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Early diagnosis of craniofacial necrotising fasciitis: Analysis of clinical risk factors

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Abstract

Necrotising fasciitis (NF) is a rapidly progressing fatal disease. Craniofacial necrotising fasciitis (CNF) is limited to the region above the mandibular margin, and early diagnosis is particularly difficult in the absence of related studies. Ten-year data of patients with craniofacial infection were collected from four separate hospitals. Based on the diagnostic criteria, patients were classified into abscess and CNF. The risk factors for early diagnosis were analysed by comparing the two groups. Simple abscess was found in 176 patients, and CNF was detected in 25 patients. The risk factors associated with CNF include old age, presence of odontogenic infection, elevated white blood cell count (WBC), increased C-reactive protein (CRP), high levels of creatinine (Cr) and glucose (Glu) and low levels of haemoglobin (Hb) and albumin (Alb). In addition, fever above 38°C and sinusitis at the time of admission and progressive sepsis after admission were also risk factors. Among the statistically significant risk factors, low Alb level showed the greatest association with CNF progression. Appropriate management of CNF via early diagnosis and extensive surgical intervention based on identified risk factors can reduce the mortality rate, complications and unnecessary medical expenses. Clinical question/level of evidence: Diagnostic, III.

KEYWORDS

craniofacial, early diagnosis, multi-centre, necrotising fasciitis, risk factor

Key Messages

- Craniofacial necrotising fasciitis is difficult to differentiate from simple abscess because the clinical features are similar in the early stage of onset. However, the sequalae of the two diseases are different, so a differential diagnosis is required.
- This study is to explore the risk factors for the progression of CNF, which has been clinically difficult so far.
- As a result of exploring risk factors through a multi-centre study, old age, presence of odontogenic infection, elevated WBC, increased CRP, high

Abbreviations: Alb, albumin; AUC, area under the curve; BMI, body mass index; CNF, craniofacial necrotising fasciitis; Cr, creatinine; CRE, carbapenem-resistant enterobacteriaceae; CRP, C-reactive protein; CT, computed tomography; Glu, glucose; Hb, haemoglobin; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; MRSA, methicillin-resistant *Staphylococcus aureus*; NF, necrotising fasciitis; POD, post-operative days; ROC, receiver operating characteristic; VRE, vancomycin-resistant enterococci; WBC, white blood cell.

levels of Cr and Glu and low levels of Hb and Alb were significantly associated with CNF progression.
- Among the proven risk factors, the risk factor that showed the highest correlation with the onset of CNF was the low Alb level.
- Based on the results revealed in this study, diagnostic criteria more suitable for CNF should be established by modifying the existing LRINEC.

1 | INTRODUCTION

Necrotising fasciitis (NF) is a fatal disease that involves rapidly progressing fascial and soft-tissue infection, accompanied by systemic toxicity such as extensive necrosis of soft tissue and in severe cases, septic shock or multi-organ dysfunction syndrome.[1,2] Generally, fascial necrosis is a key feature of NF progression, and in most wound cultures, group A streptococcus was identified as the most common pathogen.[3] Until now, it has been described by various names and forms such as hospital gangrene, necrotising erysipelas, streptococcal gangrene and suppurative fasciitis. It is called NF because of the commonality of necrosis of the fascia and soft tissue following infection, and recently, it has been designated as necrotising soft-tissue infection regardless of the location or depth of the invasion. With the recent increase in nosocomial infections, the incidence of antibiotic-resistant bacteria such as vancomycin-resistant enterococci (VRE), carbapenem-resistant enterobacteriaceae (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA) also increased, and the risk of serious infection increased accordingly.[4] Early diagnosis of NF is particularly difficult because of vague symptoms in the early stages, followed by rapid progression to severe systemic infection.[5] NF rarely affects the head and neck area.[6,7] It has an incidence of 4 cases per 100 000 people.[8] Based on the mandibular margin, head and neck NFs are classified as craniofacial NF (CNF) above and cervical NF below.[6] NF involving the craniofacial area is associated with a high rate of progression and a mortality rate of 15% to 40% because of its abundant vascular distribution.[9] Unlike the upper and lower extremities, the clinical course of severe infections and simple abscess in the craniofacial region is similar in the early stages of clinical treatment,[10] and a differential diagnosis based on physical examination is difficult, suggesting the need to develop a predictor of CNF. Currently, a haematological predictor such as the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system (Table 1) is utilised for NF involving the upper and the lower limbs. Despite studies involving disease epidemiology and risk factors, NF associated with the head and neck regions is relatively poorly investigated.[11] Cervical NF has been investigated during head and neck surgery. However, the risk factors for CNF have yet to be analysed. CNF is associated with a lower mortality rate than cervical NF but is often more difficult to treat because of extensive skin necrosis and multiple functionally and aesthetically important units.[12] However, CNF occurs frequently after oropharyngeal trauma or tooth extraction (Figure 1).[5,13]

Therefore, this study analysed CNF data above the mandibular margin, compared the clinical features in patients with simple abscess and investigated the risk factors for early diagnosis of CNF.

2 | MATERIALS AND METHODS

2.1 | Design

This study was conducted in four referral hospitals located in four separate provinces in the Republic of Korea including Seoul, Bucheon, Gumi and Cheonan. The local Institutional Review Boards (IRB) approved this retrospective and observational study.

TABLE 1 Laboratory risk indicator for necrotising fasciitis (LRINEC) score system

CRP (mg/dL)	<15	0
	≥15	4
WBC (per mm^3)	<15	0
	15–25	1
	>25	2
Haemoglobin (g/dL)	>13.5	0
	11 to 13.5	1
	<11	2
Sodium (mEq/L)	≥135	0
	<135	2
Creatinine (mg/dL)	≤1.6	0
	>1.6	2
Glucose (mg/dL)	≤180	0
	>180	1
Composite Score	Score< 6	Low risk
	Score 6 to 7	Intermediate
	Score≥ 8	High risk

Abbreviations: CRP, C-reactive protein; WBC, white blood cell.

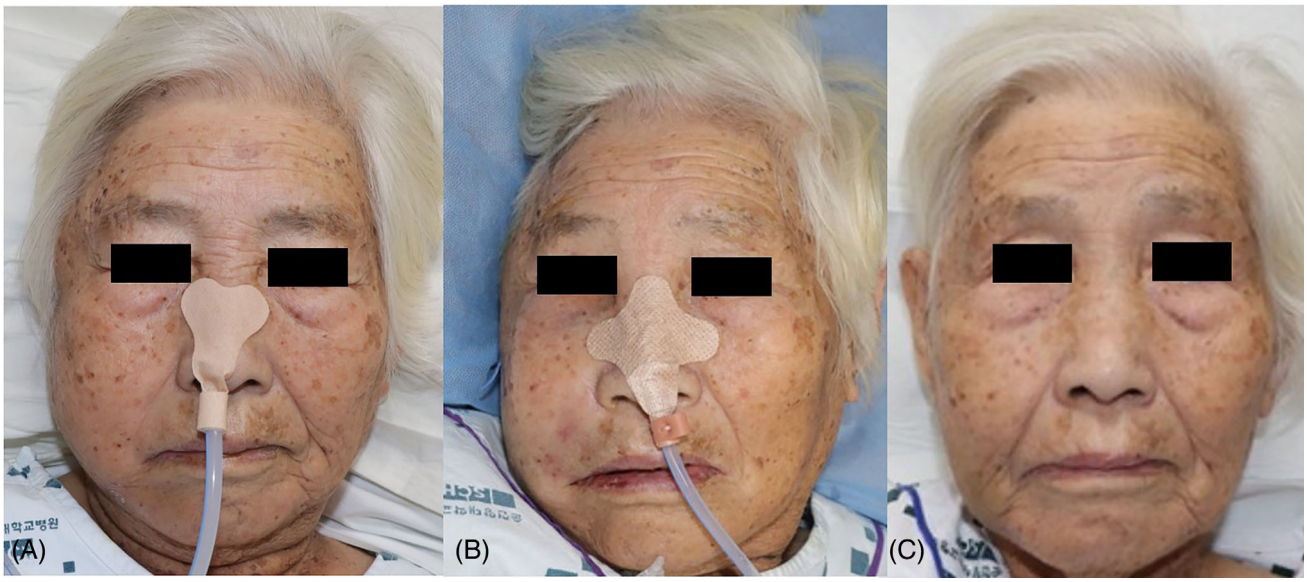

FIGURE 1 Photographic images of craniofacial necrotising fasciitis (CNF) in a 79-year-old woman because of odontogenic infection. (A) Severe swelling and induration were observed throughout in the right cheek. (B) Transient facial palsy as a result of swelling and compression of the buccal branch of the facial nerve was observed on the 5th day of post-operative days (POD) after surgical decompression. (C) On the 31st day of POD after surgical decompression, trismus was observed, but swelling and transient facial palsy improved

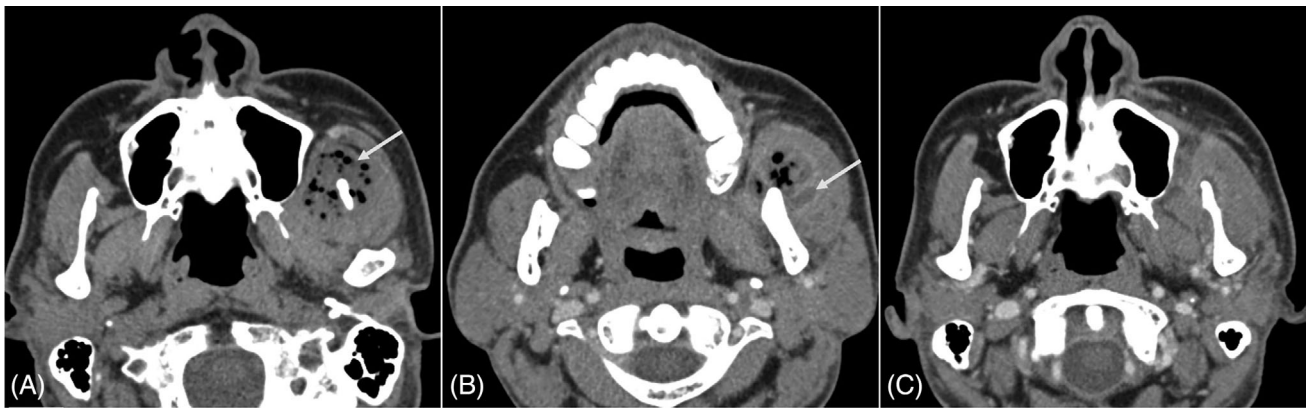

FIGURE 2 Craniofacial necrotising fasciitis (CNF) in a 58-year-old man because of unknown origin. (A) Axial computed tomography (CT) shows multiple soft-tissue abscess with air bubbles (white arrow), (B) At enhanced phase, axial CT shows polymorphic wall enhancing lesions in the muscle (white arrow), (C). CT image of POD 25, more decreased size of abscess formation in left masseter and temporalis muscle

2.2 | Patients

The authors reviewed the records of patients with NF who were treated for approximately 10 years from February 2010 to December 2019. The diagnostic criteria of CNF along with evidence of necrotising fascia and/or characteristic pathological confirmation (extensive tissue necrosis, pattern of infection spreading along the fascia) or evidence of air bubble formation in the fascia or invasive muscle necrosis in imaging tests such as facial contrast enhanced computed tomography (CT) were reviewed (Figures 2 and 3).[14] In this study, clinical data of patients manifesting CNF pattern were collected based on CT images, and the patients' biopsy results were reviewed subsequently to establish a definitive diagnosis of CNF.

2.3 | Risk factor designation

Significant risk factors for simple abscess and CNF were compared based on the patients' data. In addition to diagnostic laboratory values, the patient's comorbidities such as polymicrobial infection rate, tooth extraction history,

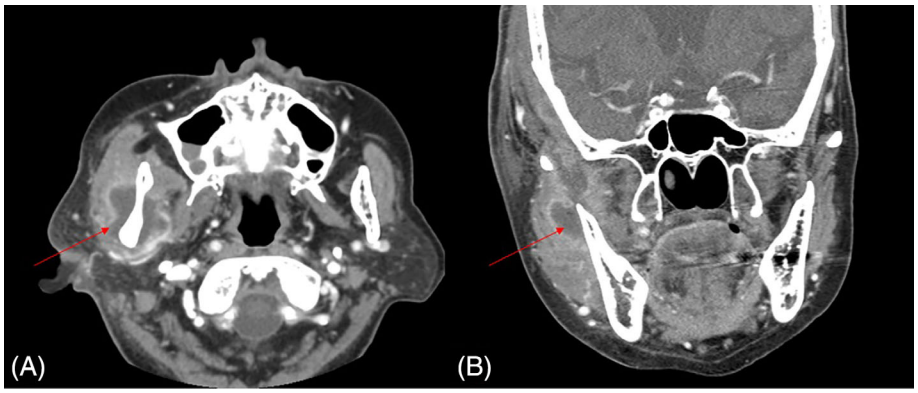

FIGURE 3 Craniofacial necrotising fasciitis (CNF) in an 89-year-old woman infected through the raw surface of the right maxilla 3 days after tooth extraction. (A) Necrotising fasciitis with multiple abscess pockets along the temporalis muscle (red arrow indicates the lesion site). (B) Findings of necrotising fasciitis spreading through the right perimandibular area and deep temporal fascia

diabetes and sinusitis were compared. The severity of infection at the time of NF diagnosis was assessed based on the LRINEC score.[15] The LRINEC score consists of C-reactive protein (CRP), white blood cell (WBC) count, haemoglobin (Hb), sodium, creatinine (Cr) and glucose (Glu). Each item was scored and patients were classified into low-, intermediate- and high-risk groups according to the sum of the scores.

2.4 | Statistics

This study was performed using SPSS (version 21.0; IBM Copatron, NY, USA). Categorical variables were compared using the χ^2-test or Fisher's exact test and Mann–Whitney *U*-test. Only variables with $P < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Based on medical records, the authors reviewed 634 patients with craniofacial area infection above the mandibular margin. Both physicians reviewed the medical records and contrast-enhanced CT images of 582 patients, excluding patients with insufficient imaging and laboratory data. Patients diagnosed with a head and neck malignancy or those who were immunosuppressed were excluded. The 201 patients who were diagnosed with cellulitis (without evidence of a definite abscess pocket) were classified into a simple abscess group of 176 patients and a CNF group of 25 patients with fascial extension associated with air bubbles and pathological evidence of necrosis (Figure 4). Thus, CNF was diagnosed in less than 4% of all patients with craniofacial infection.

Table 2 describes the demographic features of CNF and abscess groups. Of the 25 patients with CNF, 12 (48%) were males and 13 (52%) were females. The

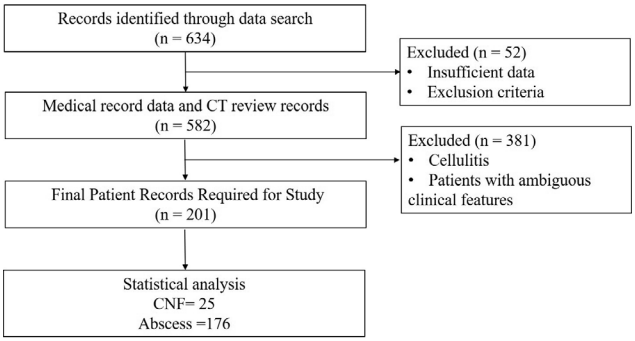

FIGURE 4 Flow diagram for selection of the craniofacial necrotising fasciitis (CNF) patient population

mean age was 67 years and the median age was 75 years (range, 57.0-79.0). Odontogenic infection was the most common mechanism of lesion reported in 8 cases (32%). No lesion mechanism was identified in 13 cases (52%). Based on CNF bacterial culture, single microbial infection was confirmed in 7 cases (28%) of Gram-positive bacteria and 6 cases (24%) of Gram-negative bacteria. Polymicrobial infection was confirmed in 1 case (4%). No bacterial infection was detected in 8 patients (32%).

3.2 | Treatments and outcomes

All patients underwent systemic antibiotics after admission and incision and drainage for the infection source on the day or 1 day after admission. In case of progressing to CNF by the LRINEC system, urgent surgical decompression was performed. After confirming the position of the abscess pocket on CT, dissection of the muscle was performed to drain the abscess, followed by massive saline irrigation. A drainage line was inserted through the incision line to the decompression site. Wound swab and tissue cultures were performed during the operation. Following the recommendation of the Division of Infectious Diseases, intravenous antibiotics were administered

TABLE 2 Demographic characteristics between CNF and simple abscess groups

Characteristic	Total (n = 201)	CNF		*P* value
		CNF (n = 25)	abscess (n = 176)	
Old age				
≥65	47 (23.4)	14 (56.0)	33 (18.8)	<.001
<65	154 (76.6)	11 (44.0)	143 (81.3)	
Sex				
Male	99 (49.3)	12 (48.0)	87 (49.4)	>.99
Female	102 (50.7)	13 (52.0)	89 (50.6)	
Infection route				
Unknown	139 (69.2)	13 (52.0)	126 (71.6)	.017
Skin trauma	36 (17.9)	4 (16.0)	32 (18.2)	
Odontogenic infection	26 (12.9)	8 (32.0)	18 (10.2)	
Culture bacteria				
Gram positive	71 (35.5)	7 (28.0)	64 (36.6)	.096
Gram negative	24 (12.0)	6 (24.0)	18 (10.3)	
polymicrobial	3 (1.5)	1 (4.0)	2 (1.1)	
no growth	54 (27.0)	8 (32.0)	46 (26.3)	
No culture test	48 (24.0)	3 (12.0)	45 (25.7)	
MRSA				
Identified	14 (7.0)	1 (4.0)	13 (7.4)	>.99
Non-identified	187 (93.0)	24 (96.0)	163 (92.6)	
Antibiotics				
Empirical antibiotics	120 (59.7)	8 (32.0)	112 (63.6)	.005
Broad spectrum antibiotics	81 (40.3)	17 (68.0)	64 (36.4)	
Medical past history				
Diabetes mellitus	35 (17.4)	7 (28.0)	28 (15.9)	.158
Solid organ cancer	5 (2.5)	2 (8.0)	3 (1.7)	.118
Liver cirrhosis	1 (0.5)	—	1 (0.6)	>.99
Surgical procedure period after onset				
≤5 days	31 (15.4)	4 (16.0)	27 (15.3)	.665
>5 days	113 (56.2)	16 (64.0)	97 (55.1)	
none	57 (28.4)	5 (20.0)	52 (29.5)	

Abbreviations: CNF, craniofacial necrotising fasciitis; MRSA, methicillin-resistant *Staphylococcus aureus*.

according to the antibiotic susceptibility test of the cultures. In most cases where the incision site was confined to the oral cavity, it healed well with secondary healing. When the incision site was located on the external skin, a skin graft or local flap was performed after the infection sign was sufficiently controlled. There was no death in CNF patients, and trismus was observed in many patients, but all improved within 6 months (Figure 5). No other symptoms suggestive of complications were observed in the craniofacial region. A clinical phase and outcome of CNF patients are described in Table 3.

3.3 | Comparison of risk factors

Several risk factors were compared and analysed between the two groups (Table 4). Among the various risk factors, old age (>65 years), odontogenic infection route, high WBC count (>10 000/μL), increased CRP (>5.0 mL/L), low sodium (≤135 mmol/L), high Cr (<1.2 mg/dL), high Glu (>110 mg/dL), low Hb (<13.0 g/dL) and low albumin (Alb) (3.0 g/dL) were significantly correlated with increased risk of CNF. Fever above 38°C was correlated with sinusitis at the time of admission and progression to

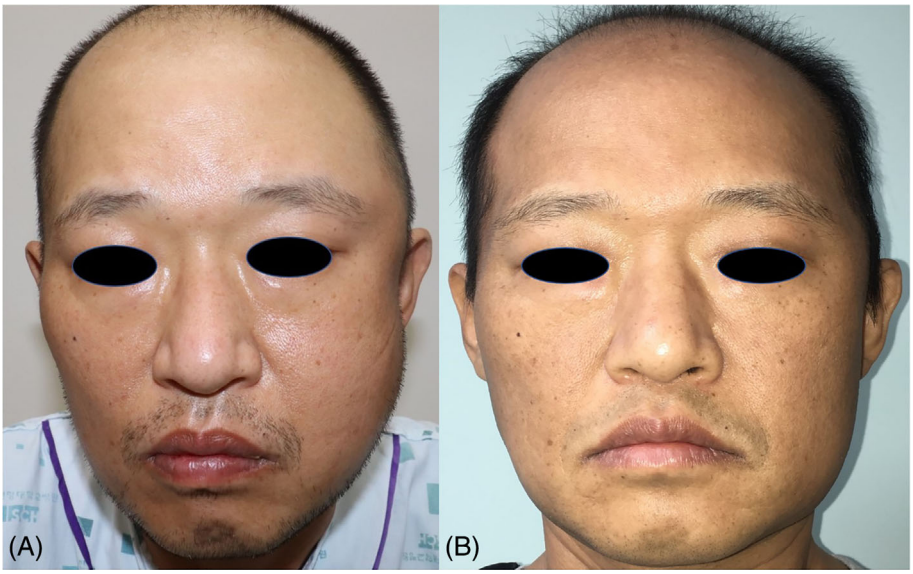

FIGURE 5 Photographic images of craniofacial necrotising fasciitis (CNF) in a 43-year-old man. (A) Severe swelling and induration were observed throughout the left cheek. (B) 6 months after surgical decompression, the patient recovered successfully without trismus

sepsis after admission. The higher the LRINEC score and the higher the risk group, the greater was the progression to NF. However, there was no significant difference between the two groups in terms of high BMI, dental procedure or history of liver cirrhosis.

3.4 | Exploration of the most significant risk factors

Among the statistically significant risk factors, low Alb level yielded the receiver operating characteristic (ROC) curve and showed the highest area under the curve (AUC) value of 0.757 (Figure 6). In addition, logistic regression analysis was utilised to identify the variable most strongly correlated with the onset of CNF among the significant risk factors. The univariable logistic regression analysis indicated that low Alb was associated with the highest odds ratio of 24.7. The results of multivariable logistic regression analysis of factors with *P*-values less than 0.05 in univariable logistic regression analysis revealed that low Alb had the highest odds ratio of 17.8 (Table 5). Thus, low Alb is the most significant risk factor for the development of CNF and is highly correlated with other significant risk factors.

4 | DISCUSSION

We investigated the risk factors for CNF progression among patients admitted to four referral hospitals located in different urban areas of South Korea. However, because of the rarity of CNF, only 25 patients with CNF were identified after reviewing data from thousands of inpatients with infectious diseases in four hospitals. Early-stage CNF is not characterised by specific symptoms.[9] However, rapid progression of CNF infection is characterised by clinical manifestations and pattern of pain inconsistent with the abscess site.[16] In fact, the diagnosis of NF requires pathological confirmation after biopsy. However, because of the rapid progression of the lesion, the treatment cannot await the results of pathological examination, and the diagnosis is often based on imaging and laboratory examinations. Findings such as soft-tissue air bubble formation and pockets of rapid and extensive abscess along the fascial plane on contrast-enhanced CT enable early detection of CNF.[16] Becker et al. investigated 14 cases of head and neck NF and reported subcutaneous fat thickening or enhancement, necrosis in the fascia and muscle layer, as well as confirmed gas formation accompanied by air bubbles in about two-thirds of all patients based on CT images.[17] Contrast-enhanced CT is most often employed as an imaging test for early diagnosis of NF.[18]

The management of NF is early recognition, followed by prompt treatment with broad-spectrum antibiotics. Various bacteria have been identified in polymicrobial infections including non-group-A streptococci, aerobic organisms, anaerobic bacteria such as *Clostridium* and *Bacteroides* and enteric bacteria, including *Escherichia coli, Klebsiella pneumoniae*, *Pseudomonas* and *Vibrio* species. However, single microbial CNFs co-exist with *Streptococcus pyogenes* or *Staphylococcus* species.[19,20] Early surgical intervention is more important than anything else. However, unfortunately, despite early and aggressive treatment, it is difficult to manage the remnant abscess pocket in CNF, and the morbidity and potential mortality are quite high because of the underlying diseases.[21]

TABLE 3 Treatments and outcomes in craniofacial necrotising fasciitis (CNF) patients

Patient	Age	Sex	Infection route	LRINEC score	Albumin (g/dL)	Days to surgical decompression	Number of surgical decompressions	Method of wound healing	Death
1	56	M	Unknown	0	4.2	5 days	1	Secondary healing	No
2	58	M	Unknown	5	2.9	5 days	1	Secondary healing	No
3	76	M	Unknown	2	3.3	3 days	1	Secondary healing	No
4	46	F	Skin trauma	0	3.4	No operation	0	Secondary healing	No
5	78	F	Unknown	2	3.2	7 days	11	Secondary healing	No
6	82	M	Unknown	1	3.3	5 days	1	Local flap	No
7	89	F	Odontogenic infection	6	2.0	9 days	8	Secondary healing	No
8	81	F	Unknown	4	2.3	No operation	0	FTSG	No
9	43	M	Unknown	6	3.3	8 days	1	Secondary healing	No
10	75	M	Odontogenic infection	3	4.5	10 days	1	FTSG, STSG	No
11	47	M	Odontogenic infection	5	3.5	10 days	1	Secondary healing	No
12	77	M	Unknown	2	3.2	20 days	1	Local flap	No
13	86	F	Skin trauma	3	2.5	No operation	0	Secondary healing	No
14	60	M	Odontogenic infection	8	2.9	9 days	1	FTSG	No
15	46	F	Unknown	5	2.2	No operation	0	Secondary healing	No
16	79	F	Odontogenic infection	5	3.0	9 days	1	Local flap	No
17	61	F	Unknown	3	3.5	8 days	1	Secondary healing	No
18	76	F	Skin trauma	5	2.5	7 days	1	STSG	No
19	79	M	Unknown	11	2.6	10 days	1	Secondary healing	No
20	39	M	Unknown	3	2.7	7 days	11	FTSG	No
21	69	M	Skin trauma	3	2.8	28 days	1	Local flap	No
22	60	F	Odontogenic infection	7	4.1	No operation	0	Secondary healing	No
23	83	M	Odontogenic infection	10	2.3	5 days	1	Secondary healing	No
24	77	F	Unknown	7	2.7	7 days	3	Secondary healing	No
25	46	M	Odontogenic infection	7	2.7	3 days	2	Secondary healing	No

Abbreviations: CNF, craniofacial necrotising fasciitis; FTSG, full-thickness skin graft; LRINEC, laboratory risk indicator for necrotising fasciitis; STSG, split-thickness skin graft.

TABLE 4 Comparison of risk factors of craniofacial necrotising fasciitis (CNF) and simple abscess

		CNF		
	Total (n = 201)	**NF (n = 25)**	**Abscess (n = 176)**	***P* value**
WBC (10 000/μL)	10 000.0 (7890.0-13 885.0)	14 590.0 (9245.0-17 500.0)	9500.0 (7840.0-12 910.0)	.011
≤10 000	100 (49.8)	6 (24.0)	94 (53.4)	
>10 000	101 (50.2)	19 (76.0)	82 (46.6)	
Crp (5.0 mg/L)	17.2 (3.0-55.0)	65.0 (17.5-186.9)	14.2 (2.8-41.6)	.011
≤5	65 (32.3)	2 (8.0)	63 (35.8)	
>5	136 (67.7)	23 (92.0)	113 (64.2)	
Sodium (136 mmol/L)	140.0 (139.0-142.0)	138.0 (135.0-142.0)	140.0 (139.0-142.0)	.003
>135	180 (90.9)	18 (72.0)	162 (93.6)	
≤135	18 (9.1)	7 (28.0)	11 (6.4)	
Creatinine (>1.5 mg/dL)	0.8 (0.6-1.0)	0.9 (0.7-1.3)	0.8 (0.6-1.0)	.005
≤1.5	194 (96.5)	21 (84.0)	173 (98.3)	
>1.5	7 (3.5)	4 (16.0)	3 (1.7)	
Glucose (>110 mg/dL)	116.0 (102.0-154.8)	147.0 (126.0-180.0)	113.0 (100.0-149.0)	.010
≤110	75 (37.3)	3 (12.0)	72 (40.9)	
>110	127 (62.7)	22 (88.0)	104 (59.1)	
Albumin (3.0 g/dL)	3.79 ± 0.6	3.02 ± 0.53	3.9 ± 0.52	<.001
≤3.0	22 (11.0)	14 (56.0)	8 (4.6)	
>3.0	179 (89.0)	11 (44.0)	168 (95.4)	
Hb (<13 g/dL)	12.1 (11.0-13.6)	10.9 (9.9-11.7)	12.3 (11.3-13.8)	.005
>13	71 (35.3)	2 (8.0)	69 (39.2)	
≤13	130 (64.7)	23 (92.0)	107 (60.8)	
LRINEC score	2.0 (1.0-2.8)	5.0 (2.5-6.5)	1.0 (1.0-2.0)	<.001
LRINEC score risk				
Low risk	185 (92.0)	17 (68.0)	168 (95.5)	<.001
Intermediate risk	11 (5.5)	5 (20.0)	6 (3.4)	
High risk	5 (2.5)	3 (12.0)	2 (1.1)	
Sepsis				
Appearance	31 (15.4)	13 (52.0)	18 (10.2)	<.001
Non-appearance	170 (84.6)	12 (48.0)	158 (89.8)	
Septic shock				
Non-appearance	2 (1.0)	1 (4.0)	1 (0.6)	.234
Appearance	199 (99.0)	24 (96.0)	175 (99.4)	
Fever				
≥38	40 (19.9)	12 (48.0)	28 (15.9)	<.001
<38	161 (80.1)	13 (52.0)	148 (84.1)	
BMI				
≥23	85 (42.5)	12 (50.0)	73 (41.5)	.747
<23	110 (55.0)	12 (50.0)	98 (55.7)	
unknown	5 (2.5)	—	5 (2.8)	
Dental procedure				
Appearance	18 (9.0)	5 (20.0)	13 (7.4)	.055
Non-appearance	183 (91.0)	20 (80.0)	163 (92.6)	

TABLE 4 (Continued)

	Total (n = 201)	CNF		*P* value
		NF (n = 25)	Abscess (n = 176)	
Sinusitis				
Appearance	22 (10.9)	8 (32.0)	14 (8.0)	.002
Non-appearance	179 (89.1)	17 (68.0)	162 (92.0)	

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CNF, craniofacial necrotising fasciitis; Hb, haemoglobin; LRINEC, laboratory risk indicator for necrotising fasciitis; WBC, white blood cell.

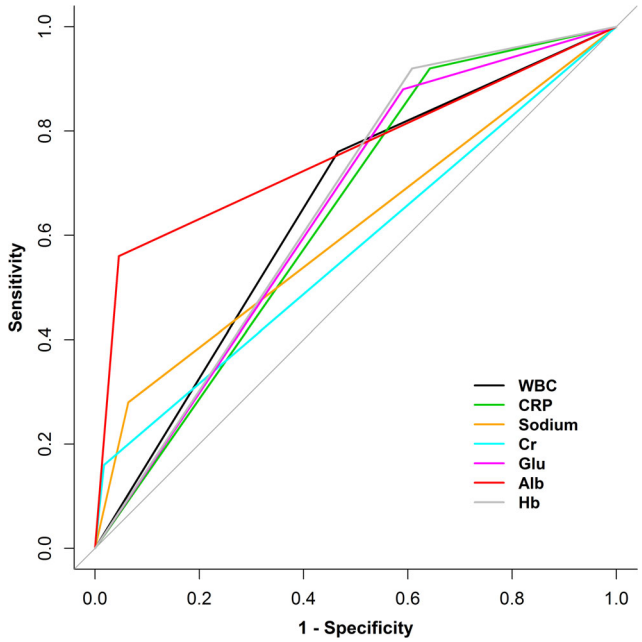

FIGURE 6 Receiver operating characteristic (ROC) curve based on laboratory risk factors. The area under the curve for low albumin is the highest at 0.757

Early diagnosis of NF was based on the LRINEC score, which can be utilised to differentiate NF from severe cellulitis/abscess according to significant haematological parameters. It has been utilised in multiple ways for severe infections of the upper and lower extremities and improves the efficiency of early diagnosis.[10,14] However, it has not been widely utilised for severe infections of the craniofacial region. The effectiveness of the LRINEC score in the craniofacial region has yet to be reported, because of the extremely low incidence of CNF. However, based on our study results, the LRINEC scoring system can be successfully applied to CNF.

In addition, several haematological parameters were associated with the CNF progression in this study. High WBC, high CRP, high Cr, high Glu, low sodium and low Hb, as well as low Alb, were strongly correlated with CNF. Low Alb is associated with a fatal prognosis in several diseases.[11,18] This laboratory marker was not included in the existing LRINEC score but must be considered additionally in the craniofacial area.

Odontogenic or oropharyngeal infection was the main cause of CNF onset in previous studies. In this study,[5,13] odontogenic infection was the main infection route. Therefore, the risk of progression to CNF is increased by wounds in the oral cavity. Interestingly, oropharyngeal infection showed limited association with CNF and manifested as deep neck infection, suggesting a preliminary diagnosis of cervical NF rather than CNF.

Fever above 38°C and sepsis suggest progression to systemic infection and are significant risk factors. However, sinusitis is characterised by chronic inflammation occurring in the maxillary sinus, which is triggered by odontogenic infection or skin trauma and promotes bacterial proliferation, suggesting a significant correlation.

A specific population of diabetes or immunocompromised patients exposed to systemic chronic steroids is at high risk for NF.[9] Obesity, alcoholism, cirrhosis, chronic kidney failure, substance abuse, atherosclerosis, malnutrition, cancer and old age are the other risk factors.[22] Liver cirrhosis was generally associated with NF in previous studies and was a significant risk factor affecting poor prognosis[3,11]; however, this was not the case in this study because of the scarcity of CNF. A significant statistical relationship could not be established because only a single patient with liver cirrhosis was included in the simple abscess group. However, other studies report that medical history was related to NF,[4,5,21] suggesting the need for further investigations into the relationship between CNF and other diseases.

The 10-year data starting from 2011 were searched in PubMed, Google Scholar and Cochrane Library to investigate CNF comprehensively (Table 6). The search term utilised the algorithm of '(cervical OR craniofacial) AND necrotising fasciitis'. A total of 816 articles were searched as a result. Overlapping studies under each database search were excluded. Articles limited to NF in the head and neck area were collected except for studies involving NF extending to the mediastinum. Collections of simple case reports involving fewer than

TABLE 5 Significance and odd ratio values of each variable through logistic regression analysis. Low albumin has the highest correlation with craniofacial necrotising fasciitis (CNF) and other risk factors

	Univariable logistic analysis		Multivariable logistic analysis	
	OR	***P* value**	**OR**	***P* value**
Old age				
≥65	Ref[a]		Ref.	
<65	0.181 (0.076-0.435)	<.001	0.305 (0.063-1.481)	.141
Sex				
Male	Ref.			
Female	1.059 (0.458–2.449)	.893		
Infection route				
Unknown	Ref.		Ref.	
Skin trauma	1.212 (0.370-3.966)	.751	0.385 (0.049-3.037)	.365
Odontogenic infection	4.308 (1.569-11.824)	.005	9.546 (1.693-53.824)	.011
Culture bacteria				
Gram positive	Ref.			
Gram negative	3.048 (0.909-10.213)	.071		
Polymicrobial	4.571 (0.366-57.049)	.238		
No growth	1.590 (0.539-4.695)	.401		
No culture test	0.596 (0.146-2.429)	.471		
MRSA				
Appearance	Ref.			
Non-appearance	1.914 (0.240-15.300)	.540		
Antibiotics				
Empirical antibiotics	Ref.		Ref.	
Broad spectrum antibiotics	3.719 (1.520-9.098)	.004	2.996 (0.732-12.273)	.127
Medical past history				
Diabetes mellitus	2.056 (0.786-5.379)	.142		
Solid organ cancer	5.015 (0.795-31.616)	.086		
Surgical procedure period after onset				
≤5 days	Ref.			
>5 days	1.113 (0.344-3.608)	.858		
None	0.649 (0.161-2.618)	.544		
WBC (10 000/μL)				
≤10 000	Ref.		Ref.	
>10 000	3.468 (1.322-9.097)	.012	6.817 (1.319-35.242)	.022
CRP (5.0 mg/L)				
≤5	Ref.			
>5	7.069 (1.615-30.947)	.009		
Sodium (136 mmol/L)				
>135	Ref.			
≤135	5.727 (1.974-16.621)	.001		
Creatinine (>1.5 mg/dL)				
≤1.5	Ref.			
>1.5	3.889 (1.412-10.710)	.009		

TABLE 5 (Continued)

	Univariable logistic analysis		Multivariable logistic analysis	
	OR	***P* value**	**OR**	***P* value**
Glucose (>110 mg/dL)				
≤110	Ref.		Ref.	
>110	4.959 (1.431-17.188)	.012	4.644 (0.624-34.543)	.134
Albumin (3.0 g/dL)				
≤3.0	24.691 (8.826-68.966)	<.001	17.794 (3.893-81.301)	<.001
>3.0	Ref.		Ref.	
Hb (<13 g/dL)				
>13	Ref.			
≤13	7.416 (1.695-32.456)	.008		
LRINEC score risk				
Low risk	Ref.			
Intermediate risk	8.235 (2.273-29.839)	.001		
High risk	14.824 (2.314-94.978)	.004		
Antibiotic period				
<14 days	ref.		Ref.	
≥14 days	0.116 (0.047-0.286)	<.001	0.228 (0.050-1.038)	.056
Sepsis				
Appearance	Ref.		Ref.	
Non-appearance	0.105 (0.042-0.265)	<.001	0.254 (0.045-1.443)	.122
Septic shock				
Non-appearance	Ref.			
Appearance	0.137 (0.008-2.265)	.165		
ICU admission				
Appearance	Ref.			
Non-appearance	0.137 (0.008-2.265)	.165		
Fever				
≥38	Ref.			
<38	0.205 (0.085-0.495)	<.001		
BMI				
≥23	Ref.			
<23	0.745 (0.317-1.753)	.500		
Dental procedure				
Appearance	Ref.			
Non-appearance	0.319 (0.103-0.989)	.048		
Sinusitis				
Appearance	Ref.		Ref.	
Non-appearance	0.184 (0.067-0.500)	<.001	0.111 (0.021-0.602)	.011

Abbreviations: BMI, body mass index; CRP, C-reactive protein; Hb, haemoglobin; ICU, intensice care unit; LRINEC, Laboratory Risk Indicator for Necrotising Fasciitis; MRSA, methicillin-resistant *Staphylococcus aureus*; WBC, white blood cell.

[a]'Ref.' is the reference standard value for statistical analysis.

TABLE 6 Extensive literature search reviews on craniofacial necrotising fasciitis (CNF)

References	Patients (N)	Age	Conclusion
Thomas AJ et al[23]	17	Average: 45.5	The utilisation of LRINEC scores and white blood cell counts and sodium levels is not useful for differentiating cervical NF from non-NF infections. Because there are many non-specific clinical courses, clinicians must maintain vigilance.
Thakur JS et al[24]	38	10 months to 82 years, Average: 55	The most important factor in determining prognosis was the time interval between the onset of CNF and surgical intervention.
Kovačić M et al[25]	15	Average: 54	Mention the importance of early diagnosis and appropriate surgical intervention, broad-spectrum antibiotics and intravenous immunoglobulin therapy.
Zhao Y et al[26]	29	Unknown	Early surgical intervention is useful in reducing complications.
Nougué H et al[27]	160	33 to 64 years Median: 50	Evidence of the usefulness of CT scan and partial efficacy of prehospital oral glucocorticoid intake.
Sandner A et al[28]	16	Average: 57	Patients with a LRINEC score ≥ 6 should be carefully evaluated for progression of CNF.
Juncar M et al[29]	55	17 to 78 years Average: 41	Odontogenic infection is the most common cause, explaining the importance of early diagnosis and aggressive surgical procedures.
Elander J et al[30]	59	17 to 89 years Average: 60	The utilisation of combination therapy with hyperbaric oxygen therapy and early surgical debridement can reduce mortality in patients with cervical NF.
Gahleitner C et al[31]	10	42 to 85 years Average: 64	Patients with acute tonsillitis with age >35 years and serum CRP >15.5 mg/dL with retropharyngeal abscess have a high association with NF.
Hernandez DA et al[5]	29	19 to 81 years	A collection of existing 24 case reports, which should be sufficiently suspected and boldly diagnosed at an early stage.
Gore, M. R.[32]	164	15 to 83 years Average: 44	A collection of existing 58 case reports. Anaemia, diabetes mellitus and malnutrition were the major systemic condition coexisting in CNF.
Gunaratne DA et al[33]	969	Average: 49.14	CNF may have subtle early clinical findings and requires active intervention to prevent fatal local and systemic morbidity and mortality.
Ogawa et al[34]	26	22 to 88 years Average: 62	CRP, WBC, Cr and skin flare in the cervical and precordial areas were extracted as independent factors. Introduced LRINEC-OC with some improvements to the LRINEC Score system.
Sideris G et al[35]	11	17 to 62 years	It was found that the presence or absence of immunosuppression was not related to the development of CNF.
Melis A et al[36]	11	9 to 87 years Average: 41	Correct clinical diagnosis and early medical and surgical treatment were crucial in reducing complications; LRNEC score, C-reactive protein, glycaemia and creatininaemia has proven to be a reliable prognostic indicator.
Fiorella ML et al[37]	118	2 to 83 years Average: 48	LRINEC and NLR (neutrophil to lymphocyte ratio) scores are useful for rapidly predicting the risk of necrotising fasciitis and systemic involvement at an early diagnostic stage.
Sideris G et al[38]	12	Unknown	LRINEC score, using 6 as a cutoff, proves to be a useful 'rule-out' tool, and among the items, CRP and Glu seem to be the most significant variables. Diagnosis of NF must be based on medical history, clinical symptoms and signs, imaging findings and laboratory tests and not according to the LRINEC score itself.
Sizer B et al[39]	16	19 to 71 years	Odontogenic infection is the most common cause, and the risk is increased in diabetic patients and broad-spectrum antibiotics should be initiated when infection is suspected.

Abbreviation: CNF, craniofacial necrotising fasciitis; CRP, C-reactive protein; CT, computed tomography.

10 patients were also excluded. As a result of search and exclusion, 19 articles were summarised, and the most common was CNF. The articles mentioned the utility of early diagnosis of CT and the LRINEC score system and stated the importance of sensitive clinical suspicion and early surgical intervention.

Our study has several strengths. To date, few systematic studies of CNF have been reported, and most of the existing articles are case reports. In this study, a relatively wide range of data from various regions was collected, and a group of patients with CNF carrying risk factors was recruited in a multi-centre study, with a 10-year follow-up. The single article analysing the largest number of patients in CNF involved 273 patients,[40] but it included both CNF and cervical NF with thoracic mediastinitis and summarised only the clinical features of CNF. In addition, only CNF involving the craniofacial area, but not NF, which mainly involves the upper and lower extremities, was investigated to demonstrate the different risk factors compared with the previous study. The previous studies of cervical NF investigated deep neck infection and NF of other facial areas separately. In addition, despite involving the four hospitals under the same foundation, a uniform methodology was adopted to review medical records, minimise errors when collecting large-scale data and increase the validity of the study.

4.1 | Study limitations

The study has a statistical limitation because it compared the data of only 25 patients with CNF with abscess even though the number was 7-fold higher. Second, the relationship between medical history and CNF could not be established, suggesting the need to analyse data from hundreds of CNF patients in a large-scale study. According to Thomas et al., studies have reported the limitations of the LRINEC system for the diagnosis of CNF and the need for improved scoring system based on data from a larger number of patients in the future.[23] In addition, a prospective study is needed to validate the effectiveness of risk factors identified in our study for early diagnosis of CNF.

5 | CONCLUSION

Risk factors suggestive of CNF progression include high levels of WBC, CRP, creatinine and Glu and low levels of sodium, Hb and Alb, in addition to wounds in the oral cavity, old age, sinusitis, fever and sepsis. Based on the study findings, prevention of complications in patients via increased early diagnosis of CNF reduces needless medical expenses and the exorbitant cost of treating severe infections.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board (IRB number: 2020–08–011-002). All the study procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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