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Original Research

Relationship Between *Acinetobacter baumannii* Pneumonia and Human *CTLA4* Gene Polymorphism (rs231775) in Relation to IL-7 Serum Levels: A Study on Host–Pathogen Dynamics

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Abstract

Background: The relationship between genetic variations and susceptibility to infection provides insight into the pathogenesis of diseases caused by infections, illustrating host–pathogen interactions, informing preventive measures, and offering a novel therapeutic approach. **Methods**: This cross-sectional study was conducted at Baghdad Medical City Hospital from April 2024 to October 2024 and involved 100 subjects referred to the laboratory for confirmatory diagnosis. Bacterial isolates were identified using routine phenotypic and biochemical tests. DNA was extracted from participants and used to genotype the rs231775 single-nucleotide polymorphism (SNP) using TaqMan® SNP Genotyping Assays; the serum levels of interleukin-7 (IL-7) were also determined for the studied groups. **Results**: A total of 32 patients were infected with *Acinetobacter baumannii*, and 68 were controls. No statistically significant difference was noted between the blood group and the infection status ($p = 0.109$). The results indicated a highly statistically significant association between genotype AA and the occurrence of disease ($p = 0.003$) and an extremely significant association between genotype GG and the occurrence of disease ($p < 0.001$), respectively. The results indicated that individuals with the AA genotype had lower odds (odds ratio (OR) = 0.217) of having the disease, as did those with the AG genotype (OR = 0.80). However, the presence of the GG genotype GG exhibited higher odds in patients compared to the controls (OR = 5.439). Serum levels of IL-7 differed significantly between patients and controls ($p < 0.001$) and between the three genotype groups in patients ($p = 0.029$). **Conclusion**: Individuals with genotypes AA and AG are characterized by protective attributes against infection with *Acinetobacter baumannii*, while those having the genotype GG are more prone to infection with this bacterium. Furthermore, an association between specific genotypes and serum levels of IL-7 can hint at the possible role of genetic polymorphism in modulating immune response in relation to bacterial infection.

Keywords: interleukin-7; *Acinetobacter baumannii*; CTLA-4 antigen; reverse transcriptase polymerase chain reaction; genetic polymorphism; single nucleotide; host–pathogen interactions; rs231775

1. Introduction

Recently, humanity has begun to face a significant issue in response to the increasing spread of antibiotic-resistant bacteria. This situation has led to a worrying rise in mortality and the introduction of increasingly difficult-to-control diseases. *Acinetobacter baumannii* is regarded as one of these flexible pathogens due to an observed increase in frequency in hospitals, resistance to therapy, and association with higher mortality and morbidity rates. The occurrences of *Acinetobacter baumannii* outside clinical settings indicate a considerable danger related to ecological contamination [1]. Thus, the remarkable capacity of *Acinetobacter baumannii* to evolve resistance to a wide range of antibiotics poses a substantial concern in healthcare settings. Indeed, *Acinetobacter baumannii* is particularly known for causing acute and invasive hospital infections, such as bloodstream infection, ventilator-associated pneumonia (VAP), skin and soft tissue infections, meningitis, and urinary tract infections (UTIs) [2,3]. Neonatal regions (hospital intensive care units, NICUs) and burns units are principal places where seriously sick patients develop infections from opportunistic pathogens [4,5].

Meanwhile, cytokines and chemokines are strictly controlled, excreted proteins that govern several cellular functions, including differentiation, migration, and growth. These proteins provide cues for the trafficking of immune cells, adjust the placement of immune cells in tissues and organs, and stimulate the progression of an immune system that has been altered in response to the immune insult. Major categories of cytokines comprise interferons, interleukins, and the tumor necrosis factor (TNF) family members [6,7]. Interleukin-7 (IL-7) is secreted from epithelial cells in host tissues, keratinocytes, stromal cells, or tumors and performs an expanded variety of immune functions controlled by the IL-7 receptor (IL-7R) [8]. The biological roles of IL-7 make this protein a pivotal adjuvant that enhances the efficiency of vaccines, as IL-7 can boost and expand systemic immune responses against microbes

by lengthening the lifespan of lymphocytes, augmenting effector cell action, and increasing the production of antigen-specific memory cells [9].

Host genetics has the potential to influence the susceptibility of a person to a disease and the ability of that individual to develop an effective immune response, particularly in cases of *Acinetobacter* infections. Research has shown that genetic variations, such as single-nucleotide polymorphisms (SNPs), in immune-related genes can significantly influence the response of the host to infections. Thus, polymorphisms in genes producing cytokines and any associated receptors, such as IL-6, TNF-α, and IL-10, can modify the inflammatory response, which is critical in treating bacterial infections, particularly those caused by *Acinetobacter* spp. [10]. A SNP is a DNA sequence polymorphism that happens because of changes to a single nucleotide in a given position at the genome level [11]. SNPs are useful indications of clinical diagnosis, and can be used to explore between-individual variances in many domains [12,13]. Thus, this study aimed to identify the frequencies and rs231775 SNP genotypes and alleles in the selected patients and to investigate the influence of this infection on IL-7 levels in people with different rs231775 SNP genotypes.

2. Materials and Methods

2.1 Subjects

This study is a cross-sectional approach that involved 100 individuals who were suffering from skin with blisters, cough, or trouble breathing, chest pain, burning feeling while urinating, and a suspected *Acinetobacter baumannii* infection, and had been referred to the laboratory. The bacteria were identified in 32 subjects, while 68 participants did not show positive culture results; thus, the 68 negative samples were considered as healthy controls.

2.2 The Study Duration and Venue

This study was conducted from April 2024 to October 2024 at the Bacteriology laboratory/Baghdad Medical City Hospital.

2.3 Sample Collection

Samples were obtained from patients who attended intensive care units, surgical wards, and outpatient clinics within the study period. The types of samples collected included blood, urine, sputum, wound swabs, and other relevant clinical specimens as indicated by the clinical presentation of the patient.

2.4 Sample Processing

Samples were processed following standard microbiological procedures.

(1) Blood samples: bottles of blood culture incubated in a blood culture system (e.g., BACTEC, BD). Positive cultures were subcultured onto MacConkey and blood agar plates. An aliquot of blood (2 mL) from each patient and control was aspirated into an ethylenediaminetetraacetic acid (EDTA) tube for later molecular investigation.

(2) Urine samples: urine samples were plated on blood agar and MacConkey agar using a calibrated loop.

(3) Sputum and wound swabs: Samples were directly plated on MacConkey agar, blood agar, and chocolate agar. To assess the quality of the samples and the preliminary identification of organisms, a Gram stain was conducted.

2.5 Identification of Acinetobacter Species

Isolates were identified as *Acinetobacter* species based on the following criteria:

(1) Colony morphology: Observations of the colony characteristics on blood agar plates and MacConkey within 24–48 hours of incubation at 37 °C.

(2) Biochemical testing: Preliminary identification was conducted using the oxidase test (*Acinetobacter* species are oxidase-negative). Further identification was performed using a series of biochemical tests, including IMViC, urease test, and motility.

2.6 Extraction of DNA

DNA isolation from patient and control blood samples was performed using Quick–DNA™ MiniPrep kit (Zymo Research, Catalog Nos. D3024 & D3025, Irvine, CA, USA). The kit included Genomic Lysis Buffer, DNA prewash buffer, DNA wash buffer, DNA elution buffer, Zymospin™ IIC columns, and collection tubes; all reagents were stored at room temperature. Before use, β-mercaptoethanol was added to the genomic lysis buffer at 0.5%. DNA was purified from $\leq$200 µL of whole blood (or other sample type) without proteinase K or organic solvent, using microcentrifugation. The typical elution volume was $\geq$50 µL, yielding up to 25 µg of DNA (A280/A260 $>$1.8), with fragment size up to $>$40 kb.

DNA quality and purity were assessed using the OD260/280 ratio with a NanoDrop spectrophotometer. Only samples with a ratio between 1.8 and 2.0 were included for genotyping.

2.7 Detection of the rs231775 SNP

Genotyping was performed using TaqMan® SNP genotyping assays (Applied Biosystem, Thermo Fisher Scientific) according to the manufacturer's instructions. Each assay contained an allele-specific (Minor Groove Binder) MGB probe labeled with VIC™ and FAM™ dyes, as well as sequence-specific primers. Additionally, TaqMan® SNP genotyping assays were used to detect the rs231775 SNP in genomic DNA, which uses allele-specific probes and primers to distinguish between two alleles at a single SNP locus. Each probe was labeled with a distinct fluorescent dye, allowing for both alleles to be detected in the same reaction.

2.8 Measurement of Interleukin-7 (IL-7)

The serum levels of IL-7 were quantified using a commercially available human IL-7 ELISA kit (Elabscience, Catalog No. E-EL-H0080) (Wuhan, Hubei, China) according to the manufacturer's instructions. Absorbance was measured at 450 nm using a microplate reader, and IL-7 concentrations were calculated using a standard curve derived from known concentrations.

2.9 Statistical Analysis

Data analyses were conducted using SPSS version 26 (IBM®, USA). Categorical information is presented as frequencies, while continuous improvement is represented by the mean ± standard error (SE). Chi-square of independence, independent samples *t*-test, and analysis of variance (ANOVA) were used wherever relevant. A p-value ≤ 0.05 was considered statistically significant.

3. Results

This study involved 100 subjects, with 32 assigned to the patient group and 68 considered as controls. Males and females constituted 57 and 43 subjects, respectively. The percentages of male patients and controls were similar, at 53.1% and 58.8%, respectively. Furthermore, the females in the patient group comprised 46.9%, while those in the control group comprised 41.2%. There was no significant association between gender and the groups of subjects under study ($p = 0.591$) (Table 1).

Table 1. Distribution of the patients and controls across gender.

Gender	Frequency (%)	Patient	Control	*p*-value
Male	Number	17	40	0.591
	%	53.1	58.8	
Female	Number	15	28	
	%	46.9	41.2	

Table 2 describes the distribution of participants in the patient and control groups in relation to the relevant blood group. The findings indicate no significant association ($p = 0.109$) between blood groups and the assigned category of the studied subjects (patients or controls). Notably, blood group A+ was the most frequently observed, while A– was the least in both patients and controls.

An independent *t*-test was used to determine the difference between the mean values of certain demographic data for patients and controls. The comparisons revealed no significant differences between the mean age of patients (40.5 ± 1.89 years) and that of the controls (42.19 ± 1.34 years) ($p = 0.474$). Moreover, there were no statistically significant differences among the mean weight, height, and body mass index (BMI) of the patients and controls: the respective values of these variables in order are as follows:

Table 2. The distribution of blood groups across participants.

Blood group	Patients	%	Controls	%	*p*-value
A+	11	34.4%	15	22.1%	0.109
B+	2	6.3%	9	13.2%	
AB+	3	9.4%	7	10.3%	
A–	4	12.5%	1	1.5%	
B–	5	15.6%	9	13.2%	
O+	3	9.4%	10	14.7%	
O–	3	9.4%	5	7.4%	
AB–	1	3.1%	12	17.6%	

93.59 ± 3.3 kg, 85.54 ± 3.03 kg ($p = 0.109$); 1.53 ± 5.85 m, 1.7 ± 0.01 m ($p = 0.147$); 32.31 ± 1.72 kg/m^2, 29.73 ± 1.10 kg/m^2 ($p = 0.198$), respectively (Table 3).

Table 3. The demographic parameter values for the patient and control groups.

Variables	Group	Mean	SE	*p*-value
Age (years)	Patients	40.5	1.89	0.474
	Controls	42.19	1.34	
Weight (kg)	Patients	93.59	3.30	0.109
	Controls	85.54	3.03	
Height (meters)	Patients	1.53	5.85	0.147
	Controls	1.7	0.01	
BMI (kg/m^2)	Patients	32.31	1.72	0.198
	Controls	29.73	1.10	

The Ct values ranged from 18 to 25 cycles for the first allele and 18 to 29 cycles for the second allele, signifying effective amplification. The curves with no anomalies or irregularities exhibited a typical sigmoid shape. Any observed minor variations in Ct values could be attributed to slight differences in sample preparation or pipetting accuracy.

An independence chi-square test was conducted to evaluate the relationship between a specific genotype and disease status. The results indicated that the AA genotype was markedly more common in the controls (85.4%) than in the patients (14.6%), suggesting a protective effect. A calculated odds ratio (OR) of 0.217 ($p = 0.003$) supports this notion, indicating that individuals with an AA genotype are significantly less likely to be patients. The possession of the AG genotype exhibited no significant association (OR = 0.800; $p = 0.647$), suggesting no influence on disease susceptibility. The GG genotype was significantly more frequent in patients (58.1%) than in controls (41.9%), with an OR of 5.439 ($p < 0.001$). The A allele was significantly more common in controls (66%) and was associated with a reduced risk of disease (OR = 0.232; $p < 0.001$). Finally, the G allele was more frequent in patients (69%) and significantly associated with a higher risk of disease (OR = 4.30, $p < 0.001$) (Table 4).

Table 4. Genotypes and allele associations with the rs231775 SNP.

rs231775 genotype	Output	Patients	Controls	OR	*p*-value	95% CI
AA	Number	6	35	0.22	0.003**	0.08–0.60
	%	14.6	85.4	0.10		
AG	Number	8	20	0.80	0.647	0.31–2.08
	%	28.6	71.4	0.38		
GG	Number	18	13	5.44	<0.001***	2.16–13.70
	%	58.1	41.9	2.56		
A	Number	20	90	0.23	<0.001***	0.12–0.44
	%	31	66			
G	Number	44	46	4.30	<0.001***	3.67–4.94
	%	69	34			

OR, odds ratio; 95% CI, 95% confidence interval.

**Highly significant $p < 0.01$, ***very highly significant at $p < 0.001$.

The mean serum concentration of IL-7 (1035 ± 62.9 pg/mL) differed very highly significantly ($p < 0.001$) from that of the controls (297 ± 32.6 pg/mL) (Table 5).

Table 5. A comparison of the IL-7 serum levels between patients and controls.

Group	Mean IL-7 concentration (pg/mL)	SE	*p*-value
Patients	1035	62.9	<0.001***
Controls	297	32.6	

***Very highly significant at $p < 0.001$.

A comparison of the mean serum levels of IL-7 was conducted among the three genotypes in the patient group, namely, AG, AA, and GG. The results clarified that the respective means of these genotypes were 498 ± 79.6 pg/mL, 417 ± 63.8 pg/mL, and 720 ± 89.7 pg/mL, respectively. A significant difference was obtained ($p = 0.029$) (Table 6).

Table 6. A comparison of the IL-7 levels among genotypes of rs231775.

rs231775 genotype	Mean IL-7 concentration (pg/mL)	SE	*p*-value
AG	498	79.6	
AA	417	63.8	0.029*
GG	720	89.7	

* Significance at $p < 0.05$.

4. Discussion

Connections between diseases and blood type have been explored since the 1900s, when scientists revealed that antigens and antibodies are innate components of the immune system. Nonetheless, due to the absence of antigens in some blood groups, there have been various contentious topics regarding the relationship between the ABO blood groups and an increased liability to specified non-infectious and infectious illnesses [14]. The results of the present work illustrate no significant relationship between blood groups and the occurrence of infection; this finding aligns with other studies that found no considerable connection between susceptibility to COVID-19 and ABO and D (Rh system) [15]. Conversely, several blood groups were observed to be statistically exclusive for *P. aeruginosa*, *S. aureus*, and *E. coli* infections [16]. Similar to age and gender, the blood group of a patient is an intrinsic factor that cannot be changed; thus, a high-risk group is defined as a blood group strongly associated with a specific disease. It is worth mentioning that the biological mechanism through which such an association occurs has yet to be completely explained [15].

Obesity, measured by BMI, has a definite but not precisely clear impact on the immune system through various immune mediators, leading to increased susceptibility to diseases and infections. The data obtained imply that obese individuals are more at risk of developing multiple types of infections, such as postoperative infections, and other hospital-acquired infections, and are more likely to develop serious infection-related complications than people of normal weight [17]. The results of the current work do not align with those presented previously [18], possibly due to the nature of the elected candidates in the study.

The SNP rs231775 in the *CTLA-4* gene has previously been investigated for its potential association with various illnesses, including microbial infections. This SNP promotes the modification of the threonine amino acid to alanine at position seventeen in the leader peptide of CTLA-4 [19]. The first evidence was provided by a separate study, which identified *CTLA-4* rs231775 as a predictive marker for human survival with sepsis [20]. This result is broadly consistent with the findings in this study, where patients were more likely than controls to have the rs231775 GG genotype.

However, we acknowledge that the cross-sectional design limits our ability to infer a causal relationship between the *CTLA-4* rs231775 polymorphism and *Acinetobacter baumannii* infection. As noted, the possibility of reverse causality and unmeasured confounding factors remains.

Interleukin-7 is a pleiotropic molecule, primarily generated by stromal cells [21], which is an important factor to T and B cell growth in primary lymphoid organs, as well as to the control of proliferation of mature T cells in the periphery [22]. The findings of the present study align with the above-mentioned discoveries, which indicate the significance of IL-7 in regulating the inflammatory response initiated by microbial infections. The rs231775 SNP, located in the *CTLA-4 gene*, can affect cytokine levels, including IL-7 [23]. This finding is supported by the present study, which demonstrated a significant difference in IL-7 serum levels among individuals with the rs231775 genotype.

IL-7 also regulates proinflammatory cytokines IFN-γ and TNF-α, both essential in the immune response to infection. Indeed, IL-7 promotes Th1 differentiation and CD8+ T cell activity, enhancing IFN-γ production. Additionally, IL-7 upregulates TNF-α in activated immune cells. Thus, IL-7 variations linked to the rs231775 SNP in the *CTLA-4* gene may impact both cellular and cytokine-mediated immunity, contributing to infection susceptibility and highlighting the broader immunological relevance of this polymorphism [24,25].

The impact of rs231775 on disease vulnerability and development underscores the significant role of genetic factors in the normal functioning of the immune system and overall disease progression. Such associations will be immensely useful for understanding how genetic variations influence the host immune response to infection, for developing evidence-based therapy practices, and for further developing treatments specifically targeted at these associations. Thus, thoroughly outlining these connections is fundamental to effectively incorporating genetic data into medical practice and care for the sick [26]. In conclusion, the present work shows the status of genetic polymorphism (rs231775) in the susceptibility to infectious diseases and emphasizes the crucial role of IL-7 in modulating immune responses.

5. Limitations of the Study

(1) A key limitation of this study is the small sample size, which may reduce statistical power and limit the detection of subtle associations. This was due to strict inclusion criteria, focus on a specific patient population (e.g., those infected with *A. baumannii*), and logistic challenges such as limited sample availability and resources. While these measures ensure data quality, these measures may also limit generalizability. Therefore, future studies with larger and more diverse cohorts are recommended to validate these findings.

(2) IL-7 levels were compared across *CTLA-4* rs231775 genotypes using appropriate statistical tests. Multiple comparison correction (e.g., Bonferroni) was not applied due to the limited number of planned, hypothesis-driven tests and the small sample size. Moreover, unadjusted *p*-values are presented due to the risk of increased Type II error, meaning the results should be interpreted with caution.

(3) Antimicrobial susceptibility testing (AST) was not performed in this study due to several limiting factors and resource and logistic limitations. Our study focused on genetic susceptibility (*CTLA-4* rs231775), and clinical isolates were limited and not preserved for further testing. Therefore, we recommended that further research include both host and pathogen factors.

6. Conclusions

In conclusion, this study presents the status of the rs231775 genetic polymorphism regarding susceptibility to infectious diseases and emphasizes the critical role of IL-7 in regulating immune responses.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

MMRA-R formulated the study design and was responsible for writing the manuscript, WA-EB and ZFA did the practical section of this work, and RSA-S was responsible for the statistical analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee of the Microbiology Department at the Medical College of Mustansiriyah University (approval number 153, dated 20/03/2024). Verbal informed consent was obtained from all participants prior to sample collection, and this procedure was specifically approved by the ethics committee.

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Conflict of Interest

The authors declare no conflict of interest.

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