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Efficacy of Early Targeted Antibiotic Therapy in Patients with Sepsis and Septic Shock

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ABSTRACT

Background and objective: Sepsis and septic shock carry a high mortality rate, necessitating prompt treatment. As antibiotic-resistant pathogens become more prevalent, genotyping offers a potential advantage by quickly identifying organisms and their resistance genes. This study evaluated whether genotyping-targeted antibiotic therapy improved outcomes over conventional bacterial culture-based treatment in sepsis or septic shock patients, with a focus on correlating Sirtuin1 levels with the inflammatory response and mortality risk. **Methods:** This single-center, prospective, open-label, randomized clinical study with 52 patients suffering from sepsis or septic shock, randomly assigned patients to either conventional bacterial culture or genotyping targeted antibiotics. Samples of blood were drawn on Days 1 and 5 to measure sepsis markers; total leukocytic count (TLC), C-reactive protein (CRP), procalcitonin (PCT), and Sirtuin 1 and changes in SOFA scores were assessed. **Results:** The intervention did not differ significantly from conventional culture-based therapy in terms of the percentage change of SOFA scores (p=0.679) or ventilator-free days (p=0.362). Similarly, changes in TLC (p=0.522), PCT (p=0.067), and Sirtuin 1 (p=0.227) revealed no differences that were statistically significant, although CRP was the only marker with a significant percentage change (p=0.042). Additionally, there was no significant difference in 30-day mortality, length of hospital stays, or death rates (p=0.668, p=0.594, and p=1.00, respectively). **Conclusion:** The research discovered that incorporating genotyping in sepsis management didn't result in differences in the prognosis and mortality of patients. Additionally, the level of Sirtuin 1 did not reflect either improvement or mortality in this specific group of individuals.

Keywords: Sepsis, Sirtuin 1, mortality, multiplex PCR, SOFA score.

1. INTRODUCTION

Sepsis and septic shock harm millions of individuals annually worldwide and kill one in three to one in six of those affected. Sepsis is a potentially fatal illness resulting from an improper reaction of the host to infection.[1] Its most serious form is septic shock. It shows up as a reduction in blood pressure, which causes hypoxia, a defining feature of shock, and lowers tissue perfusion pressure[2].

For critically ill patients in the intensive care unit (ICU), sepsis frequently ranks as the primary cause of death. It continues to rank among the world's main causes of illness and mortality. Since the initial consensus definition was

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established in 1991, sepsis and septic shock are becoming more common by the day. Sepsis definition up until recently was a clinical illness that shows up as an infection-related systemic inflammatory response syndrome (SIRS). It is now simpler to identify sepsis in routine clinical practice according to the most recent (2016) redefinition of the condition, which emphasizes the host's insufficient response to infection. [2]

The 2016 Surviving Sepsis Campaign (SCC) guidelines emphasize the importance of promptly starting intravenous broad-spectrum antibiotics, ideally within an hour of identifying sepsis. Results are improved by early detection and suitable care in the first few hours following the onset of sepsis. The 2021 Surviving Sepsis Campaign guidelines reaffirm the importance of initiating antibiotic therapy within the first hour of recognizing sepsis.[1]

The global rise in multidrug-resistant (MDR) pathogen infections has greatly expanded, which in turn has restricted the range of antibiotic treatments. Hence, increasing the efficacy of antimicrobial medications and preventing the emergence of resistant bacteria during treatment are crucial priorities in the treatment of sepsis and septic shock.[3] Rising occurrence of carbapenem-resistant Enterobacterales (CRE) is a particularly alarming form of antimicrobial resistance (AMR) that presents a significant clinical challenge. It can lead to a serious problem due to its resistance to numerous final-line antibiotics, making treatment difficult and resulting in high mortality rates and costly hospital stays.[4] Obtaining a microbiologic diagnosis enables targeted treatment, which has been proven to enhance results and can help reduce the overuse of antibiotics, prevent antimicrobial resistance, and avoid unnecessary complications, such as Clostridioides (formerly Clostridium) difficile infections.[5]

There is a growing use of molecular tests that can identify various respiratory pathogens, such as bacteria and viruses, from just one respiratory sample.[6] Traditional culture-based methods take 2 to 3 days to identify and conduct antimicrobial susceptibility testing (AST) on bacteria. Syndromic molecular diagnostic panels have transformed clinical microbiology labs by being able to identify an organism and detect important antimicrobial resistance genes at the same time, directly from different types of specimens like whole blood, cerebrospinal fluid, and respiratory samples.[7]

Regarding monitoring sepsis prognosis, many different serum sepsis indicators have been commercially available in recent decades. These include the following: neutrophil CD64 (nCD64), procalcitonin, presepsin, interleukin 6 (IL-6), lipopolysaccharide-binding protein (LBP), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), serum soluble urokinase-type plasminogen activator receptor (suPAR), and C-reactive protein (CRP). Procalcitonin and presepsin are now thought to be the most promising diagnostics for the early detection of sepsis, as well as for supplying crucial prognostic data and directing therapy choices.[8]

SIRT1, a protein of the family of sirtuin, is a well-preserved post-translational regulator deacetylase that is NAD+-dependent, influencing inflammation. By eliminating acetyl groups from a variety of proteins, including histones and non-histone proteins, SIRT1 affects a wide range of biological processes. SIRT1 and inflammation are closely related, according to recent studies, and inflammatory diseases have been linked to alterations in SIRT1 expression and activity.[9]

There is abundant evidence indicating that overactivation of ER stress contributes significantly to the development of various diseases. It is crucial to prevent this excessive stress to preserve normal physiological function. Recently, there has been a growing focus on the study of Sirtuin1 (SIRT1) in relation to endoplasmic reticulum (ER) stress. Evidence is increasingly indicating that SIRT1, as a master regulator of ER stress, exerts a beneficial influence on a range of organ damage induced by ER stress through several mechanisms. These include the inhibition of cellular apoptosis and the promotion of autophagy.[10] Several research papers have demonstrated that SIRT1 has the ability to decrease the inflammatory reaction following sepsis.[11] There is emerging evidence suggesting a correlation between Sirtuin 1 level and sepsis in terms of disease risk, severity and mortality risk. The assessment of serum SIRT1 levels could potentially aid in improving the evaluation of disease progression, development of effective management approaches, and monitoring of survival outcomes in sepsis patients.[12]

The purpose of this study is to assess how well early targeted antibiotic treatment works for sepsis and septic shock patients employing the multiplex PCR for early detection of bacteria and its genes of resistance in addition to Sirtuin 1 as a novel inflammatory biomarker. The duration of ICU stays, days free of ventilatory support and the change in SOFA score were the primary outcome because it offers a sensitive, continuous measure of organ dysfunction that reflects the dynamic changes in critically ill patients and provides immediate assessment of patient response to intervention. Secondary outcomes included mortality rate, and Sirtuin 1 level.

2. PATIENTS AND METHODS

2.1. Study design

A prospective, single-center, open-label, parallel groups, randomized controlled study was conducted in accordance with the Declaration of Helsinki. Prior to taking part in the study, each patient provided written informed consent. Patients were randomly assigned to either the genotyping group, where samples were sent for multiplex PCR to detect infectious organisms, or the control group, where patients submitted culture specimens for antibiotic susceptibility testing within 24 hours before starting empirical

antibiotic treatment. We used a simple randomization method to carry out the random assignment, and to assist in creating random numbers, a web-based randomization system and https://www.randomizer.org/ were used.

Then the antibiotic regimen has been switched or not according to the culture results yielded after 48 hours of sampling, or the multiplex PCR group, in which the specimens were sent for multiplex PCR genotyping to detect organisms and their resistant genes if any, in few hours, and the need to switch antibiotic regimen was assessed after genotyping results. Participants were chosen based on their age (18–80 years old), a confirmed diagnosis of sepsis or septic shock, and their risk of contracting carbapenemase-producing organisms, which included living in a long-term care institution, having taken wide spectrum cephalosporins and/or carbapenems within the last three months, having polytrauma, diabetes, organ transplantation, mechanical ventilation, indwelling urine or venous catheters, and generally having poor functional status. Pregnant or nursing women, hematological abnormalities, acquired immunodeficiency syndrome, deadly traumatic injury, APACHE II scores of 34 or higher because of the high anticipated death rate of 80%, as well as primary viral or fungal diseases were among the exclusion criteria.

During the research period, patients were appropriately treated in accordance with the guidelines of the surviving sepsis campaign, and their prognosis and mortality were monitored. Study was authorized by Damanhour University's Faculty of Pharmacy Research Ethics Committee (Ref. no. 522PP50) and filed as NCT05459389 on ClinicalTrials.gov.

2.2. Patients and biochemical analyses

This study involved 52 patients with sepsis or septic shock, with pneumonia including community or hospital acquired, including 27 men and 25 women, (from May 2022 to September 2023) who were randomly assigned to either a control group using conventional culture techniques or a multiplex PCR group. A separate person carried out the randomization process using Microsoft Excel's computerized random number approach. Randomization was used to ensure unbiased group allocation, even though patients and researchers knew their assigned treatment. Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Charlson comorbidity index, and Sequential Organ Failure Assessment (SOFA) score were computed at the beginning of the trial. Routine sepsis markers TLC, CRP and PCT, and biochemical tests as serum creatinine and serum albumin were collected on day 1 and again on day 5. Blood samples were prepared and stored at -80°C before analysis. As directed by the manufacturer, the enzyme-linked immunosorbent assay (ELISA) kit (Sunred Biological Technology, Shanghai, China: Catalogue No.: 201–12-2558) was used to measure SIRT1 levels.

On the first day, the microbiology lab received specimens for microbial detection for multiplex PCR analysis or classical culture. Empiric antibiotics were administered within one hour of diagnosing sepsis or septic shock based on the suspected pathogens. After identifying the bacteria, the antibiotic regimen was adjusted, escalated, de-escalated, or maintained based on the detected organisms and their antibiotic sensitivities.

2.4. Calculating sample size

To calculate the required sample size, the G*Power program version 3.1.0 (Institut für Experimentelle Psychologie, Heinrich Heine Universitat, Dusseldorf, Germany) was utilized. A 96% power was anticipated for a total sample size of 50 patients to detect a medium to high effect size of 0.96 in the key outcome measure.

2.5. Statistical analysis

A total sample size of 48 patients was expected to have an 80% power to detect a medium to high effect size of 1.05 in the primary outcome measure. Data was fed into the computer and analyzed using IBM SPSS software suite version 26.0 (Armonk, New York: IBM Corp.) The qualitative data was described using numbers and percentages. The Shapiro-Wilk test was used to verify that the distribution was normal. Quantitative data was described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). At the 5% level, the findings' significance was assessed. The subsequent statistical analyses were utilized: A correction was made using Fisher's exact test when over 20% of cells had an expected count below 5. For categorical data, the Chi-square test was used to compare groups. Quantitative variables with normal distributions were compared between two groups using the student t-test; quantitative variables with abnormal distributions were compared between two groups using the Mann-Whitney test. The correlation coefficient of Spearman's rank was used to assess the relationship between the variables. The presented results had a significant level of $P \leq 0.05$, and all analyses were conducted using the intention-to-treat (ITT) technique.

3. RESULTS

Patients underwent screened for eligibility, randomized, and followed throughout the study as depicted in **figure 1.** Initially, 105 patients suffering from sepsis or septic shock were evaluated, resulting in excluding 33 patients due to not meeting inclusion criteria. Consequently, two groups of 72 patients, each with 36 members, were chosen at random. During follow-up, 20 patients dropped out from both groups, primarily due to loss of follow-up due to early hospital discharge (n=7), death before following up (n=5), and not available samples for cultures (n=8). A total of 52 patients, 26 in each group, were incorporated into the final analysis.

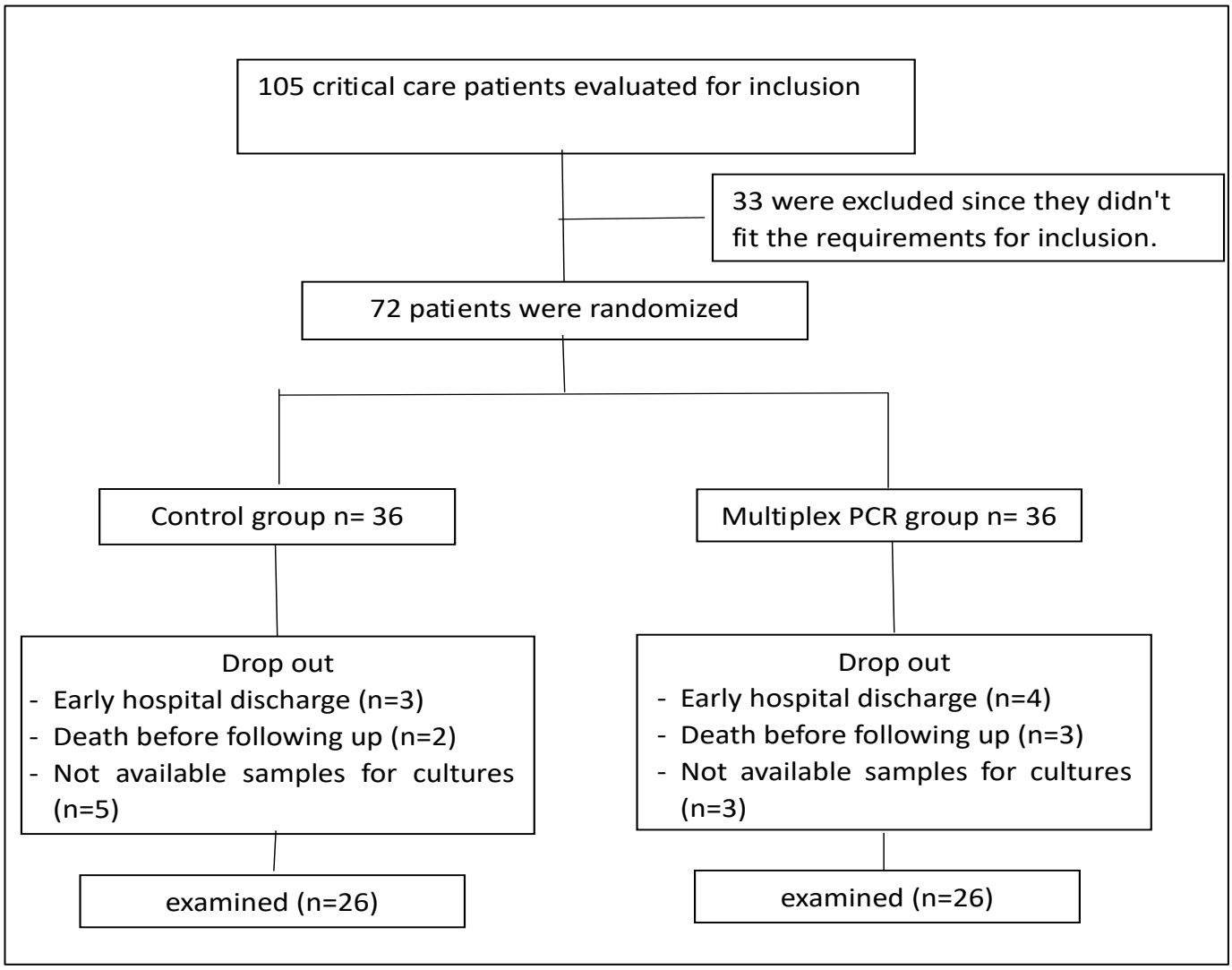

Figure 1: Diagram for the patient enrollment, randomization, and follow-up.

Regarding demographic information, no statistically significant difference found between groups at baseline, as age, sex, baseline chronic comorbidities presented by the Charlson comorbidity index, sepsis, septic shock, baseline serum creatinine and serum albumin levels, only statistically significant difference in APACHE II score with mean 12.12 ± 4.27 in the control group and 15.69 ± 6.60 in the multiplex PCR group, and the need for mechanical ventilator among control and multiplex PCR group (19.2% versus 53.8% respectively) as illustrated in **Table (1).**

Table (1): Demographics of patients at baseline in both groups under study

Demographic data	Control group	Multiplex PCR group	Test of significance	P - value
Age				
Median (IQR)	68.0 (59.0 –74.0)	68.0 (55.0 – 73.0)	U=306.0	0.558
Sex				
Male Female	46.2% 53.8%	57.7% 42.3%	$\chi 2$= 0.693	0.405
CCI				
Mean ± SD.	4.85 ± 2.24	4.15 ± 2.65	T= 1.018	0.314
Sepsis				
No Yes	23.1% 76.9%	30.8% 69.2%	$\chi 2$= 0.391	0.532
Septic shock				
No Yes	76.9% 23.1%	69.2% 30.8%	$\chi 2$= 0.391	0.532
APACHE II score				
Mean ± SD.	12.12 ± 4.27	15.69 ± 6.60	T= 2.321	0.024
S. Creatinine (mg/dl)				
Median (IQR)	1.06 (0.80 – 1.80)	1.15 (0.77 – 1.97)	U= 329.500	0.876
S. albumin (g/dl)				
Median (IQR)	3.34 (2.95 – 3.50)	3.30 (3.0 – 3.44)	U= 322.500	0.776
Ventilator				
No Yes	21 (80.8%) 5 (19.2%)	12 (46.2%) 14 (53.8%)	$\chi 2$=6.718	0.010

Data presented as mean±SD or median (range) or percentage as appropriate. P values were obtained by $\chi 2$ chi-square test or Fisher' s exact test, T Independent t test or U Mann–Whitney U test with significance set at $p < 0.05$. APACHEII: Acute Physiology and Chronic Health Evaluation II, CCI: Charlson Comorbidity Index

Among the 2 groups, Gram negative organisms were detected more frequently by both techniques such as Klebsiella, E-coli, Acinetobacter and Pseudomonas aeruginosa. The multiplex PCR technique detected 16 types of genes of resistance: KPC, CTX-M, NDM, VIM and Oxa-48 like gram negative organisms and MREJ and mecA/C for the gram-positive detected organisms mainly for MRSA. Enterobacteriaceae, extended-spectrum β-lactamases (ESBLs), such as CTX-M were detected as 50%. IMP, KPC, NDM, VIM, and OXA-48-like carbapenemase genes that provide resistance to beta-lactam antibiotics, such as carbapenems and cephalosporins were present as 38.5% NDM, 30.8% OXA-48 like, 7.7% VIM and 3.8% for KPC as illustrated in **Figures 2,3** and **4.**

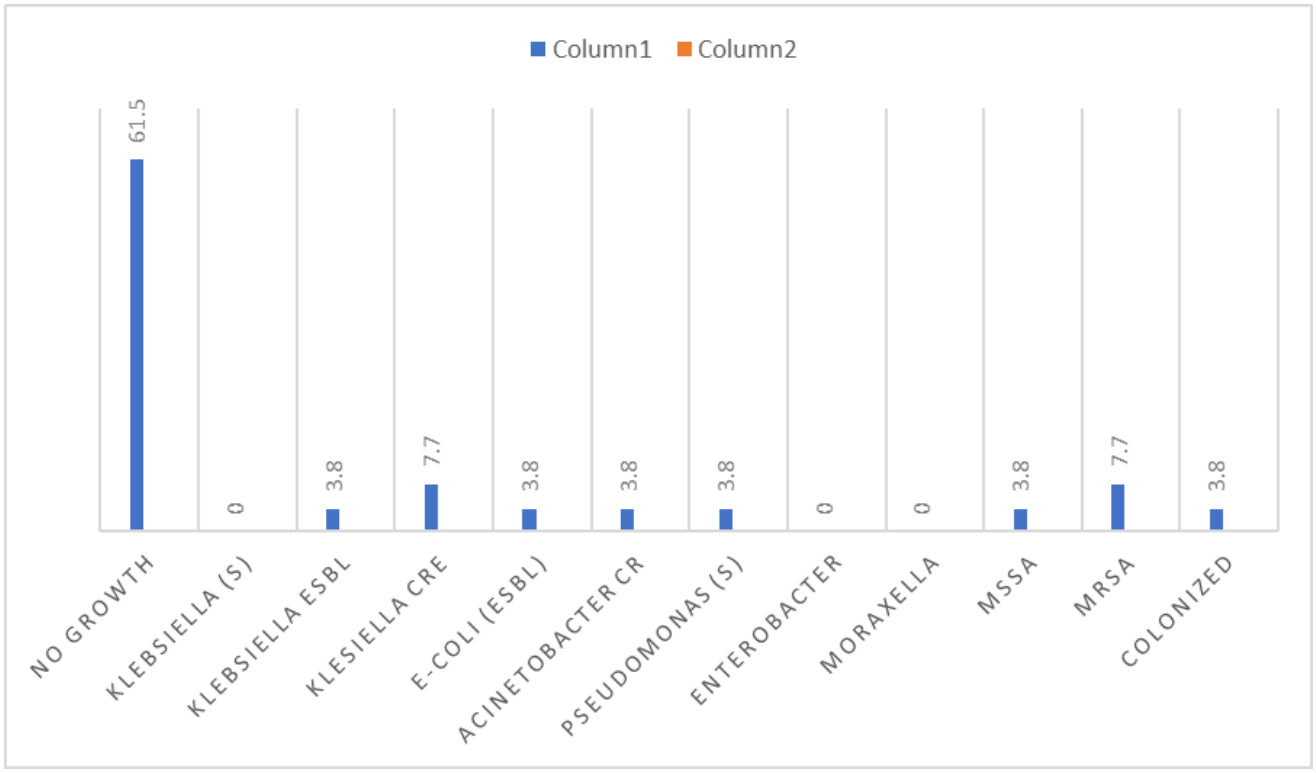

Figure 2. Culture results from conventional culture technique

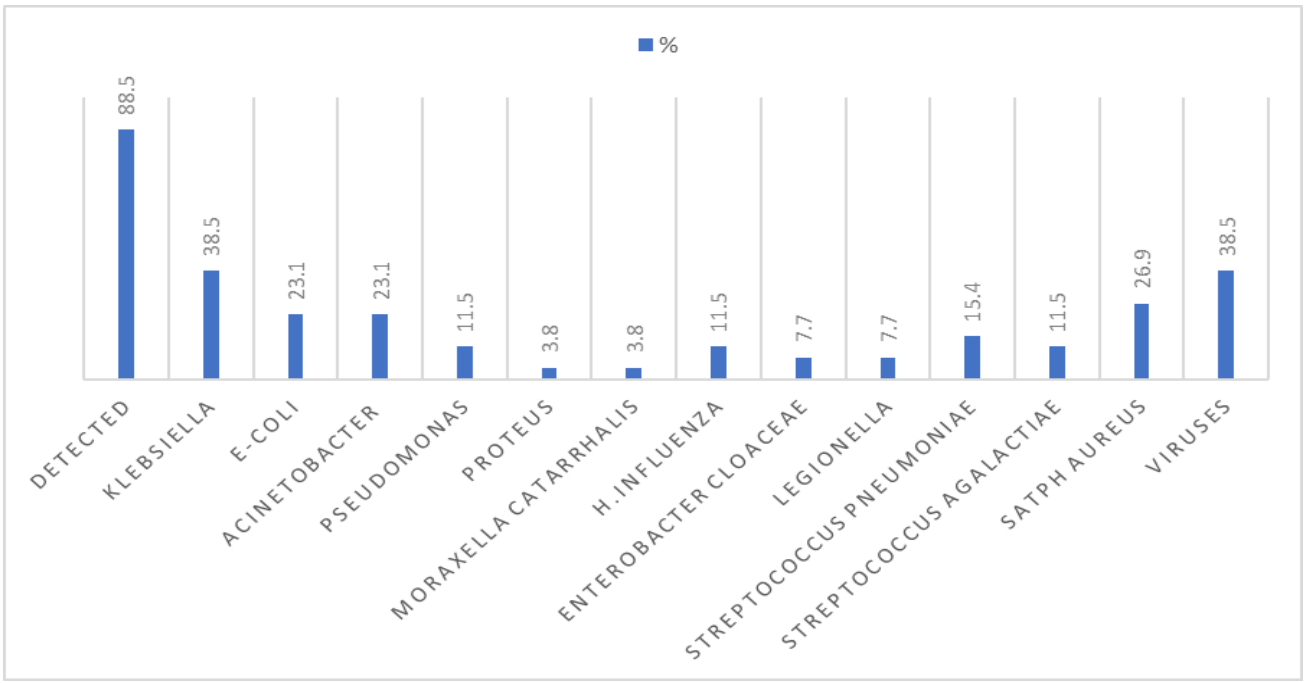

Figure 3. Organisms detected by the multiplex PCR technique

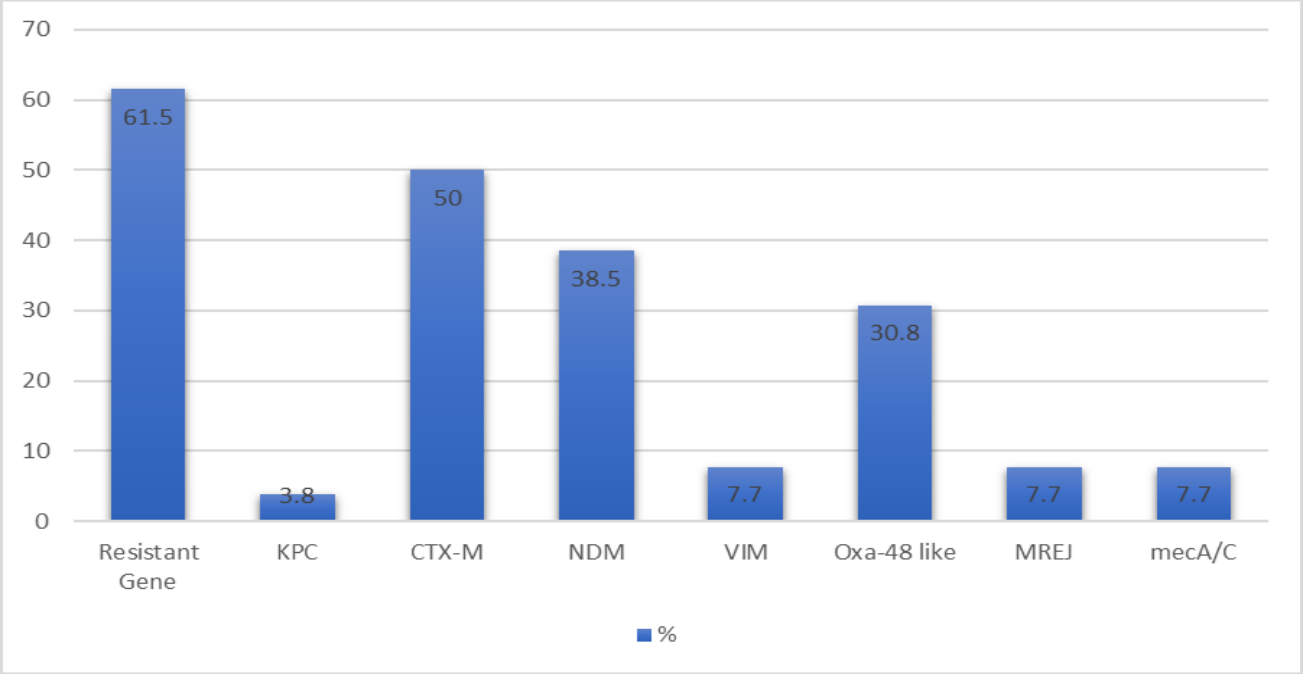

Figure 4. Distribution of the investigated cases in the intervention group based on the resistant gene (n = 26)

The new technique intervention did not differ from the widely used conventional culture technique, as there was no statistically significant difference between the two groups in terms of ventilator-free days (P-value = 0.362) or the percentage change in SOFA score from day 1 to day 5 (P-value = 0.679).

The Sirtuin 1 level was assessed on days 1 and 5, and its percentage change was not statistically significant, P-value of 0.227.

TLC and PCT showed the least amount of percent change with P-value o. 522 for TLC, whereas 0.067 was the P-value for PCT percent change, respectively. While the percentage change in CRP among studied groups was statistically significant P-value = 0.042.

Additionally, no statistically significant changes were seen between groups in terms of 30-day mortality, icu length of stay, or mortality rates. Mortality rate was 15.4%, in multiplex PCR group, while it was 7.7% in the control, the 30-day mortality rates were 11.5% and 15.4%. The corresponding P-values were 0.668 and 1 for the control and multiplex PCR groups, respectively.

There was a trend where those who died at the end of the study or at 30 days had lower median Sirtuin 1 levels compared to those who improved, nonetheless, there is no statistically significant difference; the corresponding P-values are 0.052 and 0.101.

Upon correlation of Sirtuin 1 at the start of the study with different parameters, there was a negative correlation between Sirtuin 1 and Age p 0.026 and CCI P-value = 0.003, other parameters were not statistically significant correlated with Sirtuin 1, as need for ventilator P-value = 0.555, APACHE II score P-value = 0.159, S. Creatinine (mg/dl) P-value= 0.146, S. albumin (g/dl) P-value = 0.495, SOFA score (day1) P-value = 0.109, TLC (day1) P-value = 0.661, CRP (day1) P-value = 0.540 and PCT (day1) P-value = 0.795.

There is a statistically significant difference in Sirtuin 1 levels between males and females, where males having a higher median Sirtuin 1 level (8.0) compared to females (6.5) with a p-value of 0.017 as illustrated in **figure 5.**

The univariate and multivariate linear regression analyses for the variables influencing sirtuin on day 1 are displayed in **Table 2.** At day 1, age and CCI had a significant impact on the sirtuin 1 level in both groups under study (p <0.001 and =0.001). On the other hand, sex, APACHE II score and SOFA scores were not significantly affecting sirtuin 1 level at day 1.

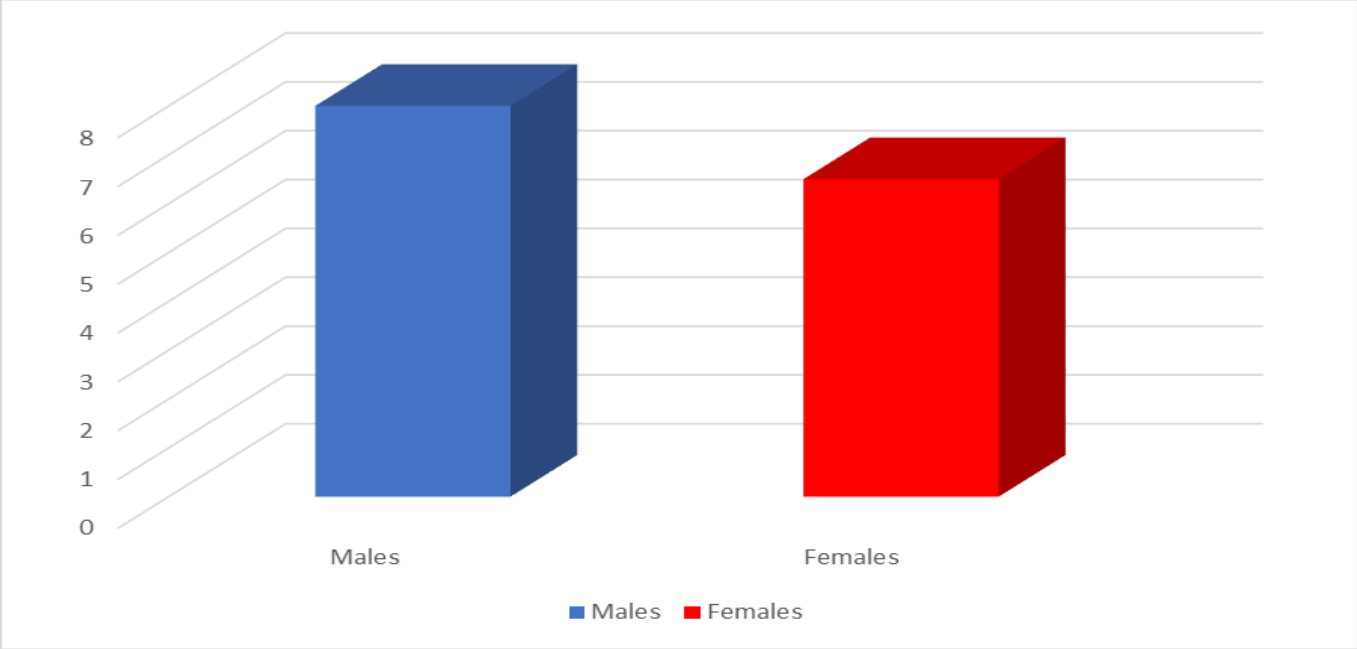

Figure 5. Relation between Sirtuin 1 level and Sex

Table (2): Univariate and multivariate linear regression for the factors influencing Sirtuin on Day 1

	Univariate		#Multivariate	
	P	B (LL – UL 95%C. I)	p	B (LL – UL 95%C. I)
Sex	**0.085**	1.615(-0.232 – 3.462)		
Age	**<0.001***	-0.113(-0.161 – -0.065)	**0.006***	-0.098(-0.166 – -0.030)
Charlson comorbidity index	**0.001***	-0.610(-0.960 – -0.259)	0.542	-0.142(-0.604 – 0.321)
APACHE II score	**0.057**	-0.155(-0.315 – 0.005)		
SOFA score day 1	**0.306**	-0.206(-0.607 – 0.194)		

B: Unstandardized Coefficients C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 were included in the multivariate*: Statistically significant at p ≤ 0.05

4. DISCUSSION

The goal of this study was to evaluate the impact of rapid detection of infectious organisms and their resistance if any in patients with sepsis and septic shock. Furthermore, serum Sirtuin 1 level was tracked in this study to be correlated with patient outcomes and mortality in sepsis and septic shock. Multiplex PCR techniques are faster than traditional culture-based techniques in detection of infectious organisms in sepsis patients. Its utility, as also declared in different studies, is mainly in early detection of the causative organisms causing sepsis and switching to the appropriate antibiotics. The detection rate can be raised through combined detection,

which offers promising performance and application opportunities.[13-17]. Its effects on hospital stay duration, death, and 30 days mortality wasn't verified by using this technique and more prospective studies are required to prove its impact on death and length of hospital stay. According to a meta-analysis and systematic review, using multiplex PCR improved the optimal antiviral and infection control therapy of patients with influenza while also reducing the overall length of stay and time to results for patients.[18]

The change in SOFA score the primary outcome, ventilator-free days and mortality, were not significant using multiplex PCR technique than the traditional culture based. Several factors might account for these findings. First, our study's sample size may have been insufficient to detect modest yet clinically relevant differences. In addition, potential baseline differences between groups could have influenced the outcomes, despite our efforts to balance confounding variables.

The multifactorial nature of sepsis, where numerous physiological and treatment-related factors play a role, may also dilute the measurable impact of our intervention on these endpoints. In addition, the change in sepsis markers did not differ in any way that was statistically significant as TLC and PCT. But only percentage change of CRP was statistically significant. CRP is a well-established biomarker for inflammation and has been correlated with sepsis severity[19].

Its significant reduction suggests that the intervention may have had an early beneficial effect on the inflammatory response. However, the clinical relevance of this finding should be interpreted with caution, as a change in CRP does not directly translate to improved long-term clinical outcomes[20]. Future studies with larger sample sizes and more comprehensive endpoints are needed to fully elucidate the impact of CRP modulation on sepsis progression and overall patient prognosis.

The promising outcome is to decrease the use of broad-spectrum antibiotics by de-escalation according to the early detection of pathogenic organisms, also, if it is confirmed that it is mainly viral infection.

The effectiveness in terms of mortality, hospital stay duration, and 30-day mortality have not been verified through this approach, and additional prospective studies are required to establish its impact on mortality and hospital stay duration.

Further investigation with randomized controlled trials is essential to address the many outstanding concerns related to using multiplex rapid molecular testing for diagnosing and treating sepsis and septic shock patients. Moreover, demonstrating its cost-effectiveness in high-risk populations with elevated mortality rates is also necessary.

Regarding the Sirtuin 1 level, the change in its level was not significant between the two groups from day 1 to day 5. The level of Sirtuin 1 did not show a significant relationship with mortality, 30-day mortality, or hospital length of stay. However, it did exhibit a significant negative correlation with age and chronic comorbid conditions as indicated by the Charlson Comorbidity index. On the other hand, the negative correlations with serum creatinine, APACHE II score, and SOFA score were not found to be significant and require further investigation. Although there were initially positive correlations between Sirtuin 1 and TLC as well as CRP on day 1, these correlations later turned negative. However, both correlations were weak and non-significant, which contrasts with previous studies that reported a negative correlation between Sirtuin 1 and CRP and TLC.[21]

PCT and Sirtuin 1 levels were found to be positively correlated, but it was not statistically significant. The initially positive correlation between Sirtuin 1 and serum albumin on day 1 changed to a negative correlation by day 5. Rebuilding or re-synthesizing SIRT1 after degradation relies on factors such as transcriptional regulation, protein synthesis rates, and cellular conditions. Obtaining precise information on the half-life of SIRT1 and its rebuilding time in adult humans may necessitate specific experimental data from studies on human cells. Both the positive and negative correlations between Sirtuin1 and serum albumin were weak and not significant.

At baseline, it was noted that males exhibited a notably higher level of Sirtuin 1 than females, but this did not have any impact on the final outcome, including improvement, mortality, or length of stay. One potential explanation for this finding is the influence of sex hormones; for example, estrogen has been demonstrated to modulate Sirtuin 1 expression in various tissues pointing out that estrogen levels may also be impacted by aging[22]. Further explaining the variation between male and female participants may be the fact that Sirtuin 1 is a crucial regulator of metabolic and inflammatory pathways, and sex differences in these processes may be innate [23]. These findings suggest that sex-specific differences in Sirtuin 1 levels might influence the efficacy of therapeutic interventions targeting this pathway. Future research should focus on elucidating the molecular mechanisms underlying these differences and exploring the potential for personalized treatment strategies based on sex-specific profiles.

5. CONCLUSION

The data collected from this study showed no significant influence of multiplex PCR on mortality, length of hospital stay, or 30-day mortality. Similarly, significant correlations were not found between Sirtuin 1 and sepsis markers. It appears to be mainly associated with age and chronic comorbid conditions. Nevertheless, these findings call for further exploration through broader scale and more longitudinal studies.

6. STUDY LIMITATIONS

The current research limitations are the small sample size and the brief follow-up period of Sirtuin 1 level. Lack of data regarding exact Sirtuin 1 pharmacokinetics in adult humans makes it difficult to follow and estimate its level. Clinical correlation was needed to establish the significance of the multiplex PCR technique in identifying multiple pathogens and detecting genes associated with antimicrobial resistance. Additionally, there were inconsistencies in polymicrobial samples.

DECLARATIONS

CONFLICT OF INTEREST

None of the authors reveal any conflicts of interest.

ETHICAL APPROVAL

The Declaration of Helsinki carried out this study. Before the study started in May 2022, it was approved by the Faculty of Pharmacy's Research Ethics Committee at Damanhour University in Egypt (Ref. no. 522PP50). Registered on ClinicalTrial.gov with code no.: NCT05459389, (The first posted July 15, 2022). https://clinicaltrials.gov/study/NCT05459389

PARTICIPATION CONSENT

Every participant gave written informed consent and consented to be included in this clinical investigation.

AVAILABILITY OF DATA

Upon reasonable request, the corresponding author will make the data available.

CONSENT FOR PUBLICATION

Not applicable.

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