Panton-Valentine leukocidin-positive methicillin-resistant Staphylococcus aureus correlates with disease severity in psoriasis: a case–control study

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ABSTRACT
Psoriasis is a chronic inflammatory cutaneous disorder, which is prone to methicillin-resistant Staphylococcus aureus (MRSA) infection. We aimed to investigate prevalence of MRSA skin colonization among psoriatic patients and if there is a relation between Panton-Valentin leukocidin (PVL) expression and disease severity. A case-control study was conducted on 90 patients with active psoriatic lesions and 90 healthy controls. Scales from psoriasis plaques and skin swabs from healthy control were collected. Identification of MRSA and antibiotic susceptibility patterns were performed using routine microbiological methods. mecA and PVL genes were detected using PCR assay and pulsed field gel electrophoresis (PFGE) was done for MRSA typing. Prevalence of MRSA among psoriatic patients was 23.3%. Significant difference was noticed in MRSA colonization between psoriasis and control groups. Five (23.8%) MRSA isolates from skin lesions were positive for mecA and PVL genes. Antibiotic resistance among PVL negative MRSA was higher, specially towards clindamycin. Patients harboring PVL positive isolates had significantly lower mean age and higher PSAI score than those with negative isolates. Fourteen PVL negative isolated MRSA from psoriasis patients were the same pulsotype. There was significant MRSA colonization in psoriasis group and presence of PVL may contribute to increased severity of this disease.

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Introduction
In the middle of the twentieth century, the advances in antibiotics development were a hope for controlling infections, but the overuse of it and the ability of bacteria to mutate resulted in drug-resistant strains. In 1959, methicillin was introduced and within 2 years hospital-acquired methicillin-resistant Staphylococcus aureus (HA-MRSA) was reported. In 1982, the first MRSA was isolated outside the hospital. By the late nineties, MRSA was isolated from people in communities with no known risk factors. By 2004, community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) had reached the proportions of a worldwide epidemic [1]. Twenty percent of individuals are persistently colonized with S. aureus, and 30% are intermittently colonized. Colonization clearly increases the risk for subsequent infection as it provides a reservoir from which bacteria can be
introduced [2]. MRSA accounted for 70% of the infections by \textit{S. aureus} strains. In the USA, MRSA causes 94,000 life-threatening infections and 19,000 deaths a year [3]. The epidemiologic changes in MRSA over the years have made the distinction between CA-MRSA and HA-MRSA is no longer clear [4]. In 2005, the prevalence of MRSA was high in Egypt (52%) [5], and even more, Abouelfetouh reported more increase in its prevalence (82%) in 2017 [6]. MRSA strains possess a mobile genetic element called staphylococcal cassette chromosome mec (\textit{SCCmec}) which includes the \textit{ccr} gene complex encoding for site-specific recombinases and the \textit{mec} gene complex which typically divided into five types of I, II, III, IV (IVA, IVB, IVC and IVD) and V. Other regions of the \textit{SCCmec} have been referred to as the J regions and contain a variety of genes, including those coding for resistance to other antibiotics [7]. \textit{SCCmec} types can be further subtyped into variants based on differences in J regions [8]. Furthermore, \textit{Staphylococcus} protein A gene (\textit{spa}) can be used for accurate and discriminatory typing of MRSA even greater than that of the multi-locus sequence typing [9]. \textit{SCCmec} also carries the Panton-Valentin leukocidin (PVL) virulence genes that compose of \textit{lukS-PV} and \textit{lukF-PV} which form the PVL toxin [10]. The presence of PVL genes appears to be associated with increased severity in some diseases and screening for it may become a routine laboratory procedure [11]. Psoriasis is a chronic inflammatory cutaneous disorder, affecting approximately 2–4% of the general population, and these patients are more prone to MRSA infection due to injured keratinocyte with impaired barrier function [12]. MRSA is characterized by enhanced ability to bind, persist, invade skin cells than other strains do and produce a unique toxin, PVL protein, with leukocytolytic activity. MRSA invades skin, increases the production of proinflammatory products inside leukocytes, and PVL produces pores in the leukocyte membranes resulting in lysis and release of inflammatory enzymes and cytokines even with low concentrations of PVL and this may induce or worsen psoriasis [13]. Furthermore, MRSA reacts with antigen-presenting cells that stimulate the T helper-cells which produce IL17 & IL22 that are well known to be important immunological mediators in psoriasis pathogenesis [14]. Panton-Valentin leukocidin toxin is uncommonly found in methicillin-sensitive \textit{Staphylococcus aureus} (MSSA) isolates but there is a strong epidemiological association between it and the emergence of CA-MRSA infections [15]. This study is to investigate the prevalence of MRSA skin colonization in psoriasis and correlate \textit{PVL} expression and the disease severity.

**Methodology**

**Subjects**

This case–control study was conducted over the period from February 2015 till April 2017 on 180 adults attending Mansoura University Hospital after informed consent. They were allocated in two groups: Gr1 (n = 90) patients with active psoriatic lesions, and Gr2 (n = 90) healthy controls with no history of psoriasis. Exclusion criteria were as follows: oral or local antibiotic, ultraviolet light therapy and systemic therapies at least 2 weeks before enrollment. All subjects were subjected to history taking and clinical examination. Psoriasis patients were diagnosed in a dermatology clinic, psoriasis area and severity index (PASI) of patients were reported [16], which involves the assessment over four body regions (head \((h)\), trunk \((t)\), upper \((u)\) and lower \((l)\) extremities) of erythema \((E)\), infiltration \((I)\), desquamation \((D)\), and body surface area involvement \((A)\), as in Table 1. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10%, 20%, 30%, and 40% of body surface area, respectively, the PASI score is calculated by the formula:
Samples collection

For psoriasis patients, skin scales were collected from psoriasis plaques after decontamination by alcohol. For normal skin in healthy control subjects, two skin swabs were collected for each person from the volar site of the elbow using cotton applicators immersed in NaCl 0.9%.

Isolation and identification of S. aureus

All samples were inoculated on blood agar and mannitol salt agar plates (Oxoid, UK) and incubated aerobically for 24 h at 37°C. After incubation, S. aureus strains were identified on the basis of their colonies morphology, catalase test, Gram staining, coagulase activity, and biochemical features using the API Staph identification test kit (Bio-Mérieux, France).

Antimicrobial resistance

Methicillin susceptibility was studied by using agar screen plates on Müller-Hinton agar (MHA) (Oxoid, UK) with 30 μg/ml of cefoxitin disc. Plates were incubated at 37°C for 18 h and zone diameters were measured. An inhibition zone diameter of ≤19 mm was reported as oxacillin resistant and ≥20 mm was considered as oxacillin sensitive [17]. Quality control strains, methicillin-sensitive S. aureus ATCC 25923 and methicillin-resistant S. aureus ATCC 43300 were used as negative and positive controls, respectively. Antibiotic sensitivity of MRSA was obtained using the agar disc diffusion method on MHA (Oxoid, UK) according to the recommendations given by the CLSI (2015). The following antimicrobial agents (Oxoid, UK) were tested: tetracycline (30 μg), erythromycin (15 μg), lincomycin (15 μg), gentamicin (10 μg), clindamycin (2 μg), rifampicin (5 μg), ciprofloxacin (5 μg), cotrimoxazole (1.25/23.75 μg), and fusidic acid (10 μg). D-test was also performed to diagnose inducible clindamycin resistance in erythromycin-resistant clindamycin-susceptible isolates. This test was performed by placing an erythromycin disk at a distance of 15–20 mm of clindamycin disk. Isolates with blunting of the inhibition zone around the clindamycin disk adjacent to the erythromycin disk (D-zone positive) considered to have inducible clindamycin resistance and are presumed to be resistant [17].

Multiplex PCR assay for detection of mecA and PVL genes among MRSA isolates

Genomic DNA was extracted by using a simple boiling method and the supernatant was used as a DNA template for PCR analysis. The multiplex PCR assay targets the ipV genes with primers Luk-PV-1 (5'-ATCATTAGTAAATGTCTGGACATGATCCA-3') and Luk-PV-2 (5'-GCATCAAGTGATTGGA TAGCAAAGC-3') [18], and the mecA gene with primers MecA1 (5'-GTAGAAATGACTGAACGT CCGATAA-3') and MecA2 (5'-CCAATTCCACATGT TTCGGTCTAA-3'). The PCR yielded fragments of the expected sizes, i.e. 433, and 310 bp for the ipV, and mecA genes, respectively. The optimized multiplex PCR conditions were, as follows: 2 μl of template DNA in a 25 μl final reaction volume containing 1 μl of each primer. The multiplex PCR conditions set at 94°C for 10 min, followed by 10 cycles of 94°C for 45 s, 55°C for 45 s, and 72°C for 75 s and 25 cycles of 94°C for 45 s, 50°C for 45 s, and 72°C for 75 s. Amplification in a single multiplex
PCR produced distinct bands, corresponding to their respective molecular sizes, that were easily recognizable in agarose gels stained with ethidium bromide [19].

**Pulse field gel electrophoresis typing (PFGE)**

The clonal relationships between the MRSA isolates were studied by evaluating the genomic DNA with PFGE analysis that was performed according to the CDC protocol [20]. DNA was restricted with the SmaI enzyme and was separated on an agarose gel using a CHEF DR III apparatus (Bio-Rad laboratories). The running conditions were 6 V per cm, with pulses ranging from 5 to 40 s for 18 h at 14°C. The DNA banding patterns were visualized under UV light after staining with ethidium bromide (0.5 mg/mL). The similarities between the isolates were determined by visual comparison of the isolates band patterns. The interpretation of the PFGE results was carried out by eye according to the criteria described by Tenover et al. [21].

**Statistical analysis**

Data were analyzed using SPSS statistical software, version 16.0 (IBM, Chicago, USA). Chi-Square test was used to assess the differences between proportions of *S. aureus* strains isolated in psoriasis and control skin. *P*-value <0.05 was considered as statistically significant. Quantitative data were presented as means and standard deviation and also described as numbers and percentages. Mann–Whitney U test was used for comparing *PVL* positive and *PVL* negative groups relation to PASI.

**Results**

Two groups were included in this study: the first was patients with psoriasis (36 ± 12.4 years, 54 females and 36 males) and the second was a control group (38 ± 11.7 years, 49 females and 41 males).

**Prevalence of *S. aureus* in psoriasis and control groups**

*S. aureus* was isolated from 31 cases (34.4%) in psoriatic skin lesions, and from 16 cases (17.8%) in the control group, which makes a statistically significant difference (*P* = 0.01).

**Prevalence of MRSA in psoriasis and control groups**

The prevalence of MRSA colonization in our psoriatic patients from skin lesions was 23.3% (21 out of 90 samples). A high statistically significance difference (*P* < 0.001) was noticed in MRSA colonization between psoriasis and control groups (23.3% versus 3.3% in psoriasis and control groups, respectively).

**Expression of meca and PVL genes in MRSA isolates from psoriasis and control groups**

In psoriasis patients, five out of 21 (23.8%) MRSA isolates from skin lesions were positive for *meca* and *PVL* genes using PCR assay. None of the isolated MRSA from the control group was positive for *PVL* genes.

**PFGE**

The restriction endonuclease patterns obtained with the PFGE following the SmaI treatment for the 24 MRSA isolates showed 10 different patterns. Fourteen isolates belonged to the same pulsotype, as in Figure 1, another two carried similar pulsotypes (control group), and other eight showed un-similar pulsotype. Of interest, the 14 MRSA isolates with similar pulsotypes were isolated from psoriasis patients out of 16 with *PVL negative*. 
Antibiotic resistance in PVL-positive and PVL-negative MRSA isolates

The results of antimicrobial susceptibility testing of 21 MRSA isolates from psoriatic skin lesions are shown in Table 2. Generally, the antibiotic resistance among PVL negative MRSA isolates was found higher as compared to PVL positive MRSA. There was a statistically significant difference in the resistance pattern only toward clindamycin.

Ten out of 16 isolates were D-zone positive and considered to have inducible clindamycin resistance and are presumed to be resistant.

Clinical comparisons of psoriatic patients with PVL-positive and -negative MRSA

Psoriatic patients with PVL-positive and PVL-negative MRSA did not show significant

Table 2. Antibiotic resistance pattern of PVL positive and PVL negative MRSA isolates.

| Antimicrobial   | PVL-positive MRSA | PVL-negative MRSA | P value |
|-----------------|--------------------|-------------------|--------|
|                 | n = 5 (%)          | n = 16 (%)        |        |
| Erythromycin    | 4 (80)             | 13 (81.3)         | 0.95   |
| Ciprofloxacin   | 3 (60)             | 13 (81.3)         | 0.330  |
| Lincomycin      | 3 (60)             | 12 (75)           | 0.517  |
| Tetracycline    | 1 (20)             | 6 (37.5)          | 0.469  |
| Gentamicin      | 2 (40)             | 8 (50)            | 0.695  |
| Cotrimoxazole   | 3 (60)             | 12 (75)           | 0.517  |
| Clindamycin     | 0 (0)              | 15 (93.8)         | <0.001*|
| Rifampicin      | 1 (20)             | 4 (25)            | 0.819  |
| Fusidic acid    | 1 (20)             | 5 (31.3)          | 0.627  |

* Significant association.
difference with respect to sex, family history, nail involvement, pruritis and arthritis. In contrast, we had noticed a significantly higher PSAI score among patients harboring PVL-positive isolates compared to PVL negative isolates (33.06 ± 0.9 vs. 22.94 ± 1.08; p < 0.001) beside a significant difference in the age in which PVL positive cases were younger than those with negative isolates as shown in Table 3 and Figure 2.

**Discussion**

In the current study, the prevalence of *S. aureus* was 34.4% among psoriasis cases, this is in agreement with Ng CY et al. who reported 35.3% and Flytström et al. who reported 37.5% [12,22]. A higher prevalence of 64% and 46.2% were reported in previous studies [23,24]. However, other studies reported lower prevalence [25,26]. In the present study, 17.8% of the control group was *S. aureus* positive; similarly was reported by Fahlén et al. [26]. On the other hand, the lower prevalence was reported in different literatures [22–26]. *S. aureus* showed a significant skin colonization in psoriasis group when compared with the control group and this is parallel to that reported by Ng CY et al. who mentioned that patients with psoriasis were 4–5 times more likely to be

| Parameter               | PVL-positive MRSA | PVL-negative MRSA | P value |
|-------------------------|-------------------|-------------------|---------|
| Age (years)             | 27 ± 10           | 39.6 ± 11.2       | 0.0369* |
| Sex (male)              | 3 (60)            | 8 (50)            | 0.696   |
| Family history          | 1 (20)            | 4 (25)            | 0.819   |
| PSAI score              | 33.06 ± 0.9       | 22.94 ± 1.08      | <0.001* |
| Nail involvement        | 2 (40)            | 2 (12.5)          | 0.172   |
| Pruritis                | 5 (100)           | 14 (87.5)         | 0.406   |
| Psoriatic arthritis     | 1 (20)            | 3 (18.75)         | 0.95    |

*Significant association.

![Figure 2. SmaI restriction endonuclease patterns obtained by PFGE: Lane 1, marker; lanes 3,4,7,8,9,10,11,12,13, 14,15,16,17,18 MRSA strains showed the same pulsotype; lanes 2, 5, and 6 showed three different pulsotypes.](image-url)
colonized by S. aureus than healthy controls [12]. There is evidence that S. aureus peptidoglycan inhibits apoptosis, and affects keratinocyte proliferation [27]. Also, staphylococcal antigens regulate inflammatory mediators such as interleukin (IL)-22, which inhibit the terminal differentiation of keratinocytes [28]. In the current study, the prevalence of MRSA positive cases was 23.3% in psoriatic patients. A lower prevalence of 11% and 9% were reported by others [12,29]. In the present study, 3.3% of the control group was positive for MRSA, a finding close to that reported by Ng CY et al. (2.6%) [12]. However, a higher prevalence (12%) was reported by others [25]. MRSA colonization was significant in psoriasis group when compared with the control group in our study and this is in agreement with Hsu et al. who reported that psoriasis patients were more susceptible to MRSA by twofolds than those without [30]. In this study, we detected five PVL positive MRSA isolates from psoriatic skin lesions and this was in parallel with Pouessel et al. study who reported an association between PVL-positive MRSA and psoriasis [31]. Our results of antimicrobial sensitivity testing revealed higher resistance trend in PVL negative MRSA isolates compared to PVL positive MRSA isolates; however, there were no statistically significant differences except in case of clindamycin. The same result was obtained by Elizuret al. and Shrestha et al. who reported that PVL genes were positively correlated with erythromycin resistance and clindamycin-susceptible phenotype which was confirmed by the presence of a macrolide efflux protein [32,33]. The current study reported an increase in the psoriasis severity score among patients harboring PVL positive isolates when compared to PVL negative isolates, this is in parallel to Zhang et al. who reported that PVL genes are more common among isolates causing a clinical problem and larger skin lesions than among isolates causing asymptomatic colonization [34]. The clinical squeal of PVL positive MRSA is more serious than those with PVL negative MRSA because this toxin stimulates the secretion of pro-inflammatory molecules as LTB4 which is a potent chemokine for macrophages, and neutrophils, decrease the percentage of Treg cells and the expression of Foxp3, and increase the expression of RORγt mRNA, that act as DNA-binding transcription factor and plays an important regulatory role by reducing apoptosis and promoting the differentiation of T-lymphocyte into pro-inflammatory T helper 17 cells [35]. In this study, 14 PVL negative MRSA isolates showed the same pulsotype pattern; however, the rest of MRSA isolates from psoriasis patients, seven isolates showed different pulsotypes. Up to our knowledge, there is no study that makes PFGE for MRSA in psoriasis patients, so this point needs further studying to clear if there is a certain type of MRSA induce or worsen the prognosis of this disease.

**Conclusion**

MRSA infections remain a significant threat to human health and our study reported a significant MRSA colonization in psoriasis group and showed that the presence of PVL contributes to increase the severity of this disease; however, the number of PVL + MRSA isolates were very limited and further work is needed to investigate these possible differences and to clear if there is a common type of MRSA infection in psoriasis patients.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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