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Effect of the Panton – Valentine leukocidin gene *Staphylococcus aureus* on the course of the infectious process in orthopedic patients

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Abstract

Introduction *Staphylococcus aureus* is a leading pathogen causing osteoarticular infections. Panton – Valentine leukocidin (*PVL*) is considered one of the key of virulence factors with its role being poorly explored in orthopedic infections.

The **objective** was to evaluate the occurrence of the *PVL* gene in *S. aureus* strains, the effect on laboratory markers of inflammation and on the course of the infectious process in orthopedic patients.

Material and methods A retrospective analysis of 130 *S. aureus* strains isolated from 100 patients was performed. The presence of the *lukS-PV* and *lukF-PV* genes was determined using PCR. Laboratory parameters (CRP, ESR, leukocytes, neutrophils, and procalcitonin) and long-term treatment outcomes were assessed.

Results *PVL* was detected in 15 % of strains *S. aureus*. No statistically significant effect of *PVL* on the levels of routine inflammatory markers was found. A key finding was that the presence of the *PVL* gene was associated with an increased risk of adverse outcome.

Discussion The findings can be associated with debates on the clinical significance of *PVL*. Despite a significant impact on outcome The absence of significant differences in systemic inflammatory markers suggests that the negative effect of *PVL* is rather mediated by other mechanisms than by global inflammation activation measured by routine tests. These include direct cytotoxic tissue damage, impaired immune cell function, and the emergence of specific immunological processes. The association identified between *PVL* and the MRSA phenotype is consistent with the global epidemiological picture, where this toxin is a marker of hypervirulent community-acquired strains.

Conclusion The presence of *PVL* is a significant risk factor for a poor outcome of orthopedic infection suggesting the need for its detection for risk stratification and optimization of patient management strategy. Conclusion The presence of *PVL* is a significant risk factor for an unfavorable outcome of orthopedic infection, which indicates the need for its detection for risk stratification and optimization of patient management tactics.

Keywords: *Staphylococcus aureus*, Panton – Valentine leukocidin, orthopedic infection, virulence factors, treatment outcome

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INTRODUCTION

Staphylococcus aureus remains one of the most significant pathogens causing musculoskeletal infections. According to our data, *S. aureus* remained high-frequency isolation (31.3 %) over a 12-year observation period between 2011 and 2022 [1]. Similar data were presented by Tsiskarashvili et al. who reported *S. aureus* as the leading causative agents of periprosthetic joint infection over a six-year period amounting to more than 30 % [2]. *S. aureus* is characterized by the ability to form biofilms and by different mechanisms of resistance to antibacterial drugs complicating the fight against infection and requiring long-term administration of drugs or their combinations [3]. A number of studies have demonstrated the tropism of staphylococci for bone tissue cells [4, 5]. This affinity is ensured by the presence of various virulence factors that allow *S. aureus* to adsorb on the surface of the bone matrix and penetrate into bone tissue cells.

The cytotoxin Panton-Valentine leukocidin (*PVL*) is one of the significant virulence factors that realizes the pathogenic potential of *S. aureus*. This two-component protein causes lysis of blood cells, including neutrophils, monocytes, and macrophages leading to tissue necrosis and enhancing the systemic inflammatory response of the body [6]. *PVL* components encode the *lukS-PV* and *lukF-PV* genes, located on mobile genetic elements, facilitating the spread of this gene among bacterial strains [7].

With the data available, the role of *PVL* in the pathogenesis of orthopedic infections remains poorly understood. Infections of other localizations caused by *S. aureus* containing *PVL* usually proceed in a more severe form, are prone to more frequent relapses, accompanied by a risk of reinfection and characterized by formation of larger abscesses [8, 9]. Considering that the *PVL* toxin mediates its action through direct cytotoxicity and modulation of inflammation, it can be assumed that its production by staphylococci will be associated with changes in the profile of laboratory markers of systemic inflammation (such as C-reactive protein, leukocytes, neutrophils and procalcitonin), but with more frequent adverse clinical outcomes [10].

The **objective** was to evaluate the occurrence of the *PVL* gene in *S. aureus* strains, the effect on laboratory markers of inflammation and on the course of the infectious process in orthopedic patients.

MATERIAL AND METHODS

Between January 1, 2023 and December 31, 2023, 104 *S. aureus* strains were isolated from 75 patients with bone infections of the limbs and major joints who underwent surgery in the Center's departments. The study included 26 *S. aureus* strains isolated from the blood of 25 patients in the Purulent Osteology Department between January 1, 2012 and December 31, 2024.

Patients were selected for the study using the Mikrob-2 microbiological monitoring program and the Across-Engineering information system based on microbiological examination of biomaterial obtained from patients.

All patients had orthopedic infection caused by *S. aureus*. Based on the medical records after discharge, a database created included:

— anthropometric data (age, gender);

— localization of the infectious process;

— laboratory blood tests at the time of admission (leukocytes, neutrophils count, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein) level, PCT (procalcitonin) in patients with bacteremia).

Patients were divided into two groups depending on the presence or absence of the *PVL* gene in the causative agent of the infection: group 1 (*n* = 19), *PVL*-positive *S. aureus*, group 2 (*n* = 81), *PVL*-negative *S. aureus*.

A separate comparison of laboratory markers of the inflammatory process was conducted in patients with bacteremia caused by *S. aureus* and with a wound infection without bacteremia. For this purpose, patients with bacteremia were divided into two subgroups based on the presence of the *PVL* gene in *S. aureus*: subgroup 1 (*n* = 7), the *PVL* gene was present, subgroup 2 (*n* = 18), the *PVL* gene was absent.

The outcome was then assessed for 47 patients (47 %). A telephone survey was conducted, asking standard questions about whether they had any clinical or laboratory signs of recurrent infection within two years of the index surgery, and whether they had undergone repeat debridement procedures. In cases of fatal outcome, interviews were conducted with the patient's relatives. A favorable outcome (according to the Delphi criteria) was defined as the absence of clinical and laboratory signs of recurrent infection and the absence of debridement procedures within two years of the index surgery [11]. As a result, patients were divided into two subgroups: group A (*n* = 29) with a favorable outcome, and group B (n = 18) with a poor outcome.

Gender- and age-related parameters and laboratory test results (leukocyte and neutrophil counts, ESR, CRP, the proportion of MR strains among *S. aureus*, and the proportion of patients with *PVL* strains of *S. aureus*) at admission were compared. The proportion of patients with *S. aureus* bacteremia was assessed in patients of the comparison groups.

Laboratory methods

Microbiological testing of patient biomaterial was performed in accordance with international standards. Until 2021, bacterial identification was performed biochemically on Microlatest panels (Erba Lachema) using an iEMS Reader MF (Labsistems, Finland). Since 2021, bacterial identification was performed using MALDI-TOF-MS, the FlexControl system and MBT Compass 4.1 software (Bruker Daltonics, Germany), with a score of ⩾ 2.0. The sensitivity of bacterial cultures to antibacterial drugs was assessed in accordance with EUCAST requirements (v.2-13).

Nucleic acids (NA) were isolated as follows: the *S. aureus* concentration required for NA isolation was diluted with distilled water to a turbidity of 1 µF (BioSan, Latvia). Then, 200 µl of the suspension were collected and additional lysis of the bacterial culture was performed in the presence of 20 mg/ml lysostaphin (Sigma Aldrich, USA) and 50 mg/ml lysozyme (Amresco, USA) in Tris-EDTA buffer for 60 minutes at 37°C. In accordance with the manufacturer's protocol, Magno-Sorb (Amplisens, Russia) was used to isolate nucleic acids using the Auto-Pure S32 system for automated nucleic acid isolation and purification (Allsheng, China). RNA was removed from DNA samples using the RNase A enzyme (Biolabmix, Russia) in accordance with the manufacturer's protocol. The concentration of isolated DNA and RNA was measured using an Implen NP80-Touch spectrophotometer (Implen, Germany). A sample was considered pure at a 260/280 ratio of 1.8–2.0 and a 260/230 ratio of ~2.0.

Real-time PCR was performed according to the manufacturer's protocol BioMaster HS-qPCR SYBR Blue (2X) (Biolabmix, Russia) using a CFX-96 amplifier (BioRad, USA). Primers for *PVL* detection were *luk-PV-f* (ATCATTAGGTAAAATGTCTGGACATGATCCA) and *luk-PV-r* (GCATCAAGTGTATTGGATAGCAAAAGC), which amplify a 433-bp fragment specific for the *lukS/F-PV* genes encoding the two-component *PVL S/F* protein, as described by McClure et al. [12]. Oligonucleotide synthesis was produced by Evrogen (Russia). PCR temperature conditions: initial denaturation at 94 °C for 4 min; 30 amplification cycles (denaturation at 94 °C for 45 s, annealing at 56 °C for 45 s, and elongation at 72 °C for 30 s); and a final elongation at 72 °C for 2 min. For visualization, 5 µl of the PCR amplicon were loaded with dye into a 1.2 % agarose gel containing ethidium bromide, followed by electrophoresis at 100 V for 1 h and visualization using the ChemiDoc MP Imaging System (BioRad, USA).

Statistical analysis

The data were recorded in the form of spreadsheets in MS Office Excel, 2007 (Microsoft, USA), visualization of the data structure and the analysis were performed using GraphPad Prism 9.0 (USA) and IBM SPSS STATISTICS (version 27). Quantitative indicators were assessed for compliance with normal distribution using the Kolmogorov – Smirnov test. With the absence of normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles (Q1-Q3). Categorical data were described using absolute values and percentages. Comparison of two groups for a quantitative indicator, the distribution of which differed from normal, was performed using the Mann – Whitney U test. To assess the risk in the comparison groups, the odds ratio (OR, 95 % CI) was calculated. Comparisons of percentages in the analysis of four-field contingency tables were performed using the Pearson chi-square (χ^2) test (for expected value greater than 10) or Fisher's exact test (for expected value less than 10). Associations were assessed using Cramer's test. Differences in the parameters between groups were considered statistically significant at $p < 0.05$.

Ethical Standards

Upon admission to the hospital, all patients signed informed voluntary consent to the processing of personal data for scientific and educational purposes, the possible presence of students during medical interventions, and the use of patient information constituting a medical secret for educational and scientific purposes.

RESULTS

Frequency of PVL-positive S. aureus isolated from biomaterial of patients with orthopedic infection

B In the studied cohort, the *PVL* gene was detected in 15 % ($n = 19$) of *S. aureus* strains. The majority of *PVL*-positive isolates were characterized by resistance to cefoxitin (58 %, $n = 11$). There were 12 % of *PVL*-positive cultures Among MSSA strains and 17 % among MRSA.

Analysis of the relationship between the presence of the PVL gene and the sex of patients

The *PVL* gene was detected among *S. aureus* strains without statistically significant differences between the male and female groups ($\chi^2 = 0.455$; $p = 0.500$). *PVL*-positive *S. aureus* were isolated from 11 of 51 male patients (21.6 %) and from eight (16.3 %) of the 49 female patients (Table 1).

Table 1

Distribution of the *PVL* gene depending on the sex of patients

Group	Males (*n* = 51)		Females (*n* = 49)		*p*
	abs.	%	abs.	%	
Group 1	11	21.6	8	16.3	0.500
Group 2	40	78.4	41	83.7	

Analysis of the relationship between the presence of the PVL gene and the age of patients

The analysis was performed for 99 patients, one patient with missing age data was excluded. There was no statistically significant difference in the mean age between groups 1 and 2 (t = 1.03; $p = 0.306$). The mean age was (58.2 ± 12.7) years (Me = 58) in the PVL^{+} group and (54.6 ± 15.3) years (Me = 54) in the PVL^{-} group (Table 2).

Table 2

Comparison of the age of patients in groups with and without the *PVL* gene

Group	*n*	Mean age ± SD	The median [Q1–Q3]	*p*
Group 1	18	58.2 ± 12.7	58 [49–66]	0.306
Group 2	80	54.6 ± 15.3	54 [41–64]	

Analysis of infection localization depending on the presence of the Panton-Valentine gene

Patients with infection caused by *PVL*$^+$ strains had knee joint involvement in half of the cases ($n = 9$), with hip involvement being less common. In contrast, hip involvement was predominant in the *PVL*$^-$ group, accounting for 45 % of cases ($n = 35$) (Fig. 1). The distribution by localization showed similar trends in both groups, with, ajor joint involvement being predominant.

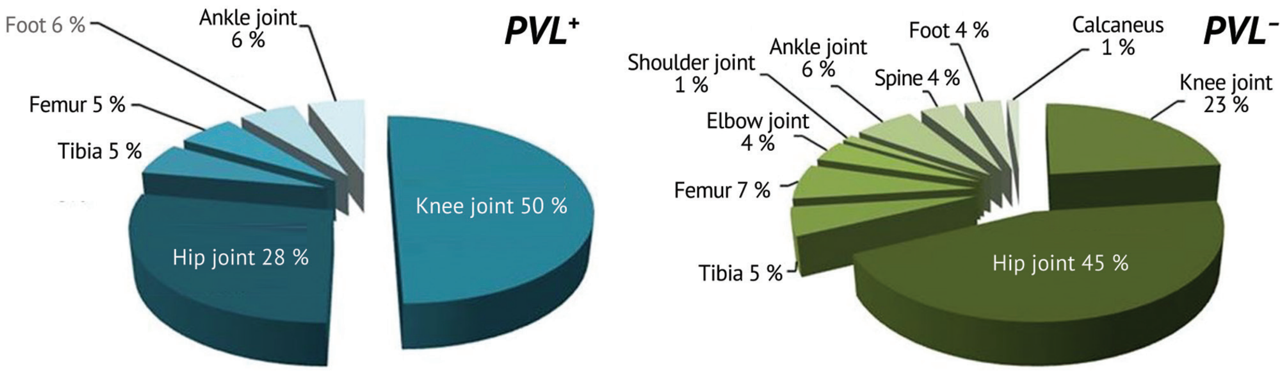

Fig. 1 Localization of the infectious process depending on the presence of the *PVL* gene

Comparison of laboratory test results in patients with PVL-positive and PVL-negative S. aureus

A comparative analysis of inflammatory markers revealed no statistically significant differences between the study groups despite the expected significant reduction in leukocyte and neutrophil levels due to the potential cytotoxic effect of *PVL*. There was a trend toward a higher median CRP level in patients of Group 1 compared to Group 2 (by 60 %) was detected which was not statistically significant (Table 3).

Table 3

Comparison of laboratory parameters of the inflammatory process in patients with *PVL*-positive (group 1) and *PVL*-negative *S. aureus* (group 2)

Description	Group 1 ($n = 19$)	Group 2 ($n = 83$)	*p*
Leukocytes, 10^9/L, Me [Q1–Q3]	9.7 [6.9–13.6]	8.6 [6.9–11]	0.587
Neutrophils (% from the level of leukocytes), Me [Q1–Q3]	5.7 [4.5–8.7]	5.5 [3.8–8.9]	0.713
CRP, mg/L, Me [Q1–Q3]	67 [12.0–215.0]	42 [12.0–117.0]	0.358
ESR, mm/h, Me [Q1–Q3]	46.0 [40.0–70.0]	48.0 [27.0–74.5]	0.649

Severity of systemic inflammation assessed by laboratory parameters in groups with different PVL status in patients with bacteremia

To evaluate the effect of the Pantone leukocidin gene on the severity of systemic inflammation, patients with bacteremia caused by *S. aureus* were divided into two subgroups: subgroup 1 ($n = 7$) *PVL*-positive strains and subgroup 2 ($n = 18$) *PVL*-negative strains (Table 4). A steady trend towards higher median values of procalcitonin (by 28 %), CRP (by 7.5 %), and ESR (by 8 %) was observed in subgroup 1, compared to subgroup 2 despite the lack of statistical significance. The median level of leukocytes was almost identical, and the level of neutrophils was higher in patients of subgroup 2. The lack of statistical differences in the comparison groups could be explained, among other things, by their small number.

Table 4

Comparison of laboratory parameters of systemic inflammation in patients with *PVL*-positive and *PVL*-negative *S. aureus* bacteremia

Description	Subgroup 1 ($n = 7$)	Subgroup 2 ($n = 18$)	p
PCT, ng/mL, Me [Q1–Q3]	0.9 [0.3–1.9]	0.7 [0.2–1.6]	0.622
Leukocytes, 10^9/L, Me [Q1–Q3]	14.0 [9.9–17.0]	14.4 [8.9–17.6]	0.949
Neutrophils (% from the level of leukocytes), Me [Q1–Q3]	8.7 [3.1–12.8]	10.3 [5.5–14.4]	0.467
CRP, mg/L, Me [Q1–Q3]	215.0 [179.5–290.0]	200.0 [145.5–310.0]	0.727
ESR, mm/h,Me [Q1–Q3]	85.0 [43.0–85.0]	78.5 [29.5–84]	0.260

Severity of systemic inflammation assessed by laboratory parameters in groups with different PVL status in patients with wound infection without bacteremia

A comparative analysis of laboratory parameters of systemic inflammation revealed no statistically significant differences between the groups ($p > 0.05$ in all cases). The leukocyte count was 7.7×10^9/L [6.7–9.8] in group 1, 8.2×10^9/L [6.6–9.7] in group 2 ($p = 0.964$). The absolute number of neutrophils was comparable: 5.4×10^9/L (group 1: 4.5–7.1; group 2: 3.7–7.1; $p = 0.587$). The level of CRP reached 25 mg/L [5.5–66.3] in group 1, 25 mg/l [6.3–54.5] in group 2 ($p = 0.940$). The ESR index showed no significant differences: 45.5 mm/hour [39.3–56.5] in group 1 and 45 mm/hour [24-71] in group 2 ($p = 0.958$).

Assessment of the impact on the outcome of complex treatment of orthopedic infection PVL

The influence of various factors was assessed in patients with the known outcome ($n = 47$) (Table 5). The patients were divided into two groups: group A having a favorable outcome ($n = 62$ %), group B featuring an unfavorable outcome ($n = 38$ %). No statistically significant differences in various parameters of laboratory test results on admission were observed. The presence of the Panton-Valentine leukocidin gene in *S. aureus* strains increased the risk of unfavorable outcome by 4 times ($p = 0.029$, 95 % CI: 1.114–13.851, Cramer's V 0.318, moderate association). The proportion of patients with bacteremia was statistically significantly lower among patients in group 1 than among patients in group 2: 10.7 % versus 38.9 % ($p = 0.02$).

Table 5

Comparison of laboratory parameters in study group A and group B

Description	Group A ($n = 29$)	Group B ($n = 18$)	p
Leukocytes, 10^9/L, Me [IQR]	8.5 [6.7–12.4]	9.7 [7.0–13.5]	0.450
Neutrophils (% from the level of leukocytes), Me [IQR]	5.6 [4.5–8.1]	5.7 [4.2–10.5]	0.609
ESR, mm/h, Me [IQR]	52 [39.3–70.0]	45 [27.0–76.0]	0.740
CRP, mg/L, Me [IQR]	42.0 [17.0–82.0]	55.0 [16.0–219.0]	0.279
The proportion of patients with *PVL* strains *S. aureus*, n (%)	7 (24.1)	10 (55.6)	**0.029***

DISCUSSION

The role of the *PVL* gene as a virulence factor remains controversial. A number of studies associate its presence with severe necrotizing infections of the skin and soft tissues, and necrotizing pneumonia [13, 14, 15]. Other studies did not reveal a significant association between the carriage of the *PVL* gene and the severity of the systemic inflammatory response or mortality [16]. Our findings showed that the presence of the *PVL* gene in *S. aureus* was a significant risk factor for the development of an adverse clinical outcome, increasing its odds by almost fourfold (OR = 3.93, 95 % CI: 1.11–13.85, $p = 0.029$). The conclusion is the central finding of our study and is consistent with the fundamental concept of *PVL* as a potent cytotoxin that damages the membranes of neutrophils and other immunocompetent cells, which can potentially lead to a more severe course of infection and disturbed innate immune system [17, 18, 19].

Our findings indicated 57.9 % (*n* = 11) of all *PVL*-positive strains being methicillin-resistant isolates (MRSA) and were fully consistent with the global epidemiological picture and could be explained by modern evolutionary concepts [20]. Despite the fact that the proportion of MRSA isolates was expectedly lower than the proportion of MSSA, the *PVL* gene was associated predominantly with the MRSA phenotype. This observation was not random and reflected the process of clonal selection and successful dissemination of specific strains [21].

A key explanation is that the *PVL* gene is a marker for so-called "community-acquired" MRSA (CA-MRSA) strains [22, 23]. These clones, the so-called biovariants, unlike "hospital-acquired" (HA-MRSA), have acquired evolutionary advantages for spreading in community settings in the absence of significant antibiotic pressure. This advantage is virulence, provided, in part, by Panton-Valentine leukocidin.

The lack of a statistically significant effect of the *PVL* gene on individual laboratory markers of systemic inflammation (CRP, ESR, leukocytes, neutrophils, procalcitonin) was an interesting and somewhat controversial finding when considered in isolation. With the trends toward increased median values in the PVL^{+} group for all parameters, the differences did not reach significance, which was likely due to the limited sample size and high variability of the parameters. However, this result does not refute the main conclusion, but rather indicates that the negative impact of *PVL* gene on outcome is likely mediated not so much by global activation of systemic inflammation measured by routine methods, but by other mechanisms, which may include:

— direct cytotoxic damage to target tissues and organs [10, 24],

— disturbed neutrophil functions (chemotaxis, phagocytosis, NET formation) even without their quantitative change [25, 26];

— induction of specific anti-inflammatory cascades that are not routinely measured [27, 28].

This assumption is consistent with the publication of Motomura et al. [29], who reported that *PVL*-associated necrotizing pneumonia was characterized by a severe course with pronounced lung damage with only a moderate increase in systemic markers of inflammation.

Our data contribute to resolving the existing debate about the clinical significance of *PVL*. On the one hand, our finding of a significant association with outcome is consistent with a number of studies linking PVL with severe necrotizing skin and soft tissue infections and pneumonia [13, 14]. On the other hand, our data on the variability of the inflammatory response echo studies that did not find a direct correlation between *PVL* and laboratory markers or mortality [15]. This discrepancy can be explained by the heterogeneity of the studied populations (type of infection, comorbid background), differences in study design and the predominant influence of other virulence factors (e.g., α-toxin), which can mask or modulate the effect of *PVL* [30].

The main limitation of our study is the small sample size, which may have resulted in a failure to achieve statistical significance in the analysis of individual laboratory parameters (type II error) and wide confidence intervals in the risk assessment. The retrospective design of the study does not allow for the complete elimination of unaccounted confounding factors. Prospective studies in larger cohorts are needed to confirm the obtained results.

CONCLUSION

The presence of the *PVL* gene in *Staphylococcus aureus* strains is an aggravating risk factor for adverse clinical outcomes in orthopedic infections. This fact confirms the role of *PVL* as an important virulence factor contributing to a more severe course of the disease and a worse prognosis in patients.

With the important role of *PVL* in determining risk, its impact on infection outcome is not always accompanied by statistically significant changes in the levels of routine laboratory markers of systemic inflammation, such as CRP, ESR, leukocytes, or procalcitonin. This suggests that the pathogenic mechanisms underlying the impact of *PVL* on clinical outcome may be mediated by global activation of inflammatory processes measured by standard markers and by other pathways. Determining the presence of *PVL* in clinical isolates of *S. aureus* represents a promising tool for risk stratification and optimization of clinical management. This approach may facilitate more accurate prognosis of the disease course and informed treatment decisions. Further investigation of the impact of *PVL* on specific patient immunological profiles and its interaction with other bacterial virulence factors is essential. Studying these aspects will allow for a better understanding of the pathogenetic mechanisms underlying severe infectious outcomes and the development of new prevention and treatment strategies.

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Informed consent *Upon admission to the hospital, all patients signed informed voluntary consent for the processing of personal data and the use of anonymized patient information for educational and scientific purposes.*

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