence network underscores the central role of sleep-related outcomes within nephrology research, particularly regarding their influence on physical and psychological well-being.

*SWOT Analysis*

The SWOT assessment provided a structured overview of the current research landscape concerning sleep quality in individuals with chronic kidney disease (Table 2).

*Strengths*

The field demonstrates a mature and well-established research core supported by substantial bibliometric density. Across 149 publications from 44 countries, high-frequency keywords such as sleep quality (33 occurrences; total link strength 118), hemodialysis (23; TLS 102), chronic kidney disease (22; TLS 93), and depression (17; TLS 66) dominate the conceptual landscape, indicating consistent scientific engagement with these

themes. The clustering structure further shows that research involving hemodialysis patients constitutes the largest and densest thematic group, benefitting from abundant citation linkages and strong inter-keyword connectivity. Countries with the highest research output include China (n=13), the United States (n=12), and Türkiye (n=11), while the United States (265 citations) and Canada (235 citations) show the strongest global citation impact. These metrics collectively demonstrate both the breadth and depth of existing literature, confirming sleep quality as an increasingly recognized and clinically relevant dimension of CKD research.

#### Weaknesses

Despite the overall richness of the dataset, several measurable gaps persist. Keywords associated with early-stage CKD—such as pre-dialysis and sleep disorders—appear infrequently and show comparatively lower total link strength, indicating limited focus on these populations. Only 18 of the 44 contributing countries produced four or more publications, suggesting that global research activity remains unevenly distributed. The presence of smaller, low-connectivity clusters (e.g., eGFR and sleep disturbance) reflects insufficient integration of objective renal markers or standardized sleep assessment methods. The dominance of subjective terms such as sleep quality, fatigue, and mental health, combined with the absence of high-frequency objective sleep terms (e.g., polysomnography, actigraphy), implies limited use of validated quantitative tools across the dataset. Together, these patterns highlight restricted methodological diversity, insufficient coverage of pre-dialysis populations, and a likely predominance of small, cross-sectional studies.

#### Opportunities

Emerging bibliometric patterns suggest clear prospects for scientific advancement. The presence of terms such as systematic review, sleep duration, and restless legs syndrome

with moderate frequencies (9–13 occurrences) indicates expanding thematic directions, particularly toward integrative symptom clusters and long-term physiological outcomes. The temporal distribution of the dataset (2020–2023) reflects consistent annual publication activity, implying continuing academic interest. Countries such as Italy and Sweden, despite having moderate publication counts (n=7 and n=6), demonstrate high total link strength (both 21), positioning them as structurally influential collaborators and indicating readiness for multinational cohort studies. The growing density of connections between sleep-related keywords (sleep quality, sleep duration, sleep disturbance) and CKD-related constructs (eGFR, chronic renal failure, quality of life) suggests opportunities for refined mechanistic research addressing cardiovascular risk, mortality, inflammation, and patient-centered outcomes. The current bibliometric landscape therefore supports the development of standardized longitudinal research frameworks and multicenter trials.

#### Threats

Several identifiable challenges pose potential barriers to future progress. The dispersion of sleep-related terminology across multiple small clusters, combined with uneven co-occurrence patterns, reflects substantial methodological heterogeneity within the field. The lack of high-frequency objective sleep keywords indicates that most studies rely on subjective instruments such as the Pittsburgh Sleep Quality Index, suggesting limited comparability across publications. Furthermore, the uneven geographic distribution of research—with only a minority of countries contributing more than four publications—may reduce the generalizability of findings and exacerbate population-level biases. The tight linkage of sleep-related keywords with multifactorial constructs such as depression, quality of life, and fatigue highlights the complexity of establishing causality in a domain heavily influenced by psychological, social, and treatment-related factors. These

Table 2. SWOT Analysis Table

Category	Summary of Key Findings
<b>Strengths</b>	A substantial and internationally distributed body of literature (149 publications from 44 countries) centers on strong conceptual anchors such as sleep quality, hemodialysis, and chronic kidney disease. Hemodialysis-related sleep research forms the densest and most methodologically developed cluster, supported by high citation activity from leading contributors (e.g., United States: 265 Canada: 235 citations).
<b>Weaknesses</b>	Early-stage CKD and pre-dialysis populations remain underrepresented, reflected by low-frequency, low-link-strength keywords and small peripheral clusters. Objective sleep assessments are rarely used, with minimal representation of polysomnography or actigraphy. Methodological variation across studies and inconsistent use of standardized tools limit cross-study comparability and hinder synthesis.
<b>Opportunities</b>	Expanding themes such as sleep duration, restless legs syndrome, and integrative symptom clusters indicate growing diversification. Strong collaborative potential exists in countries with high link strength but modest publication output (e.g., Italy and Sweden). Increasing annual publication activity (2020–2023) supports feasibility for future multicenter cohort studies and deeper exploration of cardiovascular, inflammatory, and mortality-related pathways.
<b>Threats</b>	Heterogeneous terminology, inconsistent assessment methods, and reliance on subjective tools create structural barriers to standardization. Uneven geographic distribution may introduce population biases. The multifactorial nature of sleep disturbances in CKD—spanning psychological, physiological, and treatment-related domains—complicates causal inference and risks fragmentation of future research trajectories.

structural constraints may impede the development of standardized outcome measures and complicate attempts to synthesize data across diverse study designs.

#### *Overview of Bibliometric Trends*

The clustering patterns observed in this study reveal distinct thematic research domains. The first cluster, which encompasses hemodialysis, depression, quality of life, and sleep, aligns with established evidence suggesting that hemodialysis patients exhibit some of the highest rates of sleep disruption among individuals with CKD.<sup>4,10,18</sup> This may be attributed to the cumulative burden of uremic toxins, metabolic derangements, fluid shifts, and treatment-related stress, all of which adversely affect sleep architecture.<sup>4,10</sup> The strong association between “hemodialysis” and “quality of life” within the network further reinforces the multidimensional impact of sleep problems in this population. Poor sleep quality has been linked to increased fatigue, diminished treatment adherence, and impaired psychosocial functioning, thereby contributing to the already complex morbidity profile of ESRD patients.<sup>5,11,13,14</sup>

The second and largest cluster, dominated by chronic renal failure and sleep quality, reflects the foundational research direction aimed at characterizing the extent and nature of sleep disturbances across CKD stages.<sup>5-7,9,17</sup> Notably, the presence of “systematic review” within this cluster suggests that synthesizing and consolidating evidence on sleep disorders in CKD has become an emerging priority. This indicates a maturing research field that is advancing beyond isolated observational studies toward broader theoretical and clinical frameworks.

The third cluster, comprising pre-dialysis and sleep disorders, highlights an important but understudied area: sleep disruption in earlier CKD stages. Although this study shows that these concepts are linked, the relatively limited number of publications in this domain suggests that early identification and management of sleep problems remain insufficiently addressed.<sup>4,6-9</sup> This represents a clinically meaningful gap, as sleep disturbances may precede overt renal deterioration and contribute to downstream neurocognitive, cardiovascular, and metabolic complications.

The fourth cluster links estimated glomerular filtration rate with sleep disturbance, reflecting a growing interest in integrating objective renal function indices with sleep-related outcomes. While preliminary research has demonstrated associations between lower GFR and poorer sleep metrics, these relationships are complex and may be influenced by inflammatory pathways, autonomic dysfunction, and comorbidities such as diabetes or heart failure.<sup>6,8,9,25</sup> The scarcity of studies in this domain underscores the need for methodologically rigor-

ous investigations using standardized sleep assessment tools, including actigraphy and polysomnography.

#### *Global Collaboration Patterns*

The country-level analysis reveals substantial geographical variability in research productivity and citation impact. The United States and Canada distinguish themselves with high citation counts, indicating strong international visibility and influence. In contrast, China and Türkiye demonstrate high publication output but lower collaboration strength, suggesting that expanding international partnerships may enhance global integration and research impact. European countries such as Italy and Sweden exhibit high connection strength despite modest publication volume, reflecting strong engagement in collaborative, multinational research networks. These patterns collectively point to a research landscape that is expanding but remains unevenly distributed across regions.

#### *Methodological Gaps and Limitations in the Literature*

This study also identifies notable gaps within the existing literature. Research examining the interaction between sleep quality and psychological parameters such as depression appears limited, despite evidence that depressive symptoms are highly prevalent in CKD and intricately linked with sleep physiology.<sup>5,13,15,16</sup> Additionally, the variability in renal replacement therapy modalities and their differential effects on sleep appear to be acknowledged but not comprehensively explored.<sup>10,18,21</sup> The relative scarcity of longitudinal or intervention-based studies further restricts the ability to establish temporal or causal relationships between declining kidney function and sleep impairment.<sup>22</sup>

Sleep disturbances in pre-dialysis CKD may represent an early, modifiable risk marker for adverse cardiovascular and metabolic outcomes. Identifying and managing sleep disorders at earlier disease stages could offer opportunities to mitigate symptom burden, delay disease progression, and improve long-term quality of life before irreversible renal decline occurs. The relative scarcity of research in this population therefore represents not only a bibliometric gap but also a clinically meaningful limitation in current nephrology practice.

The incorporation of SWOT analysis offers additional insight into the structural characteristics of this research field. Strengths include a solid body of evidence focusing on hemodialysis patients and increasing recognition of sleep quality as a vital component of CKD management. However, weaknesses such as small sample sizes, limited research in pre-dialysis populations, and inconsistent sleep assessment methods hinder the development of unified clinical guidelines. Opportuni-

ties exist for research exploring mechanistic pathways linking sleep quality to cardiovascular outcomes, inflammation, and mortality—areas with significant potential for advancing patient care. Conversely, threats include the multifactorial nature of sleep disturbances, which complicates causal inference, and the lack of standardized, objective sleep measurement tools specific to CKD populations.

Overall, this bibliometric analysis demonstrates that sleep quality has emerged as an important research focus in nephrology, yet several key areas remain underdeveloped. Expanding collaborative networks, enhancing methodological rigor, incorporating objective sleep assessments, and prioritizing understudied patient groups such as pre-dialysis populations will be critical for advancing the field. Addressing these gaps may ultimately contribute to a more nuanced understanding of sleep disturbances throughout the CKD continuum and inform targeted interventions aimed at improving patient outcomes.

### Conclusion

This bibliometric analysis highlights sleep quality as an increasingly recognized yet still underdeveloped research domain within chronic kidney disease. While hemodialysis populations have been the primary focus of existing studies, thematic clustering reveals that sleep disturbances affect patients across all stages of CKD and intersect with psychological well-being, quality of life, and objective markers of renal function. Despite growing global interest, significant gaps persist, particularly regarding pre-dialysis populations, the use of standardized and objective sleep assessments, and the elucidation of mechanistic links between renal dysfunction and sleep impairment. The observed disparities in research productivity and collaboration further underscore the need for broader international engagement and methodologically robust, longitudinal investigations. Advancing research in this field has the potential to inform targeted interventions and ultimately improve clinical outcomes for individuals living with CKD.

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# Endoscopic Vacuum Therapy in Boerhaave Syndrome: A Contemporary Narrative Review

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## ABSTRACT

Boerhaave syndrome remains a life-threatening condition due to rapid mediastinal contamination and sepsis, prompting growing interest in minimally invasive alternatives to surgery. Alongside surgery and endoscopic stenting, endoscopic vacuum therapy (EVT) has emerged over the past decade as an organ-preserving treatment option that combines defect closure with continuous internal drainage—an advantage over conventional stents, which often migrate and fail to control underlying contamination. This narrative review synthesizes current evidence on the role of EVT and hybrid vacuum–stent technologies in the management of spontaneous esophageal rupture. Across recent multicenter cohorts, observational studies, and case series, EVT demonstrates high defect closure rates (80–90%), particularly when applied early in contained perforations and in patients at increased operative risk. Comparative data suggest that, while stents provide effective luminal sealing, EVT offers a distinct advantage in controlling sepsis through active drainage, thereby reducing the need for adjunctive interventions in selected cases. Hybrid systems such as the VACStent further integrate luminal patency, sealing, and negative pressure, allowing nutritional intake while maintaining effective drainage. However, the available evidence remains heterogeneous and largely non-randomized, and EVT appears less effective in the presence of extensive contamination, large chronic cavities, or advanced sepsis. Current data support EVT as a central component of individualized, multimodal management strategies for Boerhaave syndrome, complementing rather than replacing surgical and stent-based approaches. Further prospective and comparative studies are required to refine patient selection and optimize treatment algorithms..

**Keywords:** Boerhaave syndrome, Esophageal perforation, Endoscopic vacuum therapy, Negative pressure therapy, Minimally invasive therapy

## Introduction

Boerhaave syndrome represents the most severe form of esophageal perforation, characterized by a spontaneous, full-thickness rupture often precipitated by sudden intraluminal pressure changes.<sup>1,2</sup> Mortality remains high, particularly when diagnosis is delayed beyond 24 hours, due to rapid contamination of the mediastinum and pleural cavity and subsequent sepsis.<sup>3,4</sup> Historically, management has relied on surgical repair with extensive drainage or endoscopic stenting.<sup>2,4</sup> While covered stents seal the luminal defect, they lack the ability to drain infected cavities

and are prone to migration, leading to persistent leakage or the need for repeated interventions.<sup>3,5</sup>

Endoscopic vacuum therapy (EVT) has emerged as a minimally invasive alternative capable of simultaneously promoting defect closure and active drainage.<sup>2,6,7</sup> EVT adapts negative pressure wound therapy to the intraluminal or intracavitary setting, encouraging granulation tissue formation, reducing cavity size, and evacuating contaminated fluids.<sup>7,8</sup> A polyurethane sponge is connected to a transnasal tube linked to a vacuum system and positioned either within the esoph-

ageal lumen (endoluminal EVT) or directly inside a cavity (intracavitary EVT).<sup>9,10</sup> Continuous negative pressure—typically around  $-125$  mmHg—collapses the defect, drains infected fluid, reduces local edema, improves perfusion, and promotes granulation tissue formation.<sup>6,7</sup> Sponges are generally exchanged every 3–5 days; some centers perform weekly exchanges in select cases.<sup>9–11</sup>

Both custom-made and commercially available EVT systems such as the EsoSPONGE®, are currently in use.<sup>9,12</sup> More recently, hybrid platforms including the vacuum-assisted covered stent (VACStent) have been developed, integrating negative pressure therapy with luminal sealing and self-expanding stent-based anchoring.<sup>13–15</sup> These allow ongoing drainage through a sponge-cylinder interface while maintaining luminal patency, a unique advantage over conventional EVT that often precludes oral intake.<sup>14</sup>

Over the last decade—and especially from 2018 onward—evidence has accumulated supporting EVT and hybrid EVT–stent technologies such as the VACStent in the management of esophageal perforations, including Boerhaave syndrome.<sup>9,11,15,16</sup> This focused review synthesizes current evidence for these modalities, emphasizing patient selection, comparative outcomes, and their role within modern management algorithms.

**Review**

*Literature Search Strategy*

A narrative literature search was conducted using the Web of Science database without time restrictions. English-language publications addressing endoscopic vacuum therapy in the management of esophageal perforations, including Boerhaave syndrome, were identified using relevant keywords. Titles and abstracts were screened for relevance, and full texts were reviewed when appropriate. Studies were selected based on their clinical relevance and contribution to understanding the indications, outcomes, technical aspects, and limitations of EVT.

*Evidence for EVT in Boerhaave Syndrome*

The most robust data originate from a multicenter German study by Wannhoff et al., which included 57 patients with Boerhaave syndrome.<sup>17</sup> EVT was used as the primary therapy in 25 patients and achieved an 80% success rate.<sup>17</sup> Mortality in the EVT group (8%) was lower than in the non-EVT group (25%), and primary EVT independently predicted treatment success in multivariable analysis.<sup>17</sup> These findings suggest that EVT not only is feasible but may be superior to stenting or primary surgery in selected cases.<sup>17</sup>

Luttikhould et al. reported on 27 patients with esophageal perforations—including iatrogenic and Boerhaave causes—treated with EVT across five European centers.<sup>16</sup> The overall success rate was 89%, with failures primarily related to underlying critical illness rather than technical EVT inadequacy.<sup>16</sup> Adverse events were infrequent but included hemorrhage and defect expansion during sponge exchange.<sup>16</sup>

In a 17-patient Norwegian series of Anundsen et al., Boerhaave syndrome was managed with stents, EVT, or a combination.<sup>5</sup> Despite a high rate of complications (88%), healing occurred in all survivors, and the 90-day mortality was only 6%.<sup>5</sup> These results support EVT’s value in multimodal management strategies.

A UK case series reported successful EVT outcomes in three surgically unfit Boerhaave patients, reinforcing its applicability in high-risk populations.<sup>10</sup> Earlier British experience demonstrated complete resolution of leakage in two frail patients, highlighting EVT’s usefulness in elderly or comorbid patients.<sup>12</sup>

Collectively, these studies demonstrate that EVT provides closure rates of approximately 80–90% and may reduce mortality compared with traditional management (Table 1).<sup>6,10,16,17</sup> Treatment duration ranges from 12 to 28 days, with the need for multiple endoscopies typical of the technique.<sup>6,9,16</sup>

*Comparative Evidence: EVT Versus Stenting*

Endoscopic stenting has long been a mainstay of less invasive therapy; however, its limitations—migration, inadequate drainage, and residual leaks—are well documented.<sup>3–5</sup> A 2025 systematic review and meta-analysis found an 86.1% pooled sealing rate for stents in esophageal defects and a 14.9% failure rate.<sup>18</sup> EVT demonstrated a pooled sealing rate of 54.1% with high heterogeneity, but sensitivity analyses yielded an improved closure rate of 89.6%.<sup>18</sup> These findings indicate that, when performed in appropriate settings and patient subsets, EVT achieves closure rates comparable to or exceeding those of stents.<sup>6,18</sup>

The tertiary-center experience from Kooij et al. emphasizes that stents often require additional surgical or percutaneous drainage and that delayed diagnosis significantly worsens outcomes.<sup>3</sup> In their cohort, stent management alone frequently required escalation to drainage procedures.<sup>3</sup> In contrast, EVT intrinsically provides drainage, potentially reducing the need for adjunct operations.<sup>6,9</sup>

Thus, EVT and stents should not be viewed as competing therapies; rather, choice depends on perforation characteristics,

**Table 1.** Key studies evaluating endoscopic vacuum therapy (EVT) in Boerhaave syndrome

Study (Year)	Study Design	Patients (Boerhaave)	EVT Role	Success / Closure Rate	Mortality	Key Notes
Wannhoff et al. (2025)	Multicenter retrospective	57 (25 EVT primary)	Primary EVT	80%	8% (EVT group)	EVT independently predicted treatment success
Luttikhould et al. (2023)	Multicenter retrospective	27 (mixed etiologies)	Primary EVT	89%	Not reported	Failures related to critical illness
Anundsen et al. (2024)	Retrospective cohort	17	EVT / stent / combined	Healing in all survivors	6% (90-day)	High complication rate, effective multimodal care
Soussi et al. (2024)	Case series	3	Primary EVT	100%	0%	Surgically unfit patients
Alakkari et al. (2019)	Case series	2 (Boerhaave and anastomotic leak)	Primary EVT	100%	0%	Frail, elderly patients

degree of contamination, and patient stability. EVT excels when drainage is critical, whereas stents may be favored when rapid luminal sealing and oral intake are prioritized—unless hybrid technologies are available.<sup>2,7,19</sup>

*Hybrid EVT–Stent Technologies: The Rise of the VACStent*

Hybrid devices aim to combine the sealing effect of covered stents with the drainage and healing advantages of EVT. The VACStent is the most widely reported system.<sup>13-15</sup>

A systematic review by Kehagias et al. identified 65 patients treated with VACStent, including 10% with Boerhaave syndrome.<sup>13</sup> Technical success was 100% and clinical success 77%, with a mean treatment duration of 8.8 days.<sup>13</sup> Notably, most patients tolerated liquid intake during therapy, an advantage over traditional EVT.<sup>13</sup>

Initial evaluations of Lange et al. showed that the VACStent can overcome stent migration through vacuum anchoring while facilitating defect healing.<sup>14</sup> Early monocentric experiences of another center reported successful outcomes in three patients, including one with Boerhaave syndrome, with exchanges required approximately every seven days.<sup>11</sup>

In a prospective case series by Pattynama et al., all ten treated patients (including one Boerhaave case) achieved defect closure, with median treatment lasting 18 days.<sup>15</sup> Similarly, Ylli et al. reported successful closure in four patients in 2025—two with Boerhaave syndrome—without procedural complications.<sup>20</sup>

These reports suggest that VACStent may reduce the number of required interventions, improve patient comfort, and permit continued nutrition while delivering effective drainage.<sup>11,13-15</sup> Although evidence remains early-phase and observational, hybrid EVT–stent technologies represent an important evolution in minimally invasive management (Table 2).

*Patient Selection and Indications for EVT in Boerhaave Syndrome*

Successful application of endoscopic vacuum therapy in Boerhaave syndrome hinges on meticulous patient selection and accurate characterization of the perforation.<sup>1,2,4</sup> Across the published series, outcomes are most favorable when EVT is initiated early—ideally within the first 24 hours after symptom onset—at a stage when mediastinal contamination remains

limited and the defect is amenable to endoscopic access.<sup>3,4,21</sup> Early-diagnosed patients tend to exhibit a contained transmural perforation or a discrete cavity that allows effective sponge placement and continuous drainage.<sup>2,10</sup> These anatomical conditions, combined with an intact hemodynamic profile, create an environment in which EVT can facilitate rapid collapse of the defect and control of the septic focus.<sup>6,7,19</sup>

EVT has demonstrated particular value in individuals who are poor candidates for major surgery.<sup>5,10,12</sup> Elderly, frail patients or those with severe comorbidities—groups represented in several case series from the United Kingdom and Europe—often derive significant benefit from this organ-preserving approach when conventional surgical repair carries prohibitive risk.<sup>5,10,12</sup> EVT is additionally advantageous when stent therapy is anticipated to be suboptimal, such as in situations with a high risk of stent migration or where sealing alone is unlikely to address the underlying sepsis due to persistent mediastinal contamination.<sup>3,5,10</sup>

Conversely, EVT proves less effective in the presence of extensive or uncontrolled contamination.<sup>4,21</sup> Patients with free perforation and gross mediastinal or pleural soilage frequently require prompt operative intervention to achieve adequate debridement and drainage before any endoscopic modality can be considered.<sup>4,21</sup> Very large or chronic cavities—typically greater than 8 cm, as noted in the early series from Ooi and colleagues—tend to respond poorly because negative pressure is insufficient to collapse the space, and sponge anchoring becomes unstable.<sup>7,19</sup> Extensive necrosis and the presence of devitalized tissue further undermine the likelihood of successful healing with EVT alone.<sup>4,21</sup> In the setting of profound hemodynamic instability or evolving multi-organ failure, immediate surgical source control remains the standard of care, with EVT reserved for later adjunctive management once physiological stability is restored.<sup>4,10,21</sup>

Across nearly all cohorts, the consistent determinant of clinical success is the adequacy of drainage.<sup>6,9,10,19</sup> EVT itself provides effective internal drainage of infected cavities, but in cases where the extent of contamination exceeds the capacity of the endoscopic system, supplemental percutaneous or surgical drainage is indispensable.<sup>3,5,7</sup> The need for thorough multidisciplinary evaluation—often involving endoscopists, thoracic surgeons, intensivists, and interventional radiologists—is underscored by rare but serious complications, such as bleeding or iatrogen-

Table 2. Hybrid endoscopic vacuum–stent (VACStent) therapy for esophageal defects

Study (Year)	Study Design	Patients	Boerhaave (%)	Technical Success	Clinical Success	Treatment Duration	Key Advantage
Kehagias et al. (2025)	Systematic review	65	-10%	100%	77%	8.8 days (mean)	Maintained oral intake
Lange et al. (2021)	Prospective case series	3	1 case	100%	100%	NR	Reduced migration
Klose et al. (2023)	Monocentric case series	3	1 case	100%	100%	-7 days/ex-change	Stable anchoring
Pattynama et al. (2023)	Prospective series	10	1 case	100%	100%	18 days (median)	Combined sealing & drainage
Ylli et al. (2025)	Case series	4	2 cases	100%	100%	NR	No complications

ic perforation during device placement, highlighted in isolated reports such as that of Halliday et al.<sup>16,22</sup> These considerations reinforce that EVT is most successful when implemented within experienced centers equipped to handle the complexity and dynamic clinical evolution characteristic of Boerhaave syndrome.<sup>2,21,22</sup>

#### *Technical Considerations and Complications*

Technical execution of EVT plays a decisive role in determining clinical efficacy and minimizing complications. The choice between endoluminal and intracavitary placement is dictated by the morphology of the perforation.<sup>2,15</sup> Endoluminal sponge placement is preferred when the defect communicates openly with the esophageal lumen, allowing the sponge to apply circumferential negative pressure.<sup>2,10</sup> Intracavitary placement becomes necessary when a sizeable paraesophageal cavity is present, permitting the sponge to conform directly to the interior of the defect. Most centers employ continuous negative pressure at approximately -125 mmHg, a level shown to promote granulation and cavity collapse without excessive mucosal trauma.<sup>6</sup>

The interval between sponge exchanges typically ranges from three to five days, reflecting the balance between maintaining adequate suction efficiency and minimizing endoscopic manipulation.<sup>11</sup> In hybrid systems such as the VACStent, exchange intervals may extend to approximately seven days due to the inherent stability and luminal patency afforded by the stent-sponge configuration.<sup>11</sup> Overall treatment duration varies widely, often spanning 12 to 28 days depending on the initial severity of contamination, the size of the defect, and the patient's physiological response.<sup>6,9,16</sup> Multiple endoscopic procedures are usually required, with series reporting between three and twelve interventions over the treatment course.<sup>6,9,15</sup>

Complications associated with EVT, although relatively uncommon, warrant careful attention.<sup>16</sup> Hemorrhage may occur during sponge removal, particularly when granulation tissue has formed densely around the device.<sup>16</sup> Defect enlargement during exchange has been reported, albeit rarely, and underscores the need for gentle manipulation and appropriate device sizing.<sup>16</sup> Anastomotic or esophageal strictures can develop during follow-up, particularly after prolonged therapy, though most are amenable to endoscopic dilation.<sup>6,9,13</sup> Iatrogenic perforation during placement—described in early reports such as the case by Halliday et al.—is an uncommon but serious risk that highlights the importance of specialized training and adherence to meticulous technique.<sup>22</sup> When EVT is performed within experienced multidisciplinary teams, these adverse events are generally manageable and do not diminish the overall therapeutic efficacy of the modality.<sup>2,21,22</sup>

#### *Outcomes and Long-Term Follow-Up*

Across the published literature, EVT achieves consistently high closure rates for esophageal defects, including Boerhaave syndrome.<sup>6,9,16</sup> Reported healing rates typically range from 80% to 94%, with several multicenter studies demonstrating that EVT can obviate the need for esophagectomy or major surgical in-

tervention in the majority of cases.<sup>6,9,16,17</sup> Mortality rates reported in EVT cohorts vary between 6% and 14%.<sup>3,5</sup> Importantly, these deaths are generally attributable to the severity of the underlying septic state or comorbid illness rather than direct complications of EVT itself, reinforcing its safety profile.<sup>5,16</sup>

Beyond short-term outcomes, EVT appears to provide durable long-term results.<sup>23</sup> A prospective study by Dhayat et al. examining quality of life after upper gastrointestinal EVT demonstrated that overall GIQLI scores approximated those observed in patients who had undergone esophagectomy without anastomotic leakage.<sup>23</sup> Except for modest reductions in social function, EVT-treated patients reported comparable symptom control, emotional well-being, and physical capacity.<sup>23</sup> These findings suggest that EVT not only resolves the acute perforation effectively but does so while preserving a satisfactory long-term quality of life, underscoring its value as an organ-preserving intervention.<sup>16,17,23</sup>

#### *Integration of EVT into Contemporary Management Algorithms*

The evolving evidence base supports a nuanced, patient-specific approach to integrating EVT into the management of Boerhaave syndrome.<sup>1,2,21</sup> In early-diagnosed cases, particularly when the perforation is contained and the degree of mediastinal contamination is limited, EVT has emerged as a highly effective primary therapy.<sup>16,17</sup> In these settings, EVT may be used alone or in combination with percutaneous or limited surgical drainage, depending on the extent of extraesophageal contamination.<sup>4,5</sup> Hybrid devices such as the VACStent offer the additional advantage of maintaining luminal patency and enabling nutrition while simultaneously providing negative-pressure therapy, making them particularly suitable when oral intake is desirable.<sup>13,14</sup>

In patients presenting more than 24 hours after perforation, the degree of contamination is typically greater, and a combined therapeutic approach becomes more appropriate.<sup>3,4,21</sup> This may include stent placement with surgical drainage, EVT with adjunctive drainage procedures, or sequential use of stents and EVT in cases where initial strategies fail.<sup>3,14,21</sup> When contamination is significant, EVT is often favored because it provides continuous drainage—addressing a limitation of stents, which may seal the defect but leave the underlying sepsis undressed.<sup>3,6,19</sup>

Severely septic or hemodynamically unstable patients remain candidates for immediate operative intervention to achieve rapid source control.<sup>1,21</sup> EVT may then be introduced in the postoperative period to facilitate ongoing drainage and promote secondary healing of persistent defects.<sup>6,14</sup> This staged approach reflects the complexity and heterogeneity of Boerhaave syndrome and mirrors the conclusions of multicenter studies and systematic reviews emphasizing early recognition, rapid control of contamination, and individualized multimodal therapy.<sup>13,17,18</sup>

#### *Shortcomings of EVT Therapy*

Despite the encouraging clinical outcomes reported with endoscopic vacuum therapy, a balanced appraisal of the available evidence highlights several important limitations and less favorable scenarios.<sup>8,18</sup> EVT appears most effective in early-diagnosed, hemodynamically stable patients with contained perforations and limited cavity size, whereas outcomes are less favorable in the presence of extensive mediastinal or pleural contamination, large or chronic cavities, or delayed presentation—settings in which prompt surgical source control remains essential.<sup>3,4,19,21</sup> Several series have demonstrated that inappropriate reliance on endoscopic therapy may necessitate subsequent escalation to surgery, underscoring that EVT should not delay definitive operative management when sepsis is uncontrolled.<sup>3,4,21</sup> Furthermore, EVT is a resource-intensive intervention, often requiring multiple endoscopic exchanges over prolonged treatment periods and extended hospital stays.<sup>5,6,9,12,22</sup> Although generally safe, procedure-related complications such as bleeding during sponge exchange, defect enlargement, esophageal strictures, and rare iatrogenic perforation have been reported.<sup>6,9,16,22</sup> From an evidence standpoint, current data are derived predominantly from retrospective cohorts and case series, with substantial heterogeneity in patient selection, technical protocols, and outcome definitions, limiting direct comparison with surgical or stent-based strategies.<sup>8,18,24</sup> These considerations emphasize that EVT should be regarded not as a universal replacement for surgery or stenting, but as a complementary modality within a multidisciplinary, patient-specific treatment algorithm implemented in experienced centers.<sup>1-3</sup>

#### *Future Directions*

Despite notable progress, several critical knowledge gaps limit the ability to standardize EVT-based management. Foremost among these is the absence of randomized controlled trials directly comparing EVT, stenting, and hybrid modalities such as VACStent.<sup>8,13,18</sup> Current evidence, though encouraging, is derived almost exclusively from observational studies and case series, making comparative effectiveness and optimal treatment sequencing difficult to define with certainty.<sup>8,13,18</sup>

Standardization of EVT technique is another pressing need. Parameters such as negative pressure settings, optimal exchange intervals, and treatment duration vary considerably between centers and studies.<sup>11,19,24</sup> Establishing harmonized protocols could improve reproducibility, reduce complications, and facilitate multicenter trials.<sup>16,22,24</sup> Advances in patient stratification—including the identification of clinical or radiologic biomarkers predictive of EVT success—would further refine selection criteria and optimize treatment pathways.

Economic evaluations are notably lacking. Given the prolonged inpatient stays and repeat endoscopic procedures often required, determining the cost-effectiveness of EVT relative to stenting or surgery will be increasingly important as its use expands. Technological innovation remains a promising avenue, with ongoing development of smaller, more adaptable sponges, integrated monitoring systems, and devices tailored to complex anatomies. Hybrid stent–vacuum platforms such as the VACStent hold substantial potential but require larger pro-

spective studies to clarify their ideal indications, durability, and long-term safety.

#### *Limitations of the Review*

This narrative review has several inherent limitations that should be acknowledged. The available evidence on endoscopic vacuum therapy in Boerhaave syndrome is dominated by retrospective cohorts, case series, and observational studies, with a marked absence of randomized controlled trials, which restricts the strength of comparative conclusions. Considerable heterogeneity exists across the included studies with respect to patient selection, timing of intervention, defect size, extent of contamination, technical execution of EVT (endoluminal vs intracavitary), negative pressure settings, exchange intervals, and definitions of technical and clinical success, limiting direct comparability and precluding formal quantitative synthesis. In addition, reporting bias cannot be excluded, as favorable outcomes are more likely to be published, particularly in early experience and single-center reports. Many reports originate from high-volume tertiary centers with specialized endoscopic and surgical expertise. Outcomes achieved in these settings may not be reproducible in lower-volume institutions, potentially limiting external validity. Furthermore, most studies combine Boerhaave syndrome with other etiologies of esophageal perforation or anastomotic leakage, making disease-specific inferences less precise. Finally, long-term outcomes, cost-effectiveness, and standardized patient-reported measures remain inconsistently reported, underscoring the need for prospective, multicenter studies with uniform protocols to more clearly define the role of EVT and hybrid technologies within contemporary management algorithms.

#### **Conclusion**

Endoscopic vacuum therapy has rapidly evolved into a first-line, organ-preserving option for many patients with Boerhaave syndrome. Across multiple cohorts and multicenter analyses, EVT achieves high defect closure rates, provides effective sepsis control, and demonstrates favorable mortality and quality-of-life outcomes. Hybrid technologies like VACStent further expand the therapeutic armamentarium by combining sealing, drainage, and luminal patency in a single platform. While EVT is not universally applicable—particularly in patients with extensive contamination or delayed presentation—it has fundamentally shifted the minimally invasive management paradigm for spontaneous esophageal rupture. Future well-designed comparative studies will be essential to refine patient selection, standardize practice, and define the optimal role of EVT and hybrid technologies in the modern management algorithm for Boerhaave syndrome.

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# Successful Conservative Management of Emphysematous Cholecystitis in a Non-Diabetic Elderly Patient with Multiple Comorbidities

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## ABSTRACT

**Background:** Emphysematous cholecystitis (EC) is a rare, fulminant variant of acute cholecystitis caused by gas-forming organisms in the setting of gallbladder ischemia and impaired mucosal defenses. It typically affects elderly diabetic men and carries a high mortality rate, particularly when associated with *Clostridium perfringens*. Although urgent cholecystectomy is considered the standard of care, emerging evidence suggests that early-stage EC may occasionally be managed non-operatively in carefully selected high-risk patients.

**Case Presentation:** A 79-year-old non-diabetic male with coronary artery disease, prior cerebrovascular accident, acute kidney injury, and hyperlipidemia presented with right upper quadrant pain and nausea. Laboratory studies revealed leukocytosis, markedly elevated CRP, and impaired renal function. Contrast-enhanced CT demonstrated Type I emphysematous cholecystitis with intraluminal gas but no mural involvement, pericholecystic extension, gallstones, or perforation. Due to his high surgical risk, the patient was treated conservatively with IV piperacillin–tazobactam, fluid resuscitation, and close hemodynamic monitoring. On day two, he developed hypotension, oliguria, and rising inflammatory markers, prompting escalation to meropenem. Following antibiotic adjustment, he exhibited continuous clinical and biochemical improvement, with normalization of renal function and resolution of inflammatory markers. Repeat imaging confirmed complete resolution, and the patient was discharged on day ten in stable condition.

**Conclusion:** This case demonstrates that early-stage emphysematous cholecystitis may be successfully managed with antibiotics alone in non-diabetic patients with significant vascular comorbidities when prompt diagnosis, close monitoring, and appropriate antimicrobial escalation are ensured. Early CT imaging and individualized, stage-based decision-making are essential to avoid progression to gangrene, perforation, or sepsis, particularly in high-risk patients and resource-limited environments.

**Keywords:** Emphysematous cholecystitis, Acalculous cholecystitis, Conservative management, Acute cholecystitis

## Introduction

Emphysematous cholecystitis is a rare but fulminant variant of acute cholecystitis characterized by the presence of gas within the gallbladder lumen, wall, or surrounding tissues.<sup>1,2</sup> Unlike uncomplicated calculous cholecystitis, emphysematous cholecystitis arises from infection with gas-forming organisms—most commonly *Clostridium*

*perfringens*, *Escherichia coli*, *Klebsiella spp.*, or anaerobic pathogens—and is driven by a combination of gallbladder ischemia, impaired mucosal defenses, and rapid bacterial proliferation.<sup>1,3-5</sup> Although EC represents only about 1% of acute cholecystitis, mortality ranges from 15%–25%, with even higher rates in fulminant Clostridial infections.<sup>3,6,7</sup>

Classically, emphysematous cholecystitis affects elderly diabetic men with vasculopathy; however, recent reports demonstrate that the condition may occur even in the absence of diabetes when alternative mechanisms—such as diffuse atherosclerosis, immunosuppression, dehydration, or microvascular injury—compromise gallbladder perfusion.<sup>1,2,8-13</sup> Early cross-sectional imaging is critical, as emphysematous cholecystitis may initially mimic uncomplicated cholecystitis, and delayed recognition contributes significantly to its lethality.<sup>2,3,6,7</sup>

Prompt diagnosis is critical, as the condition can evolve rapidly into gangrene, perforation, retroperitoneal gas spread, or fulminant septic shock.<sup>3,8,13,14</sup> Although urgent cholecystectomy remains the standard of care, the expanding body of literature includes rare but compelling examples of successful conservative management in carefully selected patients without peritonitis, perforation, abscess, or hemodynamic instability.<sup>1,10,15,16</sup>

We report a rare case of acalculous, early-stage emphysematous cholecystitis in a non-diabetic elderly male with vascular comorbidities, managed successfully with antibiotics alone in a resource-limited rural hospital, underscoring the importance of early imaging and tailored clinical decision-making.

### Case Presentation

A 79-year-old male presented with a two-day history of acute right upper quadrant pain and nausea. His medical history was notable for coronary artery disease, a prior cerebrovascular accident, acute renal failure, and hyperlipidemia. Importantly, he had no history of diabetes mellitus—a key risk factor in most reported cases—nor any previous biliary interventions.

On presentation, he was afebrile, hemodynamically stable, and exhibited no features of systemic sepsis. Physical examination revealed localized right upper quadrant tenderness without guarding or rebound.

Laboratory investigations demonstrated leukocytosis and a markedly elevated C-reactive protein (CRP) of 269 mg/L. Liver enzymes and bilirubin were mildly elevated. Serum creatinine was increased to 1.63 mg/dL, accompanied by reduced urine output, consistent with acute kidney injury.

Contrast-enhanced abdominal CT revealed marked gallbladder wall thickening, intraluminal gas, pericholecystic heterogeneity without pericholecystic air, abscess, or perforation (Figure 1).

Given the absence of peritonitis and the patient's extremely high surgical risk profile, a conservative strategy was selected. Intravenous piperacillin–tazobactam was started, along with isotonic fluids, renal support, and close monitoring.

On hospitalization day two, the patient deteriorated with hypotension, reduced urine output, and a further increase in inflammatory markers (CRP 328 mg/L), raising concern for evolving sepsis. Due to the rural setting, blood or bile cultures could not be obtained, but antimicrobial therapy was escalated to IV meropenem, hydration was intensified, and supportive measures were reinforced. The decision was made as a case-specific



**Figure 1.** Contrast-enhanced CT of the abdomen. The arrow indicates intraluminal gas within the gallbladder, characteristic of Type I emphysematous cholecystitis, without evidence of wall disruption or perforation.

decision to cover potential resistant anaerobic or Gram-negative pathogens in a deteriorating patient.

Following the antibiotic change, the patient demonstrated continuous clinical improvement: abdominal pain subsided, urine output normalized, and inflammatory markers steadily declined. Renal function and bilirubin levels returned to baseline. Serial ultrasonography confirmed the absence of fluid collections or wall defects. Ursodeoxycholic acid was initiated to support biliary physiology and prevent biliary stasis/sludge during the recovery phase, a strategy selected based on the patient's acalculous presentation and high risk of recurrence.

By day ten, CRP had decreased to 14 mg/L, and serum creatinine normalized to 1.19 mg/dL. The patient was asymptomatic, afebrile, tolerating oral intake, and was discharged after completing the antibiotic regimen. Follow-up imaging demonstrated complete resolution of emphysematous changes.

Informed consent was obtained from the patient for hospitalization, medical treatment, and the anonymous publication of the clinical details and associated imaging for scientific purposes.

### Discussion

Emphysematous cholecystitis accounts for approximately 1% of all cases of acute cholecystitis but carries disproportionately high morbidity and mortality due to its rapid progression, vascular compromise, and the virulence of gas-forming organisms.<sup>1-3</sup> Diabetes mellitus remains the most frequently reported predisposing factor; however, the literature consistently emphasizes the contribution of generalized vascular insufficiency, atherosclerotic disease, renal dysfunction, immunosuppression, and transient hemodynamic insults such as dehydration or systemic hypoperfusion.<sup>1,4,12-14,17,18</sup> In this context, EC should be understood as the result of an ischemic–infectious cascade rather than a purely metabolic complication of diabetes.

Radiologically, EC has been categorized according to the distribution of gas within the gallbladder and surrounding structures.<sup>3,19</sup> A commonly used classification divides EC into three types; Type I as the gas is confined to the gallbladder lumen,

type II as the gas as within the gallbladder wall (intramural gas) and type III as the gas is extending into the pericholecystic tissues, biliary ducts, or adjacent spaces.<sup>3,19</sup> This classification carries both diagnostic and therapeutic implications, as Types II and III are more often associated with gangrene, perforation, abscess formation, and systemic sepsis, frequently requiring urgent surgical intervention.<sup>3,19</sup> In our case, contrast-enhanced CT demonstrated intraluminal gas without mural or pericholecystic gas, corresponding to Type I emphysematous cholecystitis. There was no evidence of gallstones, pneumobilia, perforation, or abscess, and no diffuse peritonitis on clinical examination. This early, localized stage of disease likely provided a narrow therapeutic window in which conservative management could be attempted.

Although diabetes is considered the hallmark comorbidity in EC, our patient was non-diabetic, highlighting that diabetic status is neither necessary nor sufficient for the development of this entity. Instead, he had extensive atherosclerotic cardiovascular disease, prior cerebrovascular events, and acute kidney injury, all of which suggest a global microvascular and macrovascular compromise. Ischemic damage to the gallbladder wall is believed to facilitate mucosal breakdown, bacterial translocation, and the proliferation of gas-forming organisms such as *Clostridium perfringens*, *Escherichia coli*, *Klebsiella spp.*, and other facultative or obligate anaerobes.<sup>1,3,5</sup> The constellation of advanced age, vascular disease, and renal impairment in this patient is therefore pathophysiologically coherent with current concepts of EC, even in the absence of diabetes or gallstones.<sup>1,3,5,8</sup> This aligns with more recent reports describing EC in elderly non-diabetic patients with significant cardiovascular comorbidity.<sup>3,8-10</sup>

From a diagnostic perspective, computed tomography is widely regarded as the most sensitive modality for detecting even small volumes of gas in the gallbladder lumen and wall.<sup>9,15,20</sup> While ultrasonography may reveal characteristic findings such as echogenic foci with posterior “dirty” shadowing or the “champagne sign,” early EC can be subtle and is sometimes missed on initial sonography, with diagnosis made only after CT or repeat imaging.<sup>2,11,15</sup> In our patient, early CT imaging was decisive in confirming Type I EC before the onset of gangrenous changes, perforation, retroperitoneal extension, or biliary sepsis—complications that are well documented and frequently lethal. The ability to differentiate early EC from uncomplicated calculous or acalculous cholecystitis has direct consequences for both prognosis and management strategy.

Traditional management of EC has centered on urgent cholecystectomy, often via an open approach because of severe inflammation and difficulty in identifying Calot’s triangle.<sup>1,5,7</sup> However, contemporary practice has broadened the therapeutic spectrum to include emergency cholecystectomy (open or laparoscopic) in operable patients, particularly in Types II–III or when perforation, abscess, or generalized peritonitis is present, percutaneous cholecystostomy as a temporizing or definitive measure in critically ill, high-risk patients, often combined with broad-spectrum intravenous antibiotics, endo-

scopic transpapillary gallbladder drainage in selected high-risk or perforated cases where percutaneous access is contraindicated or conservative antibiotic therapy alone in rare, carefully selected patients with early-stage, localized disease and no radiologic or clinical evidence of complications.<sup>5,6,8,10,13,15,16,21,22</sup> Our patient was hemodynamically stable at presentation, had Type I intraluminal gas without wall disruption or pericholecystic extension, and was a poor surgical candidate due to age, significant cardiovascular disease, and acute kidney injury. These features supported an initial trial of conservative management.

The inclusion of Ursodeoxycholic acid in our conservative regimen was a case-specific decision aimed at improving biliary physiology and preventing further stasis in a high-risk, non-operative candidate. This approach is supported by recent literature, such as Di Stefano et al, who documented the effectiveness of ursodeoxycholic acid as part of a conservative medical treatment bundle for acute cholecystitis to avoid the need for cholecystectomy in patients where surgical intervention carries significant risk.<sup>23</sup> Furthermore, the use of ursodeoxycholic acid is recognized as a therapeutic option in managing gallbladder sludge and stasis-related disorders when surgical access is limited or contraindicated.<sup>24,25</sup>

In literature, successful non-operative or minimally invasive management strategies for EC generally rely on early, broad-spectrum intravenous antibiotic therapy targeting both aerobic Gram-negative bacteria and anaerobes.<sup>4,6,16</sup> Commonly used regimens include a B-lactam/B-lactamase inhibitor combination (such as piperacillin–tazobactam), a third- or fourth-generation cephalosporin plus metronidazole, or carbapenems (such as meropenem) in cases with clinical deterioration, high suspicion for resistant organisms, or severe sepsis.<sup>4,6,16,26</sup> In our case, we initiated IV piperacillin–tazobactam, consistent with broad coverage recommended for severe biliary infections. On day two, the patient developed hypotension, oliguria, and rising inflammatory markers, suggestive of impending sepsis. Given the rural setting and lack of culture data, antimicrobial therapy was appropriately escalated to IV meropenem, after which the patient’s condition progressively improved. This choice was made on a case-by-case basis, but there are examples. Continuous re-evaluation of the need for urgent surgery was a key component of this conservative strategy.

## Conclusion

This case highlights that emphysematous cholecystitis can develop in non-diabetic patients with significant vascular comorbidities and may be successfully treated with medical therapy alone when diagnosed early and monitored intensively even in a resource-constrained rural environment. Early CT imaging, rapid antimicrobial escalation, and meticulous hemodynamic follow-up are critical for non-operative success in selected high-risk patients. Although surgery remains the definitive treatment for most cases, individualized, stage-based decision-making can yield excellent outcomes and may prevent unnecessary operative morbidity in vulnerable populations.

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# Azathioprine-Induced Severe Myelosuppression Mimicking Disease Flare in Ulcerative Colitis: A Case Report

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## ABSTRACT

**Background:** Azathioprine is widely used as a steroid-sparing immunomodulator in the long-term management of ulcerative colitis; however, early-onset myelotoxicity remains one of its most serious and potentially life-threatening complications. The clinical presentation of azathioprine-induced marrow suppression frequently overlaps with symptoms of active ulcerative colitis, creating substantial diagnostic uncertainty. Early recognition is critical, particularly given the influence of pharmacogenetic susceptibility—most notably TPMT and NUDT15 variants—on the development of abrupt and profound cytopenias.

**Case Presentation:** We report a 68-year-old man with ulcerative colitis who presented with progressive weakness, fatigue, and profuse bloody diarrhea one month after initiating azathioprine therapy. Initial laboratory testing revealed severe pancytopenia, prompting immediate discontinuation of the drug and initiation of supportive care. Despite withdrawal of azathioprine, cytopenias continued to worsen over the following 48–72 hours, reaching a nadir of  $0.59 \times 10^3/\mu\text{L}$  WBC and  $27 \times 10^3/\mu\text{L}$  platelets. Beginning on hospital day four, hematologic recovery became evident, with rapid normalization of cell counts by day six and complete clinical resolution at early outpatient follow-up. The temporal pattern of decline and subsequent brisk rebound strongly supported acute azathioprine-induced severe myelosuppression rather than an intrinsic hematologic disorder. The patient was transitioned to mesalamine maintenance therapy, and plans were made to initiate infliximab as a safer long-term immunomodulatory strategy.

**Conclusion:** This case illustrates the diagnostic challenges posed by early azathioprine-induced marrow toxicity, particularly when symptoms mimic an ulcerative colitis flare. The predictable delayed nadir of cytopenias and rapid recovery following drug withdrawal underscore the importance of timely hematologic monitoring during the initial weeks of thiopurine therapy. Early identification enables prompt cessation of the offending agent and prevents progression to catastrophic complications. Given the severity of toxicity observed, thiopurines should not be reintroduced, and biologic agents represent a safer alternative for long-term disease control.

**Keywords:** Azathioprine, Myelotoxicity, Pancytopenia, Ulcerative colitis, Drug-induced myelosuppression

## Introduction

Azathioprine is a purine analog immunomodulator widely used in the long-term management of ulcerative colitis (UC), particularly for steroid-sparing maintenance therapy.<sup>1-3</sup> By inhibiting lymphocyte proliferation, it helps maintain remission and reduce

the need for repeated corticosteroid courses.<sup>1,2</sup> Despite its proven efficacy, azathioprine is associated with a narrow therapeutic window and several potentially serious adverse effects.<sup>2,4,5</sup> Among these, hematologic toxicity—ranging from isolated leukopenia to severe pancytopenia and, in rare instances,

es, life-threatening bone marrow aplasia—remains the most feared complication.<sup>3,4,6,7</sup> Reported rates of clinically significant myelotoxicity vary between 2% and 7%, but many studies suggest that the true incidence may be higher in real-world practice, particularly in populations with unrecognized genetic susceptibility.<sup>3,5,8-10</sup>

Myelotoxicity typically emerges during the first few weeks of therapy, often before steady-state thiopurine metabolites are reached.<sup>4,11,12</sup> Early toxicity is strongly associated with thiopurine methyltransferase (TPMT) and, more importantly in many Asian and Middle Eastern populations, nudix hydrolase 15 (NUDT15) polymorphisms.<sup>10,12-15</sup> However, severe marrow suppression can also occur in individuals without known enzymatic deficiencies, making clinical vigilance essential even when pre-treatment testing is unavailable or normal.<sup>4,11,16,17</sup>

A major diagnostic challenge arises because the early symptoms of myelotoxicity—such as fatigue, pallor, diarrhea, and mucosal bleeding—overlap substantially with those of active UC.<sup>4,8,11,18</sup> Moreover, gastrointestinal symptoms may persist or worsen despite cytopenias, misleading clinicians toward the assumption of an inflammatory flare.<sup>4,8,11,18</sup> Failure to recognize this overlap may result in inappropriate escalation of immunosuppression, delay in stopping the offending agent, and increased risk of sepsis or catastrophic bleeding.<sup>4,11,17,19</sup>

Here, we report a case of severe azathioprine-induced severe myelosuppression developing shortly after therapy initiation in a patient with ulcerative colitis. The presentation closely mimicked a disease flare, highlighting the importance of routine hematologic monitoring and careful clinical interpretation during the early phases of thiopurine therapy.

### Case Presentation

A 68-year-old male with a known diagnosis of ulcerative colitis presented to the emergency department with progressive weakness, marked fatigue, and profuse bloody diarrhea occurring more than ten times daily. These symptoms had intensified over several days. His disease had recently been managed at an outside center, where colonoscopy reportedly demonstrated left-sided colonic involvement, and azathioprine (3×50 mg daily, 3 mg/kg/day in a thin, 50-kg patient) together with mesalamine (3×1600 mg daily) was initiated approximately one month before presentation in the setting of an acute disease flare. Detailed records regarding prior treatment responses were not fully available at the time of admission. His corticosteroid regimen had been discontinued around the same time, although the exact treatment sequence at the outside center could not be fully reconstructed. He denied fever, chills, or systemic symptoms suggestive of overt infection. His medical history included cardiovascular comorbidities for which he was taking clopidogrel.

On arrival, the patient appeared pale, lethargic, and volume depleted but remained hemodynamically stable. Abdominal evaluation revealed mild left lower quadrant tenderness without guarding or rebound. Initial laboratory evaluation demonstrated severe pancytopenia, with a white blood cell (WBC) count of

$1.08 \times 10^3/\mu\text{L}$ , hemoglobin 6.7 g/dL, and platelets  $45 \times 10^3/\mu\text{L}$ . Red blood cell indices showed normocytic, normochromic anemia consistent with acute blood-loss anemia compounded by marrow suppression. CRP was mildly elevated at 5.7 mg/L, and stool occult blood test was positive.

Given the profound cytopenias and clear temporal relationship with azathioprine initiation, acute azathioprine-induced bone marrow suppression was suspected. Azathioprine was discontinued immediately. Supportive therapy was initiated with intravenous hydration, ciprofloxacin and metronidazole for neutropenia-associated infection prophylaxis, and intravenous corticosteroids (prednisolone 40 mg/day) to address presumed concurrent UC activity. Due to symptomatic anemia, he received a unit of packed red blood cells. Owing to thrombocytopenia, clopidogrel was withheld and planned for re-initiation only after platelet counts exceeded  $50 \times 10^3/\mu\text{L}$ .

Despite cessation of azathioprine, the patient's hematologic parameters continued to deteriorate over the next 48 to 72 hours. On the second hospital day, his WBC count fell further to  $0.78 \times 10^3/\mu\text{L}$  and the platelet count decreased to  $31 \times 10^3/\mu\text{L}$ , although his hemoglobin rose to 8.2 g/dL following transfusion. By the third day, marrow suppression reached its peak severity: the WBC count declined to  $0.59 \times 10^3/\mu\text{L}$ , hemoglobin dropped again to 6.4 g/dL in the setting of ongoing gastrointestinal blood loss, and platelets remained critically low at  $27 \times 10^3/\mu\text{L}$ . Throughout this period, the patient remained afebrile and hemodynamically stable, with no focal or systemic signs of infection; although extensive microbiological testing was not available, opportunistic infection was considered clinically, and the subsequent rapid hematologic recovery after azathioprine withdrawal supported drug-induced myelotoxicity rather than an infectious etiology.

Beginning on the fourth hospital day, laboratory values began to show the first signs of marrow recovery. The WBC count increased to  $0.87 \times 10^3/\mu\text{L}$ , platelets rose to  $32 \times 10^3/\mu\text{L}$ , and hemoglobin stabilized with continued supportive management. Clinically, the patient's diarrhea progressively decreased in frequency, and he reported gradual improvement in energy, appetite, and overall well-being. No infectious complications developed during hospitalization.

By the sixth day of admission, hematologic recovery was substantial: the WBC count had increased to  $2.21 \times 10^3/\mu\text{L}$ , hemoglobin to 8.6 g/dL, and platelets to  $187 \times 10^3/\mu\text{L}$ . The rapid rebound in cell counts after withdrawal of azathioprine strongly supported the diagnosis of reversible drug-induced myelosuppression rather than a primary hematologic disorder. Colonoscopy was deferred during this admission due to the elevated bleeding risk associated with thrombocytopenia and mucosal friability.

Once stabilized, the patient was transitioned to oral mesalamine for maintenance therapy, alongside proton-pump inhibitor therapy and calcium supplementation. Plans were made to initiate infliximab as a long-term steroid-sparing strategy after complete hematologic recovery. He was discharged in stable condition with close outpatient gastroenterology follow-up.

At the time of discharge, stool frequency had significantly decreased, bleeding had resolved, and laboratory values were trending toward normalization. At outpatient gastroenterology follow-up four days after discharge, his complete blood count had fully normalized, with restoration of WBC and platelet counts to within reference ranges and complete clinical resolution of diarrhea and bleeding.

## Discussion

Azathioprine-induced myelotoxicity is among the most serious complications of thiopurine therapy and remains a major barrier to its long-term use in inflammatory bowel disease.<sup>1,4,7,11</sup> Although controlled trials often cite low rates of severe cytopenia, real-world cohorts consistently report higher toxicity rates, particularly in populations with unrecognized pharmacogenetic susceptibility.<sup>3,5,11</sup>

Azathioprine-induced marrow toxicity results from the accumulation of thioguanine metabolites that disrupt DNA replication in hematopoietic progenitor cells.<sup>10,12,13,15</sup> The degree of toxicity is strongly influenced by pharmacogenetic factors—particularly TPMT and NUDT15 variants—which modulate intracellular levels of active thioguanine nucleotides.<sup>10,12-14,20</sup> Early-onset, profound pancytopenia typically reflects impaired NUDT15-mediated detoxification, leading to rapid accumulation of DNA-incorporated 6-TGNs and apoptosis of marrow precursors.<sup>12-15</sup>

Early-onset myelotoxicity, typically arising within the first two to six weeks of therapy, has become increasingly linked to genetic variants that impair thiopurine metabolism.<sup>4,10,11,21</sup> While TPMT deficiency has historically been emphasized, accumulating evidence identifies NUDT15 polymorphisms—common in Asian and Middle Eastern populations—as a principal contributor to abrupt and profound cytopenias.<sup>13-15</sup> In this respect, the clinical trajectory of our patient, who developed escalating pancytopenia approximately four weeks after initiating standard-dose azathioprine, closely mirrors the characteristic timing and severity described in NUDT15-associated early marrow toxicity. This correlation is noteworthy because pharmacogenetic screening is not routinely implemented in many regions, resulting in patients beginning thiopurine therapy without assessment of genetic vulnerability. In the present case, pharmacogenetic testing for TPMT and NUDT15 variants was not performed, reflecting real-world limitations in test availability at the treating center.

A central teaching point of this case lies in the diagnostic uncertainty generated by the overlap between symptoms of ulcerative colitis exacerbation and manifestations of marrow failure. The patient presented with progressive bloody diarrhea, weakness, and marked fatigue—symptoms that could easily be interpreted as worsening colitis. However, each of these findings may equally reflect severe anemia, thrombocytopenia, or neutropenia.<sup>17-19</sup> This convergence is well recognized in the literature and often leads to misinterpretation.<sup>4,11,18</sup> In our patient, the clinical presentation alone might have prompted escalation of corticosteroids or the addition of further immunosuppression

had an early complete blood count not been obtained. Instead, laboratory evaluation revealed severe pancytopenia—WBC  $1.08 \times 10^3/\mu\text{L}$ , hemoglobin 6.7 g/dL, and platelets  $45 \times 10^3/\mu\text{L}$ —which immediately shifted the diagnostic focus toward azathioprine toxicity rather than uncontrolled colitis. This pattern is consistent with reported cases in which early hematologic assessment was decisive in preventing inappropriate treatment intensification and avoiding the potentially catastrophic consequences of untreated marrow aplasia and severe myelosuppression.<sup>4,11,17,18</sup>

The progression of cytopenias in this patient also paralleled the expected kinetics of thiopurine-induced marrow suppression. In published series, hematologic decline often continues for several days despite cessation of azathioprine due to lingering intracellular metabolites.<sup>4,11,18</sup> This phenomenon was clearly observed in our case: the WBC count fell to a nadir of  $0.59 \times 10^3/\mu\text{L}$  and platelets to  $27 \times 10^3/\mu\text{L}$  on the third hospital day, even though the drug had been discontinued immediately upon admission. Recognition of this predictable delayed nadir is crucial, as clinicians must anticipate ongoing marrow suppression to guide monitoring intensity, transfusion thresholds, and infection prophylaxis during the early recovery period. Equally characteristic was the rapid rebound of hematologic parameters following withdrawal of the drug.<sup>4,11,18,19</sup> The literature consistently describes a prompt recovery of marrow function once the offending agent is removed, provided the stem cell compartment remains intact.<sup>4,11,18,19</sup> In our patient, WBC and platelet counts began to increase by the fourth hospital day and had nearly normalized by day six, with complete normalization confirmed at outpatient follow-up four days after discharge. This brisk recovery strongly supports azathioprine-induced myelosuppression as the underlying mechanism, effectively excluding primary hematologic malignancy, aplastic anemia, or other marrow-intrinsic disorders, which typically exhibit a slower or incomplete response.

The clinical course of this case additionally reinforces several principles in the safe use of thiopurines. International guidelines emphasize the need for frequent complete blood count monitoring during the first month of therapy (a period during which early toxicity most often emerges), consideration of lower starting doses in elderly or low-body weight patients, and heightened vigilance when pharmacogenetic testing is unavailable.<sup>4,11,12,18,19</sup> Had such surveillance occurred prior to presentation, the patient's progressive cytopenias might have been detected before reaching severe levels. Furthermore, given the degree of marrow suppression demonstrated here, rechallenge with azathioprine or related thiopurines is contraindicated. Biological therapies, particularly tumor necrosis factor inhibitors, offer safer steroid-sparing alternatives in similar cases and align with contemporary management strategies that prioritize individualized treatment based on risk stratification, comorbidities, and prior drug tolerance.<sup>1-3</sup> The transition planned for our patient reflects this shift toward precision-guided therapy. The absence of pharmacogenetic testing represents a limitation of this report and precludes definitive attribution of toxicity to an underlying enzymatic variant.

In summary, the clinical and laboratory features of this case closely parallel the patterns described in early-onset thiopurine-induced marrow toxicity, particularly in populations in which NUDT15-mediated susceptibility has been reported. The case underscores the diagnostic challenges created by overlapping symptomatology and highlights the indispensable role of early laboratory monitoring in distinguishing flare from toxicity, guiding timely intervention, and preventing life-threatening complications.

### Conclusion

Azathioprine-induced marrow myelosuppression is an uncommon but potentially life-threatening adverse effect that may closely resemble an ulcerative colitis flare, particularly during the early phase of therapy. This case underscores how overlapping clinical features—such as fatigue, bloody diarrhea, and general deterioration—can obscure the underlying diagnosis when hematologic evaluation is delayed. The patient's abrupt and profound pancytopenia, its continued progression despite immediate drug withdrawal, and the rapid hematologic recovery thereafter are characteristic of acute thiopurine toxicity, likely reflecting a pharmacogenetic predisposition. Early recognition through timely complete blood count monitoring, especially within the first month of treatment, is essential to prevent progression to severe marrow failure, sepsis, or catastrophic bleeding. Once detected, prompt cessation of azathioprine and appropriate supportive measures typically result in full recovery. Given the severity of toxicity observed, thiopurines should not be reintroduced, and alternative maintenance therapies such as biologic agents should be pursued. This case highlights the importance of integrating clinical vigilance, laboratory monitoring, and individualized treatment strategies when managing patients with ulcerative colitis receiving thiopurine therapy.

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# Comparative Analysis of Large Language Models in the Interpretation of Gynecologic Pathology Reports

## OPEN ACCESS

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Dear Editor,

The increasing availability of digital health information has enabled patients to access their pathology reports prior to clinical consultation, a phenomenon that has markedly amplified what is described in the literature as “waiting-time anxiety”.<sup>1,2</sup> In contemporary practice, patients increasingly rely on Large Language Models (LLMs) rather than conventional search engines to decipher complex medical terminology.<sup>2-5</sup> However, it remains uncertain how accurately and empathetically these models convey nuanced pathological concepts—particularly within “grey-zone” diagnoses such as Endometrial Intraepithelial Neoplasia (EIN), which cannot be classified as strictly benign or malignant—as well as how they communicate potential malignancy.<sup>1-3,6</sup> In this letter, we present a quantitative evaluation of the per-

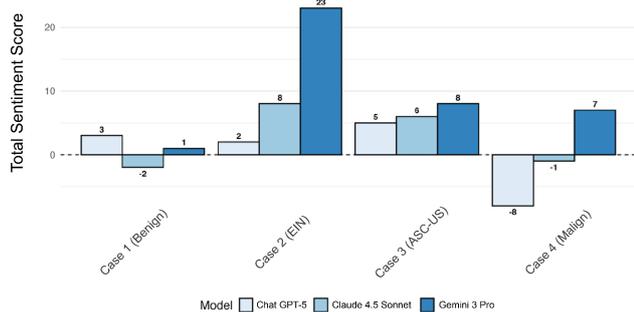
formance of three current LLMs across a series of gynecologic pathology scenarios.

In our study, we generated four synthetic pathology reports designed to represent a clinically relevant spectrum: benign (cellular leiomyoma), premalignant (endometrial intraepithelial neoplasia, EIN), indeterminate (atypical squamous cells of undetermined significance, ASC-US), and malignant (endometrioid adenocarcinoma) (Table 1). Three contemporary LLMs—Claude Sonnet 4.5, ChatGPT 5, and Gemini 3—were instructed to explain these reports to a persona defined as “a worried 45-year-old patient with no medical background.” The resulting outputs were assessed using the Ateşman Readability Index, NRC Emotion Analysis, and a jargon-density metric.<sup>7,8</sup> The language of the study was Turkish. For readability assessment, the Ateşman Readability Index, which

**Table 1.** Synthetic Gynecologic Pathology Reports Used as Model Inputs

Case No.	Clinical Category	Pathology Report Text (Model Input) <sup>1</sup>
Case 1	Benign (Cellular Leiomyoma)	Gross Description: Nodular tissue fragment measuring 8 × 6 × 5 cm, with a beige–white cut surface containing focal cystic areas.  Microscopic Description: Sections show intersecting fascicles of spindle-shaped smooth muscle cell bundles. Focal areas demonstrate edema, hyaline degeneration, and cystic change. Although mild increases in cellularity are noted in some regions, cytologic atypia is not prominent. No necrosis is identified. Mitotic activity is fewer than 1 per 10 HPF.  Diagnosis: Cellular Leiomyoma, Uterus (Myomectomy Specimen).
Case 2	Premalignant (EIN)	Specimen: Endometrial Curettage.  Microscopic Description: Examination of the entire specimen reveals increased glandular density with a gland-to-stroma ratio exceeding 1:1. Glands exhibit branching and crowding. Cytologic atypia is present, characterized by nuclear rounding, chromatin coarsening, and nucleolar prominence. The atypical glands are clearly distinguishable from the background endometrium. No evidence of invasion (myometrial involvement) is identified.  Diagnosis: Findings Consistent with Endometrial Intraepithelial Neoplasia (EIN).
Case 3	Indeterminate (ASC-US)	Specimen: Cervical Smear.  Microscopic Description: The background contains polymorphonuclear leukocytes and Döderlein bacilli. Superficial and intermediate squamous epithelial cells are present. Some squamous cells show nuclear enlargement (mildly increased nuclear-to-cytoplasmic ratio) and irregular nuclear contours; however, these findings are insufficient in quantity and quality to support a diagnosis of intraepithelial lesion (LSIL/HSIL). No cells suspicious for malignancy are identified.  Diagnosis: Atypical Squamous Cells of Undetermined Significance (ASC-US).
Case 4	Malignant (Adenocarcinoma)	Specimen: Probe Curettage.  Microscopic Description: Sections lack normal endometrial stroma. Instead, the tissue is replaced by back-to-back, cribriform, and complexly branching atypical glandular structures occupying the entire field. The neoplastic cells show marked nuclear pleomorphism, loss of polarity, and increased mitotic activity. A desmoplastic stromal reaction is present.  Diagnosis: Endometrioid-Type Adenocarcinoma, FIGO Grade 1.

HPF: High-power field, EIN: Endometrial intraepithelial neoplasia, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, ASC-US: Atypical squamous cells of undetermined significance, FIGO: International Federation of Gynecology and Obstetrics, <sup>1</sup> The content has been translated and adapted to comply with the journal's formatting and terminology guidelines.



**Figure 1.** Sentiment Load of Model Responses (NRC Sentiment Score).

Higher scores indicate a greater density of positive or reassuring language, whereas lower scores reflect negatively valenced or alarming wording. The distribution across the four clinical scenarios (Benign, EIN, ASC-US, Malignant) illustrates substantial variation in emotional tone between models.

is specifically designed for and adapted to Turkish morphology, was employed. For sentiment analysis, the validated Turkish translation of the NRC Word-Emotion Association Lexicon (Saif Mohammad’s NRC Word-Emotion Association Lexicon), accessible via the ‘syuzhet’ R package, was utilized.<sup>9</sup>

Our analyses revealed that none of the models adopted a standardized approach to patient education; instead, each demonstrated a distinct communicative profile (Table 2). Gemini 3 generated the longest and most detailed explanations (mean: 510 words) and incorporated the highest number of empathy markers (n=14), making it the model that conveyed the strongest empathetic intent (Figure 1). However, its responses were heavily laden with technical terminology, resulting in markedly poor readability (mean Atesman score: -99.9).

Conversely, Claude Sonnet 4.5 delivered the most balanced performance, offering concise yet adequately informative explanations (mean: 248 words). It achieved the highest readability scores in benign scenarios and, notably, eliminated potentially confusing terminology—such as “squamous” or “atypia”—in the ASC-US case, producing a fully jargon-free explanation (0.00% jargon density). In the EIN scenario, its use of the metaphor “This is not a red light but a yellow one” to describe diagnostic uncertainty was identified as an exemplary strategy for reducing patient anxiety.

Although ChatGPT 5 demonstrated a high degree of techni-

cal accuracy, it consistently underperformed in the domain of “emotional intelligence.” In three of the four scenarios, the model produced responses entirely devoid of empathy markers. More importantly, in the malignant scenario, its use of starkly negative language failed to incorporate the essential buffering and softening strategies emphasized in established “breaking bad news” protocols.

Taken together, our findings suggest that these three models assume distinct functional roles from the patient’s perspective: Gemini 3 resembles an “Academic Instructor” that appeals to detail-oriented users; ChatGPT 5 functions more as a detached “Technical Glossary”; and Claude Sonnet 4.5 operates as an “Empathetic Clinician” with a focus on anxiety mitigation. Ultimately, our results illustrate the diverse communicative profiles patients may encounter when independently consulting these tools. Clinicians’ awareness of these varying “AI communication styles” is critical—not only for correcting unrealistic patient expectations but also for managing secondary anxiety that may arise from digital information overload.

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**Table 2.** Quantitative Comparison of LLM Outputs Across Four Gynecologic Pathology Scenarios

Model	Clinical Scenario	Word Count	Readability <sup>1</sup>	Sentiment Score <sup>2</sup>	Jargon Density <sup>3</sup> (%)	Lexical Diversity <sup>4</sup>
Claude Sonnet 4.5	Case 1 (Benign)	208	-51.41	-2	2.54	0.75
	Case 2 (Premalignant)	240	-81.08	8	0.90	0.81
	Case 3 (ASC-US)	299	-77.90	6	0.00	0.70
	Case 4 (Malignant)	245	-79.56	-1	0.43	0.77
ChatGPT 5	Case 1 (Benign)	280	-63.88	3	1.52	0.71
	Case 2 (Premalignant)	305	-75.38	2	0.35	0.76
	Case 3 (ASC-US)	292	-76.02	5	0.00	0.76
	Case 4 (Malignant)	380	-92.01	-8	2.16	0.64
Gemini 3	Case 1 (Benign)	458	-98.51	1	2.43	0.64
	Case 2 (Premalignant)	496	-98.08	23	1.01	0.70
	Case 3 (ASC-US)	514	-100.00	8	1.78	0.64
	Case 4 (Malignant)	573	-89.86	7	1.60	0.63

Data were analyzed using R (v4.3.1). <sup>1</sup> Atesman Readability Formula: The Turkish adaptation of the Flesch Reading Ease method; higher scores (i.e., values approaching zero) denote greater readability. Negative values are expected in medically technical content due to the high density of specialized terminology. <sup>2</sup> Sentiment Score: Calculated using the NRC sentiment lexicon. Negative scores indicate alarmist or negatively valenced language, positive scores reflect reassuring or supportive language, and a score of 0 denotes a neutral tone. <sup>3</sup> Jargon Density: The proportion of predefined medical terms (e.g., “neoplasia,” “atypia”) relative to the total word count. Lower proportions indicate greater patient-centered simplification. <sup>4</sup> Lexical Diversity (Type-Token Ratio, TTR): The ratio of unique word types to the total number of words (range: 0-1). Higher values reflect reduced word repetition and greater linguistic richness.

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