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Fluoroquinolones susceptibility and gyrA variation patterns in Klebsiella pneumoniae clinical isolates from cancer patients in Kurdistan, Iraq

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ABSTRACT: Background: Klebsiella pneumoniae is a critical pathogen causing severe infections in immunocompromised cancer patients, with fluoroquinolone resistance largely driven by gyrA gene in quinolone resistance-determining region (QRDR) mutations. present study was designed to bridge the genotype to phenotype gap by investigating the relationship between gyrA gene mutations and fluoroquinolone susceptibility profiles in Klebsiella pneumoniae isolates recovered from cancer patients.

Methodolgy: In this cross-sectional study at Nanakaly Hospital, Erbil (July 2024–April 2025). 65 K. pneumoniae isolates were recovered from clinical specimens. Identification and susceptibility profiling were performed using VITEK® 2. gyrA gene mutations were identified via PCR and Sanger sequencing and correlated with ciprofloxacin susceptibility.

Results: Isolates exhibited high resistance to fluoroquinolones (ciprofloxacin, 86.27%; levofloxacin, 83.34%). gyrA gene mutations occurred in 53.84% of isolates, predominantly Ser83Phe (25%) and Asp87Asn (24%), alongside atypical substitutions (Ser83Phe, Asp87Ala). Double mutants, particularly Phe83+Asn87 showed the strongest association with resistance (81.82%) though genotype–phenotype discordance was observed where some mutant strains remained ciprofloxacin-susceptible (Fisher Freeman Halton exact p = 0.0348).

Conclusion: This study shows a high burden of K. pneumoniae resistance against fluroquinolones harboring atypical gyrA gene mutations among cancer patients in Erbil, Iraq. Highlighting the importance of combined phenotypic and genotypic surveillance to guide antimicrobial stewardship in oncology units.

INTRODUCTION

Klebsiella pneumoniae is one of the most clinically important nosocomial pathogens worldwide, this bacterium is an opportunistic Gram-negative type of bacteria in the family of *Enterobacteriaceae*. By which it can cause a wide variety of infections especially in immunocompromised patients such as pneumonia, bacteremia, septicemia, urinary tract infections (Liu *et al.*, 2023). Therefore, patients with cancer undergoing chemotherapy, radiotherapy or surgical operations are highly vulnerable to *K. pneumoniae* infections that can be fatal (Gu *et al.*, 2018). This susceptibility is due to the disruption of natural mucosal barriers, neutropenia, and the extensive use of broad-spectrum antibiotics.

As for treatment and prophylaxis of bacterial infections, fluoroquinolones have been extensively used in oncology units, especially ciprofloxacin and levofloxacin. Their mechanism of working is through inhibiting DNA gyrase, a type II

topoisomerase encoded by *gyrA* and *gyrB* genes, which is crucial to bacterial DNA replication and repair. The global rise of fluoroquinolone resistance substantially limits their therapeutic usage (Kareem *et al.*, 2021). The main molecular basis of this resistance is the presence of point mutations in the quinolone resistance determining region (QRDR) of *gyrA* gene. Mainly codons 83 and 87 by which they may cause conformational changes in the *gyrA* subunit that result in reduced binding affinity for fluoroquinolones. Thus, knowledge of the genotypic basis of resistance is essential for predicting phenotypic outcomes and guiding clinical decisions (Aldred *et al.*, 2014).

The epidemiology of antimicrobial resistance among clinical isolates of *K. pneumoniae* in Kurdistan Region of Iraq including the city of Erbil, is incompletely characterized (Naqid *et al.*, 2020). Multidrug resistant *K. pneumoniae* strains have been increasingly reported in Iraq and Middle East region (Hussein *et al.*, 2025). The knowledge gap is especially alarming in light of the increasing number of cancers diagnoses in the region and the lack of other therapeutic agents.

Therefore, the present study was designed to bridge the genotype to phenotype gap by investigating the relationship between *gyrA* gene mutations and fluoroquinolone susceptibility profiles in *K. pneumoniae* isolates recovered from cancer patients admitted to oncology centers in Erbil, Kurdistan-Iraq. Specifically, our study aimed to determine the antibiotic susceptibility patterns with detecting mutations in the *gyrA* QRDR via PCR and DNA sequencing then correlate identified genotypic mutations with observed phenotypic resistance to fluoroquinolones.

MATERIALS AND METHODS

Study Design and Sample collection

This cross-sectional study is conducted at Nanakaly Hospital for Cancer Care in Erbil city, Kurdistan Region of Iraq. After educating the patients on the study objectives and procedures, the clinical specimens including urine, blood, sputum, wound, rectal and perianal swabs were collected from 50 cancer patients (31 females and 19 males) between July 2024 and April 2025 using standard clinical techniques under aseptic conditions. 15 samples from immune-competent (non-cancer) patients were also obtained during the same period of time.

Isolation, identification, and Storage of Isolates

Clinical specimens were cultured on MacConkey and 5% sheep blood agars at 37°C for 24–48 hours. *K. pneumoniae* was preliminarily identified by standard colony morphology (pink, mucoid on MacConkey; greyish-white, non-hemolytic on blood agar) and confirmed using the VITEK® 2 Compact System. In total, 65 confirmed isolates were stored in 30% glycerol at –20°C for future analysis (de Carvalho *et al.*, 2021).

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing (AST) for all confirmed *K. pneumoniae* isolates was conducted using the VITEK® 2 Compact System with AST-GN cards to determine minimum inhibitory concentrations (MICs). Results were interpreted according to Clinical and Laboratory Standards Institute guidelines (CLSI, 2026) and classified as susceptible (S), intermediate (I), or resistant (R). Multidrug resistance (MDR) was defined as resistance to at least one agent in three or more antimicrobial categories (Othman and Baban, 2023).

Molecular Detection of *gyrA* Mutations

Detection of *gyrA* gene was performed using primers from previous studies (Khalefa *et al.*, 2025). The forward primer 5'-CGTCTATCCCTGTCGCCTTC-3' and reverse primer (5'-TCTCTTTTTCCAGGTCGGCC-3') were used to amplify a 450 bp of target *gyrA* via PCR setting as 94°C for 4 minutes for *Taq*-polymerase activation followed by 30 cycles each including denaturation at 94°C for 30 seconds, annealing at 57°C for 40 seconds and extension at 72°C for 60 seconds with a final extension at 72°C for 10 minutes. The PCR products were visualized on 1.5% agarose gel with a non-template control applied per each run. Gel purification of the excised bands was performed using (AddBio PCR purification kit, South Korea).

DNA Sequencing and Mutation Analysis

Purified PCR products were then subjected to Sanger sequencing on GeneStudio (Thermo Fisher, USA) platform. The resulting forward and reverse sequencing chromatographs were checked for read quality using Chromas V.6.6.1. After trimming low quality nucleotides. The FASTA files of each read were aligned against reference *K. pneumoniae gyrA* sequence (GenBank:

PV368874.1) on BioEdit V. 7,2,1 to detect nucleotide alterations. using ClustalW2 tool. Point mutations within the QRDR were identified.

Statistical Analysis

Data were analyzed using Microsoft Excel and GraphPad Prism v8.0.1, Descriptive statistics were reported as frequencies, percentages, means, and standard deviations. A statistical test with $p < 0.05$ was considered significant.

RESULTS

Clinical and Demographic Characteristics of Isolates

A total of 65 *K. pneumoniae* clinical isolates were collected in Erbil, Iraq, comprising 50 isolates from cancer patients at Nanakali Hospital for Cancer Care and 15 isolates from general microbiology laboratories. The most prevalent specimen source was urine (n = 39, 60.0%), followed by blood (n = 12, 18.5%) and stool or rectal swabs (n = 7, 10.8%). The patient cohort consisted of 23 males and 42 females. No statistically significant association was observed between gender and cancer status among patients with *K. pneumoniae* isolates (Fisher's exact test, OR = 0.59, p = 0.544). The majority of isolates were recovered from patients aged 18–59 years (47.7%), with age distribution showing no significant association with infection status (p = 0.193). Among the cancer cohort (n = 50), 86.0% (n = 43) were diagnosed with hematological malignancies, while 14.0% (n = 7) presented with solid tumors.

Fluoroquinolone susceptibility profile of the isolates

High rates of resistance were observed among the isolates against the evaluated fluoroquinolone class of antibiotics. Specifically, resistance to Ciprofloxacin reached 86.27%, with only 9.80% of the isolates demonstrating full susceptibility. Similarly, Levofloxacin exhibited high resistance levels at 83.34%, while 16.66% of the isolates remained susceptible. The complete distribution of susceptibility and resistance patterns for both fluoroquinolones is illustrated in Figure 1.

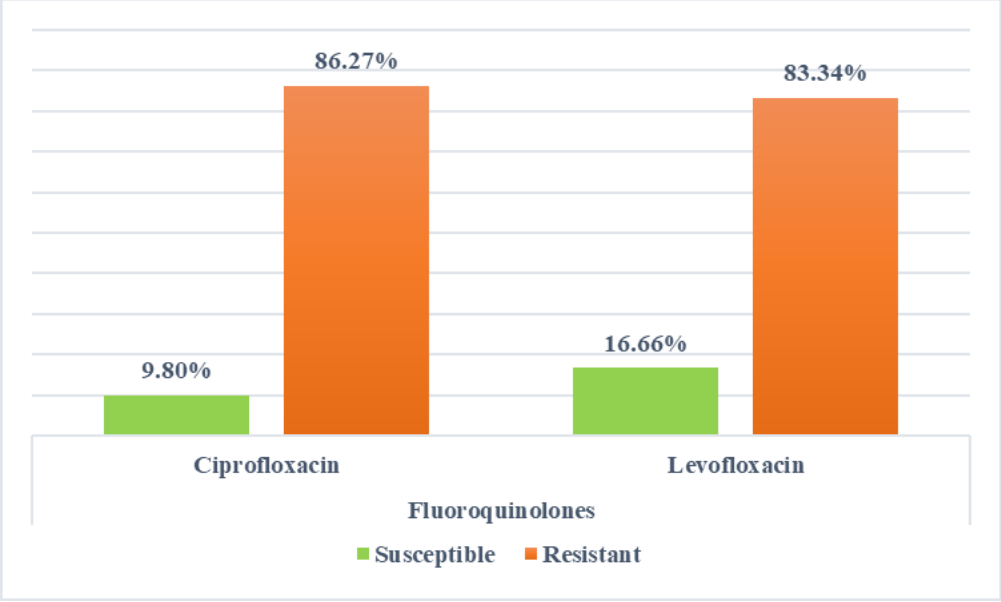

Figure 1. Susceptibility and resistance rates of *K. pneumoniae* isolates to fluoroquinolones.

Molecular Characterization and Frequency of *gyrA* Mutations

To target the amplification of the QRDR of *gyrA* gene, PCR analysis was performed across the clinical isolates, Figure 2. Since *gyrA* is an essential housekeeping gene encoding DNA gyrase subunit A, it was present across 100% of the evaluated isolates. Agarose gel electrophoresis confirmed successful targeted amplification of the *gyrA* QRDR fragment across all lanes.

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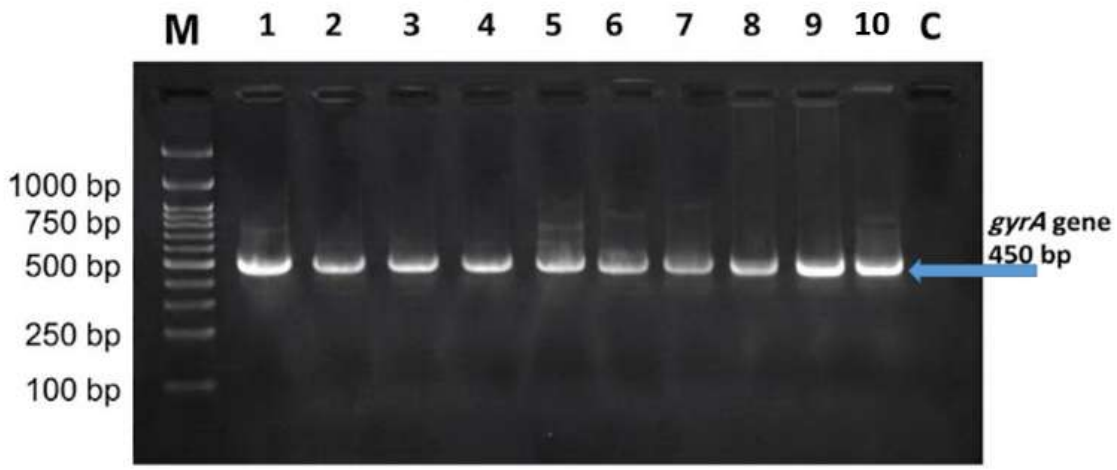

Figure 2. Molecular confirmation and PCR amplification of the *gyrA* QRDR region. Representative agarose gel electrophoresis showing specific target amplicons (~450 bp) corresponding to the QRDR of *gyrA* across evaluated clinical isolates. M: 100 bp DNA marker ladder; Lanes 1 to 10, *K. pneumoniae* isolates, C: negative control (DNase free water)

Sanger sequencing of the QRDR of the *gyrA* gene displayed mutational alterations in 53.84% of the tested isolates, whereas 30.76% exhibited the wild type strain. Analysis of the *gyrA* QRDR across 50 clinical strains showed that mutant alleles were common at both resistance determining codons. At codon 83, 60% (30/50) of isolates carried substitution mutations replacing the wild-type serine, most commonly with phenylalanine (25%, n=13), followed by equal proportions of leucine and isoleucine (10% each, n=5) and tyrosine (8%, n=4). The remaining 40% (20/50) retained the wild-type residue. A similar pattern was observed at codon 87, where 44% (22/50) of strains carried a substitution of the wild-type aspartate. Predominantly asparagine (24%, n=12) and, less frequently alanine (16%, n=8), while 56% (28/50) remained wild-type. Overall, codon 83 showed a higher rate of amino acid substitution and greater variant diversity than codon 87, with Phe83 and Asn87 representing the dominant mutant alleles at each position, respectively.

Genotypic-Phenotypic Discordance in Fluoroquinolone Susceptibility

Correlating *gyrA* genotype with susceptibility phenotype showed a clear resistance gradient. Single mutants at codon 83 (Phe83/Leu83/Ile83) were predominantly resistant (71.43%). Double mutants showed the strongest resistance association, (Phe83+Asn87) was 70% resistant and 30% intermediate with no susceptible strains, while (Tyr83+Ala87), (Tyr83+Phe87), and (Leu83+Asn87) combinations were uniformly resistant. (Phe83+Ala87) n=4 showed a mixed profile (1 susceptible, 3 resistant). Other mutations, including insertions/deletions (n=5), were also uniformly resistant. Overall, accumulation of *gyrA* mutations particularly double substitutions correlated with increasing phenotypic resistance ($p<0.05$), Table 1.

Table 1. Ciprofloxacin phenotype distribution across *gyrA* mutation profiles.

gyrA Mutation Profile	Genotype	Ciprofloxacin Sensitive n (%)	Ciprofloxacin Intermediate n (%)	Ciprofloxacin Resistant n (%)	Total Strains n (%)
Wild-type	No mutations	8(40.00%)	1(5.00%)	11(55.00%)	20 (30.76%)
Single Mutation	Phe83/Leu83/ile83	2(20%)	2(20%)	6(60%)	10 (15.38%)
Double Mutation	Phe83 + Ala87	2(33.34%)	0	4(66.67%)	6(9.23%)

	Phe83 + Asn87	0	2(18.18%)	9(81.82%)	11(16.92%)
	Tyr83 + Ala87	0	0	4(100%)	4(6.15%)
	Tyr83 + Phe87	0	0	3(100%)	3(4.61%)
	Leu83 + Asn87	0	0	5(100%)	5(7.69%)
Other Mutations	(Ins./ Del)	0	0	6(100%)	6(9.23%)
Fisher–Freeman–Halton exact test (p = 0.0348)					

CIP resistance associated with different genotypes of the *gyrA* gene

The relationship between *gyrA* mutation and ciprofloxacin resistance is further examined in Figure 3. The wild type (no mutation group) exhibited the lowest ciprofloxacin resistance rate (55%). Resistance increased with the accumulation of point mutations. Single amino acid (Phe83/Leu83/Ile83) substitutions carrying the 60% CIP resistance rate. 67% in those with (Phe83+Ala87) and 82% in isolates harboring (Phe83+Asn87). Notably, isolates with double substitutions (Tyr83+Ala87, Tyr83+Phe87, and Leu83+Asn87) as well as those carrying (insertion/deletion) mutations displayed the highest ciprofloxacin resistance rate 100%. Statistically significant association is observed between *gyrA* mutation category and ciprofloxacin susceptibility phenotype, Monte Carlo exact p=0.035.

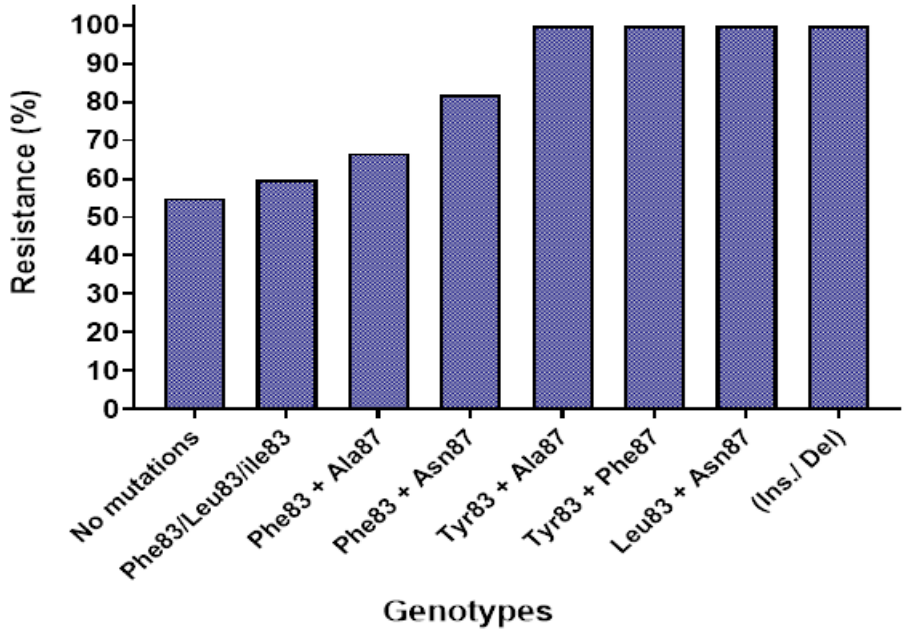

Figure 3. Percentage of CIP resistance associated with different genotypes of the *gyrA* gene.

DISCUSSION

The rapid dissemination of MDR *K. pneumoniae* strains represent a critical challenge to global public health (Irusan *et al.*, 2026). Especially, within a high-risk clinical setting such as oncology wards. Therefore, in this study, we investigated the resistance patterns and molecular characteristics of *K. pneumoniae* isolates recovered from cancer patients in Erbil, Kurdistan region of Iraq.

This study approached the immunocompromised patients as they are the most clinically vulnerable groups to microbial infections in view of the fact that standard empiric antimicrobial regimens often intersect with increased risks of multidrug

resistance (Naghavi *et al.*, 2024). Thus, in order to find out the impact of antibiotic resistance among this group, out of 65 collected *K. pneumoniae* isolates 50 (76.92%) were from cancer patients and the rest were taken from non-cancer immunocompetent control group with active bacterial infections. Both groups were enrolled in the same period to compare their antibiotic resistance profiles and *gyrA* mutation patterns. The vulnerability of cancer patients to opportunistic infections initially caused by chemotherapy induced neutropenia, recurrent hospitalization, prolonged usage of antibiotics, and invasive therapeutic interventions (Shelke *et al.*, 2024), Making them a critical group to compare against immunocompetent controls.

According to the source of specimens, urine (60.00%, n = 39) was the predominant specimen source. The urinary bias indicates the elevated prevalence of urinary tract infections (UTIs) and catheter related UTIs in hospitalized individuals. Importantly, the considerable percentage (18.46%) of bacteremia underscores *K. pneumonia*'s ability to penetrate mucosal barriers especially in cancer patients with reduced mucosal integrity resulting in severe, sometimes fatal bloodstream infections (Souza *et al.*, 2024). The detection of gut colonization through stool suggests that the gastrointestinal tract may serve as an internal reservoir for systemic dissemination in immunocompromised individuals. Among the group of n = 50 cancer related isolates, a significant proportion were derived from individuals with hematological malignancies (86.00%, n = 43), whereas solid tumors represented 14.00% (n = 7). Hematological cancers, including leukemia's and lymphomas, together with associated rigorous conditioning treatments, cause significant and extended neutropenia and mucosal damage, greatly compromising innate immunity and rendering patients particularly vulnerable to *K. pneumoniae* colonization and invasive infections (Chen *et al.*, 2021).

One of the important findings of this study is the presence of atypical amino acid substitutions at key positions in the QRDR of *gyrA*. Specifically, Ser83Phe and Asp87Ala. While the typical Ser83Leu and Asp87Asn mutations are well documented drivers of high level fluoroquinolone resistance globally as reported in Iraq (Kareem *et al.*, 2021), Iran (Rezaei *et al.*, 2024), and China (Zhan *et al.*, 2021). The identified substitution shows different epidemiological and structural features. interestingly, we observed a genotypic to phenotypic discordance, wherein a subset of isolates harboring these verified *gyrA* point mutations retained phenotypic susceptibility to ciprofloxacin. A study done by (Robert *et al.*, 2025) was in agreement with our results by which it mentioned the antibiotics susceptibility phenotype detected is linked to a likely efflux-pump overexpression mechanism and not fluoroquinolone target mutation.

This Difference shows the multifactorial and complex nature of fluoroquinolone resistance in *K. pneumoniae*. QRDR target-site mutations typically reduce the binding affinity of fluoroquinolones to DNA gyrase complex (Kherroubi *et al.*, 2024). But Phenotypic resistance often requires synergistic mechanisms, such as secondary mutations in parC, upregulation of active efflux pumps or down-regulation of OmpF/OmpC porins (Zgurskaya *et al.*, 2021). Meanwhile, Susceptibility in *gyrA* mutated strains reflects a mutation's position, certain substitutions alter the QRDR binding pocket insufficiently to exclude ciprofloxacin, particularly when no secondary resistance determinants are present (Khan *et al.*, 2024).

These results have important implications for regional infection control and surveillance programs from a diagnostic approach. Depending on molecular resistance screening or genotypic panels solely may result in inaccurate results of clinical susceptibility profiles. Therefore, integration of comprehensive diagnostic workflows through merging conventional phenotypic AST with focused QRDR sequencing is crucial for precise clinical decision making.

It is important to note that our study faced a number of limitations. While we successfully characterized *gyrA* substitutions, whole-genome sequencing (WGS) and comprehensive screening of secondary targets (such as *parC, parE*, and plasmid-mediated quinolone resistance (PMQR) genes like *qnr, oqxAB*) was not performed, which could further elucidate the full resistome of these isolates. Further research using structural docking modelling is needed to understand how ciprofloxacin binds to these particular *gyrA* variants.

At last, this study provides an important regional baseline data on the molecular epidemiology of *K. pneumoniae* in Erbil city, Iraq. The detection of atypical *gyrA* mutations alongside high MDR rates in oncology patients underlines the serious action for improving regional genomic surveillance, strict antimicrobial stewardship, and tailored empirical treatment guidelines.

CONCLUSION

This study found high rates of MDR *K. pneumoniae* in cancer patients in Erbil, Iraq, driven partly by *gyrA* QRDR mutations, including atypical substitutions (Ser83Phe, Asp87Ala) not commonly reported elsewhere. A notable genotype phenotype discordance was observed in isolated taken from cancer patients, where some mutation carrying isolates remained ciprofloxacin

susceptible, indicating that additional resistance mechanisms (eg: efflux pumps, porin loss) likely contribute alongside target-site mutations. These findings highlight the need for combined phenotypic and genotypic testing, rather than genotypic screening alone, to guide treatment decisions, and call for expanded surveillance (including whole genome sequencing) and stronger antimicrobial stewardship in oncology settings to protect this vulnerable patient population.

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Conflict of Interests

The authors declare that they have no competing financial interests, personal relationships, or professional involvements that could have appeared to influence the work reported in this paper.

Ethical Approval

Ethical approval was granted by the Hawler Medical University (No. 66, on 24-Jun-2024). All the experimental protocols were conducted in strict adherence to the institutional guidelines for the handling of clinical pathogens. In accordance to the standards of the Helsinki Declaration (World Medical Association, 2025).

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