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Breast

Alpha Defensin-1 Level Correlates with Periprosthetic Infection Severity following Implant-based Breast Reconstruction

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Background: Accurate diagnosis of periprosthetic infections following breast reconstructions is paramount to reduce morbidity. Alpha defensin-1 (AD-1) is an antimicrobial peptide released by neutrophils. This study evaluates the relationship between quantitative AD-1 levels and infection severity in patients with suspected periprosthetic infection.

Methods: Retrospective review was conducted of patients with prior breast implant reconstruction undergoing surgery for either suspected infection or prosthesis exchange and revision. The AD-1 level in periprosthetic fluid was sent for quantitative analysis. Association between AD-1 levels with outcomes, management, systemic markers of infection, and overall infection severity was evaluated.

Results: Thirty-eight breasts were included. Infected breasts had higher AD-1 levels (3.91 versus 0.14, $P < 0.01$), greater odds of erythema [odds ratio (OR) 2.98 (1.53–5.82), $P = 0.01$], purulence [OR 2.84 (1.51–5.35), $P = 0.01$], fever [OR 1.84 (1.15–2.93), $P = 0.01$], threatened implant exposure [OR 2.97 (1.48–5.95), $P < 0.01$], and true implant exposure [OR 1.79 (1.04–3.08), $P = 0.04$]. Increasing AD-1 was an independent risk factor for washout ($P < 0.01$), and explant [OR 2.48 (1.47–4.2), $P < 0.01$]. AD-1 positively correlated with white blood cell count ($\beta = 1.81$ cells/μL, $P < 0.01$), and serum lactate ($\beta = 0.19$ meq/L, $P < 0.04$). Increasing AD-1 level was an independent predictor of infection severity ($\chi^2 = 22.77$, $P < 0.01$).

Conclusions: AD-1 levels correlate with infection severity, highlighting its potential both when clinical examination is ambiguous and when treatment response is being monitored. Although further evaluation is warranted, AD-1 may demonstrate utility in novel breast implant salvage algorithms. *(Plast Reconstr Surg Glob Open 2024; 12:e5543; doi: 10.1097/GOX.0000000000005543; Published online 23 January 2024.)*

INTRODUCTION

Prosthesis-based breast reconstruction remains the leading method of correcting mastectomy defect following oncological management of breast cancer, which routinely yields favorable aesthetic outcome and psychosocial benefit.[1–3] However, nearly one-fifth of breast reconstructions become complicated by periprosthetic infection.[4] This may result in prolonged antibiotic therapy duration, multiple operations, and implant loss.[5–7] The current paradigm for implant salvage relies on stratification of infection severity, primarily based on clinical assessment, which may be inherently subjective or variable among providers.[5,8] Furthermore, bacterial culture, which represents the gold standard for diagnosis, is dichotomous, where the extent of colonization rarely correlates with infection severity, especially in the setting of empirical antibiotic administration.[5,9]

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Therefore, identification and development of a reliable diagnostic test is of critical importance to facilitate appropriate gradation and management of periprosthetic infection.

Alpha defensin-1 (AD-1) is an antimicrobial peptide released by neutrophils that confers bactericidal effects through disruption of pathogen cellular membranes.[9] AD-1 targets metabolically active microbes in the setting of on-going infection (versus colonization), and, as such, may serve as a novel biomarker for periprosthetic infection. In fact, AD-1 has become a critical component in the diagnosis of prosthetic joint infection following orthopedic intervention, as it is routinely found within infected peri-implant fluid collections and remains uniquely unchanged in the setting of indolent infections or previous antibiotic exposure.[9–12] Its use in the diagnosis of breast implant-associated infection remains limited; however, in two prior studies performed by our group, we demonstrated superior sensitivity and specificity of AD-1 in the identification of periprosthetic breast infection when compared with standard bacterial culture or Gram stain.[13,14]

Whereas AD-1 stands to supplant bacterial culture as a point-of-care resource to identify periprosthetic infection, there remains a gap in our ability to differentiate between mild, moderate, and severe infections with current diagnostic tools.[8,13] It stands to reason that relative AD-1 concentrations within fluid samples may serve as a surrogate marker for the extent of pathogenic metabolic activity and innate inflammatory response, thereby demonstrating utility as a marker of infection severity. The aim of this study is to evaluate the relationship between quantitative AD-1 levels and infection severity in patients who present with suspected periprosthetic infection. We hypothesize that levels of AD-1 within peri-implant fluid samples will correlate with degree of infection.

Takeaways

Question: What is the relationship between quantitative values of alpha defensin-1 (AD-1), an antimicrobial peptide released by neutrophils, and infection severity in breast reconstruction patients who present with suspected periprosthetic infection?

Findings: A retrospective cohort study demonstrated that quantitative AD-1 correlated with the presence of signs and symptoms of infection and that it was an independent predictor of infection severity ($\chi^2 = 22.77$, $P < 0.01$).

Meaning: AD-1 correlates with infection severity and may have utility as a potential marker when clinical examination is ambiguous, and when treatment response is being monitored. Studies utilizing AD-1 to guide implant salvage are necessary.

METHODS

Study Design and Population

Retrospective review of a prospectively maintained database was conducted of consecutive patients with prior breast implant reconstruction undergoing surgery for either suspected infection or prosthesis exchange and revision between June 2018 and June 2019 at a tertiary academic medical center. Patients undergoing surgery for prosthesis exchange and revision served as noninfected controls. Institutional review board approval was obtained from the Lifespan Institutional Review Board (Providence, Rhode Island), with a waiver of informed consent for retrospective chart review. Periprosthetic fluids were sampled intraoperatively in both infected patients and noninfected controls, and sent for Gram stain, bacterial culture, AD-1 assay, and surgical pathology. Each AD-1 assay requires approximately 0.5 mL of fluid. AD-1 levels were sent directly postoperatively to an independent laboratory (Citrano Diagnostic Labs, Baltimore, Md.) for quantitative analysis, defined as a relative signal strength of AD-1 concentration when compared with a noninfected control. The AD-1 calibration curves generated by this method were previously described and validated in our pilot study.[14]

Data Collection and Analysis

Patient demographic and characteristic data were recorded, including age at surgery, body mass index, history of smoking or breast irradiation, and plane of reconstruction (prepectoral versus subpectoral). The presence of surgical adjunct, defined as human or xenograft acellular dermal matrix, was also recorded. The following postoperative signs and symptoms of infection were identified: erythema; purulence; implant exposure; threatened exposure, defined as wound breakdown along mastectomy incision without visibility of underlying implant; and fever. Periprosthetic infection was defined as cellulitis with or without abnormal drainage found intraoperatively. Methods of infection management, namely antibiotic course, implant washout, or explantation, were extracted from the medical record. Body mass index was calculated as mass/meters squared (kg/m^2).

Systemic markers of inflammation and infection were recorded when laboratory values were available. These markers included maximum temperature (°F), white blood cell (WBC) count (10^9 cells/L), C-reactive protein (mg/L), hemoglobin (g/dL), percentage polymorphonuclear cells, percentage monocytes, and serum lactate levels [milliequivants (meq)/L]. Each patient was assigned an infection score, as previously described by Spear et al.[15] Herein, patients were classified into eight categories based on clinical and systemic characteristics on presentation: infection score of 0, no clinical or laboratory markers concerning for infection; score of 1, mild infection, localized erythema at the surgical site or in the skin overlying the implant; score of 2, severe infection defined as significant generalized erythema, purulent drainage, and/or systemic signs of infection; score of 3, threatened implant exposure without signs of infection; score of 4, threatened implant exposure with mild infection; score of 5, threatened implant exposure with concurrent severe infection; score of 6, true implant exposure with no or mild signs

of infection; and score of 7, true implant exposure with severe infection.

This categorization schema presented by Spear et al[15] does not imply ascending grade of infection; instead, it classifies by degree of implant exposure: 1, 2 as no device exposure; 3, 4, 5 as threatened implant exposure; and 6, 7 as true implant exposure. Given AD-1 is a marker of neutrophil activity, it stands to reason that AD-1 levels increase with systemic infection severity. As such, we created a modification of Spear's infection categorization, now placing emphasis on infection severity rather than degree of implant exposure. Our modified Spear criteria are ordered as follows: 1, 3—no signs of infection; 4, 6—minor infection; and 2, 5, 7—severe infection. The degree of implant exposure then serves to stratify within a particular bracket of infection severity.

Statistical Analysis

Data were analyzed using SPSS 25 (IBM Corp., Armonk, N.Y.). The datasets generated and analyzed during the current study are not publicly available but are available from the authors on reasonable request. Results were analyzed by breast, assuming outcomes for each breast were independent events. Univariate analysis was conducted to compare patient characteristics, operative management, and outcomes between infected and noninfected groups. Pearson chi-square testing was used for categorical variables if cell numbers were 5 or higher; otherwise, the Fisher exact test was utilized. A Shapiro-Wilk test was used to test for normality among continuous variables. Variables that were nonnormally distributed were analyzed using a Mann-Whitney test. The remaining continuous variables were compared using Student *t* test. Unadjusted logistic regression was utilized to evaluate outcomes by breast with increasing quantitative AD-1 levels. For each outcome, an odds ratio (OR), 95% confidence interval (CI), and *P* value were calculated and reported as [OR, (95% CI), *P* value]. Subgroup analysis was conducted to evaluate distribution of AD-1 levels based on clinical sign of infection, namely erythema or purulence. Univariate linear regression modeling was performed to identify the relationship between AD-1 levels and systemic markers of inflammation or infection. Each breast was assigned an infection score, as previously described by our modified Spear criteria, and ordinal logistic regression analysis was performed to evaluate the correlation between infection severity and AD-1 level. A receiver operator curve was generated for our logistic regression, and the area under the curve was calculated to investigate fitting behavior of the model. Adjusted linear regression analyses were conducted, controlling for either implant exposure level or degree of systemic infection, to evaluate the relationship between each of these variables and AD-1 level. Statistical significance was set at *P* value less than 0.05.

RESULTS

Patient Characteristics

Twenty-nine patients met inclusion criteria (nine bilateral cases), resulting in 38 breasts for analysis. Median age was 58 [interquartile range (IQR) = 51–64] years. History of smoking was present in 60.5% of patients, and history of radiation was present in 47.4%. Patient demographics and operative characteristics are presented in Table 1.

Postoperative Outcomes

Postoperative outcomes are depicted in Table 1. Erythema (n = 16, 42.1%) was the most common sign concerning for infection. Nine breasts (23.7%) demonstrated gross purulence on exploration and washout. Eight breasts (21.0%) presented with threatened implant exposure, although four (10.5%) demonstrated complete exposure. Fifteen breasts (38.4%) were found to have periprosthetic infection diagnosed intraoperatively. On culture data, the most isolated organism was methicillin-sensitive *Staphylococcus aureus* (26.7%), followed by methicillin-resistant *S. aureus* (20%), and coagulase-negative *Staphylococcus* (13.3%). Sixteen breasts required washout (42.1%), and 12 required explantation (31.6%). Oral antibiotic therapy were utilized for treatment of 16 breasts (42.1%). Four infected breasts (10.5%) received intravenous (IV) antibiotics before operative washout.

Among noninfected breasts (n = 23), the most common indication for surgery was breast asymmetry (n = 11, 47.8%). Other operative indications included implant rupture (n = 4, 17.4%), recurrent sterile seroma (n = 4, 17.4%), explantation for cosmesis (n = 2, 8.7%), and breast implant illness (n = 2, 8.7%).

When comparing infected and noninfected groups, demographics were well matched (Table 1). Infected breasts had higher rates of surgical adjunct use (100% versus 65%, $P < 0.01$). Infected breasts had significantly higher quantitative AD-1 levels (3.97 versus 0.12, $P < 0.01$). Clinical signs of infection and use of oral antibiotic therapy, IV antibiotic therapy, and operative intervention were all significantly higher in infected breasts (Table 1).

Quantitative Analysis of AD-1

On univariate logistic regression analysis, increasing quantitative AD-1 demonstrated greater odds of erythema [OR 2.98 (1.53–5.82), $P = 0.01$], purulence [OR 2.84 (1.51–5.35), $P = 0.01$], fever [OR 1.84 (1.15–2.93), $P = 0.01$], threatened exposure [OR 2.97 (1.48–5.95), $P < 0.01$], and implant exposure [OR 1.79 (1.04–3.08), $P = 0.04$] (Table 2). Interestingly, the range of quantitative AD-1 level was widely distributed in breasts with erythema (median = 3.79, IQR 0.12–5.83, min = 0.05) (Fig. 1), whereas variance was minimal for breasts with purulence (median = 4.10, IQR 3.0–5.7, min = 2.7). Finally, regarding management, patients with increasing AD-1 levels demonstrated greater odds of requiring oral antibiotics [OR 2.96 (1.53–5.73), $P = 0.01$], IV antibiotics [OR 2.02 (1.1–3.71), $P = 0.02$], explant [OR 2.48 (1.47, 4.2), $P < 0.01$], and washout ($P < 0.01$).

Results of unadjusted linear regression of systemic markers of infection relative to quantitative AD-1 levels are contained in Table 3. Increasing AD-1 positively correlated with WBC count ($\beta = 1.81$ cells/mL, $P < 0.01$) and lactate ($\beta = 0.19$ meq/L, $P < 0.04$).

Table 1. Comparison of Demographics and Outcomes between Patients with and without Clinically Diagnosed Infection, by Breast

Variable	Total (%)	Infection (%)	No Infection (%)	*P*
No. patients	29	15 (51.7)	14 (48.3)	
No. breasts	38	15 (39.5)	23 (60.5)	
Median age [IQR], y*	58 [51, 64]	58 [47, 59]	58 [52, 68]	0.30
No. obese†	13 (34.2)	7 (46.6)	6 (26.1)	0.30
History of smoking	23 (60.5)	8 (53.3)	15 (65.2)	0.51
Radiation	18 (47.4)	9 (60.0)	9 (39.1)	0.32
Plane of reconstruction				>0.90
Prepectoral	28 (71.1)	11 (73.4)	16 (69.6)	
Subpectoral	11 (28.9)	4 (26.6)	7 (30.4)	
Timing of reconstruction				0.68
Immediate	31 (81.6)	13 (86.7)	18 (78.3)	
Delayed	7 (18.4)	2 (13.3)	5 (21.7)	
Reconstruction technique				0.02§
Expander	34 (89.5)	11 (73.3)	23 (100)	
Direct to implant	4 (10.5)	4 (26.7)	0 (0)	
ADM used	30 (78.9)	15 (100)	15 (65)	0.01§
Quant. AD-1 level [IQR]*‡	0.18 [0.11, 3.38]	3.97 [2.66, 5.61]	0.12 [0.08, 0.16]	<0.01§
Clinical signs of infection				
Erythema	16 (42.1)	13 (86.7)	3 (13.0)	<0.01§
Purulence	9 (23.7)	9 (60.0)	0 (0)	<0.01§
Threatened exposure	8 (21.0)	8 (53.3)	0 (0)	<0.01§
Implant exposure	4 (10.5)	4 (26.7)	0 (0)	0.02§
Fever¶	6 (15.8)	6 (40.0)	0 (0)	<0.01§
Management of infection				
Oral antibiotics	16 (42.1)	13 (86.6)	3 (13.0)	<0.01§
IV antibiotics	4 (10.5)	4 (26.7)	0 (0)	0.02§
Washout	16 (42.1)	15 (100)	1 (4.35)	<0.01§
Explant	12 (31.6)	12 (80.0)	0 (0)	<0.01§

ADM, acellular dermal matrix; BMI, body mass index.
*Nonparametric continuous variables are reported as median [IQR].
†BMI > 30.
‡Quantitative AD-1 level.
§Statistically significant ($P < 0.05$).
¶Fever defined as temperature ≥100.4°F.

Table 2. Logistic Regression of Postoperative Outcome and Infection Management Relative to Quantitative AD Levels, by Breast

		OR Per Unit Increase in AD-1	
Outcome	OR	(95% CI)	*P*
Infection	—	—	<0.01*
Clinical signs of infection			
Erythema	2.98	[1.53, 5.82]	0.01*
Purulence	2.84	[1.51, 5.35]	0.01*
Exposure	1.79	[1.04, 3.08]	0.04*
Fever	1.84	[1.15, 2.93]	0.01*
Threatened exposure	2.97	[1.48, 5.95]	<0.01*
Management of infection			
Oral antibiotics	2.96	[1.53, 5.73]	0.01*
IV antibiotics	2.02	[1.10, 3.71]	0.02*
Explant	2.48	[1.47, 4.2]	<0.01*
Washout	—	—	<0.01*

*Statistically significant ($P < 0.05$). Binomial regression of odds of postoperative complication versus none for adjunct type.

Comparison of Spear Infection Scoring versus Quantitative AD-1

Ordinal logistic regression analysis demonstrated the quantitative AD-1 level was an independent predictor of infection severity ($\chi^2 = 22.77$, $P < 0.01$). (**See table, Supplemental Digital Content 1**, which displays the modified infection scores and clinical information for each breast, **http://links.lww.com/PRSGO/D22**.) Figure 2 demonstrates the ordinal regression model. The quantitative AD-1 level was a significant predictor of infection severity (Wald = 22.77, $P < 0.01$), with higher levels associated with greater infection severity. The parameter

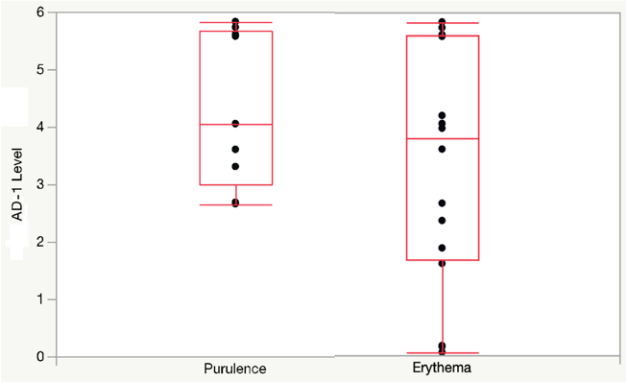

Fig. 1. Box and whisker plots depicting the distribution of AD-1 levels for breasts found to have purulence (right), and those found to be erythema (left). The range of AD-1 level is widely distributed in breasts with erythema (IQR 0.12–5.83), whereas variance in AD-1 is minimal for breasts with purulence (IQR 3.0–5.7). This highlights the broad range of outcomes possible in the erythematous breast, and thus, a limitation of the clinical examination.

Table 3. Linear Regression of Systemic and Local Markers of Infection Relative to Quantitative AD-1 Levels, by Breast

Systemic Markers	β	SE	*P*	R^2 (%)
Tmax (n = 35)*	0.28	0.16	0.09	8.7
WBC, 10^9 cells/L (n = 31)	1.81	0.33	<0.01†	51.5
CRP (n = 6)	3.99	3.0	0.26	30.6
HgB (n = 38)	−0.33	0.13	0.02†	14.3
PMN% (n = 34)	0.91	1.08	0.41	2.1
Mono% (n = 34)	−0.21	0.62	0.45	1.8
Lactate, meq/L (n = 9)	0.19	0.07	0.04†	48.9

*Temperature as measured in °F.
†Statistically significant. Linear regression of breast and blood markers relative to quantitative AD levels.
CRP, C-reactive protein (mg/L); HgB, hemoglobin (g/dL); mono%, percentage monocytes; PMN%, percentage polymorphonuclear cells; RBC/μL, red blood cells per microliter; Tmax, maximum recorded temperature.

estimate for AD-1 suggests the average infection score increased by 1.20 [95% CI (0.73–1.78)] for every one-unit increase in AD-1. **Supplemental Digital Content 2** depicts the receiver operator curve for this ordinal logistic regression model, with calculated areas under each curve being 0.90 or higher, indicating reliable fit of the model (**http://links.lww.com/PRSGO/D23**).

Subgroup analysis controlling for infection severity demonstrated that degree of implant exposure correlated with increasing AD-1 levels in breasts with no infection [$\beta = 0.86$, $P < 0.01$, R^2(adjusted) = 0.74], mild infection [$\beta = 0.92$, $P < 0.01$, R^2(adjusted) = 0.82], and severe infection [$\beta = 0.84$, $P = 0.03$, R^2(adjusted) = 0.65] (Fig. 3). Similarly, when controlling for degree of implant exposure, infection severity correlated with increasing AD-1 levels in breasts with no implant exposure [$\beta = 0.82$, $P < 0.01$, R^2(adjusted) = 0.66]. Degree of infection also correlated with increasing AD-1 levels in breasts with threatened implant exposure [$\beta = 0.34$, $P = 0.31$, R^2(adjusted) = 0.03], and actual implant exposure [$\beta = 0.58$, $P = 0.42$, R^2(adjusted) = 0.01]; however, these results were not statistically significant.

DISCUSSION

The management of periprosthetic infection in implant-based breast reconstructions following mastectomy remains complex, ranging from oral antibiotic therapy to prosthesis explantation and washout.[5,6,16,17] Algorithmic approaches to implant salvage have been suggested, often relying on subjective criteria to stratify by infection severity.[15–18] However, variability in surgeon assessment of potential periprosthetic infection limits generalizability, resulting in a salient need for objective parameters. As such, the use of AD-1 as a biomarker to grade breast implant infection confers a unique opportunity to introduce a quantitative metric for infection severity that may be used to guide implant salvage.

There have been attempts to develop and validate tools to grade surgical site infection.[19–24] The Centers for Disease Control and Prevention criteria are routinely cited when defining infection for scientific investigation, to minimize ambiguity and standardize reporting.[19] However, the Centers for Disease Control and Prevention criteria remain limited in scope, offering qualitative descriptions of superficial and deep-space infections, without specifying the index operation or stratifying by severity. Moreover, scoring systems, such as ASEPSIS or the Southampton Scale, attempt to quantitatively grade wound appearance, but were primarily developed for the assessment of cardiothoracic and abdominal wound infections, respectively.[25,26] It is reasonable to speculate the presentation of surgical site infection may vary based on anatomic region or use of prosthetic device and, therefore, scoring systems should be interrogated through the lens of the procedure being performed. As such, these commonly used scoring tools may hold little clinical utility for guiding the diagnosis and treatment of breast implant infections.

Sampling of periprosthetic fluid for a discrete biomarker obviates the subjectivity of clinical assessment and allows for precise determination of infection severity. AD-1 has several characteristics that render it uniquely suited as a diagnostic target for infection. Although present in circulating mature neutrophils throughout the body, it is not detectable in high concentrations until pathogen-mediated degranulation.[10,27] AD-1 responds to bacteria with a directed, local tissue response, which is readily differentiated from baseline extracellular tissue concentrations.[27] As such, it stands to reason AD-1 levels may vary with the extent of innate immune response to active microbes, thereby serving as a marker of infection severity. The results of our study confirm this hypothesis, as quantitative AD-1 concentrations were associated with grade of infection. We used the criteria introduced by Spear et al[15] in their seminal work detailing implant salvage techniques based on severity of infection. Although this scoring system is not ubiquitously utilized, it has served as a comparison group in prior implant salvage work and combines many aspects that are foundational to the evaluation of periprosthetic breast infection.[15,18,28–31]

Importantly, the presence of erythema along the skin flap often belies the extent of infection within the mastectomy pocket, especially in the absence of wound breakdown or gross purulence.[8,25] AD-1 levels varied widely with the presence of erythema in our study, where the distribution

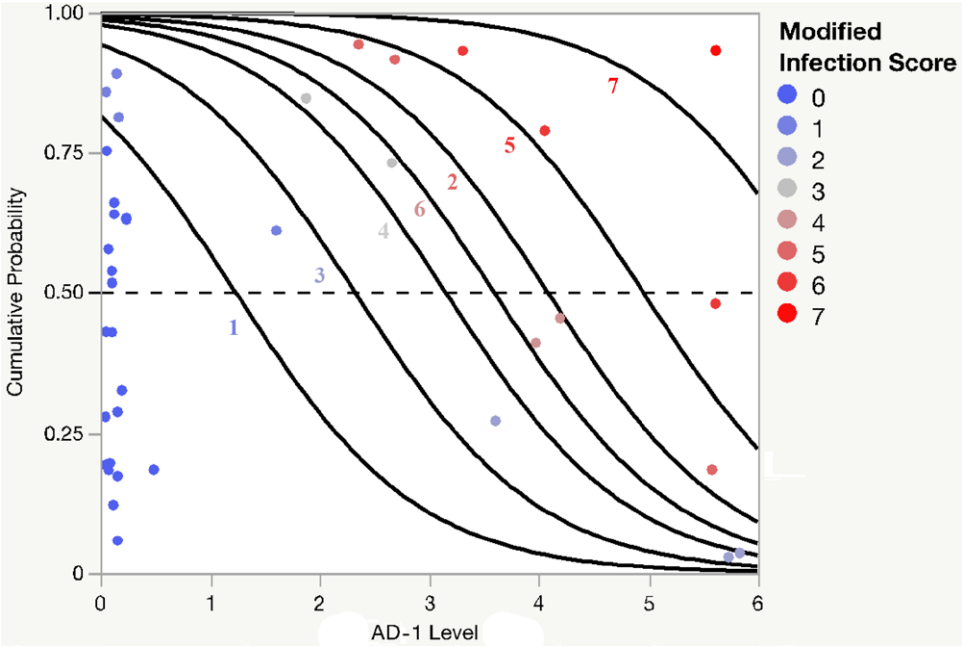

Fig. 2. Ordinal logistic regression evaluating the association between AD-1 levels and infection severity by a modified version of the criteria set forth by Spear et al.[15] The modified Spear criteria are ordered as follows: 1, 3—no signs of infection; 4, 6—minor infection; and 2, 5, 7—severe infection. Each curve is a cumulative distribution function and represents the probability that given an AD-1 level, a patient will have an infection score at or below corresponding curve. For example, at an AD-1 level of 1.3, a patient has a 50% chance of being at or above an infection score of 1. Note that as AD-1 levels increase, the probability of being at or below a given infection score decreases. The AD-1 level was an independent predictor of infection severity ($\chi^2 = 22.77$, $P < 0.01$). The AD-1 level was a significant predictor of infection severity (Wald = 22.77, $P < 0.01$), with higher levels associated with greater infection severity.

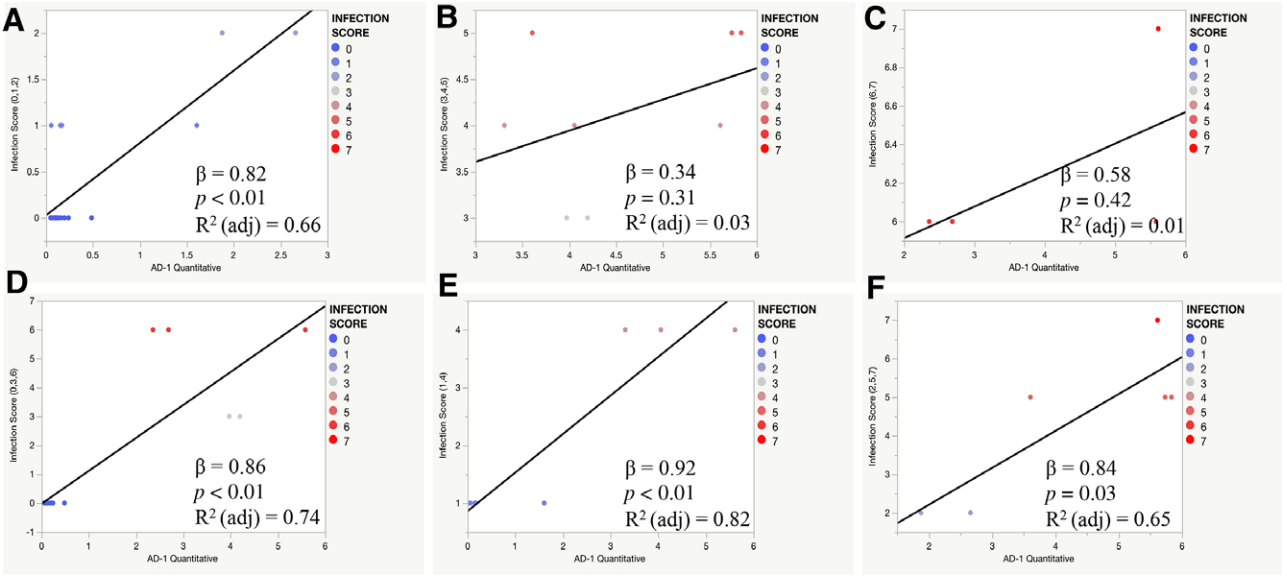

Fig. 3. Adjusted linear regression analyses, controlling for either implant exposure level or degree of systemic infection. R^2 (adj): Adjusted R^2. A, Correlation between AD-1 levels and infection severity in patients with no implant exposure, (B) correlation between AD-1 levels and infection severity in patients with threatened implant exposure, (C) correlation between AD-1 levels and infection severity in patients with actual implant exposure. D, correlation between AD-1 levels and degree of implant exposure in patients with no infection, (E) correlation between AD-1 levels and degree of implant exposure in patients with mild infection, and (F) correlation between AD-1 levels and degree of implant exposure in patients with severe infection.

tightly clustered when evaluating by purulence. These results suggest reliance on the outward appearance of a red breast may not accurately reflect degree of infection. This becomes particularly important in intermediate infections, where a systemic response has not yet mounted, and sampling of the internal environment becomes necessary to appropriately gradate severity and subsequently guide management. Therefore, quantitative analysis of AD-1 may serve to bridge the gap between physical examination and operative exploration for breast implant-related infection.

The results of our study suggest the bioavailability of AD-1 in infected periprosthetic fluid strongly correlates with systemic inflammatory markers. Interestingly, the AD-1 level was an independent predictor of maximum temperature and leukocytosis in those presenting with breast implant-associated infection. We posit these systemic signs are likely due to saturation of local neutrophil response, resulting in recruitment of circulating polymorphonuclear leukocytes, and a need to mount a disseminated response to severe infection. As such, serial evaluation of AD-1 concentration, possibly from closed suction drains, may inform infection trajectory and treatment response without the need for needle aspiration.[32,33]

Given no prior literature existed utilizing AD-1 as a marker of infection severity, we solely evaluated AD-1 levels in breasts that were returning to the operating room, rather than use it as a tool to guide operative intervention. This may have skewed our patient population to more severe cases of infection. Nevertheless, the strong correlation found in this study confirms the need for future evaluations utilizing percutaneous and drain based sampling of AD-1 as a means of guiding management in low-risk patients with ambiguous clinical examination.

An additional limitation of this study is sample size, which was restricted by availability of AD-1 test kits and relative infrequency of breast implant infections across the study period. This prevented multivariate analyses and could limit statistical power to draw conclusions or establish management criteria based on the AD-1 level. Our small sample size also precluded collection of a robust control group, thus requiring inclusion of bilateral cases and patients with history of antibiotic administration. In addition, retrospective chart review was performed, which is subject to recall bias, as heterogenous reporting of infectious signs and symptoms could introduce a systematic error that cannot be controlled for via statistical analysis. AD-1 testing requires a small amount of fluid in the breast pocket for sampling, which may be difficult to sample without the presence of a dual-port tissue expander or closed suction drain. Furthermore, if implant exchange has already occurred and minimal fluid is present, there is risk of implant rupture with percutaneous sampling. Furthermore, the Spear infection classification system was used as a primary endpoint, which has not been validated as a tool to stratify by severity and is inherently subjective. However, the criteria proposed by Spear et al[15] combine aspects of the clinical examination, laboratory markers, and vitals to guide evaluation and management of breast implant infection and, therefore, may provide a more accurate measure of degree of infection than previously validated, albeit nonspecific, grading systems. Still, further evaluations correlating AD-1 with bacterial metabolites or alternative markers of local inflammation are warranted. Despite these limitations, the results of this study serve as a framework and proof of principle to guide future investigation.

To the best of our knowledge, this work is the first to demonstrate a relationship between relative AD-1 concentration and infection grade within plastic surgery and across all surgical domains. A multi-institutional, randomized trial is necessary to increase generalizability and prospectively validate AD-1 as a maker for periprosthetic breast infection. Subsequently, it may be utilized to gradate and guide management of patients with intermediate signs and symptoms of infection. As identification of reliable biomarkers remains paramount to overcome limitations in bacterial culture and nonspecific laboratory values, these data can be utilized to help guide development of an infection scoring system and novel implant salvage algorithm for patients with breast cancer undergoing prosthesis-based breast reconstruction.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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IRB approval was obtained from the Lifespan institutional review board with a waiver of informed consent for retrospective chart review.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICAL APPROVAL STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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