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Retrospective Analysis of Antibiotic Resistance Patterns of Uropathogenic *Escherichia coli* With Focus on Extended-Spectrum β-Lactamase at a Tertiary Central Hospital in Saudi Arabia

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ABSTRACT

Background and Aims: Urinary tract infections (UTIs) are a prevalent bacterial infection that has substantial implications for healthcare on a global scale. *Escherichia coli* (*E. coli*) is a gram-negative rod responsible for most UTI cases. ESBL-producing *E. coli* is widely recognized as a significant contributor to antibiotic resistance. This study aims to evaluate the prevalence and antibiotic resistance trends of ESBL-producing *E. coli* in patients with UTIs at a tertiary hospital in Jazan, Saudi Arabia.

Methods: A retrospective cross-sectional analysis was conducted on 347 urine specimens collected between January 2022 and March 2023.

Results: The study found that 31% of *E. coli* specimens were positive for ESBL. Among patients with ESBL-producing *E. coli*, 78.9% were females, and the majority of ESBL-producing *E. coli* cases were observed in the outpatient clinic departments. Among all *E. coli* isolates, ampicillin exhibited the highest resistance rate at 69.3%, aztreonam at 66.7%, and colistin at the lowest resistance. ESBL-producing *E. coli* strains exhibited higher resistance rates than non-ESBL-producing *E. coli* strains.

Conclusion: The study agrees with others in the region and shows a higher prevalence of ESBL-producing *E. coli* in the region, emphasizing the importance of antibiotic stewardship programs and infection control measures to mitigate the prevalence and spread of ESBL-producing *E. coli* in our region.

1 | Introduction

Urinary tract infections (UTIs) are a prevalent bacterial infection that physicians frequently encounter. They are the community's second most common bacterial infectious diseases [1, 2]. According to 2022 estimates, there are 400 million cases and 230,000 deaths worldwide caused by these bacterial infections [3]. UTI accounts for up to 35% of hospital-acquired infections, making it the most common, and also it is the second leading cause of bacteremia in hospitalized patients [4]. UTIs

persist as a substantial obstacle to the healthcare system in Saudi Arabia, constituting approximately 10% of the total infections within the nation. Moreover, UTIs rank as the second most prevalent cause of admissions to the emergency department, as prompt intervention is imperative to avert grave complications [4–6].

UTIs are prevalent in women, with approximately 60% encountering it at least once during their lifetime. Women are also more likely to experience recurring UTIs. Conversely, anatomical differences make men less vulnerable to UTIs and complications. *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis*, and *Proteus mirabilis* are the primary causative agents associated with UTIs [7]. Uropathogenic *E. coli* (UPEC) is the most frequently encountered among these pathogens, accounting for approximately 60%–90% of all UTI cases. Around 30%–50% of these infections occur in healthcare settings, whereas 80% are acquired in the community [1, 8]. In addition to female anatomy, other factors can increase the susceptibility to UPEC infections, including frequent sexual activity, certain contraceptive use, urinary tract abnormalities, and compromised immune function [9, 10].

Amid the global landscape, the impact of antibiotic resistance assumes a formidable magnitude, resulting in approximately 700,000 deaths annually, and projections indicate that this number could exceed 10 million by 2050 [11]. Recognizing this imminent threat, the World Health Organization has identified the urgent need for anti-microbial agents targeting various pathogens, including extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) [12]. Compounding the urgency, community-acquired infections and ESBL-E infections have witnessed an alarming increase of approximately 50% in the past decade [13]. These trends necessitate intensified efforts to curb and counteract the dissemination of antibiotic resistance to prevent dire consequences within healthcare settings and the larger community.

The escalating trend of antimicrobial resistance in UTIs, particularly among UPEC strains, poses a significant concern. UPEC strains are becoming more resistant to commonly prescribed antibiotics, including broad-spectrum antibiotics such as fluoroquinolones, cephalosporins, and aminoglycosides, facilitated by antibiotic-resistance genes carried on mobile genetic elements [14–17]. UPEC strains have a range of virulence factors encoded within their virulence genes, which enhance their ability to circumvent defense mechanisms and cause disease. These virulence factors include fimbriae, aiding in bacterial attachment and invasion, iron-acquisition systems for survival in the iron-limited environment of the urinary tract, as well as flagella and toxins, which facilitate the dissemination of the bacteria. Virulence genes can be found on transferable genetic elements such as plasmids or within the chromosome [18], enabling non-pathogenic strains to acquire novel virulence factors from accessory DNA [19]. This rise in resistance is linked to factors such as overuse or misuse of antibiotics, inadequate empirical antibiotic therapies without antibiotic susceptibility testing, overconsumption of antibiotics by the general population, and lack of adherence to medical prescriptions [15, 20, 21]. UPEC can develop multidrug resistance (MDR) and produce ESBL. Delayed or ineffective treatment of ESBL-UTIs can lead to severe complications like sepsis, renal scarring, and prolonged hospital stays compared to non-ESBL infections [22–25].

The global prevalence of ESBL-*E. coli* is rising, with geographical factors significantly influencing the rates [26, 27]. To accurately estimate the incidence of antibiotic resistance or ESBLs, it is crucial to consider criteria for including or excluding isolates [28, 29]. ESBLs have enzymes that degrade penicillins, cephalosporins, and monobactams like aztreonam [26–29]. MDR is observed in these bacteria due to the presence of antibiotic resistance genes for cotrimoxazole, quinolones, and aminoglycosides [30]. The prompt identification of ESBL-producing strains is crucial in healthcare settings to ensure the efficacy of therapy and disease control, particularly in situations where selecting an appropriate antibiotic regimen can be intricate.

To effectively manage UTIs, it is essential to conduct comprehensive research on antimicrobial resistance patterns and carefully choose the most appropriate empirical antibiotic therapy [28, 31, 32]. The primary objective of this study is to analyze and assess the antibiotic resistance profiles of ESBL-producing *E. coli* and non-ESBL-producing *E. coli* strains in patients with UTIs at a tertiary hospital in Jazan, Saudi Arabia. The aim is to provide valuable insights for developing practical treatment approaches and support infection control efforts.

2 | Materials and Methods

2.1 | Study Design, Settings, and Population

This retrospective study was conducted at a tertiary hospital in Jazan, Saudi Arabia. In order to investigate the prevalence of UTIs caused by ESBL-producing *E. coli* compared to non-ESBL-producing *E. coli*, we analyzed the results of urine sample culture and sensitivity testing from January 2022 to March 2023. Adult patients of both sexes diagnosed with UTI based on obtaining a positive urine culture at various clinical settings, including emergency rooms (ERs), clinics, hospital wards, and intensive care units (ICUs), were included in the study. The excluded populations were pediatrics, pregnant women, patients who had catheter-associated UTIs, and cases with incomplete or missing medical files.

2.2 | Bacterial Detection

Samples were collected from mid-stream “clean catch” urine, following the hospital's internal protocols at the specified collection sites. The urine samples underwent culturing on blood agar, cystine lactose electrolyte deficient agar, and MacConkey agar plates. The plates were then placed in an incubator and maintained at 35°C–37°C for 24–48 h. Bacterial growth was monitored daily by examining the plates, while smears were prepared for initial analysis using Gram staining. The presence of a single type of bacterium with a bacterial growth of 10^5 CFU/mL of urine defines a positive urine culture. The

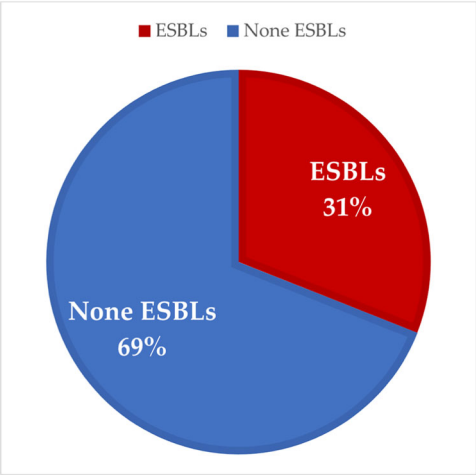

FIGURE 1 | The overall frequency of ESBL-producing *E. coli* and none-ESBL-producing *E. coli* in UTI cases ($n = 347$). ESBL, Extended-spectrum β-lactamase.

organisms were identified and validated using MicroScan and VITEK 2.

2.3 | Antimicrobial Susceptibility Testing

An automated Vitek 2 system (VITEK, bioMérieux; Phoenix, BD) was utilized for antibiotic susceptibility testing and determining the minimum inhibitory concentration against an array of antibiotics. Isolates were screened for ESBL production using the Vitek 2 system. All data were interpreted according to the guidelines provided by the Clinical Laboratory Standards Institute in the 30th Edition of M100, 2020.

2.4 | Study Approval and Data Collection

The Health Ethics Committee approved the study in Jazan, Saudi Arabia (IRB No. 2307) on January 12, 2023. The study followed the ethical guidelines of the Helsinki Declaration and Saudi Arabia's National Committee of Bioethics. A predesigned data collection sheet was created to collect and organize patients' data from the hospital database and laboratory results. The collected variables include the patient's gender, date of specimen collection, bacterial isolate, and antibiotic susceptibility testing. Information was gathered from patient records and laboratory databases, with personal details omitted to ensure privacy.

2.5 | Statistical Analysis

The statistical analysis was conducted using SPSS version 23, developed by IBM Corporation, Armonk, NY, USA. Frequencies and percentage tables were generated using descriptive statistics. Categorical variables underwent univariate analysis using statistical tests such as the Chi-squared test ($\chi 2$). A p value less than 0.05 was considered to be statistically significant.

3 | Results

Throughout the study, a total of 347 urine specimens were gathered from individuals with UTIs in different departments at KFCH. All of these specimens satisfied the criteria for inclusion. Among them, 109 (31%) samples were found to have ESBL-producing *E. Coli*, whereas 238 (69%) samples had non-ESBL-producing *E. Coli*, as shown in Figure 1.

Based on the study's results, 78.9% of patients diagnosed with ESBL-producing *E. coli* were female, and 21.1% were male. However, 68.1% of patients diagnosed with non-ESBL-producing *E. coli* were female, and 31.9% were male ($p = 0.038$). Concerning the isolation location, the outpatient clinics had the highest rate of ESBL-producing *E. coli* cases, at 60 (55%), followed by the ER at 47 (43.1%), and both the ICU and wards, each with a single case (0.9%) ($p = 0.935$) (Table 1).

The comprehensive analysis of resistance rates and number of tested isolates, as presented in Table 2, provides a deeper understanding of the performance of different antibiotic classes against these pathogens. The study involved eight distinct classes of antibiotics, each targeting different mechanisms of action against *E. coli* bacteria. Among these classes, four were subclasses of β-lactam antibiotics (penicillins, carbapenems, cephalosporins, and monobactams), while the others included

TABLE 1 | Descriptive analysis of the included data ($n = 347$).

		ESBL-*E. coli*		None-ESBL-*E. coli*			
Factor	***n***	**%**	***n***	**%**	***n* = 347**	**Total**	***p***
Gender							
Male		23	21.1%	76	31.9%	99 (28.5%)	0.038*
Female		86	78.9%	162	68.1%	248 (71.5%)	
Location							
Clinic		60	55%	129	54.2%	189 (54.5%)	0.935
ER		47	43.1%	105	44.1%	152 (43.8%)	
ICU		1	0.9%	3	1.3%	4 (1.1%)	
Ward		1	0.9%	1	0.4%	2 (0.6%)	

Abbreviations: ER, Emergency room; ESBL, Extended-spectrum β-lactamase; ICU, intensive care unit.
*$p < 0.05$.

TABLE 2 | The level of resistance exhibited by all *E. coli* strains isolated from the urine samples of patients diagnosed with urinary tract infections ($n = 347$).

Antimicrobial drug	Number of tested isolates	Resistant rate (number of resistant isolates)
β-Lactam antibiotics		
Subclass (penicillins)		
Amoxicillin-clavulanate (AMC)	114	43% (49)
Ampicillin (AMP)	140	69.3% (97)
Piperacillin-tazobactam (TZP)	92	45.7% (42)
Subclass (carbapenems)		
Meropenem (MEM)	123	21.1% (26)
Subclass (cephalosporins)		
Ceftazidime (CAZ)	78	43.6% (34)
Ceftriaxone (CRO)	125	44% (55)
Cefotaxime (CTX)	69	52.2% (36)
Cefepime (FEP)	227	55.1% (125)
Subclass (monobactams)		
Aztreonam (ATM)	15	66.7% (10)
Sulfonamides		
Trimethoprim-sulfamethoxazole (SXT)	181	33.7% (61)
Aminoglycosides		
Amikacin (AMK)	226	1.7% (4)
Gentamicin (GEN)	284	9.2% (26)
Tobramycin (TOB)	164	12.2% (20)
Tetracyclines		
Tigecycline (TGC)	7	14.3% (1)
Fluoroquinolones		
Ciprofloxacin (CIP)	298	40.6% (121)
Levofloxacin (LVX)	268	41.8% (112)
Nitrofurantoin		
Nitrofurantoin (NIT)	166	14.5% (24)
Polymixin		
Colistin (COL)	3	0.0% (0)

sulfonamides, aminoglycosides, tetracycline, fluoroquinolones, nitrofurantoin, and polymyxin. Penicillins displayed varying resistance rates, with amoxicillin-clavulanate exhibiting the lowest resistance rate (43%). Among carbapenems, meropenem showed a relative resistance increase of 21.1%. The cephalosporin class showed resistance rates of 43.6% for ceftazidime, 44% for ceftriaxone, 52.2% for cefotaxime, and 55.1% for cefepime. In the subclass of monobactams, aztreonam has a resistance rate of 66.7%. Sulfonamides (trimethoprim-sulfamethoxazole) exhibited a resistance rate of 33.7%. Aminoglycosides, including amikacin, gentamicin, and tobramycin, showed resistance rates between 1.5% and 12.2%. Tetracycline, represented by tigecycline, showcased a resistance rate of 14.3%. Resistance rates of fluoroquinolones, specifically ciprofloxacin and levofloxacin, are 40.6% and 41.8%, respectively. Nitrofurantoin displayed a resistance rate of 14.5%. Colistin exhibited the lowest resistance rate of 0% for all *E. coli* isolates.

Table 3 displays the resistance rates of isolates to some clinically relevant tested antimicrobials categorized by ESBL-producing *E. coli* and non-ESBL-producing *E. coli*. Ceftriaxone, cefotaxime, and cefepime showed 100% resistance rates for ESBL-producing *E. coli*, while with non-ESBL-producing *E. coli*, their resistance rates ranged between 9% to 14% ($p = 0.0001$). Followed by piperacillin-tazobactam (94%), ciprofloxacin (62%), levofloxacin (62%), and trimethoprim-sulfamethoxazole (54%), while with non-ESBL-producing *E. coli* their resistance rates were 14%, 29%, 31%, and 23%, respectively ($p = 0.0001$). The antibiotics that exhibited the lowest resistance rates with ESBL-producing *E. coli* were amikacin (1%), while non-ESBL-producing *E. coli* resistance rates ranged between 0% and 8%.

4 | Discussion

The worldwide emergence and escalating prevalence of multidrug-resistant Enterobacteriaceae, precisely strains that produce ESBLs, have generated significant concerns on a global scale, including within our region [33]. In this study, we investigated the prevalence of ESBL-producing *E. coli* in UTIs, and our findings revealed that 31%. Comparing our data with prevalence rates reported in different cities in Saudi Arabia, it is evident that ESBL-producing *E. coli* is prevalent across the country with notable variations related to study design, period, population and year of the study [34–45]. ESBL-producing *E. coli* has been detected in various regions of the country, exhibiting prevalence rates varying from 10.32% to 62.70%, as shown in Table 4. The significant prevalence of ESBL-producing *E. coli* in UTIs, regardless of geographical location, underscores the pressing necessity for a nationwide intervention to tackle this issue in public health. A comprehensive strategy is required to tackle the growing issue of MDR and its implications for managing and treating UTIs in Saudi Arabia.

For this study, we examined 347 strains of *E. coli* that were obtained from urine samples. Among these strains, 31% were found to produce ESBLs. Out of the *E. coli* strains that were examined, 248 (71.5%) females reported UTIs, while 99 (28.5%) males reported UTIs. A total of 86 (78.9%) cases of ESBL-producing *E. coli* were identified in females, while 23 (21.1%) cases were found in males. The elevated prevalence of UTIs in females has been previously examined and can be ascribed to various factors. The anatomical structure of their sexual organs, which includes a shorter urethra and the proximity of the urethra to the rectum, makes them more susceptible to UTIs. Pregnancy and

TABLE 3 | Resistance rates of selected clinically relevant antibiotics against ESBL-producing vs. non-ESBL *E. coli* isolates.

Antimicrobial drug	ESBL-*E. coli* Resistant rate (number of resistant isolates/total isolates)	Non-ESBL *E. coli* Resistant rate (number of resistant isolates/total isolates)	*p*
Amikacin (AMK)	1% (1/85)	1% (3/163)	0.57
Gentamicin (GEN)	18% (19/103)	4% (7/181)	0.0001*
Ciprofloxacin (CIP)	62% (65/105)	29% (56/193)	0.0001*
Levofloxacin (LVX)	62% (58/94)	31% (54/174)	0.0001*
Meropenem (MEM)	24% (16/67)	18% (10/56)	0.415

Abbreviation: ESBL, Extended-spectrum β-lactamase.
*$p < 0.05$.

aging make women more susceptible to UTIs due to hormonal, mechanical, and physiological changes. These changes can weaken the bladder and pelvic floor muscles, leading to urinary retention or incontinence and spreading ESBL-producing *E. coli* more likely [46–50]. Given the importance of gender as a possible risk factor for UTIs, it is crucial to recognize and deal with this factor while studying and treating UTIs caused by ESBL-producing *E. coli*. Among these risk factors that were not sought here and could explain this higher prevalence are the prior use of antibiotics, previous hospitalization, and a history of UTIs [51–53].

A previous study conducted in the Jazan region revealed that *E. coli* was the leading cause of UTIs, accounting for almost half of the isolates. Furthermore, 30.13% of *E. coli* strains showed ESBL production [50]. The current study expands on these findings by specifically focusing on the antimicrobial suitability testing of ESBL-producing *E. coli*. In addition, the ESBL-producing *E. coli* strains exhibited some resistance to fluoroquinolones, precisely 62% for both levofloxacin and ciprofloxacin, consistent with previous studies. This finding indicates the limited effectiveness of fluoroquinolones in treating infections caused by ESBL-producing pathogens, unless proven otherwise to be sensitive [35, 38]. The study also identified a higher degree of resistance to carbapenem (24% for meropenem) compared to what was reported in prior studies [34, 35, 38]. However, Brek et al. discovered that 74.4% of carbapenemase-producing *Klebsiella pneumoniae* are present in our region, highlighting the need for further investigation into carbapenemase-producing *E. coli* in the same area [54]. This suggests that carbapenem resistance could be an emerging challenge in the treatment of infections caused by ESBL-producing bacteria, warranting the use of alternative therapeutic strategies and reinforcing the importance of robust antimicrobial stewardship programs. We also found that antibiotics that have less resistance against ESBL-producing *E. coli* were aminoglycosides (1% for amikacin and 18% for gentamicin). Despite only three isolates being tested, it appears that colistin maintains robust activity against *E. coli*, as evidenced by a 0% resistance rate. Consequently, colistin is often regarded as a last-resort drug in accordance with numerous guidelines, given its 100% sensitivity. This finding aligns consistently with earlier national and international studies [34, 35, 38, 55]. However, the limited number of tested isolates warrants cautious interpretation, and further surveillance is needed to ensure ongoing effectiveness of colistin, particularly in regions with rising multidrug-resistant pathogens. Furthermore, the results of this study emphasize the significance of choosing the right antibiotics, as the improper use of empirical antibiotics can have adverse effects on recurrent UTIs, as well as on bacterial ecology and the dissemination of antibiotic resistance [56]. Therefore, it is crucial to gather knowledge on antimicrobial resistance rates through national, regional, and hospital studies, and to prescribe empirical agents with resistance levels not exceeding 10%–20% [57].

Our study has provided valuable insights into the prevalence of UTIs caused by ESBL-producing *E. coli* in comparison to non-ESBL-producing *E. coli* within our specific study population. However, it is essential to acknowledge the limitations of our retrospective study, which was conducted at a single tertiary hospital, potentially limiting the generalizability of our findings to the larger population. This study primarily examined *E. coli* isolates and their resistance patterns based on extracted data that some may not be validated by a consultant microbiologist. Plus, we did not consider other factors contributing to developing drug-resistant UTIs, such as host immune responses, virulence factors, clinical histories, and patient demographics. Besides, Future research should aim for a larger sample size and multicenter methodology to comprehensively understand drug-resistant UTIs. Molecular identification, characterization, and further disc tests such as the use of cefoxitin to detect ampC β lactamase isolates can benefit future research. National prevention strategies should be implemented to decrease the prevalence of ESBL UTIs, including promoting hygiene practices, raising awareness of risk factors, and improving antimicrobial stewardship programs nationwide.

5 | Conclusion

UTIs are a common bacterial infection that threatens global healthcare. Antibiotic resistance in UPEC strains, especially those that produce ESBL, is a significant healthcare issue. Misuse of antibiotics, inappropriate empirical antibiotic therapies, and excessive antibiotic consumption by the general population contribute to antibiotic resistance. Thus, studying antimicrobial resistance patterns and choosing the best empirical antibiotic treatment is crucial. Our study highlights the need for robust antibiotic stewardship programs in healthcare facilities across the county. Implementing stricter infection control measures can aid in reducing the prevalence of ESBL-producing *E. coli*.

TABLE 4 | Prevalence of ESBL-producing *E. coli* of different cities in Saudi Arabia.

First author [reference]	Year	City	ESBLs prevalence %	Notes
Khalid M. Alameer [current study]	2022	Jazan	31%	—
Samiyah A. Alghamdi [34]	2023	Al-Baha	15%	—
Adil Abalkhail [35]	2022	Riyadh	33.49%	—
Abdulrahman S. Bazaid [36]	2022	Ha'il	15.70%	—
Mohammed Y. Alasmary [37]	2021	Najran	6.50%	Isolated from adult females
Ahmad A. Majrashi [38]	2020	Riyadh	35.50%	—
Mohammed A. Alzahrani [39]	2020	Al-Baha	10.32%	—
Fethi Ben Abdallah [40]	2020	Taif	30%	—
Saleh M. Al-Garni [41]	2018	Taif	62.70%	The prevalence of ESBL-producing *E. coli* (62.7%, $n = 220$) from all ESBL-producing isolates ($n = 351$).
Fahad A. Mashwal [42]	2017	Dhahran,	23.10%	—
Sulaiman A. Al Yousef [43]	2016	Hafr Al Batin	41.90%	ESBL prevalence is according to PCDDT results.
TA El-Kersh [44]	2015	Khamis Mushayt	44%	The prevalence of ESBL-producing *E. coli* (44%, $n = 91$) from all ESBL-producing isolates ($n = 269$).
Fawzia E. Al-Otaibi [45]	2013	Riyadh	33.30%	—

Author Contributions

Khalid M. Alameer: writing–original draft, formal analysis. **Bandar M. Abuageelah:** formal analysis, writing–original draft. **Rena H. Alharbi:** writing–review and editing. **Mona H. Alfaifi:** writing–review and editing. **Eman Hurissi:** writing–review and editing. **Moayad Haddad:** writing–review and editing. **Nabil Dhayhi:** writing–review and editing. **Abdulelah S. Jafar:** writing–review and editing. **Mousa Mobarki:** writing–review and editing. **Hassan Awashi:** writing–review and editing. **Shaqraa Musawi:** writing–review and editing. **Abdulaziz M. Alameer:** writing–review and editing. **Shatha H. Kariri:** writing–review and editing. **Abdulaziz H. Alhazmi:** supervision.

Disclosure

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics Statement

The study was approved by the Jazan Health Ethics Committee (REC) at the Ministry of Health.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data presented in this study are available on request from the first author.

Transparency Statement

The lead author, Abdulaziz H. Alhazmi, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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