Epidemiology of Panton-Valentine Leukocidin harbouring *Staphylococcus aureus* in cutaneous infections from Iran: a systematic review and meta-analysis

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SUMMARY

Panton-Valentine Leukocidin (PVL) producing *Staphylococcus aureus* has been associated with severity of skin infections and pathology that suggest a major role in pathogenicity. The present study aimed to determine the overall prevalence of PVL harbouring *S. aureus* isolates from cutaneous infections in Iran. A systematic search was performed by using Medline electronic databases (PubMed) from the papers published by Iranian authors to the end of March 2017. Ten publications which met our inclusion criteria were then selected for data extraction and analysis by Comprehensive Meta-Analysis Software. The pooled prevalence of PVL in cutaneous infections was estimated at 27.9% (95% CI: 17.9-40.6). The range of PVL positivity among *S. aureus* isolates obtained from cutaneous infections was from 7.4% to 55.6%. In summary, despite the emergence of multiple-drug resistant strains, it seems that the overall prevalence of PVL carrying *S. aureus* in Iran remains steady regardless of methicillin resistance. However, further research is required to elucidate the interplay between the risk of invasive disease and PVL, especially in Iran.

Keywords: Panton-Valentine Leukocidin, *Staphylococcus aureus*, MRSA, meta-analysis, Iran.

INTRODUCTION

Staphylococcus aureus is considered as one of the main causes of nosocomial and community acquired infections with symptoms ranging from mild skin infections to life threatening disease [1-3]. The pathogenicity of *S. aureus* depends on the presence of numerous bacterial surface components and extracellular proteins [4, 5]. Some of these potential virulence factors are expressed by the genes located on mobile genetic elements (MGEs) such as Pantone Valentine Leukocidin (PVL) which is located on lysogenic bacteriophages [6]. PVL is a bi-component toxin consisting of the LukS and LukF proteins [4]. This dimeric cytolytic toxin belongs to the beta-barrel pore-forming toxin family which has a high affinity to human leukocytes [4]. In several studies, *S. aureus* isolates carrying PVL toxin are linked to severe disease pathology that suggests a major role in their pathogenicity [4]. In the literature, the fre-

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quent isolation source of PVL-producing *S. aureus* are necrotizing pneumonia and cutaneous infections, including abscesses, furuncles, and surgical wounds [7, 8].

The emergence of specific community-associated methicillin-resistance *S. aureus* (CA-MRSA) clone significantly increases the burden of soft skin and soft tissue infections (SSTIs) in epidemic areas [9-11]. MRSA strains are characterized by the presence of the *mecA* gene coding for modified penicillin-binding proteins 2a (PBP2a) with lower affinity to β-lactam antibiotics [12]. MRSA strains related to both CA-MRSA and healthcare-associated MRSA (HA-MRSA) have been increasing dramatically [13]. MRSA isolates producing PVL toxin may cause more severe and complicated infections with a higher rate of mortality when compared to strains that do not produce PVL toxin [14]. Epidemiologically, PVL carrying isolates are mostly associated with CA-MRSA infections, so raising the concerns of both microbiologists and clinicians [15]. Despite the significance of PVL as a virulence factor, there is no study looking at the overall prevalence of PVL-producing *S. aureus* in Iran. The aim of this study was to investigate the prevalence of PVL harboring *S. aureus* isolates from cutaneous infections in Iran by using a systematic review and meta-analysis based method.

MATERIALS AND METHODS

Search strategies

We performed a systematic search by using Medline electronic databases (PubMed) from papers published by Iranian authors to the end of March 2017.

"Panton-Valentine leukocidin", "Panton-Valentine", "PVL", "*S. aureus* toxin" and related terms in combination with "Iran" were searched as scientific keywords in the present survey. Two reviewers independently screened the databases with the related keywords and reviewed the titles, abstracts, and full texts to find the articles which met the inclusion criteria. The articles published in English which met our inclusion criteria considered in our survey. A standard method was used to detect *S. aureus* and the presence of PVL gene (Polymerase chain reaction (PCR) or Real-time PCR), data on the number of *S. aureus* and PVL positive isolates, and samples obtained from cutaneous infections. Studies which had not used standardized methods and studies which had not specified PVL positivity in cutaneous samples were excluded.

Extracted data and definitions

The following details were extracted from the included articles: first author's name, study duration, publication date, study setting, sample size, frequency of MRSA, *S. aureus* and MRSA identification methods and PVL positivity rate.

Statistical analysis

Analysis of data was performed by Comprehensive Meta-Analysis Software Version 2.2 (Bio stat Company). Meta-analysis was performed by using random effects model to estimate the pooled prevalence and corresponding 95% confidence interval (CI). Statistical heterogeneity between and within groups was estimated with the Q statistic and the I^2 index. The funnel plot, Begg's rank correlation test, and Egger's weighted regression tests were used to evaluate possible publication bias ($P<0.05$ was considered as a statistically significant publication bias). Chi-square tests were used to determine the significance of the differences by using SPSS™ software, version 21.0 (IBM Corp., USA). A difference was considered statistically significant if the p value was less than 0.05. The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS

In the present study, out of 117 title found by the mentioned search strategies, 10 publications met our inclusion criteria and were selected for data extraction and analysis (Figure 1) [16-25]. According to the included publications, the overall prevalence of PVL was estimated 22.8% (95% CI: 13.8-35.3). Moreover, the prevalence of PVL in MRSA strains was investigated in 8 studies. The pooled prevalence of PVL in MRSA strains estimated 18.7% (95% CI: 11.3-29.5) ranging from 5.5% to 60.6%.

The pooled prevalence of PVL in cutaneous infections was estimated 27.9% (95% CI: 17.9-40.6). The range of PVL positivity among *S. aureus* isolates obtained from SSTIs ranged from 7.4% to 55.6%.

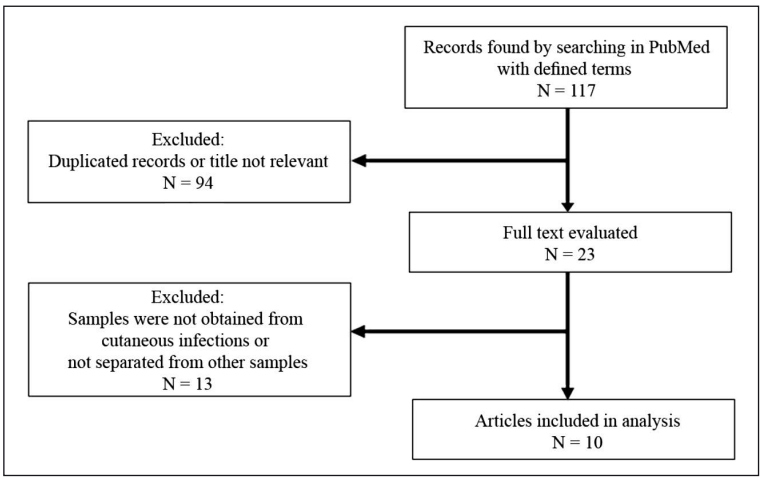


Figure 1 - Summary of the literature search strategy and study selection.

Table 1 - Characteristics of studies included in the meta-analysis

Name	*Performed/ published years*	*Study area*	*Sample size*	*MRSA No. (%)*	*Source of isolation*	*PVL in Cutaneous Positive/ Total No.*	*PVL in MRSA/ MSSA No.*	*PVL total Positive/ Total No.*
Havaei et al.	UN[a]/2010	Tehran	149	UN	Skin	21/52	ND[c]	36/149
Khosravi et al.	Jan to Nov 2010/2012	Ahvaz	95	83 (87.4)	Burn wound	10/95	6 /4	10/95
Momtaz et al.	Feb to May 2013/2014	Tehran	66	53 (80.3)	Superficial and surgical wound	19/41	ND	27/66
					Abscess	3/7		
Havaei et al.	Jan to May 2010/2014	Isfahan	50	8 (16)	Wound	8/19	2/9	11/50
					Abscess	0/1		
Hoseini Alfatemi et al.[b]	2012-2013/2015	Shiraz	345	146 (42.3)	Wound	2/18	8/ND	8/146
					Other skin infections	3/8		
Dormanesh et al.[b]	UN/2015	Khorasan	56	13 (23.1)	Wound	1/3	47/ND	47/79
		Tehran	66	19 (28.8)		3/5		
		Isfahan	67	22 (32.8)		3/5		
		Shiraz	66	25 (37.9)		3/5		
Shariati et al.	UN/2016	Shahrekord	196	96 (49)	Wound	4/54	18/3	21/196
Fagheei Aghmiyuni et al.	UN/2016	Tehran	116	49 (42.2)	Pemphigus	25/116	14/11	25/116
Goudarzi et al.	2015-2016/2017	Tehran	106	106 (100)	Burn wound	16/106	16/ND	16/106
Mehrshad et al.	2013-2014/2017	Shiraz	55	33 (60)	Superficial and burn wound	30/55	20/10	30/55

[a]UN: Unknown; [b]PVL report was only in MRSA isolates; [c]ND: Not determined.

There was a significant heterogeneity among the included studies (χ^2=69.423; P<0.001; I^2=87%). The full results of the included articles, containing sample size, prevalence of MRSA and overall PVL positivity are presented in Table 1.

Sample size and 95% confidence interval (CI) of all analyzed articles are illustrated in a forest plot (Figure 2). Moreover, a funnel plot of the included articles is shown in Figure 3. From this plot no evidence of publication bias was observed and confirmed by Begg's rank correlation analysis (z=0.53, p=0.59) and Egger's regression analysis (t=0.25, p=0.81).

DISCUSSION

There is strong evidence that PVL is associated with SSTIs and has negative effects on the clinical outcome of infections [14, 26]. To the best of our knowledge, this study is the first comprehensive systematic review on the prevalence of PVL carrying *S. aureus* isolates from cutaneous infections in Iran. Based on the meta-analysis results, the overall estimate of PVL prevalence among Iranian SSTIs was 27.9%, and was slightly higher than the overall

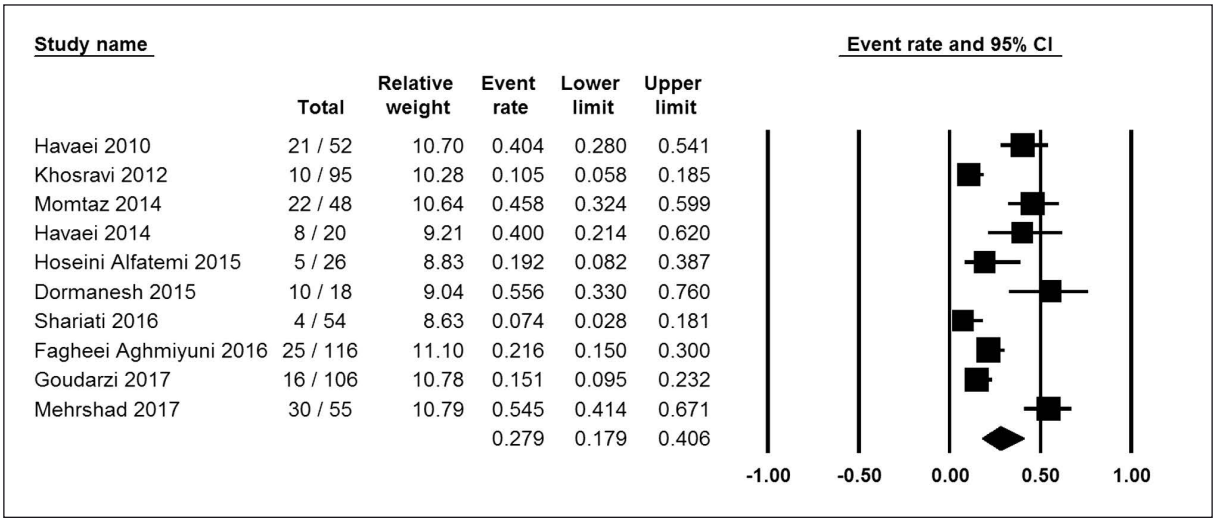
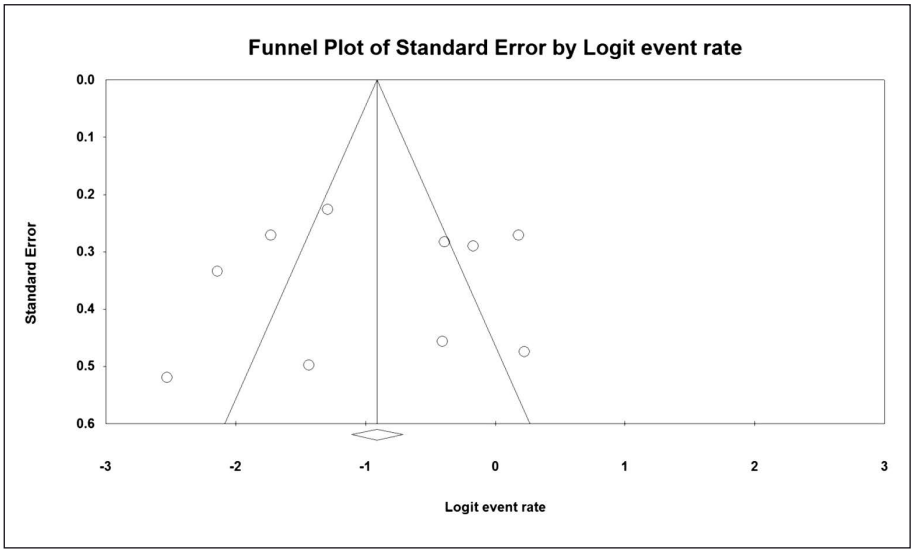


Figure 2 - Forest plot of the meta-analysis of Panton-Valentine Leukocidin (PVL) carrying *Staphylococcus aureus*.

Figure 3 - Funnel plot of the meta-analysis on Panton-Valentine Leukocidin (PVL) carrying *Staphylococcus aureus*.



prevalence of PVL estimated to be 22.8% (P=0.39). The international comparison of PVL prevalence is challenging, since the prevalence of PVL-positive strains is multifactorial, and most of the reports are regional. The high prevalence of PVL in the United States is mainly due to the higher prevalence of CA-MRSA, particularly the USA300 lineages [26, 27]. Conversely, in Europe the prevalence remains low, except in countries where PVL-positive MRSA strains belonging to ST80 clone prevail [27]. The estimated prevalence of PVL in Iran with 27.9% was lower than several reports from France, Netherlands, Turkey, New Zealand, Taiwan, and Benin [7, 28-32]. Although there are reports that showed lower rate of PVL-positive strains in SSTIs compared to our findings, such as England, Wales and Ireland [33, 34].

It must be considered that our estimates could not fully indicate the prevalence of PVL in cutaneous infections in Iran, since as seen in our results the geographical distribution of the studies was limited to a few regions. However, some reasons may explain the observed discrepancies in the prevalence of PVL neither in Iran nor in other parts of the world. The variation in the prevalence of PVL may arise from the differences in time periods, sample size, type or source of infections, rate of MRSA, and geographical distribution. Meanwhile, the included Iranian studies were performed on hospital patients so the burden of PVL-associated infection would be expected to be higher in the community. Moreover, the lower prevalence of PVL in Iran, compared to other reports, may be related to methicillin-resistance background of *S. aureus* isolates; since it has been shown that CA-MRSA and healthcare-acquired MRSA (HA-MRSA) isolates may have different virulence patterns [35]. For example, higher prevalence of PVL was mostly reported in association with CA-MRSA types, which may be due to the predominance of staphylococcal cassette chromosome *mec* (SCC*mec*) types IV or V among CA-MRSA strains [15, 35]. Based on published articles the predominant SCC*mec* types among MRSA isolates obtained from Iranian patients were HA-MRSA types, which are different from the observed patterns from countries with high PVL background [36-42].

Despite some reports about association of methicillin-sensitivity and PVL occurrence, and their reservoir role for PVL carrying MRSA strains, still there is controversy about the prevalence of PVL among methicillin-sensitive *S. aureus* (MSSA) and MRSA isolates [27, 43, 44]. In our findings, among the included articles, 4 study reported higher incidence of PVL among MRSA isolates while Khosravi et al. showed higher incidence in MSSA isolates [17, 19, 22, 23, 25].

Regarding the prevalence of PVL among *S. aureus* isolates whether in Iran or foreign countries, with some exceptions, the isolates obtained from cutaneous infections showed higher rates of PVL compared to other infection sites, including respiratory, musculoskeletal and bloodstream [16, 18, 20, 26].

Finally, as a main limitation related to the present study, we did not include the articles from other database such as Scopus and Google scholar, because of the more reliability of articles extracted from PubMed database.

In summary, because of a worse clinical outcome estimation the burden of PVL associated infections provide good epidemiological background for effective infection control of the public health. Meanwhile, despite the emergence of multiple-drug resistant strains, it seems that the overall prevalence of PVL carrying *S. aureus* in Iran remains steady regardless of methicillin resistance. However, further research is required to elucidate the interplay between the risk of invasive disease and PVL, especially in our country.

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Conflict of interest
None declared.

Statement of authorship
The conception or design of the work: Sedigh H., Shahini M.; the acquisition, analysis, or interpretation of data: Sedigh H., Shahini M., Hoseini S.M., Malekzadegan Y.; drafting the work or revising it critically for important intellectual content: Sedigh H., Nikokar I., Azizi A.; final approval of the version to be published: Sedigh H., Shahini M., Nikokar I., Hoseini S.M., Malekzadegan Y., Azizi A.

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