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The Characteristics of Oro-cervical Necrotizing Fasciitis Comparison with Severe Cellulitis of Oro-cervical Region and Necrotizing Fasciitis of other Body Regions

Eiji Iwata (eiwata@med.kobe-u.ac.jp)
Kakogawa Central City Hospital https://orcid.org/0000-0002-4010-8062

Junya Kusumoto
Kobe University

Naoki Takata
Kakogawa Central City Hospital

Shungo Furudoi
Konan Medical Center

Akira Tachibana
Kakogawa Central City Hospital

Masaya Akashi
Kobe University

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Abstract

Background: Necrotizing fasciitis (NF) is an acute and life-threatening soft-tissue infection rarely seen in oro-cervical region. Therefore, the details of oro-cervical NF (OCNF) are not well known. The purpose of this report was to investigate the characteristics of OCNF by comparing it with severe cellulitis of oro-cervical region (OCSC) or NF of other body regions (e.g., limb, perineum, and trunk) (BNF), respectively.

Methods: First, various risk factors for OCNF in oro-cervical severe infection (OCSI; composed of OCNF and OCSC), including neutrophil-to-lymphocyte ratio (NLR) and Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, were investigated by univariate and multivariate analyses. Next, the differences between OCNF and BNF, including inflammatory markers and mortality, were investigated.

Results: In the present study, 14 out of 231 OCSI patients had OCNF. Multivariate analyses of OCSI showed that NLR ≥15.3 and LRINEC score ≥6 points were significantly related to OCNF. During the same period, 17 patients had BNF. The OCNF group had significantly higher inflammatory markers than the BNF group, but significantly lower clinical stages and mortality.

Conclusion: We found that compared to BNF, OCNF can be detected at lower clinical stage by using indexes, such as NLR and LRINEC score, besides clinical findings, which may help contributing to patient relief.

1. Introduction

Necrotizing fasciitis (NF) is a severe form of infection involving rapidly spreading inflammation and extensive necrosis of the skin, subcutaneous tissue, and superficial- fascia [1, 2]. If diagnosis and surgical treatment are delayed, NF can lead to systemic toxicity, multisystem organ failure, and eventual death [3-5]. In the past, many studies have investigated the characteristics of NF of the limb, perineum, and trunk, such as prognosis and severity [6-12]. Therefore, many surgeons are aware of the characteristics of NF in these regions.

On the other hand, NF is rarely seen in oro-cervical region (OCNF). Sepulveda et al. reported that the incidence of OCNF is less likely because of the abundant blood supply in the oro-cervical region [13]. However, the spread of oro-cervical infection creates a risk of asphyxiation and because the retropharyngeal space and the spaces, adjacent to the oro-cervical region are continuous with the mediastinum, delayed diagnosis and treatment may lead to fatal conditions, such as mediastinitis. Unfortunately, because of its low incidence, many surgeons are unfamiliar with this condition.

In the present study, we compared the characteristics of OCNF with those of severe cellulitis of oro-cervical region (OCSC) and NF of other body regions (e.g., limb, perineum, and trunk) (BNF).

2. Patients And Methods

2.1 Patients

In this study, the following inclusion criteria were set: patients above 18 years of age, and patients who were hospitalized for the treatment of OCSC with drip antibiotics for over 48 hours. The following exclusion criteria were set: patients with cancer, patients who were transferred to other hospitals for some reasons, and patients who did not wish to participate after the publication of this study. We examined patients who were treated for oro-cervical severe infection (OCSI; composed of OCSC and OCNF) or BNF between April 2012 and March 2020 in Kakogawa Central City Hospital.

2.2 Necrotizing fasciitis (NF)

Patients corresponding with Fisher et al. ’s definition of NF [14] and Mathieu et al. ’s definition of CNF [15] were defined as NF. Fisher et al. [14] defined the following features: (1) necrosis of extensive superficial-fascia and surrounding tissues, (2) moderate or severe systemic intoxication with psychiatric symptoms, (3) muscle layer is not affected, (4) clostridium is not detected in wounds and blood, (5) no obstruction of large vessels, (6) severe leukocyte infiltration, fascia and surrounding tissue necrosis, and microvascular thrombosis observed on histopathological examination. Mathieu et al. [15] defined the following features: (1) inflammation in the submandibular space, with little or no pus and with spread to the neck beyond the level of the hyoid bone; (2) involvement of more than one neck space, usually bilaterally; (3) tissue necrosis with serosanguineous, putrid infiltration; (4) involvement of connective tissue and fasciae and, in a secondary manner, muscles and skin, but not of glandular structures; and (5) contiguous—not lymphatic—spread. Even if all items of Fisher et al. ’s definition and Mathieu et al. ’s definition were not satisfied, NF was finally defined when the case in which fascial necrosis was confirmed by intraoperative findings and histopathology.

NF is broadly classified into type 1, which is a polymicrobial infection containing anaerobes (e.g., *Bacteroides fragilis, Prevotella spp., Escherichia Coli*), and type 2 which is a monomicrobial infection (e.g., *Streptococcus pyogenes, Staphylococcus aureus*) [16-18]. NF does not originally produce gas; however, some anaerobes, which are the causative bacteria of type 1 NF, produce gas. Since type 1 NF has almost the same disease state as non-Clostridium gas gangrene, NF with gas production is almost synonymous with non-Clostridium gas gangrene [19]. Therefore, in the present study, patients in whom gas production was observed on CT images were also included in the NF for the above reasons.

2.3 Severe cellulitis of oro-cervical region (OCSC)

The following patients were defined as OCSC: patients with clinical findings in the oro-cervical region, such as erythema, swelling, and heat, who had difficulty eating or breathing, and who were hospitalized for treatment with intravenous antibiotics for over 48 hours. Patients diagnosed with OCNF were excluded.

2.4 Variables

The following variables from medical records were retrospectively reviewed and investigated: (1) patient factors—sex, age, body mass index (BMI), and compromised host; (2) clinical findings factors—body temperature when the patients visited our hospital, creatine kinase (CK), C-reactive protein (CRP), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), hemoglobin (Hb), serum creatinine (Cr), sodium (Na), blood glucose (Glu), albumin (Alb), and LRINEC score; and (3) treatment progress—hospitalization periods and outcomes. Moreover, the cases of NF were additionally investigated for 3 clinical findings; partial pressure of arterial oxygen (PaO_2) in arterial blood gas analysis, image in computed tomography (CT), and clinical stages.

In patient factors, “compromised host” was defined as a patient with the following diseases; e.g., rheumatoid arthritis, kidney failure, osteoporosis, and diabetes. In clinical finding factors, we used 2 risk scores and 1 clinical stage. NLR and LRINEC score, both developed to predict the severity and prognosis of NF, such as Fournier’s Gangrene [20, 21]. LRINEC score is a clinical tool first described by Wong et al. The tool is based on 6 common serum parameters: CRP, WBC, Hb, Alb, Cr and Glu (Tables 1 and 2). The cutoff values for NLR and LRINEC score in OCSI were determined using receiver operating characteristic (ROC) curve analysis. “Clinical stages” were used in a study by Wong et al. [22] (Table 3). It is classified into 3 stages based on changes in the skin as the disease progresses (Table 3). Finally, regarding the presence of gas production images in CT, the cases in which the abscess self-collapsed and cases in which gas was continuous with the outside in CT were excluded because they are likely to be air bubbles.

Table 1
LRINEC score

Variable	Value	Points
CRP (mg/dL)	≥15	4
WBC (/μL)	≥15,000	1
	>25,000	2
Hb (g/dL)	<13.5	1
	<11.0	2
Na (mmol/dL)	<135	2
Cr (mg/dL)	>1.59	2
Glu (mg/dL)	>180	1

Table 2
Diagnostic criteria of LRINEC score

Total points	Possibility of occurring NF
≥5	Low risk (<50%)
6, 7	Intermediate risk□50−75□□
8 ≥	High risk (>75%)

Table 3
Clinical features of NF as the disease progress through clinical stages

Stage 1 (Early)	Stage 2 (intermediate)	Stage 3 (Late)
Tenderness to palpation (extending beyond the apparent area of skin involvement)	Blister or bullae formation (serious fluid)	Hemorrhagic bullae Skin anesthesia
Erythema Swelling Warm to palpation	Skin fluctuance Skin induration	Crepitus Skin necrosis with dusky discoloration progressing to frank gangrene

2.5 Statistical analyses

Statistical analyses were performed using SPSS 26.0 (SPSS, Chicago, IL). The association of each variable with the post-extraction hemorrhage was analyzed by the non-parametric Mann-Whitney U test for ordinal variables, and either Fisher's exact test or chi-squared test was used for categorical variables. Probabilities of less than 0.05 were considered significant.

3. Results

3.1 Comparison of OCNF with OCSC

OCNF occurred in 14 of 231 patients with OCSI (6.1%) (Table 4). The remaining 219 patients were defined as having OCSC. NLR ≥15.3 had a sensitivity of 92.9%, a specificity of 90.0%, and area under curve (AUC) of 0.94 (Figure 1A). LRINEC score of ≥6 points had a sensitivity of 71.4%, a specificity of 93.5%, and an AUC of 0.94 (Figure 1B). We set these as cutoff values of NLR or LRINEC score, respectively.

Age, compromised host, CK, CRP, WBC, Hb, Cr, Alb, NLR≥15.3, and LRINEC score≥6 points had a statistically significant correlation with OCNF according to the univariate analysis outcomes (Table 4).

The OCNF group was hospitalized for significantly longer period than the OCSC group (Table 4). One of the 14 patients died due to OCNF (Table 4).

Table 4
Results of univariate analysis of the risk factors for OCNF in OCSI

Variables		OCNF group (n=14)	OCSC group (n=217)	*P* value
Sex	Male	5 (35.7)	110 (50.7)	0.410
	Female	9 (64.3)	107 (49.3)	
Age	Mean ± SD	69.1 ± 17.3	56.0± 21.2	0.025*
BMI	Mean ± SD	21.9 ± 3.6	22.9 ± 4.0	0.333
Compromised host	No	6 (42.9)	160 (73.7)	0.027*
	Yes	8 (57.1)	57 (26.3)	
Body temperature (℃)	Mean ± SD	37.3 ± 1.0	37.2 ± 0.8	0.804
CK (U/L)	Mean ± SD	247.3 ± 608.2	115.1 ± 178.7	0.035*
CRP (mg/dL)	Mean ± SD	26.4 ± 10.2	10.0 ± 5.9	<0.001*
WBC (10^3/μL)	Mean ± SD	22.5 ± 10.6	12.4 ± 3.6	<0.001*
Hb (g/dL)	Mean ± SD	11.7 ± 1.6	13.5 ± 1.8	<0.001*
Na (mmol/L)	Mean ± SD	137.2 ± 4.6	138.3 ± 5.1	0.442
Cr (mg/dL)	Mean ± SD	1.2 ± 0.6	0.9 ± 0.5	0.031*
Glu (mg/dL)	Mean ± SD	138.6 ± 51.1	125.7 ± 45.6	0.308
Alb (g/dL)	Mean ± SD	2.8 ± 0.4	3.7 ± 0.6	<0.001*
NLR	<15.3 (cut off value)	1 (7.1)	195 (89.9)	<0.001*
	≥15.3	13 (92.9)	22 (10.1)	
LRINEC score	<6 points (cut off value)	4 (28.6)	203 (93.5)	<0.001*
	≥6 points	10 (71.4)	14 (6.5)	
Hospitalization periods (days)	Mean ± SD	24.3 ± 14.2	9.6 ± 6.3	<0.001*
Outcomes	Survival	13 (92.3)	217 (100.0)	1.000
	Mortality	1 (7.7)	0 (0.0)	

Multivariate analysis showed that NLR≥15.3 (OR: 63.4, 95% CI: 7.4–545.7) and LRINEC score≥6 points (OR: 14.8, 95% CI: 3.1–69.7) were significant risk factors for OCNF in OCSI (Table 5).

Table 5
The results of the multivariate logistic regression analysis of the risk factors for OCNF in OCSI

			95% CI	
Variable	P value	Odds ratio	Lower	Upper
NLR ≥15.3	<0.001	63.4	7.4	545.7
LRINEC score ≥6 points	<0.001	14.8	3.1	69.7
CI. Confidence interval				

3.2 Comparison OCNF with BNF

NF occurred in 31 patients, of which 14 had OCNF and 17 had BNF (Table 6). The sites where NF occurred the most were mandible (92.3%) in the OCNF group and lower limbs (47.1%) in the BNF group, respectively (Table 6).

Table 6
Comparison of OCNF group and BNF group

Variables		OCNF group (n=14)	BNF group (n=17)	*P* value
Site of infection	Lower limb	—	8 (47.1)	—
	Upper limb	—	3 (17.6)	
	Perineum	—	5 (29.4)	
	Trunk	—	1 (5.9)	
	Maxilla	1 (7.7)	—	
	Mandible	13 (92.3)	—	
Sex	Male	5 (35.7)	9 (52.9)	0.473
	Female	9 (64.3)	8 (47.1)	
Age	Mean ± SD	69.1 ± 17.3	63.8 ± 18.4	0.424
BMI	Mean ± SD	21.9 ± 3.6	21.7 ± 2.4	0.900
Compromised host	No	6 (42.9)	12 (70.6)	0.157
	Yes	8 (57.1)	5 (29.4)	
Body temperature (℃)	Mean ± SD	37.3 ± 1.0	37.6 ± 1.1	0.410
PaO_2 (mmHg)	Mean ± SD	94.3 ± 43.0	91.9 ± 34.5	0.690
CK (U/L)	Mean ± SD	247.3 ± 608.2	350.0 ± 638.8	0.653
CRP (mg/dL)	Mean ± SD	26.4 ± 10.2	18.8 ± 10.2	0.048*
WBC (10^3/μL)	Mean ± SD	22.5 ± 10.6	13.5 ± 6.6	0.007*
Hb (g/dL)	Mean ± SD	11.7 ± 1.6	11.5 ± 2.2	0.765
Na (mmol/L)	Mean ± SD	137.2 ± 4.6	133.9 ± 5.3	0.081
Cr (mg/dL)	Mean ± SD	1.2 ± 0.6	2.4 ± 3.0	0.135
Glu (mg/dL)	Mean ± SD	138.6 ± 51.1	167.7 ± 134.5	0.452
Alb (g/dL)	Mean ± SD	2.8 ± 0.4	2.6 ± 0.7	0.447
NLR	Mean ± SD	26.0 ± 14.0	25.8 ± 19.6	0.967
LRINEC score	Mean ± SD	6.9 ± 2.5	6.1 ± 2.9	0.423
Gas production	No	9 (64.3)	14 (82.4)	0.413
	Yes	5 (35.7)	3 (17.6)	

Clinical stages	Stage 1	14 (100.0)	6 (35.3)	<0.001*
	Stage 2	0 (0.0)	4 (23.5)	
	Stage 3	0 (0.0)	7 (41.2)	
Hospitalization periods (days)	Mean ± SD	24.3 ± 14.2	30.1 ± 19.9	0.376
Outcomes	Survival	13 (92.3)	11 (64.7)	0.094
	Mortality	1 (7.7)	6 (35.3)	

Univariate analyses showed that CRP, WBC, and clinical stages had a statistically significant correlation between the OCNF and BNF groups (Table 6). The OCNF group had significantly higher inflammatory marker levels than the BNF group, but significantly lower disease progression (Table 6). The hospitalization periods were almost the same among 2 groups; however, the OCNF group had much lower mortality than the BNF group. (Table 6).

4. Discussion

In the present study, we investigated the characteristics of OCNF in comparison with OCSC and BNF. Multivariate analyses showed that NLR ≥15.3 and LRINEC score ≥6 points were significantly related to OCNF in OCSI. On the other hand, univariate analyses of NF showed that CRP, WBC and clinical stages were significant factors. Furthermore, the OCNF group had much lower mortality than the BNF group.

In the patients with OCSI, univariate analyses showed that age, compromised host, CK, CRP, WBC, Hb, Cr, Alb, NLR ≥15.3, LRINEC score ≥6 points were significantly associated with OCNF. Simonart et al. reported that CK is important for the early diagnosis of BNF [23]. Several reports have shown that infection-driven inflammation correlates with markers of malnutrition and inflammation, such as CRP, WBC, Hb, Cr, and Alb in blood tests [24, 25]. When inflammation becomes severe, CRP, WBC, and Cr tend to increase, while Hb and Alb tend to decrease [24, 25]. In the present study, OCNF showed such a tendency significantly when compared with OCSC. Several reports have shown that LRINEC score is useful for predicting BNF [26-30]. Most of the reports set LRINEC score cutoff value at 6 points, which is similar to the present study. However, only 2 reports have investigated the usefulness of LRINEC score for predicting OCNF [31, 32]. Although both reports both set LRINEC score cutoff value at 6 points and the same definition of OCNF and OCSC, opinions on the usefulness of the score were exact opposite [31, 32]. This may be because both reports were quite different in the proportion of OCNF in OCSI patients (17 vs. 70 and 16 vs. 595) [31, 32]. In this study, the proportion was 14 vs. 217 and the definitions of OCNF and OCSC were also similar to previous studies [31, 32]. No reports have investigated the relationship between NLR and NF. Several reports have shown that NLR can predict the outcomes of patients with cancers [33-37]. We found that NLR is also useful for predicting OCNF in OCSI.

In the patients with NF, the OCNF group had significantly higher inflammatory markers than the BNF group, but significantly lower clinical stages when diagnosed clinically. Furthermore, the OCNF group

(7.7%) had much lower mortality than the BNF group (35.3%) These findings showed that when compared with BNF, OCNF can be detected at a lower clinical stage and therefore, the surgeons may be better prepared to save lives. This may be because, compared to BNF, OCNF is easily noticed at an earlier stage (in the state of OCSC or early stage of OCNF), by patients themselves or their family members, as a complication in the oro-cervical region, such as trismus, dysphagia, and skin flare. NF makes superficial-fascia with poor blood flow the main base of bacterial infection; however, several reports showed that because of the abundant blood supply in oro-cervical regions, OCNF is rare in comparison to BNF [13, 38, 39]. In addition, some reports have shown that the superficial cervical fascia is thinner than those of other parts including limbs and trunk [40, 41]. The thinness of the superficial cervical fascia may be associated with the patient's increased awareness of symptoms and, consequently, the rareness of OCNF. In fact, OCNF is reported in 2.6-5.0% among all cases of NF [1, 42]. Next, we considered the difference between OCNF and BNF from the aspect of NF type. Type 1 NF which is 70-80% of NF, occurs in immunocompromised individuals, such as patients with diabetes mellitus or chronic renal failure, infection of the oro-cervical region, abdominal wall, and surgical wounds is common, and gas production can be sometimes seen [16-18]. Type 2 NF can be caused by trauma to the limbs (especially lower limbs) even in young healthy people, with a very high mortality rate of 40% when it occurs [16-18]. In the present study, the causative bacteria were identified in half of the OCNF group (7 out of 14 cases), in which multiple bacterial species including anaerobic bacteria, such as *Prevotella spp.* and *Peptostreptococcus spp.* Most of the OCNFs were probably type 1 NF because the cases in which causative bacteria were not detected were also accompanied by a strong anaerobic odor and anaerobic bacteria are actually difficult to culture. In the BNF group, the causative strain was identified in 14 out of 17 cases. Of these, 9 were *Streptococcus pyogenes*, 5 were multiple strains including *Bacteroides fragilis* and *Escherichia coli*. In other words, more than half of the BNFs were type 2 NFs. In fact, the OCNF group (57.1%) had a higher number of compromised host patients than the BNF group (29.4%). In addition, the OCNF group (35.7%) had much more gas production than the BNF group (17.6%). This may be because OCSI is a dental infection that spreads through "spaces" of the oro-cervical regions, unlike BNF. When the infection reaches the fascia (i.e., OCNF), the infection has already spread to the spaces, which may also have been accompanied by gas production due to some anaerobes. This infection route of OCNF, which is different from that of BNF, may cause severe local symptoms early and may have led to different results regardless of the same NF.

However, this study has some limitations. First, there is a possibility of unknown confounding factors because this was a retrospective study. Next, a few BNF patients were excluded because they transferred to other hospitals for various reasons during this study. If they were added to the BNF group, other results may have been obtained (e.g., mortality of BNF group may have been significantly higher than that of the OCNF group).

5. Conclusions

This is the first report to have investigated the characteristics of OCNF by comparing it with OCSC and BNF. We found that compared to BNF, OCNF can be detected at a lower clinical stage using indexes,

including NLR and LRINEC score, besides clinical findings, which may contribute to patient relief.

6. Abbreviations

Necrotizing fasciitis (NF), oro-cervical NF (OCNF), severe cellulitis of oro-cervical region (OCSC), NF of other body regions (BNF), oro-cervical severe infection (OCSI), neutrophil-to-lymphocyte ratio (NLR), Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC), creatine kinase (CK), C-reactive protein (CRP), white blood cell count (WBC), hemoglobin (Hb), serum creatinine (Cr), sodium (Na), blood glucose (Glu), albumin (Alb), partial pressure of arterial oxygen (PaO_2), computed tomography (CT), receiver operating characteristic (ROC)

7. Declarations

7.1. Ethics approval and consent to participate

This study has been conducted in full accordance with the World Medical Association Declaration of Helsinki and was approved by the institutional review board of Kakogawa Central City Hospital (authorization number: 2019-85).

7.2.Consent to publish

Not Applicable.

7.3. Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [INSERT REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

7.4. Competing interests

The authors declare that they have no competing interest.

7.5. Funding

No funding was obtained for this study.

7.6. Authors' contributions

EI designed the study, performed the data analyses, and drafted the manuscript. JK contributed to study design and data analysis. NT, SF, and AT contributed to data collection and analysis. MA revised the article for important intellectual content. All authors approved the final manuscript.

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7.8. *Authors' Information*

[1]Department of Oral and Maxillofacial Surgery, Kakogawa Central City Hospital, Kakogawa, Japan. [2]Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, Kobe, Japan. [3]Department of Oral and Maxillofacial Surgery, Konan Medical Center, Kobe, Japan.

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Figures

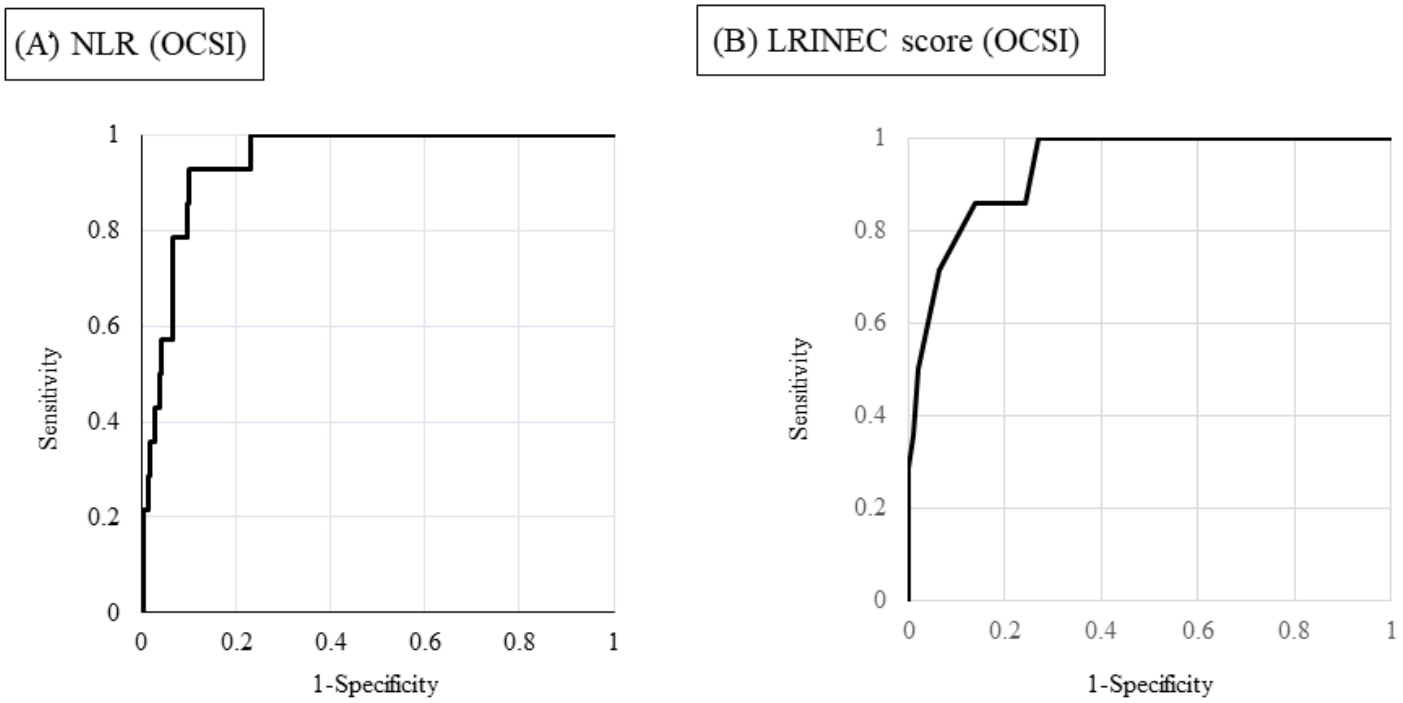

Figure 1

(A)The ROC curve for accuracy of NLR in predicting the presence of OCNF in OCSI. The AUC for our model was 0.944 (95% confidence interval 0.907 to 0.982). (B)The ROC curve for accuracy of LRINEC score in predicting the presence of OCNF in OCSI. The AUC for our model was 0.938 (95% confidence interval 0.889 to 0.987).