Brief Communications

Concentration standardization improves the capacity of drainage CRP and IL-6 to predict surgical site infections

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Impact statement

The ability to predict surgical site infections (SSIs) early would be advantageous. Previous studies have investigated the use of inflammatory factors in fluids drained from surgical sites to predict SSI, but the diagnostic efficacy of this method requires improvement. Baseline levels of inflammatory factors vary between individuals, but this variation tends to differ in patients with and without SSIs. Therefore, we standardized subsequently acquired concentrations of interleukin 6 and C-reactive protein in fluids drained from surgical sites by dividing them by the concentrations determined at day 1 to preclude the confounding effects of differences in baseline levels. The standardized concentrations had higher predictive efficacy than the absolute concentrations. Standardizing the data rendered SSI prediction more precise and practical in a diverse group of real patients. This translational study suggests that inflammatory factors in fluid drained from injury sites are promising tools for the prediction of SSI in the clinic.

Abstract

The early detection of surgical site infection (SSI) remains an unsolved problem. Inflammatory factors in fluids drained from surgical sites may be a promising tool for predicting SSI. Previous attempts to predict SSI via such factors have not taken baseline concentrations into account. However, this may have comprised predictive efficacy. In the current study, concentrations of C-reactive protein (CRP) and interleukin 6 (IL-6) in fluid samples drained from surgical sites in 20 patients with SSI and 60 matched controls were assessed, and concentrations from day 2 to day 4 were divided by the concentration at day 1 to achieve concentration standardization. There were no significant differences of CRP or IL-6 concentrations at day 1 or day 2 ($p > 0.05$), but there were significant differences at day 3 and day 4 ($p < 0.05$). The areas under the curve (AUCs) for SSI of standardized concentrations were higher than those of the corresponding absolute concentrations of CRP and IL-6 in fluid drained at days 3 and 4. Standardized concentrations of CRP at day 4 yielded the highest AUC (0.92; 95% confidence interval: 0.84–0.97), with a sensitivity of 90% and specificity of 80% at the best cutoff. Concentration standardization may improve the efficacy of predicting SSI via CRP and IL-6 in fluids drained from surgical sites. Although the sample size was small, the study demonstrated the feasibility of non-invasive, accurate, and early detection of postoperative SSI in a diverse real population. Further studies are needed to validate the results of the present study and investigate their broader applicability.

Keywords: Cytokine, diagnostic efficacy, neck dissection, oral cancer, postoperative infection, translational medicine

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Introduction

Surgical site infections (SSIs) are a common cause of morbidity, mortality, and increased lengths of hospital stays and costs in hospitalized patients.[1] A reliable method for the early detection of SSIs remains to be identified. Fluids drained from surgical sites may reflect local conditions at those surgical sites. Bacterial culture of these drained fluids has been investigated as a potential method for predicting

SSIs,[2] but its sensitivity was poor.[3] The concentrations of interleukin 6 (IL-6) and C-reactive protein (CRP) are increased in patients with SSIs.[4] In a pilot study, IL-6 in fluid drained immediately after neck dissection facilitated highly sensitive SSI detection.[5] Baseline cytokine levels vary substantially among individuals, and they may be increased in patients with cancer or systemic inflammation. Data standardization may minimize the effects of differences in baseline concentrations on the capacity of cytokines in fluid drained from surgical sites to predict SSIs. In the current study, the capacities of absolute and standardized concentrations of IL-6 and CRP in fluid drained from surgical sites to predict SSIs were compared.

Materials and methods

The study was a case–control study nested in a cohort of oral cancer patients, who underwent neck dissection and postoperative vacuum sealing drainage at the West China Hospital of Stomatology between February 2017 and June 2019 (see 'Supplementary Methods' for additional details). Each patient with SSI was matched by sex and age ($\pm$5 years) with three non-SSI control patients from the same cohort. Standardized concentrations from day 2 to day 4 were calculated via the following formula

$$SC(X)_n = \log\frac{C(X)_n}{C(X)_1}$$

where

$$\mathrm{X} = \mathrm{CRP\ or\ IL} - 6,\ n \le 4$$

$C(X)_n$ = absolute concentration of X on postoperative day n as determined via enzyme-linked immunosorbent assay (Abcam, Cambridge, UK)

Student's t-test was used to compare mean $C(X)_n$ and $SC(X)_n$ in SSI patients and non-SSI patients' (GraphPad Prism 8.30, San Diego, CA, USA). The receiver operating characteristic curve and area under the curve (AUC) were analyzed to assess the efficacy of predicting SSI via $C(X)_n$ and $SC(X)_n$ (STATA 14.0, Texas, USA; MedCalc 19.1, Ostend, Belgium).

Results

Twenty patients with SSI and 60 matched non-SSI control patients were identified in a cohort of 172 patients. There were no significant differences in baseline characteristics between the two groups ($p > 0.05$) (Table 1). With regard to comorbidities, there were more patients with diabetes in the control group ($p = 0.182$) and more patients with hepatitis in the SSI group ($p = 0.141$), but these differences were not statistically significant.

There were no significant differences in $C(X)_1$, $C(X)_2$, or $SC(X)_2$ between the two groups ($p > 0.05$). $C(X)_3$, $C(X)_4$, $SC(X)_3$, and $SC(X)_4$ were significantly lower in the control group ($p < 0.01$) (Figure 1). All $SC(X)_n$ AUCs were higher than the corresponding $C(X)_n$ values (Figure 2). $SC(CRP)_4$ yielded the highest predictive efficacy. At the best cutoff, $SC(IL\text{-}6)_3$ had the highest sensitivity (95%), and $SC(CRP)_4$ and $SC(IL\text{-}6)_4$ had the highest specificity (80%) (Table 2).

Table 1. The baseline characteristics of cases and controls.

	Control (n = 60)	Case (n = 20)	*p* value
Sex	–	–	0.495
Female	19	8	–
Male	41	12	–
Age (y)	–	–	0.796
Median	57.5	54.5	–
Range	23–80	21–79	–
Tumor position	–	–	0.854
Tongue	22	7	–
Tongue base	3	3	–
Buccal	18	6	–
Floor of mouth	4	1	–
Gingiva	4	1	–
Palatal	3	0	–
Mandibular	2	1	–
Others	4	1	–
Histopathology	–	–	1.000
Squamous	57	19	–
Adenoid	3	1	–
Recurrence	–	–	0.470
Absent	50	18	–
Present	10	2	–
Vascularized flaps	–	–	0.281
No	23	4	–
ALTF	28	14	–
Forearm	7	1	–
Fibular	2	1	–
Neck dissection	–	–	0.236
Radical	58	18	–
Functional	2	2	–
Antibiotics	–	–	0.115
Piperacillin	24	6	–
Cefuroxime	33	10	–
Others	3	4	–
Comorbidity	–	–	–
Hypertension	8	4	0.851
Diabetes	5	0	0.182
Hepatitis	3	3	0.141

ALTF: anterolateral thigh flap.

Discussion

The results of the present study further verified the potential capacity of using cytokine concentrations in fluid drained from surgical sites to predict SSIs. A previously reported study was compromised by imbalanced confounding factors and a limited sample size of just six patients.[5] In that study, IL-6 concentration in fluid drained from surgical cites exhibited low specificity with regard to predicting SSI. In the current study, the specificity of absolute IL-6 concentration was 63.3%, but it increased to 80.0% after concentration standardization. $SC(CRP)_4$ could achieve 100% specificity with 50% sensitivity. $SC(IL\text{-}6)_3$

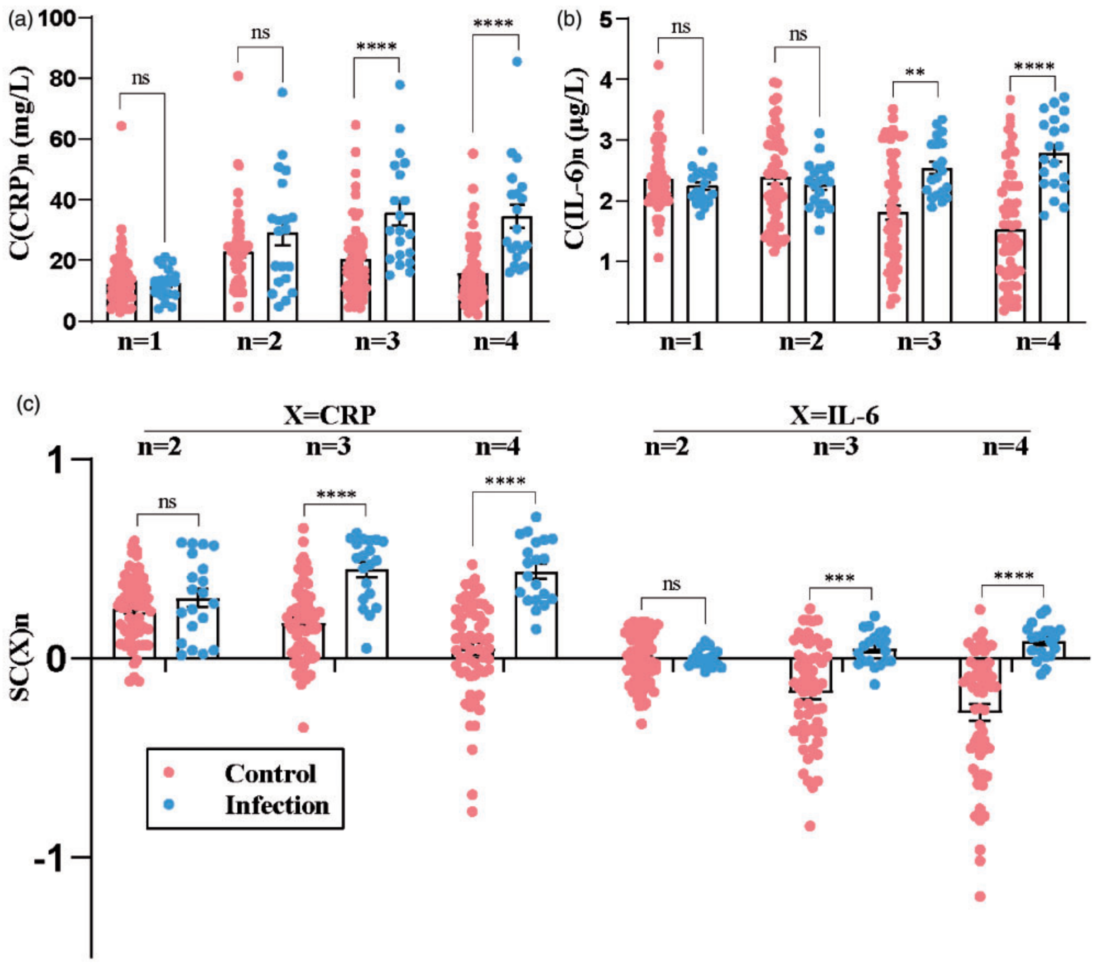

Figure 1. Absolute and standardized CRP and IL-6 concentrations in fluid drained from surgical sites in patients with surgical site infections and patients without surgical site infections. (a) Absolute drainage CRP concentrations, $C(CRP)_n$, $n = 1$ to 4. (b) Absolute drainage IL-6 concentrations, $C(IL\text{-}6)_n$, $n = 1$ to 4. (c) Standardized drainage CRP and IL-6 concentrations, $SC(CRP)_n$ and $SC(IL\text{-}6)_n$, $n = 2$ to 4. The *x*-axis of $SC(X)_n = 0$, indicating that the concentration was the same at day *n* and day 1. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. CRP: C-reactive protein; IL-6: interleukin 6. (A color version of this figure is available in the online journal.)

may assist early screening on day 3, and $SC(CRP)_4$ could help to confirm SSI on day 4.

Standardizing cytokine concentrations substantially reduced potential confounding due to inter-patient variation in baseline concentrations. In the absence of SSI, inflammatory cytokines decrease gradually during the postoperative period—but they remain high or increase if SSI occurs. The individual cytokine levels could be variable in the real world, but the changing model would be comparatively fixed according to the general pattern of inflammatory reactions, which may underlie the efficacy improvement of concentration standardization.

Stimulation of IL-6 may promote CRP production, the elevation of which is reportedly associated with cardiovascular diseases, obesity, diabetes, and inflammation.[6] In the present study, the distributions of diabetes and hepatitis differed in the two groups. Generally, the diagnostic specificity of absolute cytokine concentrations may have been reduced by elevations in the control group, whereas corresponding effects on sensitivity would be comparatively lower (refer to the Supplementary Discussion for further detail). Moreover, in the real world, the population is not composed solely of ‘healthy’ people. Absolute cytokine concentrations have shortcomings because there is substantial variation in baseline levels among the general population. Hence, we believe that compared with absolute concentrations, the advantages of data standardization will prove to be more marked in populations with variable systemic diseases.

Prediction models used in clinical practice are required to exhibit acceptable predictive efficacy. Early detection and early intervention could reduce the incidence, severity, and associated complications of SSI and enhance patients’ quality of life. The prescription of extended courses of antibiotics is not generally recommended,[7] but it may be applicable when drainage CRP and IL-6 have not decreased by postoperative day 4. Randomized controlled trials and real-world observations are needed to confirm the internal and external validity of this study.

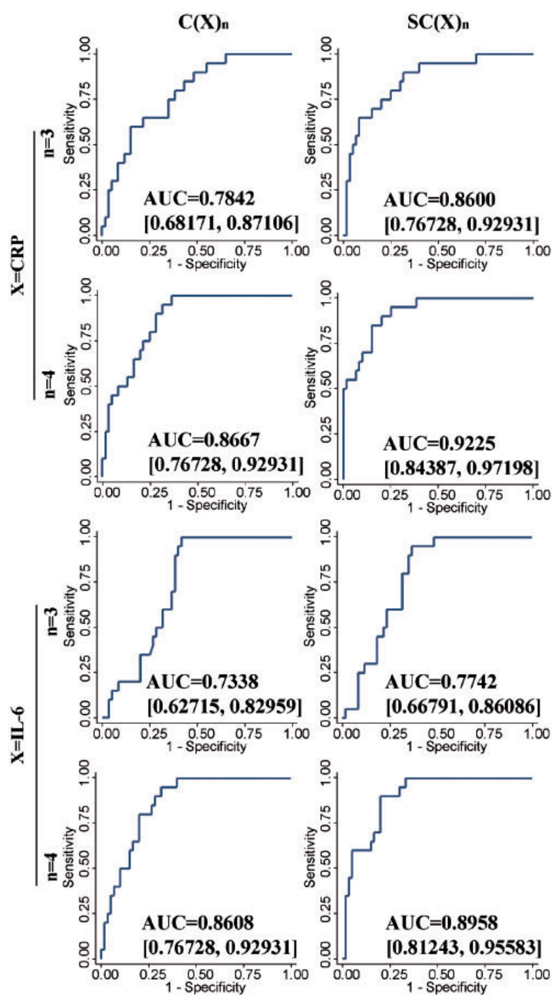

Figure 2. Receiver operating characteristic curve and AUC values of C(X)*n* and SC(X)*n* as predictors of surgical site infections (X = CRP or IL-6, n = 3 or 4). The 95% confidence intervals of AUC values are shown in square brackets. AUC: area under the curve.

Conclusions

Standardizing the concentrations of CRP and IL-6 in fluid drained from surgical sites may improve the capacity of those cytokines to predict SSI. Although the sample size was relatively small, the present study demonstrated the application of a non-invasive and accurate method for predicting postoperative SSI in a diverse sample of real patients that can be utilized early. Future studies are needed to validate the results of the current study and their broader applicability.

Authors' contributions: XB, YL, J-Li, and YC participated in designing the study and interpreting the results. XB and YL conducted the experiments. YC was primarily responsible for the data analysis, and wrote the manuscript. J-Lin and CL assisted with data analysis and contributed to the review and revision of the manuscript. XB, YL, and YC contributed equally to this work.

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DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, or publication of this article.

ETHICAL APPROVAL

The Institutional Review Board of West China Hospital of Stomatology, China, approved the study protocol (reference number WCHSIRB-D-2016-006R1). All patients provided written informed consent to participation in the study.

Table 2. Criterion values and coordinates of the ROC curve.

Marker	Cutoff	Criterion	SEN	95% CI	SPE	95% CI	+LR	−LR
$SC(CRP)_3$	SEN_{max}	>0.045	100	83.2–100.0	30	18.8–43.2	1.43	0
	Best	>0.245	90	68.3–98.8	68.33	55.0–79.7	2.84	0.15
	SPE_{max}	>0.656	0	0.0–16.8	100	94.0–100.0	–	1
$SC(CRP)_4$	SEN_{max}	>0.114	100	83.2–100.0	61.67	48.2–73.9	2.61	0
	Best	>0.258	90	68.3–98.8	80	67.7–89.2	4.5	0.13
	SPE_{max}	>0.472	50	27.2–72.8	100	94.0–100.0	–	0.5
$SC(IL\text{-}6)_3$	SEN_{max}	>−0.147	100	83.2–100.0	51.67	38.4–64.8	2.07	0
	Best	>−0.060	95	75.1–99.9	63.33	49.9–75.4	2.59	0.079
	SPE_{max}	>0.250	0	0.0–16.8	100	94.0–100.0	–	1
$SC(IL\text{-}6)_4$	SEN_{max}	>−0.093	100	83.2–100.0	66.67	53.3–78.3	3	0
	Best	>−0.018	90	68.3–98.8	80	67.7–89.2	4.5	0.13
	SPE_{max}	>0.246	0	0.0–16.8	100	94.0–100.0	–	1

SEN: sensitivity; 95% CI: 95% confidence interval; SPE: specificity; +LR: positive likelihood ratio; −LR: negative positive ratio; SEN_{max}: the point with 100% sensitivity; Best: the point at the best cutoff of ROC curve; SPE_{max}: the point with 100% specificity.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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