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Bacterial skin infections among inpatients with autoimmune blistering diseases and their association with other risk factors

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Background: Autoimmune blistering diseases (AIBDs) are rare and potentially life-threatening conditions that are often associated with various bacterial infections. This study aimed to assess the prevalence of bacterial skin infections and their association with other risk factors in patients with infected AIBDs.

Methods: This study was conducted on 47 patients with AIBDs. Two swabs for bacterial culture were obtained from each patient: one from wound secretions and the other from the nose. To determine the association between bacterial infections and other risk factors, patient information—including demographic data, AIBD types, hospitalization details, medical history, symptoms, and medications—was collected.

Results: Pemphigus vulgaris and bullous pemphigoid were identified as the most common immunobullous diseases, with prevalences of 61.7% and 25.6%, respectively. Twenty-three of 47 patients (48.9%) were found to be nasal carriers of *Staphylococcus aureus*, with the predominant strain being methicillin-susceptible *Staphylococcus aureus* (MSSA) at 42.6%. Bacterial skin infections were detected in 72.3% of patients, of whom 59.6% had infections at the time of admission, while 12.7% acquired nosocomial infections.

Conclusion: MSSA was the most frequently isolated bacterial strain from wound secretions, followed by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Klebsiella pneumoniae*. Most MSSA and MRSA isolates exhibited resistance to erythromycin and clindamycin. No significant association was found between the incidence of bacterial infections and the severity of AIBDs, comorbidities, immunosuppressive medication use, or the duration and frequency of hospitalizations.

Keywords: autoimmune diseases; bacterial infections; skin diseases; risk factors; pemphigus

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What is already known on the subject?

- Pemphigus vulgaris and bullous pemphigoid were identified as the most common immunobullous diseases.

The study's main messages:

- There was no significant association between the incidence of bacterial infection and the severity of autoimmune blistering diseases (AIBDs),

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comorbidities, use of immunosuppressive medications, or the number of hospitalizations.
- methicillin-susceptible *Staphylococcus aureus* was the most frequently isolated bacterial strain from AIBD patients.

INTRODUCTION

Autoimmune blistering diseases (AIBDs) are organ-specific autoimmune bullous disorders characterized primarily by the presence of blisters on the skin and mucous membranes. Blister formation results from the loss of tissue-bounds (cell adhesion) and the presence of autoantibodies targeting adhesion components of the skin [1,2]. The two main categories of AIBDs are the pemphigus group and bullous pemphigoid, classified based on the level of skin cleavage [3]. Pemphigus is caused by autoantibodies against desmosomes in the intraepidermal zone, whereas bullous pemphigoid results from autoantibodies targeting hemidesmosomes in the cutaneous basement membrane zone [3]. The pemphigus group includes pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus [2,4]. Additionally, pemphigus vegetans is the rarest clinical variant of pemphigus, accounting for only 1–2% of cases [5].

Immunosuppressive medications and systemic corticosteroids are the primary treatments recommended for AIBDs. However, prolonged use of these medications can lead to an immunocompromised state, increasing patients' susceptibility to various types of infections [6]. In a cohort study involving a large number of pemphigus patients, infections were identified as the most common complication, with skin infections being the primary cause [7]. Generally, these infections account for 34–55% of all deaths [8,9]. Moreover, 25.4% of inpatients without symptoms of AIBDs experience severe infections, which is significantly lower compared to 50.4% of inpatients with AIBDs [10]. In patients with AIBDs, the skin is the primary source of infections, which prolong hospital stays and increase healthcare costs [10]. Various factors contribute to the development of AIBDs; however, bacterial infections have not traditionally been considered as causative agents of these diseases. Nevertheless, during immunosuppressive therapy, septicemia caused by *Staphylococcus aureus* and other microorganisms can occur as a complication [11]. Moreover, similar to the pathogenic mechanism of pemphigus foliaceus, *Staphylococcus aureus* produces a specific toxin that binds selectively to desmoglein 1. This toxin disrupts cell adhesion in the superficial epidermis [12].

In a study involving 155 patients with AIBDs, the most common infections were skin infections, particularly those caused by *Staphylococcus aureus*, as well as oral candidiasis and herpes simplex infections [6]. Furthermore, a cohort study of 835 pemphigus patients reported that 18% of mortality was associated with various infections [13]. AIBDs are rare and severe autoimmune diseases characterized by multiple contributing factors and coexisting conditions. These include genetic, immunologic, endocrine, and environmental factors, as well as other internal conditions that facilitate their coexistence [2]. Additionally, several other diseases—such as rheumatoid arthritis, thyroid disorders, diabetes, alopecia areata, systemic lupus erythematosus, vitiligo, and rarer conditions like myasthenia gravis and scleroderma—have been reported to be associated with bullous dermatoses [14].

Among various AIBDs, pemphigus vulgaris exhibits a high incidence of 30 cases per 100,000 individuals in Iran. Additionally, the etiology of AIBDs in the northwestern regions of the country remains largely unknown. Therefore, this study aimed to investigate the prevalence of different types of bacterial skin infections and their association with other risk factors in patients with AIBDs.

METHODS

This study was conducted on 47 patients with AIBDs admitted to the Department of Dermatology at Sina Educational, Research and Treatment Center, Tabriz, Iran, from April 2020 to March 2021.

Patients who were clinically diagnosed with AIBDs and had skin lesions were included in the skin. The diagnosis of AIBDs was confirmed by direct immunofluorescence and histopathology [15]. Exclusion criteria included AIBD patients who had received antibiotics within two weeks prior to enrollment and those who declined to participate in the study.

A simple grading system was used to assess the extent of clinical involvement. According to this system, three grades were defined for disease severity: grade 1 corresponds to less than 25% body surface area (BSA) involvement, with or without mucosal involvement; grade 2 corresponds to 25% to 50% BSA

involvement, with or without mucosal involvement; and grade 3 corresponds to more than 50% BSA involvement with any degree of mucosal involvement. A questionnaire collecting demographic information, disease history, comorbidities, hospitalization details, and medication use was completed to gather patient data.

Within the first 24 hours of hospitalization, two swabs were collected from each patient: one nasal swab to evaluate the frequency of *Staphylococcus aureus* nasal carriage, and one wound swab (from vesicle, bulla, or pustule secretions) to assess the presence of other bacterial strains. Within 1-2 hours after sample collection, the specimens were processed in the Microbiology Division of Sina Educational, Research and Treatment Hospital. Nasal swabs were cultured by streaking on mannitol salt agar (Oxoid, Hampshire, UK), and wound swabs were streaked on MacConkey agar and blood agar plates (Oxoid, Hampshire, UK). Subsequently, the inoculated culture media were incubated at 37°C for 24 hours. Subculturing was performed on the aforementioned media to obtain pure colonies.

Staphylococcus aureus and other bacterial strains were identified using traditional microbiological methods and biochemical tests, including Gram staining, standard culture techniques with selective and differential media, colony morphology assessment, IMViC tests, catalase and coagulase tests, among others, as previously described. Following bacterial identification, the disk diffusion method was performed to determine antibiotic susceptibility on Mueller-Hinton agar, in accordance with Clinical and Laboratory Standards Institute guidelines [16]. The names and contents of all antibiotics tested in this study, which were purchased from Mast Diagnostics (United Kingdom), are listed in Table 1. The cefoxitin disk diffusion method (using 30 µg cefoxitin disks) was employed to detect methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA). An inhibition zone diameter of 21 mm or less around the cefoxitin disk indicated MRSA [16]. Microbial tests were repeated within one week during hospitalization or whenever the patient became clinically symptomatic. Additional information, including disease severity, type of immunobullous disease, symptoms, and results of nasal swab and wound secretion cultures, was recorded during hospitalization.

Table 1. Mast Diagnostics disks for antibiotic susceptibility testing

Antibiotic disks	Disk content
AMP: ampicillin	10 µg
AN: amikacin	30 µg
CAZ: ceftazidime	30 µg
CM: clindamycin	2 µg
CP: ciprofloxacin	5 µg
CRO: ceftriaxone	30 µg
CTX: cefotaxime	30 µg
ERY: erythromycin	15 µg
GM: gentamicin	10 µg
IMI: imipenem	5 µg
LEV: levofloxacin	5 µg
MEM: meropenem	10 µg
NIF: nitrofurantoin	100 µg
OX: oxacillin	5 µg
PTZ: piperacillin-tazobactam	100/10 µg
RIF: rifampin	30 µg
SRT: streptomycin	10 µg
SXT: co-trimoxazol	1.25/23.75 µg
TET: tetracycline	10 µg
VAN: vancomycin	30 µg

Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS, Chicago, IL, USA). Quantitative data were presented as mean ± standard deviation (SD), while qualitative data were reported as frequency (percentage). To investigate the association between bacterial infections and risk factors, Chi-square and Spearman correlation tests were used. Additionally, variables were compared using the Chi-square test and Fisher's exact test when appropriate. All tests were two-sided, and a P value ≤ 0.05 was considered statistically significant.

Ethical considerations

The present study was approved by the Institutional Review Board and the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (Ethical No. IR.TBZMEDE.REC.1396.927). All 47 patients provided written informed consent to participate in the study.

RESULTS

Patient information

The mean age of the 47 patients was 55 ± 17.2 years (ranging from 25 to 95 years). Among them, 28

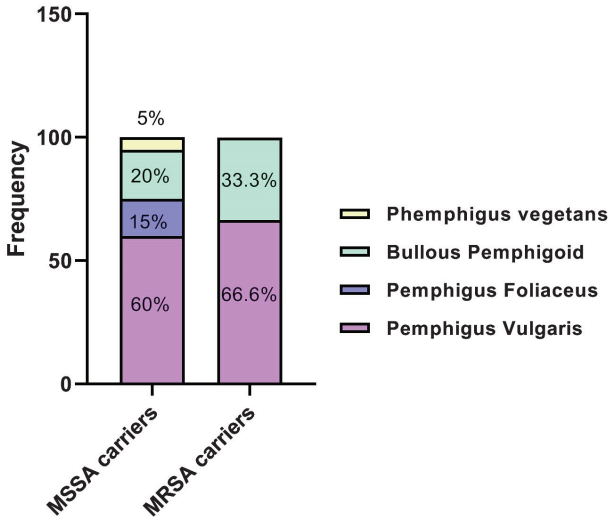

Figure 1. The types of immunobullous diseases
MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

(59.6%) were female and 19 (40.4%) were male. Of the 47 patients diagnosed with AIBDs, 29 (61.7%) had pemphigus vulgaris, 12 (25.6%) had bullous pemphigoid, five (10.6%) had pemphigus foliaceus, and one (2.1%) had pemphigus vegetans. The types of immunobullous diseases are shown in Figure 1.

Bacterial infections in AIBDs

Based on the nasal swab analysis conducted at the beginning of hospitalization, among 47 patients, 23 (48.9%) tested positive for *Staphylococcus aureus* culture, while 24 (51.1%) tested negative. Of the 23 positive nasal carriers, 20 (86.9%) were carriers of MSSA, and three (13.1%) were carriers of MRSA. In contrast, wound secretion swab cultures taken at both the beginning and follow-up stages of hospitalization showed that 35 (74.4%) patients had infectious skin lesions, whereas 12 (25.5%) patients had negative

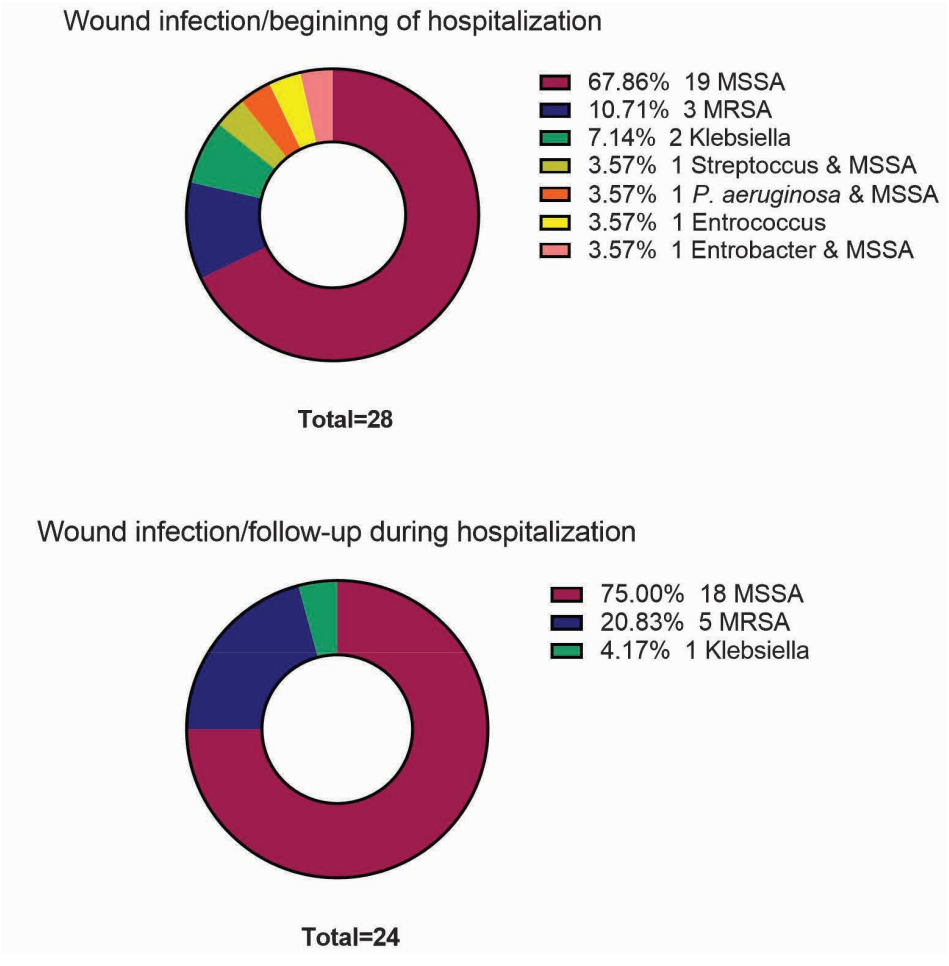

Figure 2. The prevalence of bacterial isolates from wounds at different stages of hospitalization. (A) Wound bacterial isolates at the beginning of hospitalization; (B) Wound bacterial isolates during follow-up throughout hospitalization.
MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

culture results at both stages. At admission, 28 of 47 (59.6%) wound swabs were culture-positive, while 24 of 47 (51.1%) remained positive at follow-up. Notably, six (12.7%) patients who initially had negative wound cultures developed positive cultures at follow-up, indicating nosocomial infections. Additionally, 12 (25.53%) patients showed no evidence of wound infection at either stage. The prevalence of wound bacterial isolates at both hospitalization stages is illustrated in Figure 2.

Antibiotic resistance patterns of various bacterial isolates in AIBDs

In the present study, bacterial skin infections were identified in 35 (74.4%) wound specimens collected from patients at admission and one week thereafter. Of these, 29 (61.7%) infections were present at admission, while six (12.7%) developed during hospitalization. MSSA was the most common organism, found in 26 (55.3%) patients with skin infections. Among these 26 MSSA positive cases, 22 (84.61%) were infected with MSSA at admission, whereas 4 (15.39%) acquired MSSA infections after hospitalization in the skin ward. The prevalence of other bacteria isolated from wound specimens was as follows: MRSA nine (19.14%) [three (37.5%) at admission, six (66.6%) after admission], *Klebsiella pneumoniae* four (8.51%), *Streptococcus spp.* two (4.25%), *Enterococcus spp.* two (4.25%), *Pseudomonas aeruginosa* one (2.12%), *Escherichia coli* one (2.12%), and *Enterobacter spp.* one (2.12%). Resistance to the tested antibiotics for MSSA and MRSA is shown in Figure 3. The highest resistance was related to erythromycin and clindamycin in both strains, while all MSSA and MRSA isolates were susceptible to vancomycin. The results of antibiotic susceptibility tests for other bacterial strains isolated from the wound secretions of AIBD patients are presented in Table 2.

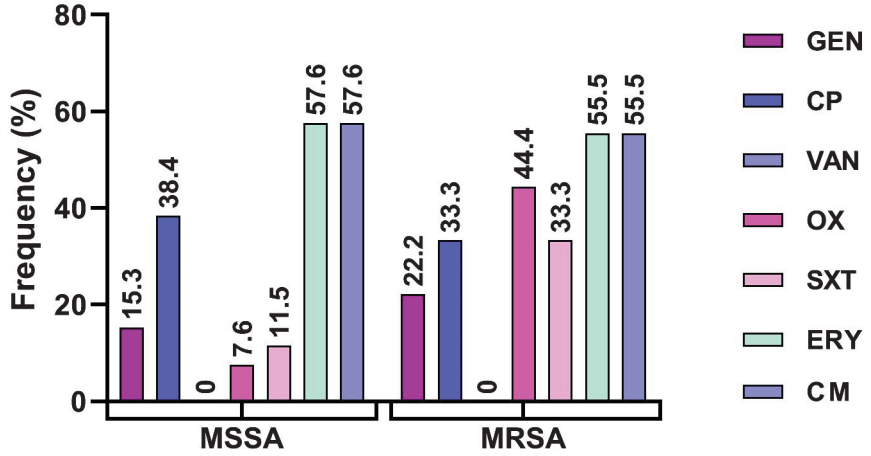

Figure 3. Antibiotic resistance patterns of *Staphylococcus aureus* isolates (MSSA and MRSA) obtained from wound secretions
MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus;* GM: gentamicin; CP: ciprofloxacin; VAN: vancomycin; OX: oxacillin; SXT: co-trimoxazol; ERY: erythromycin; CM: clindamycin.

Table 2. Antibiotic resistance patterns of other bacterial strains isolated from wound secretions

Bacterial strains	Number of antibiotic resistance
Klebsiella pneumoniae (n=4)	Res: CAZ= 3, CTX= 3, CP= 2, SXT= 2, PTZ= 2, GM= 2, AN= 2, LEV= 1 Sen: IMI= 4, MEM= 4
Streptococcus spp. (n=2)	Res: ERY= 2, CTX= 1 Sen: OX= 2, CTX= 1, RIF= 2, CRO= 2, LEV= 2
Entrococcus spp. (n=2)	Res: ERY= 2, NIF= 2, TET= 1 Sen: GEN= 2, AMP= 2, VAN= 2, STR= 2
P. aeroginosa (n=1)	Sen: CAZ, CTX, CP, PTZ, GM, AN, LEV, IMI, MEM, SXT
Escherichia coli (n=1)	Res: SXT Sen: CAZ, CTX, CP, PTZ, GM, AN, LEV, IMI, MEM
Entrobacter spp. (n=1)	Res: CZ Sen: CAZ, CTX, CP, PTZ, GM, AN, LEV, IMI, MEM, SXT

Res: Resistant; Sen: Sensitive; CTX: cefotaxime; CAZ: ceftazidime; CP: ciprofloxacin; SXT: co-trimoxazole; PTZ: piperacillin-tazobactam; AN: amikacin; GM: gentamicin; IMI: imipenem; MEM: meropenem; LEV: levofloxacin; ERY: erythromycin; OX: oxacillin; RIF: rifampin; CRO: ceftriaxone; NIF: nitrofurantoin; TET: tetracycline; AMP: ampicillin; VAN: vancomycin; SRT: streptomycin.

The frequency of comorbidities in AIBDs

The prevalence of comorbidities among 47 patients with AIBDs is presented in Table 3. The most common comorbidities included cardiovascular diseases such as hypertension and cardiac ischemia, diabetes, hyperlipidemia, asthma, and cataracts. Among the AIBD patients, none of the comorbidities showed a statistically significant association with bacterial skin infections ($P > 0.05$). Of the 47 patients, 23 (48.9%) had a history of drug use; among these, 16 (34%) had used immunosuppressive medications. There was no significant relationship between bacterial skin infections and a history of immunosuppressive drug use ($P > 0.05$).

The association between immunobullous disease severity and bacterial skin infection

The severity of immunobullous disease among 47 patients was distributed as follows: 30 individuals (63.8%) had less than 25% BSA involvement, eight patients (17%) had disease severity between 25% and 50% BSA, and another eight patients (17%) had severity ranging from 50% to 75% BSA. One patient had disease severity above 75% and died during the first days of hospitalization. Statistical analysis showed no significant correlation between bacterial skin infection and disease severity ($P > 0.05$).

The association between the number of hospitalizations and bacterial skin infections

Based on hospitalization data, 20 patients (42.5%) were hospitalized for the first time, 10 patients (21.3%) for the second time, seven patients (14.9%) for the third time, four patients (8.5%) for the fourth time, three patients (6.4%) for the fifth time, one patient (2.1%) for the sixth time, and two patients (4.3%) for the seventh time. In total, 27 patients had a history of more than one hospitalization. No significant relationship was found between the incidence of bacterial skin infections and the total number of hospitalizations ($P > 0.05$). Additionally, the average length of hospitalization was 11 days, ranging from one to 50 days. Similarly, no significant relationship was observed between bacterial skin infections and length of hospitalization among patients ($P > 0.05$).

DISCUSSION

The global incidence of pemphigus disease is estimated to be between one and five cases per million people per year. Females have been slightly

Table 3. Prevalence of comorbidities among 47 patients with AIBDs

Disease classification Total number (%)	Type of disease	Number (%)
Cardiovascular diseases 16 (34.8)	Hypertension	11 (23.9)
	Cardiac ischemia	5 (10.9)
Endocrine, nutritional and metabolic diseases 9 (19.6)	Diabetes	4 (8.7)
	Hyperlipidemia	4 (8.7)
	Hyperthyroidism	1 (2.2)
Pulmonary and respiratory diseases 5 (10.9)	Asthma	3 (6.5)
	Lung nodules	1 (2.2)
	Chronic obstructive pulmonary disease	1 (2.2)
Eye diseases 4 (8.7)	Cataract	3 (6.5)
	Glaucoma	1 (2.2)
Neoplasmic diseases 3 (6.6)	Nasopharyngeal carcinoma	1 (2.2)
	Squamous cell carcinoma of the esophagus	1 (2.2)
	Lymphoma	1 (2.2)
nervous system diseases 2 (4.4)	Transient ischemic attack	1 (2.2)
	Alzheimer's	1 (2.2)
Gastrointestinal diseases 2 (4.4)	Peptic ulcer	1 (2.2)
	Inguinal hernia	1 (2.2)
Skeletal, muscular and connective tissue diseases 2 (4.4)	Discopathy	1 (2.2)
	Rheumatoid Arthritis	1 (2.2)
Mental and behavioral disorders 2 (4.4)	Dementia	1 (2.2)
	Schizophrenia	1 (2.2)
Infectious and parasitic diseases 1 (2.2)	Tuberculosis	1 (2.2)

more affected by AIBDs. The highest incidence peak occurs in patients aged between 60 and 70 years [17]. In the present study, women comprised the majority of patients (59.6%). These findings are consistent with studies conducted in Iran [18].

The study by Daneshpazhooh *et al.* involving 1,402 patients diagnosed with AIBDs over 10 years in Iran revealed that pemphigus vulgaris was the most common AIBD (81.2%), followed by bullous pemphigoid (11.6%) and pemphigus foliaceus (4.4%) [19]. Our study aligns closely with these findings, identifying pemphigus vulgaris (81.2%) and bullous pemphigoid (11.2%) as the most prevalent AIBDs, followed by pemphigus foliaceus (10.6%).

In patients with AIBDs in this study, the most commonly isolated bacterial strain was *Staphylococcus aureus,* followed by *Klebsiella spp*. This finding is consistent with previous studies [20-23]. A high rate of MSSA colonization/infection was observed among AIBD patients both at the beginning and during follow-up hospitalization, with incidences of 67.8% and 75.0%, respectively. Similarly, a study conducted by Fagheei Aghmiyuni *et al.* reported that MSSA skin infections (57.7%) were more prevalent than MRSA infections (41.3%) [20]. Another study from India reported a prevalence of MSSA infection at 69.2%, which was higher than MRSA infection at 30.8%, consistent with our findings [23]. Various other percentages *Staphylococcus aureus* infections have been previously reported [20-24]. Among our AIBD patients, 86.9% had positive MSSA cultures from nasal swabs at the time of admission. Similarly, Mohamed *et al.* found MSSA-positive nasal swabs in 68.5% of patients [25]. Conversely, Thomas and Nair reported a lower MSSA nasal swab positivity rate of 18.6% [22]. In a study conducted in Tehran on *Staphylococcus aureus* carriers among patients with pemphigus, the carrier frequency was 58.3%, of which 73.3% were MRSA carriers [6]. Various factors, including hygienic practices, environmental conditions, differences in sample sizes, and the effectiveness of hospital infection control policies across countries, may contribute to this discrepancy.

In recent years, a clear correlation between autoimmune diseases and infections has been well established. In addition to blisters caused by AIBDs, which can serve as a source of bacteremia and life-threatening sepsis, several factors increase the risk of infection in these patients. Studies have shown that hospitalization, corticosteroid and immunosuppressive treatments, and certain comorbidities—such as cardiovascular disease, neurological and mental disorders, liver and gastrointestinal diseases, diabetes, cancer, chronic respiratory disease, endocrine disorders, urological conditions, and chronic kidney disease—predispose patients to infections [6,26,27]. A 19-year study of pemphigus patients in Croatia found that corticosteroid and immunosuppressant treatments were associated with skin infections in 16.3% of patients, sepsis in 5.7%, and an 8.8% mortality rate during hospitalization [28]. Additionally, a study conducted in the United States on risk factors affecting the survival rate of pemphigoid patients showed that sepsis was the leading cause of death among the majority of patients [29]. In a study of 155 Iranian patients with pemphigus vulgaris, 21.3% had an infection at the time of admission, and 5.8% developed an infection during follow-up starting from the fourth day of hospitalization. These infections were nosocomial in origin, and a significant relationship was observed between infection and disease severity, number of hospitalizations, and diabetes as a comorbid condition [29]. In contrast to the study by Esmaili *et al.*, the present study found no significant relationship between the number of hospitalizations or the length of hospitalization based on hospitalization data.

In the studies by Ljubojević *et al.* and Mourellou *et al.*, it was reported that the mortality rate in patients is directly related to higher disease severity [28,30]. Although Esmaili *et al.* found a significant relationship between infection and disease severity, the present study did not find a significant relationship between bacterial skin infections and the severity of blistering disease [6].

Our results showed that the most frequently occurring comorbidities of AIBDs included hypertension, cardiac ischemia, diabetes, and hyperlipidemia. In this survey, none of the comorbidities were significantly associated with AIBDs. Approximately one-quarter of our patients had a history of hypertension. According to a retrospective case–control study from Greece, hypertension was more prevalent among patients with AIBDs [31]. Additionally, contrary to our findings, another study investigated the association between pemphigus and the use of antihypertensive

medications [32].

Based on the findings of Heelan *et al.*, a high incidence of comorbidities such as hypothyroidism, diabetes, and inflammatory bowel disease was observed among patients with pemphigus compared to the general population [14].

The limitations of our study include a small sample size and the analysis of patients from a single tertiary care center. Additionally, many recorded comorbidities and diseases in our AIBD patients were excluded from statistical analysis due to the lack of comparator groups.

CONCLUSION

Regarding the severity of complications and consequences of infections in patients with AIBDs, early diagnosis and treatment of skin infections are crucial. Additionally, given the significance of risk factors associated with these infections, further studies with larger sample sizes are recommended to identify them in patients with AIBDs.

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Authors' contributions

Study conception: **AG**, **AR**; data collection: **AA**, **AH**; analysis and interpretation of results: **ES**; manuscript preparation: **ES**, **SR**.

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Conflict of interest: None declared.

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