Ann Ig 2018; 30: 391-400 doi:10.7416/ai.2018.2239

Epidemiology of toxic shock syndrome toxin-1 harboring *Staphylococcus aureus* obtained from clinical samples in Iran: A Systematic Review and Meta-analysis

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Key words: TSST-1, Staphylococcus aureus, MRSA, Meta-analysis, Iran
Parole chiave: TSST-1, Staphylococcus aureus, MRSA, Meta-analysis, Iran

Abstract

Background. *S. aureus strains, with the capability of producing toxic shock syndrome toxin-1 (TSST-1), are more likely to cause complicated infections. However, due to lack of comprehensive local data on the prevalence of TSST-1, we aimed to determine the prevalence of TSST-1 harboring S. aureus isolates in Iran.*
Methods. *A systematic search was performed by using PubMed and Scopus databases from papers published by Iranian authors from January 2000 to the end of March 2017. Then, 10 publications which were matched with inclusion criteria were selected for data extraction and analysis by Comprehensive Meta-Analysis Software.*
Results. *The overall prevalence of TSST-1 carrying S. aureus in Iran was 21.3% (95% CI: 7.9%-46.1%), ranging from 0% to 68%. Moreover, from the included studies, the pooled prevalence of TSST-1 producing MRSA isolates was estimated to be 25.2% (95% CI: 13.3%-42.5%), ranging from 0% to 69.8%. From those studies which showed the distribution of toxin-harboring S. aureus it was found that the skin and soft tissue, respiratory and bloodstream infections were the common sites of TSST-1 harboring S. aureus.*
Conclusion. *In summary, it seems that emergence of MRSA strains leads to higher prevalence of TSST-1 carrying strains in the north of Iran. However, further research is required to elucidate the interplay between the outcome of diseases and TSST-1 producing strains, especially in our country.*

Introduction

Staphylococcus aureus is a ubiquitous Gram-positive bacteria found as part of the normal flora in many sites of the human body (1). *S. aureus,* as an opportunistic pathogen responsible for a broad spectrum of infections in both community and healthcare setting, ranging from a mild superficial skin to severe systemic infections (2, 3). A broad range of virulence factors are produced by *S. aureus* activated against a variety of host cell types, which facilitates its pathogenicity (3).

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Staphylococcal toxic shock syndrome (TSS) is a relatively rare condition mainly caused by *S. aureus* toxic shock syndrome toxin-1 (TSST-1) which is known as a superantigen (4). TSS is a life-threatening disease which often progress to multiple-organ involvement and eventually death in some cases (4).

The emergence of multiple-drug resistant bacteria, particularly methicillin-resistant *S. aureus* (MRSA) has become a serious challenge of global health (5). Toxin producing MRSA strains may be more inclined to cause invasive infections and are associated with a higher mortality among hospitalized patients (6).

Despite the significance of TSST-1, as a virulence factor, there is no comprehensive local data available on its prevalence to estimate the burden of *S. aureus* toxin producing isolates. The aim of this study was to investigate the prevalence of TSST-1 harboring *S. aureus* isolates from Iran by using a systematic review and meta-analysis based method.

Materials and Methods

1. Search strategies

We performed a systematic search by using Medline electronic databases (PubMed), Scopus and Google scholar from papers published by Iranian authors from January 2000 to the end of March 2017.

"Toxic shock syndrome" or "TSST-1" or "*tst* gene" or related terms and "Iran", with and without "*S. aureus*", 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 determine the articles which met the inclusion criteria. The articles published in English or Persian language with English abstract indexed in Pubmed and Scopus which had the inclusion criteria were considered in our survey. Standard methods were used to detect *S. aureus* and the presence of TSST-1 encoding gene, data on the number of *S. aureus* and MRSA isolation rate. Studies that had not used standardized methods, their sample size was less than 10 isolates, and studies which had not detected toxin gene were excluded.

2. Extracted data and definitions

The following details were extracted from the included articles: the first author's name, the study's performing time, publication date, the study setting, sample size, frequency of MRSA, TSST-1 positivity rate, and clinical source of TSST-1 harboring isolates.

3. 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 the possible publication bias (P <0.05 was considered as 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). The p value less than 0.05 was considered to be statistically significant. The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

The database search yielded 365 non-duplicate abstracts. Among them, 344 were removed from the title and abstract

screening and 21 were accessed in full text. Of 21 reviewed studies, four studies had a sample size less than 10 isolates, four studies only detected the presence of TSST-1 by serological methods, two study had no clear identification methodology and sample size, and the results of one study were duplicated in their most recent study. Ten studies matched with inclusion criteria and were included in this meta-analysis (7-16). Searching procedure for selection of the eligible studies is demonstrated in Figure 1.

Six studies were multicenter, and four were single-center based studies. The full results of the included articles, containing sample size, the prevalence of MRSA and rates of toxin positivity are presented in Table 1. Two studies did not report primary *S. aureus* sample size and prevalence of MRSA (8, 15). For the remaining studies, the pooled prevalence of MRSA was 73.9% (95% CI: 55.5%-86.5%), ranging from 26.9% to 100%. There was a significant heterogeneity among the eight studies (χ^2 = 173.594; P <0.001; I^2 = 96%).

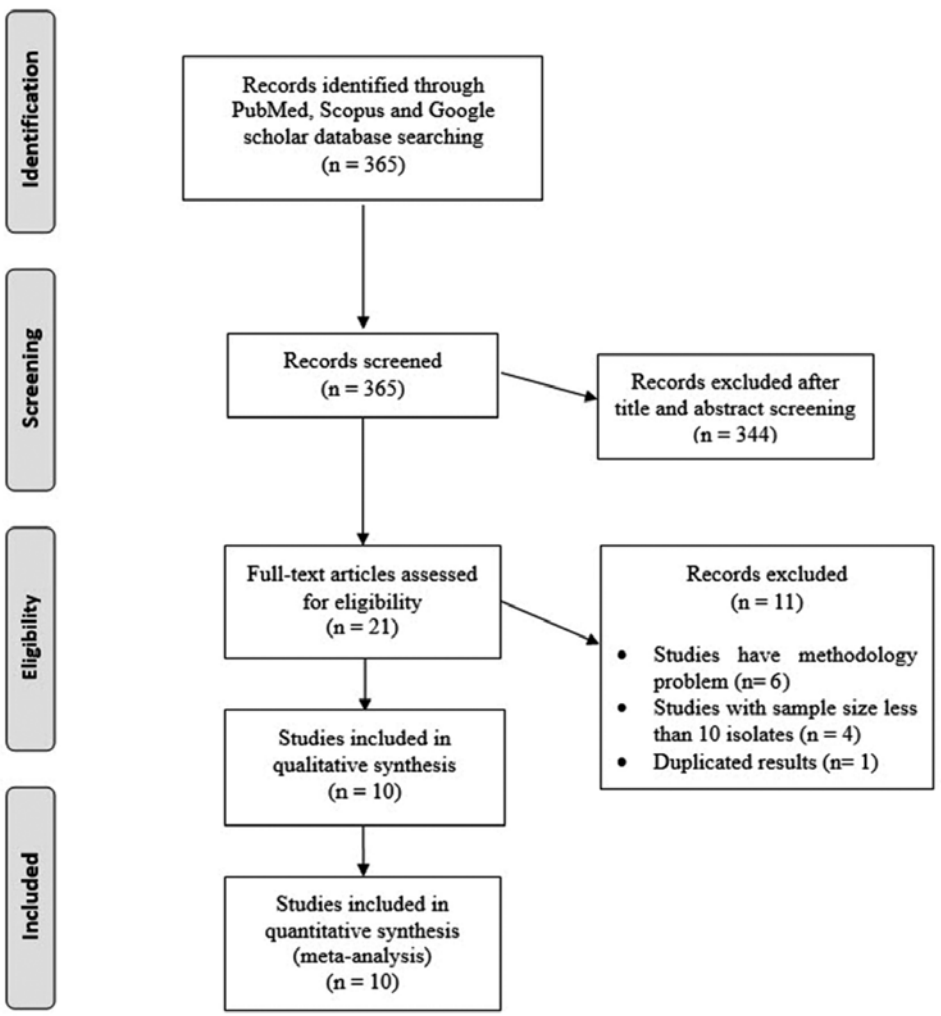

Figure 1 - Summary of the literature search strategy and study selection

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

First author, publication year	Study period	Location	Source of isolation	Sample size	MRSA rate [a] (No.)	Total TSST-1 (No.)	TSST-1 in MRSA (No.)	TSST-1 in MSSA [b] (No.)	*P* value [c]	Ref
Sabouni, 2014	UN [d]	Tehran	Clinical	133	64	17	0	17	P <0.05	(7)
Arabestani, 2015	2013-2014	Hamadan	Clinical	UN	100	22	10	12	P = 0.058	(8)
Motamedifar, 2015	2012-2013	Shiraz	Clinical	345	146	53	17	36	P = 0.136	(9)
Eftekhar, 2016	2015	Tehran	Clinical	70	70	30	30	ND [e]	ND	(10)
Goudarzi, 2016	2014-2015	Tehran	Clinical	75	70	ND	36	ND	ND	(11)
Zarei Koosha, 2016	2011-2012	Tehran	Clinical	197	172	134	120	14	P = 0.126	(12)
Motallebi, 2016	2013-2014	Tehran	Burn wound	128	77	ND	0	ND	ND	(13)
Akhi, 2017	2015	Tabriz	Urogenital tract infection	26	7	0	0	0	ND	(14)
Goudarzi, 2017	2015-2016	Tehran	Clinical	UN	128	ND	75	ND	ND	(15)
Rashidi Nezhad, 2017	2015-2016	Tehran	Clinical	105	95	ND	31	ND	ND	(16)

a) MRSA: methicillin-resistant *S. aureus*; b) MSSA: methicillin-sensitive *S. aureus*; c) significant level of TSST-1 rate in MRSA vs. MSSA strains; d) UN: unknown; e) ND: not determined

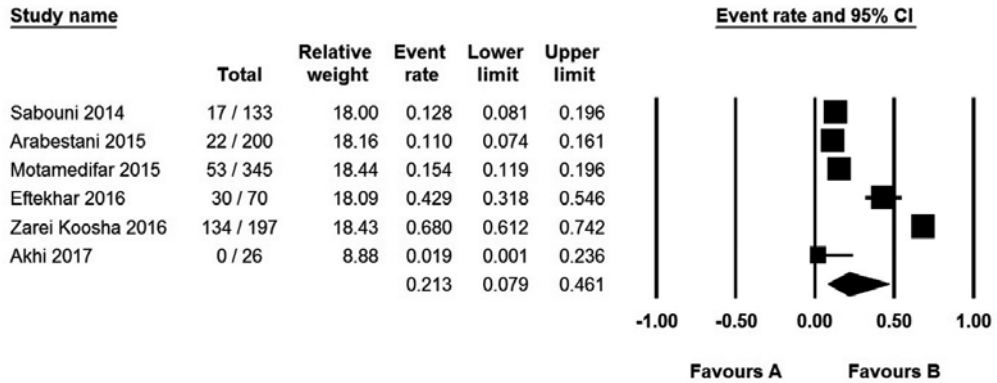

Figure 2 - Forest plot for prevalence of TSST-1 harboring *S. aureus* and 95% CI for all enrolled studies

According to the included publications, in four studies the prevalence of TSST-1 was investigated only among MRSA strains. For the remaining six studies, the overall prevalence of TSST-1 was 21.3% (95% CI: 7.9%-46.1%), ranging from 0% to 68% (Figure 2). There was a significant heterogeneity among the six studies ($\chi^2 = 200.561$; $P < 0.001$; $I^2 = 97.5\%$). The symmetric funnel plot showed no evidence of publication bias. Additionally, Begg's and Egger's tests were performed to quantitatively evaluate the publication biases. According to the results of Begg's test ($z = 0.38$, $P = 0.71$) and Egger's test ($t = 0.64$, $P = 0.56$), no evidence of publication bias was observed.

In the 10 included studies, the pooled prevalence of TSST-1 in MRSA isolates was 25.2% (95% CI: 13.3%-42.5%), ranging from 0% to 69.8% (Figure 3). Based on Q statistic and the I^2 index, heterogeneity was significant ($\chi^2 = 166.541$; $P < 0.001$; $I^2 = 94.6\%$). Moreover, the funnel plot

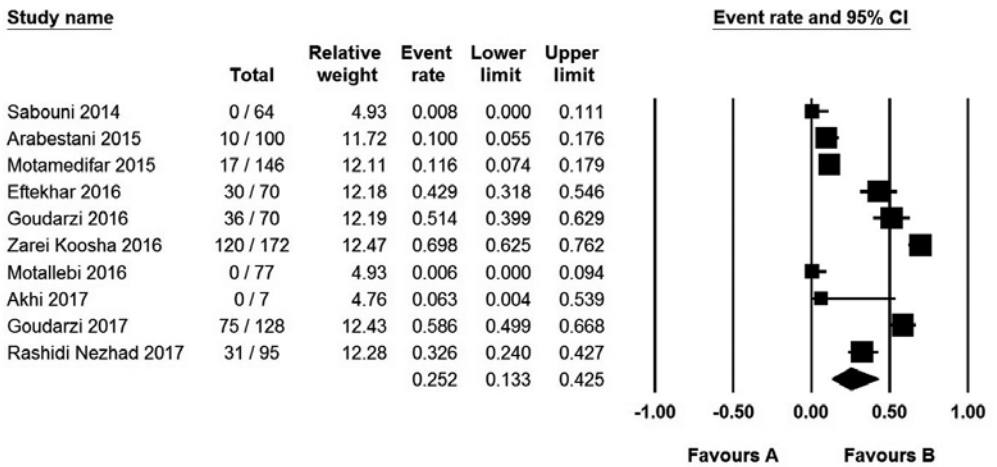

Figure 3 - Forest plot for prevalence of TSST-1 harboring MRSA and 95% CI for all enrolled studies

showed no evidence of publication bias and was confirmed by Begg's rank correlation analysis (z = 1.61, P = 0.11) and Egger's regression analysis (t = 2.32, P = 0.05).

Of the totally included articles, only in five studies the distribution of toxin-harboring *S. aureus* based on the sites of infection was documented (data not shown). From those studies, it seems that the skin and soft tissue, respiratory and bloodstream infections were common sites of TSST-1 harboring *S. aureus*.

Discussion

Colonization or infection by superantigens producing *S. aureus* strains has adverse effects on the clinical outcome of patients (8, 15). To the best of our knowledge, this study is the first comprehensive systematic review on the prevalence of TSST-1 harboring *S. aureus* isolates recovered from clinical samples in Iran. Based on the results of the present study, the overall estimate of TSST-1 harboring *S. aureus* among Iranian patients was 21.3% with a wide range from 0% to 68%. This variation in prevalence of TSST-1 in clinical samples was almost the same in other parts of the world, ranging from European countries including France (2.7%) (17); Turkey (14.2%) (18); Germany (16.7%) (19); South-American countries like Colombia (18%) (20) and Brazil (46.7%) (21); African countries like Algeria (0%) (22), Libya (7.5%) (23), Nigeria (16%) (24) and Congo (19.4%) (25); and Asian countries such as Taiwan (4.8%) (26), South-Korea (25.5%) (27) and China (31.4%) (28). However, our estimates could not fully indicate the prevalence of TSST-1 harboring *S. aureus* in Iran since, as seen in our results, the geographical distribution of studies were limited to a few regions.

According to our estimation, the pooled prevalence of MRSA was 73.9%, which showed a slight increase from the previous estimate in Iran (52.7%) (29), although our estimate was limited to studies which investigated the prevalence of TSST-1. The overall prevalence of TSST-1 harboring MRSA among Iranian patients was estimated to be 25.2%. Similar to the prevalence of TSST-1 harboring *S. aureus*, the reported rates are highly variable. Previously, prevalence of TSST-1 harboring MRSA in clinical samples from China was 24.1% (28), Colombia 27% (20), South-Korea 43.2% (27), France 60.7% (30), Congo 67% (25), Japan 75.7% (31), and more than 75% in Taiwan (32).

However, some reasons may explain the variation in prevalence of TSST-1 producing *S. aureus* in Iran. First, the differences may arise from variations in the geographical distribution, the source of infections or sample size. For example, the high rate of TSST-1 in the study of Zarei Koosha et al. may be due to the samples' origin, which mostly were from wounds (12), since skin and soft tissue infections are documented as a common site of toxin-producing *S. aureus* strains (33-35).

Second, the prevalence of TSST-1 in Iran may lie in the epidemiological background of *S. aureus* isolates, since it has been shown that TSST-1 may be more prevalent in certain clonal lineages or methicillin-susceptible *S. aureus* (MSSA) strains (36). From the included articles, four studies compared the prevalence of TSST-1 between MSSA and MRSA isolates, and only Sabouni et al. showed significant differences regarding the methicillin-resistance background of the isolates (7). Previously, it was documented that certain toxins may be associated with specific SCC*mec* types, such as Panton–Valentine leukocidin (PVL) which are frequently linked to community-associated MRSA (CA-MRSA) types (types IV, V) (37). In the present study, most of the included studies showed predominance of healthcare-associated MRSA (HA-MRSA) types (1-III); however, there was no strong

evidence of an association between TSST-1 positivity and specific SCC*mec* type (38). Based on MLST typing, *S. aureus* can be designated into different sequence types (ST) or clonal complex (CC) (39). TSST-1 appears to be limited to certain clonal lineages globally, such as CC30, CC5, and CC22 (39). Despite the limited information about colonel distribution of *S. aureus* in Iran, it seems that STs has a more prefunded effect than other epidemiological factors on the prevalence of TSST-1. In this regard, multicenter-based studies of Goudarzi et al. from Tehran (capital of Iran) showed a higher prevalence of TSST-1 in association with certain STs (ST22 and ST239) (11, 15). These findings and the observations by others (40, 41) may explain the higher prevalence of TSST-1 in the north of Iran (Tehran) compared to Southern cities (Shiraz and Hamadan). Meanwhile, the observed controversy among the results of Sabouni et al. and Motallebi et al. with other studies conducted in Tehran may arise from the single-hospital based design of their studies and restricted nature of patients, which was hospitalized children and burn patients, respectively (7, 13).

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

Conclusion

In summary, because of higher risk of complications in infections caused by TSST-1 producing strains, estimation of the burden of TSST-1 harboring strains can provide good epidemiological background for the development of practical guidelines for infection control in healthcare settings. Moreover, it seems that emergence of MRSA strains leads to higher prevalence of TSST-1 carrying strains in the north of Iran. However, further research is required to elucidate the interplay between the outcome of diseases and TSST-1 producing strains, especially in our country.

Acknowledgment
The authors wish to thank Dr. Nasrin Shokrpour at the Research Consolation Centre (RCC) at Shiraz University of Medical Sciences for her invaluable assistance in editing this manuscript, and Mr. A. Azizian from Department of Epidemiology, Shiraz University of Medical Sciences, Shiraz, Iran for his technical advise.
Funding support
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflict of interest
None declared.
Ethical approval
Not applicable.
Informed consent
Not applicable.

Riassunto

Epidemiologia dello Staphylococcus aureus produttore della tossina-1 responsabile della sindrome tossica in campioni clinici raccolti in Iran: una revisione sistematica e meta-analisi

Background. I ceppi di *S. aureus*, capaci di determinare la syndrome tossica da tossina-1 (TSST-1), sono più spesso responsabili di infezioni complicate. Comunque, a causa della mancanza di dati epidemiologici locali sull aprevalenza di TSST-1, noi abbiamo volute ricercare tale prevalenza in isolate dall'Iran.

Metodi. È stata condotta una ricerca sistematica su PubMed e Scopus riguardo ad articoli scientifici pubblicati da autori iraniani dal gennaio 2000 al marzo 2017. Quindi, 10 pubblicazioni, che rispettavano i criteri di inclusione sono state selezionate per l'estrazioe dei dati e l'analisi mediante Software.

Risultati. In generale la prevalenza di *S. aureus* produttori di TSST-1 in Iran era del 21.3% (95% CI: 7.9%-46.1%), variando da 0% a 68%. Inoltre, dagli studi inclusi. Dagli studi che mostravano una distribuzione di *S. aureus* produttori di TSST-1, è stato rilevato come le infezioni di cute, tessuti molli, tratto respiratorio e setticemie fossero la sorgente più frequente.

Conclusioni. Appare che la diffusione di ceppi di MRSA conduca ad una più elevata prevalenza di ceppi produttori di TSST-1 nell'Iran settentrionale. Comunque, ulteriori ricerche sono richieste per chiarire l'interazione tra l'esito delle infezioni ed i ceppi produttori di TSST-1 in Iran.

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