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Association of TLR7 Variants with Secondary Bacterial Pneumonia in COVID-19 Patients

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ABSTRACT

Variations in the TLR7 gene have been linked to impaired immune signaling, which may increase a person's risk of developing secondary infections and developing severe COVID-19. **Objectives:** To investigate the relationship between variations in the TLR7 gene and the prevalence of co-infections and secondary bacterial pneumonia among hospitalized COVID-19. **Methods:** A case-control study was a hospital-based study done among 200 RT-PCR-confirmed COVID-19 patients. The secondary bacterial pneumonia (SBP) was determined as another type of clinical deterioration that appeared over 48 hours of admission and was proven by radiological infiltrates and the increase of inflammatory factors; the microbiological confirmation was viewed as supportive but not obligatory. Hardy-Weinberg equilibrium of the female control group was checked, and the genotype was determined with the help of Taqman SNP assays. **Results:** The average age of the participants was 45.6 ± 12.3 years, and 60 percent of them were men. Among the SBP cases, 85% had microbiological confirmation, while 15% fulfilled predefined clinical, radiological, and inflammatory marker-based criteria for SBP despite negative cultures. Hence, pathogens in SBP cases were *Klebsiella pneumoniae* 25%, as well as *Staphylococcus aureus* 35%. **Conclusions:** TLR7 gene polymorphisms were substantially linked to a roughly three-fold higher risk of secondary bacterial pneumonia in this cohort of hospitalized COVID-19 adults, ages 18 to 65. These results imply that bacterial superinfection may be predisposed by compromised TLR7-mediated antiviral innate responses.

INTRODUCTION

Coronavirus is one of the most important disease-causing organisms, specifically infections in adults and children associated with the upper respiratory tract [1]. Coronavirus outbreaks have been associated with Pneumonia, Middle East respiratory disease (MERS), severe acute respiratory syndrome (SARS), and an emerging coronavirus that originated in Wuhan, China [2, 3]. These early investigations either reported very few cases, found no cases at all, or failed to note the presence of secondary infections or co-infections [4, 5]. Though host factors such as age, comorbidity, mechanical ventilation, and corticosteroid use are reported risk factors that regulate the occurrence of SBP in COVID-19, there is little information regarding how the host genetic susceptibility regulates the susceptibility to secondary infections by bacteria. The X-linked toll-like receptor 7 (TLR7) is a vital part of early antiviral immunity, detecting single-stranded RNA viruses and triggering type I interferon responses, which are required to initially clear viruses and regulate immunity. Research using both human and murine models shows that TLR7 loss-of-function or deficiency variants are linked to worse COVID-19, higher

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viral loads, and impaired interferon activation [6]. The role of the innate immune system in regulating the intensity and course of viral infections has been highlighted by the COVID-19 pandemic [7]. To recognize the receptor on the pattern, a Toll-like receptor 7 (TLR7) on the X chromosome is a very important requirement against RNA viruses for the host's defense [8]. Hence, type I interferon (IFN) responses depend on Antiviral immunity, which is usually triggered when single-stranded RNA is detected by TLR7 [9]. TLR7 genetic variants assist in overcoming the interference in IFN signaling and render the individual vulnerable to a severe form of COVID-19 and secondary infections, which disrupts the signaling of interferon and prolongs the viral replication [10]. A recent study revealed that variants in the TLR7 gene have been linked to the severity of COVID-19. A study conducted by Zhang *et al.* revealed that inborn errors were observed in type I IFN immunity [11]. As a result, the early antiviral response is affected, leading to increased chances of secondary bacterial infections, such as pneumonia, which ultimately leads to death and is one of the causes of morbidity among patients of COVID-19 [12]. Hence, an association exists between bacterial co-infections and higher mortality rates among COVID-19 patients, emphasizing that initial identification of disease is essential along with definitive care [13]. The host immune system is weakening, leading to serious infections of the respiratory tract due to a combination of various viral and bacterial pathogens. Understanding of genetic variables, specifically those that cause secondary infections are essential as they help to develop treatment regimens [14].

According to physiological principles, a lack of early antiviral defense may allow for prolonged viral replication, epithelial damage, and dysregulated innate immunity, all of which are favorable conditions for bacterial colonization and superinfection. It is of great interest to evaluate TLR7 genetic variation as a risk factor for SBP in COVID-19 because of this biological plausibility and the clinical implications. The study aimed to determine the connection between functional TLR7 single-nucleotide polymorphisms (rs179008, rs179009, rs179010), specific TLR7 gene polymorphisms, and incidence of secondary bacterial pneumonia in patients with COVID-19 aged 18 to 65 years who had controlled the known clinical risk factors.

METHODS

The study took place in Ziauddin University Hospital, Karachi, Pakistan, from June 2022 to March 2023 as a case-control study at a hospital. Ziauddin University Ethical Review Committee granted ethical approval to the study (Reference Code: 5360522BKBC). Informed consent of all the participants was carried out in written form, and the confidentiality of patient information was upheld during the study. Consecutive enrolment of 200 COVID-19 patients admitted to the hospital and confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) was used. The conventional formula to compute sample size was n=Z2P(1-P)/ d 2, where prevalence is assumed to be 42 percent among COVID-19 patients hospitalized with secondary bacterial pneumonia (SBP), where Z=1.96 is a 95 percent confidence interval, and d=5 represents the margin of error. Operationally, secondary bacterial pneumonia was defined as a clinical deterioration that was new, more than 48 hours after admission, and had new or progressive radiologic infiltrates, with an increase in the level of inflammatory markers. Microbiological culture positivity was regarded as supportive and not obligatory in the diagnosis of SBP, especially in patients who had prior experience with broad-spectrum antibiotics, which are known to lower the bacterial culture yield. Patients who met these clinical and radiological criteria were included in the cases, and COVID-19 patients who never developed SBP during hospital stay as controls. Those patients who showed a case of bacterial infection in the first 48 hours of admission were classified as co-infected and were disqualified from the study. Patients more than 65 years, patients with pre-existing immunodeficiency disorders, patients who had received systemic antibiotics in the 48 hours before admission, and patients who had bacterial co-infection documented at admission were excluded to reduce the confounding factors. It included patients aged between 18 and 65 years as the final study population. Hospital medical records were used to gather demographic and clinical data, such as age, sex, comorbidities (diabetes mellitus and hypertension), smoking status, intensive care unit admission, mechanical ventilation, steroid use, as well as the severity of the disease based on World Health Organization criteria, on a structured data collection form. In suspected patients of SBP, aseptic collection of sputum and /or blood samples was done after 48 hours of admission to the hospital and subjected to processing in the microbiology laboratory by the use of standard culture techniques. The identification of bacteria was done through Gram staining, morphology, and biochemical identification through the API 20E system (bioMérieux). The Kirby-Bauer disk diffusion test was used to perform the antibiotic susceptibility test in line with Clinical and Laboratory Standards Institute guidelines. Genetic analysis of approximately 3 mL of peripheral blood in EDTA tubes was done on each participant. The QIAamp DNA Mini Kit (Qiagen) was used to extract the genomic DNA according to the directions of the manufacturer. The Nanodrop spectrophotometer was used to determine the concentration and purity of DNA. TLR7 SNP genotyping. Geno-typing of TLR7 SNP genotyping assays, including pre-

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designed TaqMan SNP genotyping assays, was completed on a QuantStudio 5 Real-Time PCR System. The assays involving the primer and probes are highly confidential and thus are not publicly revealed. The thermal cycling conditions were as follows: denaturation at 95 °C/10 minutes, 40 cycles of denaturation at 95 °C/15s and annealing/extension at 60 °C/1min with a final extension at 72 °C/5min. QuantStudio Design and Analysis Software was used to perform allelic discrimination and genotype calling. The fluorescence signal clustering was used to assign genotypes and categorize them as homozygous wild-type, heterozygous, or homozygous variant. The samples that had unclear amplification curves or low levels of fluorescence intensity were resampled, and only the sample with a conclusive genotype was incorporated into the final analysis. Since TLR7 is an X-linked gene, the Hardy-Weinberg equilibrium was evaluated in female-only participants who were considered as controls. There was no major difference in the Hardy-Weinberg equilibrium. The independent t-test was used when comparing continuous variables, and the chi-square or Fisher's exact test was used to compare the categorical variables, depending on the type. TLR7 polymorphic variations of developing secondary bacterial pneumonia were assessed using logistic regression analysis and adjusted in the presence of appropriate confounding variables. Additive and dominant models of genetic interactions were used. Multiple testing was corrected by Bonferonni test, the statistical significance of which was $p < 0.017$. There were odds ratios and 95 percent confidence intervals.

RESULTS

The total number of patients included was 200 hospitalized RT-PCR-confirmed COVID-19 patients, including 100 cases of secondary bacterial pneumonia (SBP) and 100 controls who did not have SBP. Among the 100 SBP cases, 85 patients (85%) were microbiologically confirmed bacterial pneumonia, and 15 patients (15 percent) had predefined clinical, radiological, and inflammatory marker-based criteria of SBP even in negative cultures. The average age of the study population was 45.6 ± 12.3 years, and there was no significant variance in age between the SBP cases and the controls (46.2 ± 11.9 vs. 45.0 ± 12.7 years; $p > 0.05$) (Table 1).

Table 1: Clinical and Demographic Characteristics of COVID-19 Patients (n=200)

Variables	Cases (n=100)	Controls (n=100)	Total (n=200)
Age (Mean ± SD)	46.2 ± 11.9	45.0 ± 12.7	45.6 ± 12.3
Male Sex, n (%)	62 (62%)	58 (58%)	120 (60%)
Hypertension, n (%)	38 (38%)	32 (32%)	70 (35%)
Diabetes Mellitus, n (%)	30 (30%)	26 (26%)	56 (28%)
Smoking History, n (%)	20 (20%)	16 (16%)	36 (18%)
Severe/Critical Disease, n (%)	35 (35%)	25 (25%)	60 (30%)

The identification of the bacterial pathogen was conducted only among culture-confirmed cases of SBP (n=85). The most isolated ones were *Staphylococcus aureus* (35%), *Klebsiella pneumoniae* (25%), then *Pseudomonas aeruginosa* (15%), and *Escherichia coli* (10%) (Table 2).

Table 2: Microbiological Profile of Culture-Confirmed SBP Cases (n=85)

Variables	p-value
Staphylococcus aureus	30 (35%)
Klebsiella pneumoniae	21 (25%)
Pseudomonas aeruginosa	13 (15%)
Escherichia coli	9 (10%)
Others	12 (15%)

Variants of TLR7 were much more common in SBP cases than in the controls (21% vs. 7%, p=0.004). The most common SNP identified in the analysis is the most common variant; 12 per cent of the cases of SBP carried the SNP rs179008. Female control genotype was in Hardy-Weinberg equilibrium (kh^2=0.49, p=0.48) (Table 3).

Table 3: Distribution of TLR7 Variants in COVID-19 Patients (n=200)

SNP	Cases n (%)	Controls n (%)	p-value
rs179008	12 (12%)	4 (4%)	0.037
rs179009	4 (4%)	2 (2%)	0.420
rs179010	5 (5%)	1 (1%)	0.090
Any TLR7 Variant	21 (21%)	7 (7%)	0.004

The multivariate logistic regression analysis revealed that the presence of the TLR7 variant was directly linked with a secondary bacterial pneumonia, with the possibility to control the potential confounders (adjusted OR=3.2, 95% CI 1.5-6.8, p=0.002). Mechanical ventilation and ICU admission were also important predictors; age, sex, diabetes, hypertension, and steroid use were statistically not important (Table 4).

Table 4: Multivariable Logistic Regression Analysis of Factors Associated with SBP

Variables	Adjusted OR	95% CI	p-value
Presence of TLR7 Variant	3.2	1.5–6.8	0.002
ICU Stay	2.3	1.1–4.8	0.028
Mechanical Ventilation	2.9	1.3–6.6	0.011
Age (>50 years)	1.4	0.8–2.4	0.210
Male Sex	1.1	0.6–2.0	0.790
Diabetes Mellitus	1.6	0.8–3.1	0.170
Hypertension	1.4	0.7–2.8	0.290
Steroid Use	1.2	0.6–2.5	0.590

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DISCUSSION

This study assessed the relationship between secondary bacterial pneumonia development and polymorphisms of the X-linked receptor gene TLR7 in hospitalized COVID-19 patients. To improve generalizability and evaluate age-related immune effects, future research involving senior populations is necessary. The fact that there are clinically diagnosed cases of SBP that are not culture-confirmed is indicative of what is happening in the real world of the diagnosis of SBP in hospitalized COVID-19 patients. The carriers of any of the three assayed SNPs (rs179008, rs179009, rs179010) had significantly higher odds (adjusted OR 3.2, 95 % CI 1.5–6.8, p=0.002) of developing secondary bacterial pneumonia after adjusting for known confounders (age, sex, diabetes mellitus, hypertension, ICU stay, mechanical ventilation, steroid use). The genotype frequency in cases (21%) was substantially higher than in controls (7%). These results imply that in the context of a severe viral respiratory infection, TLR7 genetic variation may increase susceptibility to bacterial super-/secondary infection. When single-stranded RNA viruses are detected, the endosomal pattern recognition receptor TLR7 initiates the production of type I interferon (IFN-α and IFN-β), which is crucial for antiviral defense [10]. This gene's variations may affect the antiviral response, resulting in delayed viral clearance and heightened susceptibility to bacterial infections [11]. The most common TLR7 variant in our cohort was rs179008, which was present in 12% of patients. According to the analysis, even after controlling for comorbidities, age, and sex, patients with TLR7 variants had more than three times the chance of getting secondary bacterial pneumonia than patients without variants (OR=3.2, 95% CI: 1.5–6.8, p=0.002). analysis. According to earlier research, rare TLR7 mutations make people more vulnerable to severe COVID-19 outcomes because they impair type I IFN responses. These findings are in line with those findings [15, 16]. According to previous studies, the high prevalence of Gram-positive and Gram-negative co-infections in severe COVID-19, *Staphylococcus aureus* (35%) and *Klebsiella pneumoniae* (25%), made up most secondary bacterial infections [17, 18]. Significantly, 40% of the bacterial isolates showed signs of antibiotic resistance, highlighting the need for targeted antimicrobial therapy and the clinical difficulties in treating co-infections. The impaired TLR7-mediated type I IFN signaling can enhance early antiviral responses, which prevent epithelial injury and bacterial colonization and therefore augment the probability of secondary pneumonia [19, 20]. Notably, SBP inclusion was intentional and predefined. This is true to the reality of hospitalized COVID-19 patients, as it is difficult to diagnose in the real world, where previously exposed antibiotics cause the culture yield to decrease substantially. The same diagnostic methods have been generally adopted within the research of hospital-acquired and ventilator-associated pneumonia, especially in the case of critically ill patients. These findings suggest that genetic predisposition plays a significant role in the clinical course of COVID-19 and highlight the significance of TLR7 as a crucial modulator of both antiviral and antibacterial defense pathways [21, 22].

This study has some limitations as the sample size of the study was less due to which the results may not be as broadly applicable. Another limitation of the study design itself due to which the causal relationship between TLR7 variants and secondary bacterial pneumonia was not possible. Furthermore, a thorough assessment of the host's genetic characteristics, environmental exposures, and viral load that could influence susceptibility to co-infections was lacking. Due to the limited number of TLR7 variants that were analyzed, additional polymorphisms or epigenetic modifications might also increase the risk of developing a disease. These findings allow for several recommendations. Furthermore, the study protocol specifically included clinically diagnosed, culture-negative SBP cases to replicate actual diagnostic procedures. This method has been extensively employed in comparable clinical investigations and is in line with recognized diagnostic standards for hospital-acquired and ventilator-associated pneumonia in critically sick patients. Hence, routine genetic screening for TLR7 variants may help identify hospitalized COVID-19 patients who are more susceptible to secondary bacterial infections, particularly those who are at risk of severe illness. Early intervention strategies like timely antiviral and targeted antibacterial therapy may be beneficial for patients with harmful TLR7 variants.

CONCLUSIONS

The study concludes that the carriers of TLR7 gene polymorphisms showed a notably higher predisposition to secondary bacterial pneumonia in patients with COVID-19 infection hospitalized between 18 and 65 years. These data points on the correlation between defective antiviral innate immunity and vulnerability to bacterial superinfection. Although the findings highlight how host genetic factors may play a significant role in disease development, it will take additional large-scale, multicenter research before TLR7 genotyping is factored into a regular clinical risk assessment or customized antimicrobial treatment plans.

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Authors' Contribution

Conceptualization: BK, SB
Methodology: HF, AB
Formal analysis: BK, FA, AJ
Writing and Drafting: SB, HF
Review and Editing: BK, SB, FA, HF, AJ, AB

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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