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Morphological Features of Complications from Purulent-Necrotic Processes in the Maxillofacial Region Arising on the Background of Polyangiitis, Post-COVID Conditions, and Chronic Kidney Failure

Abstract

Purulent-necrotic processes of the maxillofacial region remain among the most severe complications in oral and maxillofacial surgery because they are frequently associated with extensive tissue destruction, prolonged hospitalization, and increased mortality. The clinical course becomes considerably more aggressive in patients with systemic disorders such as polyangiitis, post-COVID conditions, and chronic kidney failure, all of which are characterized by immune dysregulation, endothelial injury, microvascular thrombosis, and impaired tissue regeneration. Despite increasing recognition of these comorbidities, the combined morphological mechanisms responsible for the progression of maxillofacial necrosis have not been comprehensively characterized. This study aimed to investigate the morphological features of purulent-necrotic complications in the maxillofacial region associated with polyangiitis, post-COVID conditions, and chronic kidney failure and to develop an integrated morphological diagnostic framework for precision pathology. A comparative observational study was conducted using surgical tissue specimens obtained from patients with purulent-necrotic maxillofacial lesions and healthy control tissues. Histopathological examination, hematoxylin-eosin staining, Masson's trichrome staining, immunohistochemical evaluation of endothelial and inflammatory biomarkers, and digital morphometric analysis were performed to assess vascular injury, inflammatory infiltration, fibrosis, osteonecrosis, endothelial dysfunction, and tissue remodeling. The findings demonstrated pronounced endothelial damage, diffuse inflammatory cell infiltration, extensive microvascular thrombosis, progressive bone necrosis, increased fibrotic remodeling, and impaired angiogenesis in patients with systemic comorbidities. Digital morphometric assessment revealed significantly greater structural tissue destruction and vascular abnormalities in comparison with conventional histopathological evaluation. Based on these observations, an original Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF) was developed by combining histopathological, immunohistochemical, vascular, inflammatory, and digital pathological parameters into a unified precision diagnostic model. This framework provides a comprehensive approach for individualized pathological assessment, improves diagnostic accuracy, facilitates early identification of high-risk patients, and supports personalized therapeutic planning for complex maxillofacial infections associated with systemic diseases. The proposed model may contribute to the advancement of precision pathology and optimize multidisciplinary management strategies in oral and maxillofacial surgery.

1. Introduction

Purulent-necrotic diseases of the maxillofacial region represent one of the most challenging conditions encountered in oral and maxillofacial surgery because of their rapid progression, complex pathogenesis, and high risk of severe local and systemic complications. These pathological processes encompass odontogenic infections, osteomyelitis of the jaws, necrotizing soft tissue infections, deep fascial space abscesses, and extensive bone destruction, all of which may lead to functional impairment, facial deformity, septic complications, and increased mortality if diagnosis or treatment is delayed. Although advances in antimicrobial therapy, imaging techniques, and surgical management have significantly improved patient outcomes, purulent-necrotic lesions continue to pose a major clinical burden, particularly in individuals with systemic inflammatory or immunocompromising diseases (AAOMS, 2023).

Odontogenic infections remain the leading cause of maxillofacial purulent-necrotic complications worldwide. Most infections originate from untreated dental caries, periodontal disease, periapical lesions, or traumatic dental injuries and may spread rapidly through fascial spaces of the head and neck. In severe cases, bacterial invasion extends beyond local tissues, resulting in osteomyelitis, extensive soft tissue necrosis, mediastinitis, septic thrombosis, or systemic inflammatory response syndrome. The increasing prevalence of antimicrobial resistance and the growing number of medically compromised patients have further complicated disease management and increased hospitalization rates (Hupp et al., 2022).

Jaw osteomyelitis represents one of the most destructive complications of odontogenic infection. It is characterized by progressive inflammatory destruction of cortical and cancellous bone accompanied by vascular compromise, impaired osteogenesis, and tissue necrosis. Chronic osteomyelitis frequently demonstrates persistent inflammatory infiltrates, sequestrum formation, fibrosis, and impaired vascular regeneration. Histopathological examination remains the gold standard for evaluating disease severity because radiographic findings often underestimate microscopic tissue destruction. Recent studies indicate that osteomyelitic lesions occurring in patients with systemic inflammatory disorders exhibit considerably more aggressive morphological changes than those observed in otherwise healthy individuals (Marx, 2023).

Necrotizing soft tissue infections of the maxillofacial region constitute surgical emergencies requiring prompt diagnosis and aggressive intervention. Their progression is largely determined by interactions among microbial virulence, host immune responses, microvascular perfusion, and systemic health status. Tissue ischemia, endothelial injury, inflammatory cytokine release, and microthrombosis collectively accelerate necrosis while limiting antibiotic penetration into infected tissues. Consequently, understanding the underlying histopathological mechanisms has become increasingly important for improving therapeutic strategies and reducing morbidity.

Among systemic diseases influencing maxillofacial pathology, ANCA-associated polyangiitis has attracted considerable attention because of its direct effects on small- and medium-sized blood vessels. Polyangiitis is characterized by autoimmune-mediated vasculitis resulting in endothelial injury, fibrinoid necrosis, inflammatory infiltration, and progressive vascular occlusion. These pathological alterations compromise tissue perfusion and impair normal wound healing, thereby increasing susceptibility to chronic infection, osteonecrosis, and extensive soft tissue destruction. Oral manifestations including gingival ulceration, mucosal necrosis, delayed healing, and jaw involvement have been increasingly reported in patients with systemic vasculitis, highlighting the importance of multidisciplinary management (Yates et al., 2022).

The emergence of the COVID-19 pandemic introduced additional challenges to oral and maxillofacial pathology. Although acute SARS-CoV-2 infection primarily affects the respiratory system, accumulating evidence demonstrates persistent immunological and vascular abnormalities following recovery. Post-COVID syndrome is characterized by chronic immune dysregulation, endothelial dysfunction, complement activation, persistent cytokine production, coagulation abnormalities, and widespread microvascular injury. These mechanisms may significantly impair tissue repair and increase vulnerability to secondary bacterial infections. Histopathological studies have demonstrated diffuse endothelial inflammation, microvascular thrombosis, capillary rarefaction, and prolonged inflammatory activity in multiple organs, suggesting that similar mechanisms may contribute to severe purulent-necrotic lesions within the maxillofacial region (Nalbandian et al., 2023).

Chronic kidney disease (CKD) represents another major systemic condition influencing oral and maxillofacial health. Progressive renal dysfunction results in profound metabolic disturbances affecting bone remodeling, mineral metabolism, immune regulation, vascular integrity, and wound healing. Patients with CKD frequently exhibit secondary hyperparathyroidism, renal osteodystrophy, impaired collagen synthesis, chronic inflammation, and increased oxidative stress. These abnormalities weaken osseous structures and reduce resistance to infection while simultaneously impairing postoperative tissue regeneration. Consequently, purulent-necrotic maxillofacial infections occurring in patients with chronic kidney disease often demonstrate greater tissue destruction and delayed healing compared with the general population (KDIGO, 2024).

A common pathological denominator linking polyangiitis, post-COVID syndrome, and chronic kidney disease is microvascular injury**.** Healthy tissue regeneration depends upon adequate vascular perfusion, oxygen delivery, and

endothelial homeostasis. In contrast, endothelial dysfunction leads to reduced nitric oxide production, leukocyte adhesion, platelet activation, increased vascular permeability, and thrombus formation. These processes compromise tissue oxygenation and accelerate ischemic necrosis. Histologically, affected tissues demonstrate endothelial swelling, fibrinoid degeneration, capillary obstruction, inflammatory infiltration, and progressive fibrosis. Such vascular alterations are increasingly recognized as major determinants of disease severity in maxillofacial infections.

Inflammatory cytokines further amplify tissue destruction. Elevated concentrations of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and other pro-inflammatory mediators stimulate osteoclast activation, extracellular matrix degradation, endothelial injury, and apoptosis. Persistent cytokine activation also disrupts normal bone remodeling by promoting osteoclastic resorption while suppressing osteoblastic activity, thereby facilitating progressive osteonecrosis. These mechanisms suggest that inflammatory regulation represents an important therapeutic target for preventing severe complications.

Recent advances in histopathology **and** digital pathology **have** transformed morphological assessment of inflammatory diseases. Conventional light microscopy remains indispensable for evaluating necrosis, inflammatory infiltration, fibrosis, vascular injury, and bone destruction. However, digital pathology now enables quantitative morphometric analysis, automated cell counting, vascular density assessment, fibrosis quantification, and integration of immunohistochemical biomarkers. Artificial intelligence-assisted image analysis further enhances diagnostic reproducibility and facilitates objective characterization of complex tissue alterations. These technologies support the transition from descriptive pathology toward precision pathology, where microscopic findings are integrated with clinical and molecular information.

Within the broader framework of precision medicine**,** morphological analysis should no longer be considered an isolated diagnostic procedure but rather a component of integrated clinical decision-making. Combining histopathological findings with systemic disease characteristics, inflammatory biomarkers, endothelial injury, and digital image analysis offers opportunities for individualized risk stratification and personalized therapeutic planning. Such multidisciplinary integration is particularly relevant for patients presenting with complex maxillofacial infections complicated by autoimmune vasculitis, post-COVID immune dysfunction, or chronic kidney disease.

Despite growing recognition of these systemic influences, important knowledge gaps remain. Most previous studies have examined odontogenic infections, ANCA-associated vasculitis, post-COVID pathology, or chronic kidney disease independently, whereas few investigations have evaluated their combined effects on the morphology of purulent-necrotic maxillofacial lesions. Furthermore, standardized histopathological frameworks capable of integrating vascular injury, inflammatory activity, bone remodeling, and digital morphometric analysis are lacking. This limitation restricts accurate prediction of disease severity and individualized therapeutic decision-making.

Therefore, the present study aims to investigate the morphological characteristics of purulent-necrotic complications of the maxillofacial region arising in patients with polyangiitis, post-COVID conditions, and chronic kidney failure through comprehensive histopathological, immunohistochemical, and digital morphometric evaluation. The study further introduces the Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**,** an original precision pathology model that integrates vascular injury, inflammatory infiltration, endothelial dysfunction, osteonecrosis, fibrosis, and digital pathology into a unified diagnostic system. It is hypothesized that systemic vascular and immune disorders produce distinctive morphological signatures that can improve disease stratification, pathological diagnosis, and personalized management of complex maxillofacial infections. The proposed framework seeks to bridge the gap between conventional pathology and precision medicine while providing a novel scientific basis for future translational research in oral and maxillofacial surgery.

3. Literature Review

Purulent-necrotic diseases of the maxillofacial region remain among the most severe conditions encountered in oral and maxillofacial surgery because of their rapid progression, destructive biological behavior, and substantial morbidity. Odontogenic infections continue to represent the predominant etiological factor, accounting for the majority of deep fascial space infections, osteomyelitis, and necrotizing soft tissue lesions. Despite considerable advances in antimicrobial therapy and surgical management, mortality and complication rates remain high in patients with systemic inflammatory disorders, autoimmune diseases, metabolic dysfunction, or immune suppression. Recent epidemiological studies indicate that increasing life expectancy, widespread chronic diseases, antimicrobial resistance, and post-pandemic immune abnormalities have significantly altered both the clinical presentation and pathological progression of maxillofacial infections (Hupp et al., 2022).

Contemporary evidence demonstrates that purulent-necrotic lesions should no longer be regarded solely as localized bacterial infections. Instead, they represent multifactorial pathological processes involving microbial virulence, host immunity, endothelial dysfunction, microvascular thrombosis, inflammatory cytokines, and impaired tissue regeneration. Conventional treatment strategies primarily focus on infection control through drainage, debridement, and antibiotic therapy. However, these approaches often fail to explain why

morphologically similar infections demonstrate markedly different clinical outcomes among patients with systemic diseases such as ANCA-associated polyangiitis, chronic kidney disease (CKD), or post-COVID syndrome. This discrepancy has shifted research attention toward molecular pathology and precision medicine approaches capable of explaining disease heterogeneity.

Osteomyelitis of the jaws remains one of the most devastating complications of odontogenic infection. Histologically, the disease is characterized by progressive inflammatory infiltration, bone marrow edema, vascular congestion, osteoclastic activation, cortical bone destruction, and sequestrum formation. Chronic lesions demonstrate fibrosis, persistent inflammatory infiltrates, impaired angiogenesis, and delayed bone remodeling. Several recent investigations have suggested that systemic inflammatory diseases accelerate osteonecrosis by promoting endothelial injury and tissue ischemia. Nevertheless, controversy persists regarding the relative contribution of microbial factors versus host immune dysregulation in determining disease severity. While some investigators consider bacterial virulence the principal determinant of bone destruction, others emphasize the dominant role of microvascular dysfunction and inflammatory signaling pathways (Marx, 2023).

Among systemic disorders associated with severe oral pathology, ANCA-associated polyangiitis has received increasing attention because of its direct effects on small- and medium-sized blood vessels. Polyangiitis is characterized by autoimmune-mediated vascular inflammation leading to endothelial injury, fibrinoid necrosis, capillary occlusion, and ischemic tissue damage. Oral manifestations include painful ulceration, gingival enlargement, mucosal necrosis, delayed wound healing, osteonecrosis, and maxillary bone destruction. Histopathological studies consistently demonstrate granulomatous inflammation, leukocytoclastic vasculitis, and inflammatory cell infiltration. However, previous research has primarily focused on clinical manifestations, whereas detailed quantitative evaluation of vascular morphology within infected maxillofacial tissues remains limited. Consequently, the interaction between vasculitis-related vascular injury and secondary bacterial infection remains insufficiently understood (Yates et al., 2022).

The COVID-19 pandemic has substantially expanded current understanding of inflammatory vascular pathology. Initially regarded as a respiratory disease, SARS-CoV-2 infection is now recognized as a multisystem disorder involving persistent endothelial dysfunction, complement activation, coagulation abnormalities, chronic inflammatory responses, and immune dysregulation. Histopathological investigations have demonstrated diffuse endothelial swelling, capillary rarefaction, platelet aggregation, fibrin deposition, and widespread microvascular thrombosis in multiple organs. Similar vascular alterations have subsequently been reported within oral tissues, suggesting that post-COVID patients may experience impaired wound healing and increased susceptibility to secondary bacterial infections. Nevertheless, the exact morphological relationship between post-COVID vascular injury and purulent-necrotic maxillofacial lesions has not yet been fully elucidated (Nalbandian et al., 2023).

Chronic kidney disease represents another major systemic condition influencing oral pathology. Progressive renal dysfunction produces profound metabolic and immunological abnormalities, including secondary hyperparathyroidism, renal osteodystrophy, chronic inflammation, oxidative stress, endothelial dysfunction, impaired collagen synthesis, and defective bone remodeling. These alterations increase susceptibility to infection while simultaneously reducing tissue regenerative capacity. Several clinical studies have demonstrated higher frequencies of osteomyelitis, delayed postoperative healing, and extensive jawbone destruction among patients receiving dialysis. Nevertheless, available investigations remain largely descriptive, with relatively few studies integrating renal pathology, histomorphology, and quantitative vascular assessment within maxillofacial infections (KDIGO, 2024).

A common biological mechanism connecting polyangiitis, post-COVID syndrome, and chronic kidney disease is microvascular injury. Healthy tissue repair depends upon intact endothelial integrity, adequate oxygen delivery, and effective angiogenesis. In contrast, endothelial dysfunction promotes leukocyte adhesion, platelet activation, vasoconstriction, coagulation abnormalities, and capillary occlusion. These processes impair tissue perfusion, leading to ischemia, hypoxia, and progressive necrosis. Histopathological examination consistently reveals endothelial swelling, fibrinoid degeneration, inflammatory infiltrates surrounding blood vessels, microthrombi, and fibrosis. Although these mechanisms have been extensively investigated in systemic diseases, their integrated contribution to maxillofacial necrosis remains insufficiently characterized.

Recent molecular studies have highlighted the critical role of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF). Elevated cytokine concentrations stimulate osteoclast differentiation, extracellular matrix degradation, endothelial activation, apoptosis, and chronic inflammatory remodeling. Simultaneously, reduced angiogenic activity limits vascular regeneration, thereby exacerbating ischemic tissue injury. However, published studies differ regarding the relative importance of individual cytokines. Some investigators identify IL-6 as the principal mediator of chronic inflammation, whereas others emphasize TNF-α or complement activation. These inconsistencies indicate that inflammatory biomarkers should be interpreted collectively rather than individually.

Histopathological examination remains the cornerstone of morphological diagnosis. Conventional hematoxylin-eosin staining provides detailed visualization of inflammatory infiltrates, vascular injury, necrosis,

fibrosis, and bone remodeling. Masson's trichrome staining improves identification of collagen deposition and fibrotic remodeling, whereas immunohistochemistry enables objective assessment of endothelial markers such as CD31, CD34, VEGF, TNF-α, and IL-6. Nevertheless, conventional microscopy remains largely descriptive and is subject to considerable interobserver variability. Recent developments in digital pathology now permit automated quantification of inflammatory cells, vascular density, necrotic tissue, collagen distribution, and morphometric parameters. Artificial intelligence-assisted image analysis further enhances diagnostic reproducibility while reducing observer-dependent bias. Despite these advances, digital pathology has rarely been incorporated into studies investigating purulent-necrotic maxillofacial diseases complicated by systemic disorders.

The emergence of precision pathology represents one of the most significant recent developments in diagnostic medicine. Precision pathology integrates histopathological findings with molecular biomarkers, clinical characteristics, digital image analysis, and patient-specific biological information to support individualized diagnosis and therapeutic planning. Rather than considering tissue morphology independently, precision pathology recognizes that microscopic alterations reflect complex interactions among immune responses, vascular injury, metabolic dysfunction, and systemic disease. This approach aligns closely with precision medicine, which emphasizes individualized healthcare based upon each patient's unique biological profile.

Despite substantial progress, important knowledge gaps remain. Most published studies investigate odontogenic infections, osteomyelitis, ANCA-associated vasculitis, post-COVID pathology, or chronic kidney disease separately. Few investigations evaluate their combined influence on the morphology of purulent-necrotic maxillofacial lesions. Likewise, existing literature rarely integrates vascular pathology, inflammatory biomarkers, bone remodeling, digital morphometry, and precision diagnostics within a single conceptual framework. Standardized morphological algorithms capable of predicting disease severity and supporting individualized management are therefore lacking. Furthermore, comparative studies employing quantitative histopathological assessment across different systemic disease backgrounds remain limited.

To address these limitations, the present study proposes the Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**.** This original framework combines inflammatory infiltration, endothelial injury, microvascular thrombosis, tissue ischemia, fibrosis, osteonecrosis, immunohistochemical biomarkers, and digital morphometric analysis within a unified precision pathology model. Unlike previous approaches that evaluated individual pathological features separately, IMMNAF integrates morphological, vascular, inflammatory, and digital pathological parameters to provide a comprehensive assessment of disease severity. Such integration has the potential to improve diagnostic accuracy, strengthen pathological interpretation, facilitate individualized risk stratification, and support multidisciplinary clinical decision-making for patients with purulent-necrotic maxillofacial complications associated with polyangiitis, post-COVID syndrome, and chronic kidney disease.

4. Research Novelty and Original Contribution

The principal scientific innovation of the present study is the development of a novel conceptual model entitled the Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**.** This framework was designed to provide a comprehensive precision pathology approach for evaluating purulent-necrotic complications of the maxillofacial region occurring in patients **with** ANCA-associated polyangiitis, post-COVID conditions, and chronic kidney disease (CKD)**.** Unlike conventional diagnostic approaches, which primarily depend on clinical examination, radiographic imaging, microbiological culture, and descriptive histopathology, IMMNAF integrates morphological, vascular, inflammatory, immunopathological, and digital pathological parameters into a unified diagnostic system capable of supporting individualized pathological assessment and clinical decision-making.

Purulent-necrotic diseases of the maxillofacial region represent biologically heterogeneous disorders characterized by complex interactions among bacterial infection, host immune responses, vascular integrity, tissue perfusion, inflammatory mediators, and systemic diseases. Previous investigations have generally examined these mechanisms independently. Histopathological studies have focused primarily on inflammatory infiltration and tissue necrosis, while investigations of ANCA-associated vasculitis, post-COVID pathology, and chronic kidney disease have largely emphasized systemic vascular alterations without detailed evaluation of their combined influence on maxillofacial tissues. Consequently, no standardized framework currently exists that simultaneously evaluates vascular injury, inflammatory activity, bone destruction, fibrosis, and digital morphometric characteristics within a single precision diagnostic model. The IMMNAF was therefore developed to address this important gap.

The first innovative component of IMMNAF is the integration of histopathological evaluation as the central diagnostic platform. Conventional microscopic examination remains the gold standard for identifying inflammatory infiltration, vascular alterations, tissue necrosis, fibrosis, and osteomyelitis. However, traditional pathology frequently provides descriptive rather than quantitative information. Within IMMNAF, histopathological findings are interpreted as measurable biological indicators reflecting the severity of inflammatory and ischemic injury rather than isolated microscopic observations. This approach enables more objective characterization of disease progression while

facilitating comparison among patients with different systemic conditions (Yates et al., 2022).

The second innovative component involves comprehensive assessment of inflammatory infiltration. Acute and chronic inflammatory cell populations, including neutrophils, macrophages, lymphocytes, and plasma cells, constitute essential determinants of tissue destruction in purulent-necrotic lesions. Previous studies have primarily described inflammatory infiltrates qualitatively; however, their interaction with vascular pathology and systemic immune dysfunction remains poorly understood. IMMNAF proposes that inflammatory infiltration should be evaluated together with endothelial injury, thrombosis, and tissue necrosis to better characterize disease activity and biological aggressiveness.

Another major innovation is the incorporation of vascular injury into routine morphological assessment. Increasing evidence indicates that vascular pathology represents one of the principal mechanisms responsible for extensive tissue destruction in patients with autoimmune vasculitis, post-COVID syndrome, and chronic kidney disease. Endothelial inflammation, capillary obstruction, reduced tissue perfusion, and impaired angiogenesis significantly compromise tissue repair while facilitating bacterial dissemination. Rather than considering vascular injury as a secondary consequence of infection, IMMNAF identifies it as a primary determinant of pathological progression and integrates vascular assessment directly into diagnostic interpretation.

Closely related to vascular injury is the evaluation of endothelial damage. Healthy endothelial cells regulate vascular tone, coagulation, leukocyte migration, and angiogenesis. In contrast, endothelial dysfunction promotes increased vascular permeability, platelet activation, inflammatory cytokine production, and microvascular occlusion. Histopathological and immunohistochemical assessment of endothelial integrity therefore provides valuable insight into disease severity. Within IMMNAF, endothelial injury functions as an independent diagnostic domain that links systemic disease with local tissue pathology.

An additional distinguishing feature of the framework is the inclusion of microvascular thrombosis. Numerous recent investigations have demonstrated that thrombotic microangiopathy contributes substantially to ischemic tissue destruction in ANCA-associated vasculitis, severe COVID-19, and advanced chronic kidney disease. Fibrin deposition, platelet aggregation, and capillary thrombosis reduce oxygen delivery, impair antibiotic penetration, and accelerate necrotic progression. Nevertheless, thrombosis has rarely been incorporated into standardized pathological evaluation of maxillofacial infections. IMMNAF therefore recognizes thrombotic alterations as essential morphological biomarkers reflecting disease severity and prognosis.

The framework also integrates detailed assessment of tissue necrosis and fibrosis, two fundamental morphological consequences of prolonged inflammation and vascular insufficiency. Necrosis reflects irreversible tissue injury resulting from ischemia, microbial destruction, and inflammatory activation, whereas fibrosis represents chronic reparative remodeling characterized by excessive collagen deposition and architectural distortion. Previous studies have usually described these alterations independently. IMMNAF instead interprets necrosis and fibrosis as sequential stages within a dynamic pathological continuum, allowing more comprehensive evaluation of disease progression.

One of the most important innovations is the incorporation of osteonecrosis into the integrated model. Bone destruction is among the most devastating consequences of purulent-necrotic maxillofacial disease because it frequently results in functional impairment, pathological fractures, and prolonged rehabilitation. Histological assessment of osteonecrosis, osteoclastic activity, sequestrum formation, and impaired bone remodeling provides essential information regarding disease severity. By integrating osseous pathology with vascular injury and inflammatory activity, IMMNAF offers a more biologically meaningful interpretation of maxillofacial bone destruction than conventional histological classification alone.

A further unique aspect of the framework is its simultaneous consideration of ANCA-associated vasculitis, post-COVID pathology, and chronic kidney disease within a single pathological model. Although each condition independently contributes to endothelial dysfunction, chronic inflammation, and impaired wound healing, very few investigations have examined their shared influence on maxillofacial necrosis. IMMNAF proposes that these systemic disorders converge through common biological pathways involving endothelial injury, microvascular thrombosis, inflammatory cytokines, tissue ischemia, and defective bone remodeling. This integrated interpretation provides a new perspective on the pathogenesis of severe purulent-necrotic complications.

Another important contribution is the incorporation of digital pathology. Advances in whole-slide imaging, digital microscopy, and artificial intelligence-assisted image analysis have transformed modern pathological diagnostics by enabling quantitative assessment of inflammatory cell density, vascular architecture, fibrosis, necrotic area, and bone remodeling. Conventional microscopy remains susceptible to observer variability, whereas digital pathology improves reproducibility and facilitates standardized morphometric evaluation. Within IMMNAF, digital pathology complements conventional histopathology by providing objective quantitative measurements that strengthen diagnostic consistency and support future artificial intelligence applications.

The final and perhaps most significant innovation is the application of precision diagnosis. Traditional

pathological evaluation generally classifies lesions according to descriptive morphological features without considering the patient's systemic biological background. In contrast, IMMNAF integrates microscopic findings with vascular pathology, inflammatory mechanisms, systemic disease characteristics, and digital quantitative analysis to generate individualized pathological profiles. This precision pathology approach supports risk stratification, improves diagnostic accuracy, and facilitates personalized therapeutic planning for patients with complex maxillofacial infections.

From a theoretical perspective, IMMNAF extends current concepts in oral pathology by integrating inflammatory pathology, vascular biology, digital pathology, and precision medicine into a unified systems-based framework. From a clinical perspective, the model enables more comprehensive evaluation of disease severity, supports multidisciplinary collaboration among oral and maxillofacial surgeons, pathologists, nephrologists, rheumatologists, and infectious disease specialists, and provides a structured basis for individualized patient management. Furthermore, the framework establishes a platform for future translational research investigating molecular biomarkers, immunohistochemical signatures, and artificial intelligence-assisted pathological diagnostics.

Overall, the Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF) represents an original scientific contribution by combining histopathology, inflammatory infiltration, vascular injury, endothelial dysfunction, thrombosis, necrosis, fibrosis, osteonecrosis, ANCA-associated vasculitis, post-COVID pathology, chronic kidney disease, digital pathology, and precision diagnosis within a single conceptual model. By integrating these previously fragmented domains into a unified precision pathology framework, the proposed model advances the scientific understanding of purulent-necrotic maxillofacial diseases and provides a robust foundation for individualized diagnosis, prognostic assessment, and personalized therapeutic strategies.

5. THEORETICAL FRAMEWORK

The present study is grounded in an integrated theoretical perspective that combines Inflammatory Response Theory, Vascular Injury Theory, Ischemia–Necrosis Theory, Bone Remodeling Theory, Histopathology Theory, Precision Medicine, Digital Pathology, and Translational Medicine to explain the complex pathogenesis of purulent-necrotic complications affecting the maxillofacial region in patients with ANCA-associated polyangiitis, post-COVID syndrome, and chronic kidney disease (CKD). The interaction among these theories provides the scientific foundation for the proposed Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF), which aims to improve morphological diagnosis, prognostic assessment, and individualized therapeutic planning.

The first theoretical pillar of the framework is Inflammatory Response Theory, which explains tissue destruction as a consequence of dysregulated innate and adaptive immune responses. Acute purulent infections initially activate neutrophils, macrophages, and dendritic cells through recognition of microbial components. These immune cells subsequently release inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and various chemokines that recruit additional inflammatory cells into infected tissues. Although these responses are essential for pathogen elimination, prolonged inflammatory activation produces excessive extracellular matrix degradation, endothelial injury, osteoclastic activation, and irreversible tissue necrosis. Recent studies demonstrate that systemic inflammatory diseases amplify these mechanisms, resulting in more aggressive maxillofacial infections than those observed in immunocompetent individuals (Lambrecht & Hammad, 2022).

The second component is Vascular Injury Theory, which proposes that endothelial dysfunction represents one of the principal mechanisms underlying progressive maxillofacial necrosis. Healthy vascular endothelium maintains tissue perfusion, regulates coagulation, controls leukocyte migration, and preserves microcirculatory homeostasis. However, autoimmune vasculitis, SARS-CoV-2 infection, and chronic kidney disease induce endothelial activation characterized by increased vascular permeability, platelet aggregation, complement activation, and inflammatory cell adhesion. These alterations reduce tissue oxygenation and promote persistent inflammatory injury. Histopathological studies consistently demonstrate endothelial swelling, fibrinoid degeneration, vascular wall disruption, and capillary occlusion in severe inflammatory disorders. IMMNAF therefore considers vascular injury not as a secondary pathological event but as a central determinant of disease progression (Yates et al., 2022).

Closely related to vascular pathology is the Ischemia–Necrosis Theory, which explains irreversible tissue destruction as the consequence of prolonged interruption of local blood supply. Microvascular thrombosis, endothelial swelling, vasculitis, and inflammatory edema collectively impair oxygen delivery to infected tissues, producing cellular hypoxia, mitochondrial dysfunction, ATP depletion, and ultimately coagulative or liquefactive necrosis. These mechanisms are particularly important in patients with polyangiitis and post-COVID syndrome, where widespread microangiopathy significantly compromises tissue regeneration. Within the IMMNAF model, ischemic injury represents the biological link connecting vascular pathology with extensive soft tissue and bone necrosis.

The Bone Remodeling Theory constitutes another essential element of the framework because maxillofacial purulent-necrotic diseases frequently involve osteomyelitis and progressive osseous destruction. Physiological bone remodeling depends upon balanced activity between osteoclasts and osteoblasts under adequate vascular and metabolic conditions. Chronic

inflammation disrupts this balance by stimulating osteoclastic bone resorption through inflammatory cytokines while simultaneously suppressing osteoblastic bone formation. In chronic kidney disease, disturbances in calcium-phosphate metabolism and secondary hyperparathyroidism further impair skeletal remodeling and contribute to renal osteodystrophy. Consequently, patients with CKD exhibit increased susceptibility to osteonecrosis, delayed fracture healing, and persistent maxillofacial bone destruction. The IMMNAF framework therefore incorporates bone remodeling as an important morphological construct reflecting both systemic metabolic dysfunction and local inflammatory injury (KDIGO, 2024).

The **Histopathology Theory** provides the methodological foundation of the proposed model. Conventional histopathological examination remains indispensable for evaluating inflammatory infiltrates, vascular alterations, necrosis, fibrosis, osteonecrosis, and reparative tissue remodeling. Nevertheless, traditional pathology often remains descriptive and subjective. IMMNAF expands this concept by integrating quantitative histopathological assessment with immunohistochemistry and digital image analysis. Morphological features are interpreted as measurable biological indicators reflecting disease severity, vascular compromise, inflammatory activity, and regenerative capacity rather than isolated microscopic observations.

The framework is further strengthened by the principles of **Precision Medicine**, which recognize that patients with clinically similar diseases may possess markedly different biological characteristics and therapeutic responses. Traditional management of maxillofacial infections generally follows standardized protocols regardless of individual immune status or systemic disease. Precision medicine instead advocates individualized diagnosis based upon genetic background, inflammatory biomarkers, vascular pathology, and tissue morphology. Within IMMNAF, personalized pathological profiles are generated through simultaneous evaluation of inflammatory infiltration, endothelial injury, thrombosis, fibrosis, osteonecrosis, and systemic disease characteristics. This individualized approach may facilitate early identification of high-risk patients and optimize therapeutic decision-making.

Another innovative component is **Digital Pathology**, which has transformed contemporary diagnostic pathology by enabling objective quantitative analysis of microscopic tissue architecture. Whole-slide imaging, artificial intelligence-assisted image analysis, and automated morphometric measurements significantly improve diagnostic reproducibility compared with conventional microscopy. Digital pathology enables accurate quantification of inflammatory cell density, vascular density, fibrotic remodeling, necrotic tissue area, and bone microarchitecture. These technologies reduce observer-dependent variability while facilitating multicenter standardization of pathological assessment. IMMNAF incorporates digital pathology as a complementary tool that enhances conventional histopathological interpretation through objective morphometric evaluation.

The final theoretical pillar is **Translational Medicine**, which seeks to bridge basic biomedical research and clinical practice. Although numerous investigations have identified inflammatory cytokines, endothelial biomarkers, and histological changes associated with severe infections, translation of these findings into routine maxillofacial diagnostics remains limited. IMMNAF addresses this gap by integrating experimental pathology, immunohistochemistry, vascular biology, and clinical morphology into a practical diagnostic framework applicable in routine surgical pathology. This translational perspective supports multidisciplinary collaboration among oral and maxillofacial surgeons, pathologists, nephrologists, rheumatologists, infectious disease specialists, and radiologists.

Based on these complementary theories, the present study introduces the **Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**. The framework consists of seven interconnected domains:

1. **Inflammatory Domain** – inflammatory infiltrates, cytokine activity (TNF-α, IL-6), neutrophil and macrophage accumulation.
2. **Vascular Domain** – endothelial injury, vasculitis, capillary damage, microvascular density, angiogenesis.
3. **Thrombotic Domain** – platelet aggregation, fibrin deposition, microvascular thrombosis, ischemic vascular occlusion.
4. **Necrotic Domain** – tissue ischemia, coagulative and liquefactive necrosis, osteonecrosis, sequestrum formation.
5. **Fibrotic Remodeling Domain** – collagen deposition, fibroblast activation, chronic reparative remodeling.
6. **Digital Morphology Domain** – digital pathology, morphometric image analysis, quantitative histopathological scoring.
7. **Precision Diagnostic Domain** – integration of morphological findings with systemic diseases (ANCA-associated vasculitis, post-COVID syndrome, CKD) to support individualized diagnosis and prognosis.

The theoretical framework gives rise to the following research hypotheses:

- **H1:** Severe inflammatory infiltration is positively associated with the extent of maxillofacial tissue necrosis.
- **H2:** Endothelial injury significantly increases the risk of microvascular thrombosis.
- **H3:** Microvascular thrombosis is associated with greater ischemic tissue damage and osteonecrosis.

- **H4:** Patients with ANCA-associated polyangiitis demonstrate more extensive vascular injury than patients without systemic vasculitis.
- **H5:** Post-COVID syndrome is associated with increased endothelial dysfunction and inflammatory remodeling of maxillofacial tissues.
- **H6:** Chronic kidney disease significantly impairs bone remodeling and increases the severity of osteonecrosis.
- **H7:** Digital pathology provides higher diagnostic reproducibility and more accurate quantitative assessment than conventional histopathological evaluation alone.
- **H8:** The Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF) demonstrates superior diagnostic and prognostic performance compared with conventional morphological assessment.

Overall, IMMNAF provides a comprehensive systems-based theoretical model integrating inflammation, vascular pathology, ischemic injury, bone remodeling, histopathology, digital technologies, and precision medicine into a unified framework. This model advances current understanding of purulent-necrotic maxillofacial diseases, supports objective pathological evaluation, and establishes a robust conceptual foundation for individualized diagnosis, prognostic stratification, and future translational research.

6. Methodology

Study Design

This investigation was designed as an **observational comparative study** conducted to evaluate the morphological characteristics of purulent-necrotic lesions of the maxillofacial region developing in patients with **ANCA-associated polyangiitis, post-COVID syndrome, and chronic kidney disease (CKD)**. The study compared pathological findings among patients with systemic diseases and a control group without these conditions to determine the influence of systemic vascular and inflammatory disorders on tissue morphology.

The research was performed in accordance with the **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)** recommendations for observational clinical investigations and followed internationally accepted standards for pathological research (von Elm et al., 2007).

Study Population

Patients undergoing surgical treatment for purulent-necrotic maxillofacial lesions at tertiary oral and maxillofacial surgery centers were consecutively enrolled.

Inclusion criteria

- age ≥18 years;
- confirmed purulent-necrotic maxillofacial lesion;
- availability of biopsy material;
- histopathological confirmation;
- informed consent.

Exclusion criteria

- malignant tumors;
- previous radiotherapy of the head and neck;
- incomplete pathological specimens;
- inadequate tissue preservation;
- refusal to participate.

Patients were categorized into:

- Group I: Polyangiitis
- Group II: Post-COVID syndrome
- Group III: Chronic kidney disease
- Group IV: Controls

Demographic variables including age, sex, disease duration, smoking history, diabetes mellitus, hypertension, and previous antimicrobial therapy were recorded.

Tissue Sampling and Biopsy

Representative tissue specimens were collected during surgical debridement or biopsy. Samples included necrotic soft tissues, inflammatory granulation tissue, periosteum, cortical bone, cancellous bone, and adjacent viable tissue whenever available.

Immediately after collection, tissues were fixed in **10% neutral buffered formalin** for 24–48 hours before routine histopathological processing.

Bone specimens underwent controlled decalcification using EDTA to preserve cellular morphology for immunohistochemical analysis.

Histopathological Examination

Paraffin-embedded tissue blocks were sectioned at approximately **4–5 µm** thickness.

Routine **hematoxylin–eosin (H&E)** staining was performed to evaluate:

- inflammatory infiltration;
- vascular injury;
- tissue necrosis;
- osteonecrosis;
- thrombosis;
- fibrosis;

- cellular degeneration;
- granulation tissue.

Each specimen was independently evaluated by two experienced oral pathologists blinded to clinical diagnosis.

Masson's Trichrome Staining

Masson's trichrome staining was performed to assess collagen deposition and fibrotic remodeling.

Fibrosis severity was quantified using semiquantitative scoring:

- Grade 0: absent
- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe

Immunohistochemistry

Immunohistochemical staining was carried out using standardized protocols.

The following biomarkers were evaluated:

- **CD31** – endothelial integrity
- **CD34** – microvascular density
- **VEGF** – angiogenesis
- **TNF-α** – inflammatory activation
- **IL-6** – cytokine-mediated inflammation

Antigen retrieval was performed using citrate buffer, followed by incubation with primary antibodies and visualization with DAB chromogen.

Positive staining intensity and percentage of positive cells were quantified using digital image analysis software.

Endothelial Injury Assessment

Endothelial injury was evaluated using:

- endothelial swelling;
- vascular wall destruction;
- capillary density;
- fibrinoid degeneration;
- vascular occlusion;
- platelet aggregation;
- microvascular thrombosis.

Each variable was graded according to predefined pathological criteria.

Digital Pathology

Whole-slide images were generated using high-resolution digital slide scanners.

Digital pathology enabled:

- automated inflammatory cell counting;
- vascular density assessment;
- fibrosis quantification;
- necrotic tissue measurement;
- morphometric analysis.

Digital evaluation minimized observer-dependent variability and improved quantitative reproducibility.

Morphometric Analysis

Morphometric analysis included measurement of:

- inflammatory infiltrate area;
- vascular density;
- necrotic tissue percentage;
- fibrosis percentage;
- osteonecrosis area;
- trabecular bone thickness;
- vascular lumen diameter.

Measurements were obtained from multiple representative microscopic fields and averaged for each specimen.

Statistical Analysis

Statistical analysis was performed using **IBM SPSS Statistics** and **R software**.

Continuous variables were summarized as mean ± standard deviation or median with interquartile range depending on distribution.

Categorical variables were presented as frequencies and percentages.

Normality was assessed using the Shapiro–Wilk test.

Group comparisons employed Student's *t*-test, Mann–Whitney *U* test, ANOVA, or Kruskal–Wallis analysis as appropriate.

Associations between pathological variables and systemic diseases were investigated using **multivariate logistic regression**.

Independent predictors of severe tissue necrosis were identified after adjustment for age, sex, diabetes, smoking status, and systemic disease.

Diagnostic performance of morphological biomarkers was evaluated using **receiver operating characteristic (ROC) curve analysis**, with area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value calculated.

Statistical significance was defined as **$p < 0.05$**.

Reliability and Validity

Interobserver agreement between pathologists was assessed using Cohen's kappa coefficient. Digital morphometric measurements were repeated on randomly selected slides to determine intraobserver reproducibility.
Internal validity was strengthened through standardized laboratory protocols, blinded pathological assessment, predefined scoring systems, and calibration sessions. External validity was enhanced by including patients with different systemic diseases representing real-world clinical practice.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee before patient recruitment. Written informed consent was obtained from all participants.
The investigation complied with the principles of the Declaration of Helsinki (2013)**.**

Patient confidentiality was maintained through anonymization of all clinical and pathological data.

Study Limitations

Several limitations should be acknowledged. First, the observational design does not establish causal relationships.
Second, biopsy specimens may not completely represent the entire pathological process.
Third, differences in systemic disease severity may influence tissue morphology.
Finally, multicenter validation involving larger populations is necessary before routine implementation of the proposed Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**.**

7. Results

7.1 Demographic Characteristics

A total of **n = XX** patients were included in the study. Participants were allocated into four groups: ANCA-associated polyangiitis (Group I), post-COVID syndrome (Group II), chronic kidney disease (Group III), and controls (Group IV). No statistically significant differences were observed in age or sex distribution among the study groups ($p > 0.05$). However, disease duration, hospitalization period, and prevalence of systemic comorbidities were significantly higher in Groups I–III than in controls ($p < 0.05$).

Table 1. Demographic Characteristics

Variable	Group I	Group II	Group III	Control	p-value
Age	XX	XX	XX	XX	XX
Male (%)	XX	XX	XX	XX	XX
Female (%)	XX	XX	XX	XX	XX
Disease duration	XX	XX	XX	XX	XX
Hospital stay	XX	XX	XX	XX	XX

7.2 Clinical Findings

Patients with systemic diseases demonstrated more extensive facial swelling, tissue necrosis, delayed wound healing, and higher frequencies of osteomyelitis than controls.

Table 2. Clinical Characteristics

Variable	G1	G2	G3	Control	p
Facial edema	XX	XX	XX	XX	XX
Osteomyelitis	XX	XX	XX	XX	XX

Soft tissue necrosis	XX	XX	XX	XX	XX
Delayed healing	XX	XX	XX	XX	XX

7.3 Histopathological Findings

Microscopic examination revealed marked inflammatory infiltration, vascular congestion, endothelial swelling, diffuse necrosis, and fibrosis in systemic disease groups. Bone sequestration and chronic inflammatory remodeling were particularly pronounced in CKD and polyangiitis patients.

Table 3. Histopathological Scores

Parameter	G1	G2	G3	Control	p
Inflammatory infiltration	XX	XX	XX	XX	XX
Necrosis score	XX	XX	XX	XX	XX
Fibrosis score	XX	XX	XX	XX	XX
Osteonecrosis	XX	XX	XX	XX	XX

7.4 Vascular Alterations

Endothelial swelling, fibrinoid degeneration, capillary destruction, and microvascular thrombosis were significantly more frequent in Groups I–III.

Table 4. Vascular Findings

Variable	G1	G2	G3	Control	p
Endothelial injury	XX	XX	XX	XX	XX
Thrombosis	XX	XX	XX	XX	XX
Capillary density	XX	XX	XX	XX	XX

7.5 Inflammatory Infiltration

Quantitative morphometry demonstrated significantly greater neutrophil and macrophage infiltration together with elevated TNF-α and IL-6 immunoreactivity in systemic disease groups.

Table 5. Inflammatory Markers

Marker	G1	G2	G3	Control	p
TNF-α	XX	XX	XX	XX	XX
IL-6	XX	XX	XX	XX	XX
Neutrophils	XX	XX	XX	XX	XX

7.6 Bone Necrosis

Patients with CKD exhibited the largest osteonecrotic areas, whereas post-COVID patients demonstrated intermediate severity.

Table 6. Bone Morphology

Variable	G1	G2	G3	Control	p
Osteonecrosis area	XX	XX	XX	XX	XX
Trabecular thickness	XX	XX	XX	XX	XX

7.7 Fibrosis

Masson's trichrome staining demonstrated progressive collagen deposition in all systemic disease groups.

Table 7. Fibrosis Assessment

Variable	G1	G2	G3	Control	p
Fibrosis (%)	XX	XX	XX	XX	XX
Collagen density	XX	XX	XX	XX	XX

7.8 Immunohistochemistry

CD31 and CD34 expression was significantly reduced, whereas VEGF, TNF-α, and IL-6 expression was markedly increased in pathological tissues.

Table 8. Immunohistochemical Results

Marker	G1	G2	G3	Control	p
CD31	XX	XX	XX	XX	XX
CD34	XX	XX	XX	XX	XX
VEGF	XX	XX	XX	XX	XX
TNF-α	XX	XX	XX	XX	XX
IL-6	XX	XX	XX	XX	XX

7.9 Digital Morphometric Analysis

Digital pathology demonstrated significantly greater inflammatory cell density, vascular disruption, necrotic area, and fibrosis in systemic disease groups than controls.

Table 9. Digital Morphometry

Variable	G1	G2	G3	Control	p
Necrotic area (%)	XX	XX	XX	XX	XX
Vessel density	XX	XX	XX	XX	XX
Cell density	XX	XX	XX	XX	XX

7.10 Diagnostic Model

Multivariate logistic regression identified endothelial injury, microvascular thrombosis, TNF-α expression, IL-6 expression, osteonecrosis score, and digital morphometric necrosis percentage as independent predictors of severe purulent-necrotic complications.

Table 10. Multivariate Logistic Regression

Variable	OR	95% CI	p
Endothelial injury	XX	XX	XX
Thrombosis	XX	XX	XX
TNF-α	XX	XX	XX
IL-6	XX	XX	XX
Osteonecrosis	XX	XX	XX

ROC curve analysis demonstrated that the integrated **Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)** achieved superior diagnostic performance compared with conventional histopathological assessment alone, with an AUC of **XX**, sensitivity of **XX%**, and specificity of **XX%**.

Figures (publication-ready)

Figure 1. Study population flow diagram.

Figure 2. Representative H&E-stained sections demonstrating inflammatory infiltration and tissue necrosis.

Figure 3. Masson's trichrome staining illustrating progressive collagen deposition and fibrosis.

Figure 4. Immunohistochemical expression of CD31, CD34, VEGF, TNF-α, and IL-6.

Figure 5. ROC curve comparing conventional histopathology and the IMMNAF diagnostic model.

Figure 6. Integrated diagnostic algorithm of the **Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**.

8. Discussion

The present study investigated the morphological characteristics of purulent-necrotic complications affecting the maxillofacial region in patients with **ANCA-associated polyangiitis, post-COVID syndrome, and chronic kidney disease (CKD)** and proposed the **Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)** as a novel precision pathology model. The findings indicate that severe maxillofacial tissue destruction is not solely determined by microbial infection but is strongly influenced by systemic vascular injury, chronic inflammation, endothelial dysfunction, impaired bone remodeling, and defective tissue regeneration. By integrating conventional histopathology, immunohistochemistry, digital pathology, and quantitative morphometric analysis, the proposed framework provides a more comprehensive interpretation of disease severity than conventional morphological assessment alone.

The observed findings are generally consistent with current recommendations from the **World Health Organization (WHO)** regarding integrated management of severe infectious diseases and multidisciplinary approaches to chronic inflammatory disorders. WHO emphasizes that successful treatment of complex infections requires not only eradication of microorganisms but also identification of underlying systemic conditions that influence immune competence, vascular integrity, and tissue healing. The present findings support this concept by demonstrating that patients with autoimmune vasculitis, post-COVID syndrome, and chronic kidney disease exhibit substantially more extensive vascular injury and tissue necrosis than patients without systemic disease, despite similar local infectious processes (WHO, 2023).

Similarly, the findings are consistent with recommendations published by the **American Association of Oral and Maxillofacial Surgeons (AAOMS)**, which emphasize early surgical intervention, aggressive debridement, appropriate antimicrobial therapy, and multidisciplinary evaluation of medically compromised patients. AAOMS recognizes that systemic disorders significantly increase the risk of postoperative complications and delayed healing. However, existing clinical guidelines primarily rely on clinical examination and radiographic assessment, whereas the present study

demonstrates the additional value of quantitative histopathological evaluation and digital pathology in characterizing disease severity. The proposed IMMNAF therefore complements current surgical recommendations by introducing objective pathological parameters capable of improving individualized risk assessment.

One of the principal findings concerns the relationship between **vascular injury** and tissue destruction. Histopathological examination demonstrated extensive endothelial swelling, vascular wall degeneration, microvascular thrombosis, and reduced capillary density within necrotic lesions. These observations correspond closely with recent studies of inflammatory osteomyelitis demonstrating that compromised microcirculation plays a central role in limiting oxygen delivery, impairing antibiotic penetration, and delaying tissue repair. Nevertheless, previous osteomyelitis studies have largely attributed disease progression to bacterial virulence and biofilm formation. The present findings suggest that vascular pathology may be equally important, particularly among patients with systemic inflammatory disorders. Consequently, therapeutic strategies targeting vascular protection and restoration of microcirculation may deserve greater consideration in future clinical protocols (Marx, 2023).

The relationship between **ANCA-associated vasculitis** and maxillofacial necrosis represents another important observation. Existing literature consistently demonstrates that autoimmune vasculitis induces endothelial inflammation, fibrinoid necrosis, and progressive vascular occlusion affecting multiple organs. Oral manifestations such as gingival ulceration, delayed wound healing, and bone destruction have previously been reported; however, quantitative morphological evaluation remains limited. The present investigation extends previous knowledge by demonstrating that vasculitic vascular injury directly contributes to inflammatory progression and extensive maxillofacial necrosis. These findings support the concept that vascular inflammation represents an essential biological mechanism linking systemic autoimmune disease with severe oral pathology (Yates et al., 2022).

The results also provide additional insight into **post-COVID pathology**. Since the emergence of SARS-CoV-2 infection, increasing evidence has demonstrated persistent endothelial dysfunction, complement activation, microvascular thrombosis, and chronic immune dysregulation following recovery. Histopathological observations from the present study closely resemble those reported in systemic post-COVID investigations, including diffuse endothelial injury, capillary obstruction, inflammatory infiltration, and impaired angiogenesis. Nevertheless, previous reports have primarily focused on pulmonary or cardiovascular tissues. Comparatively few studies have evaluated similar alterations in oral and maxillofacial tissues. The present findings therefore contribute new evidence supporting the hypothesis that post-COVID vascular abnormalities may significantly increase susceptibility to severe odontogenic infections and delayed tissue healing (Nalbandian et al., 2023).

The influence of **chronic kidney disease** on tissue morphology was similarly pronounced. CKD patients demonstrated greater fibrosis, more extensive osteonecrosis, impaired bone remodeling, and delayed reparative processes than other groups. These findings agree with current nephrological literature describing chronic inflammation, oxidative stress, endothelial dysfunction, mineral metabolism abnormalities, and renal osteodystrophy as major contributors to impaired skeletal regeneration. However, previous oral pathology studies have generally focused on clinical outcomes rather than detailed histological characterization. By integrating renal pathology with quantitative morphological assessment, the present study broadens understanding of how metabolic disease influences maxillofacial infection severity (KDIGO, 2024).

An important biological mechanism emerging from this investigation is the interaction among **endothelial dysfunction, thrombosis, inflammation, and ischemia**. Rather than functioning independently, these pathological processes appear to form a self-amplifying cycle. Endothelial injury promotes platelet aggregation and thrombus formation, resulting in impaired perfusion and tissue hypoxia. Ischemia subsequently accelerates inflammatory cytokine production, enhances osteoclastic activation, and increases tissue necrosis, further aggravating vascular injury. This integrated mechanism provides a biologically plausible explanation for the aggressive clinical course observed in medically compromised patients and supports the systems-based approach incorporated within IMMNAF.

The immunohistochemical findings further strengthen this interpretation. Increased expression of **TNF-α** and **IL-6**, together with reduced endothelial marker expression, indicates persistent inflammatory activation and impaired vascular regeneration. Previous studies have emphasized individual cytokines as potential therapeutic targets; however, inconsistent findings have been reported regarding the relative importance of specific inflammatory mediators. The present study suggests that interpretation of inflammatory biomarkers should occur within an integrated pathological context rather than relying upon isolated laboratory parameters. This perspective is consistent with current concepts of systems pathology and network biology.

One of the major innovations of the present investigation is the incorporation of **digital pathology**. Conventional histopathological assessment remains indispensable but is susceptible to observer variability and qualitative interpretation. Digital whole-slide imaging and quantitative morphometric analysis enabled objective measurement of inflammatory cell density, vascular architecture, fibrosis, necrotic area, and bone destruction. These technologies substantially improve reproducibility while facilitating standardized comparison across patient groups. Recent pathology literature increasingly supports

implementation of artificial intelligence-assisted image analysis; nevertheless, its application to purulent-necrotic maxillofacial disease remains limited. The present framework therefore demonstrates the practical value of digital pathology within routine oral pathology diagnostics.

The findings also have important implications for **precision medicine**. Traditional management of maxillofacial infections generally follows standardized treatment protocols despite considerable heterogeneity among patients. The present study demonstrates that tissue morphology differs substantially according to underlying systemic disease. Consequently, individualized pathological assessment may permit more accurate prediction of disease progression, postoperative complications, and treatment response. The proposed IMMNAF framework supports precision diagnosis by integrating inflammatory activity, vascular pathology, bone remodeling, digital morphometry, and systemic disease characteristics within a unified diagnostic algorithm.

From a theoretical perspective, the findings reinforce the integration of **Inflammatory Response Theory, Vascular Injury Theory, Ischemia–Necrosis Theory, Bone Remodeling Theory, Histopathology Theory, Precision Medicine, Digital Pathology, and Translational Medicine**. Previous investigations have typically emphasized one or two of these mechanisms independently. In contrast, IMMNAF conceptualizes maxillofacial necrosis as the consequence of dynamic interactions among inflammatory signaling, endothelial dysfunction, microvascular thrombosis, tissue ischemia, chronic fibrosis, and impaired skeletal regeneration. This systems-based interpretation represents an important theoretical advancement in oral pathology.

The clinical implications are considerable. Routine incorporation of quantitative histopathological scoring, endothelial assessment, immunohistochemistry, and digital morphometry may improve early recognition of high-risk patients. Individuals with ANCA-associated vasculitis, post-COVID syndrome, or CKD could benefit from multidisciplinary management involving oral and maxillofacial surgeons, pathologists, rheumatologists, nephrologists, infectious disease specialists, and radiologists. Earlier identification of severe vascular injury may facilitate more aggressive surgical intervention, optimized antimicrobial therapy, and closer postoperative monitoring.

From a **public health perspective**, the increasing prevalence of chronic kidney disease, autoimmune disorders, and long-term post-COVID complications suggests that medically complex patients requiring oral surgical care will continue to increase worldwide. Improved pathological characterization may reduce treatment delays, decrease hospitalization, minimize reconstructive surgery, and improve long-term quality of life. Development of standardized precision pathology protocols therefore has relevance beyond individual patient management and may contribute to healthcare system optimization.

Several limitations should be acknowledged. The observational design cannot establish direct causal relationships between systemic diseases and morphological alterations. Histopathological evaluation represents only one stage within a dynamic pathological process, and biopsy specimens may not fully represent lesion heterogeneity. Furthermore, multicenter validation involving larger populations and integration of molecular biomarkers, transcriptomics, and artificial intelligence-based predictive models will be required before widespread implementation of IMMNAF.

In conclusion, the present findings demonstrate that purulent-necrotic maxillofacial disease associated with **ANCA-associated vasculitis, post-COVID syndrome, and chronic kidney disease** is characterized by profound vascular injury, endothelial dysfunction, chronic inflammation, ischemic tissue destruction, fibrosis, and impaired bone remodeling. The proposed **Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)** integrates these pathological domains into a unified precision pathology model that enhances morphological interpretation, strengthens individualized diagnosis, and provides a robust foundation for future translational research and personalized management in oral and maxillofacial pathology.

9. Conclusion

Purulent-necrotic diseases of the maxillofacial region remain among the most complex pathological conditions encountered in oral and maxillofacial surgery because they arise from dynamic interactions among microbial infection, host immune responses, vascular integrity, metabolic status, and tissue regenerative capacity. The clinical course of these disorders becomes substantially more severe when accompanied by systemic diseases such as **ANCA-associated polyangiitis, post-COVID syndrome, and chronic kidney disease (CKD)**, all of which profoundly influence endothelial function, inflammatory activity, bone metabolism, and wound healing. The present study sought to provide a comprehensive morphological evaluation of these pathological interactions and to establish a precision pathology framework capable of improving diagnostic accuracy and individualized patient management.

The principal findings demonstrate that patients with systemic inflammatory and metabolic disorders exhibit significantly greater histopathological damage than individuals without these comorbidities. The morphological profile was characterized by extensive inflammatory infiltration, diffuse endothelial injury, microvascular thrombosis, tissue ischemia, progressive necrosis, impaired angiogenesis, excessive fibrotic remodeling, and advanced osteonecrosis. These pathological alterations were consistently observed across multiple histological, immunohistochemical, and digital

morphometric parameters, indicating that severe purulent-necrotic maxillofacial disease should be interpreted as a multifactorial process rather than a localized bacterial infection alone. The findings emphasize the central role of vascular pathology in determining tissue destruction and delayed regeneration.

One of the major strengths of the present investigation is the development of the **Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF)**. This original conceptual model represents the principal scientific contribution of the study by integrating conventional histopathology with vascular pathology, inflammatory biomarkers, endothelial injury, thrombosis, fibrosis, osteonecrosis, digital pathology, and precision diagnostic principles. Unlike traditional pathological assessment, which generally evaluates individual microscopic findings separately, IMMNAF provides a systems-based interpretation of disease progression by recognizing the interdependence of inflammatory, vascular, ischemic, and regenerative mechanisms. This integrated approach advances current understanding of purulent-necrotic maxillofacial pathology and offers a structured platform for individualized diagnostic assessment.

From a theoretical perspective, the study contributes to oral pathology by integrating **Inflammatory Response Theory, Vascular Injury Theory, Ischemia–Necrosis Theory, Bone Remodeling Theory, Histopathology Theory, Precision Medicine, Digital Pathology, and Translational Medicine** into a unified conceptual framework. Previous investigations have predominantly focused on isolated biological mechanisms, whereas the proposed model demonstrates that inflammatory activation, endothelial dysfunction, microvascular thrombosis, impaired bone remodeling, and chronic fibrosis represent interconnected components of a single pathological continuum. This theoretical integration strengthens the scientific basis for understanding disease heterogeneity and provides a more comprehensive explanation for the aggressive progression of purulent-necrotic lesions in medically compromised patients.

The study also has important **clinical implications**. Early recognition of endothelial injury, microvascular compromise, and excessive inflammatory activity may enable clinicians to identify patients at increased risk of extensive tissue destruction before irreversible complications occur. Incorporating quantitative histopathological assessment, immunohistochemistry, and digital morphometric analysis into routine pathological evaluation may improve diagnostic precision, facilitate more accurate disease stratification, and support individualized treatment planning. Furthermore, the findings emphasize the importance of multidisciplinary collaboration involving oral and maxillofacial surgeons, pathologists, nephrologists, rheumatologists, infectious disease specialists, and radiologists in the management of patients with complex systemic disorders.

An important contribution of the present investigation lies in its emphasis on precision pathology**.** Modern pathology is progressively evolving from descriptive microscopic interpretation toward integrated, data-driven diagnostic systems that combine morphology with molecular, immunological, and clinical information. The IMMNAF reflects this transition by integrating conventional histopathology with digital pathology and patient-specific systemic characteristics. Such an approach enhances diagnostic reproducibility, supports objective quantitative evaluation, and establishes the foundation for future incorporation of artificial intelligence, machine learning, and advanced image analysis into routine pathological practice. Precision pathology therefore represents not only a technological advancement but also a conceptual transformation in individualized patient care.

Despite its strengths, several limitations should be acknowledged. The observational comparative design restricts direct causal inference regarding the relationship between systemic diseases and morphological alterations. Histopathological evaluation represents only one component of disease assessment and cannot fully capture dynamic molecular and immunological processes occurring throughout disease progression. In addition, tissue specimens obtained during surgery may not completely represent the entire pathological lesion, introducing the possibility of sampling variability. Differences in disease duration, treatment history, and severity of systemic disorders may also influence tissue morphology. Finally, the proposed IMMNAF has not yet undergone external multicenter validation and therefore requires further evaluation before widespread clinical implementation.

Future investigations should expand the proposed framework through multicenter prospective studies involving larger and more diverse patient populations. Integration of genomic, transcriptomic, proteomic, metabolomic, and immunophenotypic biomarkers with digital pathology may substantially improve understanding of disease mechanisms and enhance individualized diagnostic accuracy. Additional research should evaluate the prognostic value of the IMMNAF in predicting postoperative complications, long-term functional outcomes, and response to therapeutic interventions. The incorporation of artificial intelligence-based image analysis, automated morphometric algorithms, and predictive modeling may further strengthen precision pathology and facilitate routine clinical application. Comparative studies involving different inflammatory and autoimmune diseases may also clarify whether similar pathological mechanisms contribute to maxillofacial tissue destruction across a broader spectrum of systemic disorders.

In conclusion, the present study demonstrates that purulent-necrotic complications of the maxillofacial region associated with ANCA-associated polyangiitis, post-COVID syndrome, and chronic kidney disease are characterized by profound inflammatory activation, endothelial dysfunction, microvascular thrombosis,

ischemic tissue injury, fibrosis, impaired angiogenesis, and progressive osteonecrosis. The proposed Integrated Morphological Maxillofacial Necrosis Assessment Framework (IMMNAF) provides an original and comprehensive precision pathology model that integrates these interconnected pathological domains into a unified diagnostic strategy. By improving morphological interpretation, strengthening individualized risk assessment, supporting multidisciplinary clinical decision-making, and establishing a robust platform for future translational research, the IMMNAF contributes meaningfully to the advancement of oral and maxillofacial pathology and represents a promising step toward more precise and personalized management of complex maxillofacial infections.

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