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Evaluation of New Biomarkers in The Diagnosis of Herpes Zoster Infections

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Abstract

Background: Herpes Zoster is a neurotropic viral disease with notable inflammatory and neurological complications. And early diagnosis and treatment is still the way to go. **Aims**: This study was designed to investigate the diagnostic value of new biomarkers such as procalcitonin, neuron-specific enolase (NSE), and miR-155 among Herpes Zoster infection patients. **Methods**: The study was a case–control cross-sectional study involving 44 patients diagnosed with Herpes Zoster and 66 healthy controls. Serum levels of procalcitonin and NSE were detected by ELISA, and expression levels of miR-155 was analyzed using qRT-PCR. Statistical analysis was performed to assess differences between groups, correlations and diagnostic performance using ROC curve analysis. **Results**: The study identified significantly higher concentrations of procalcitonin (PC), NSE and miR-155 levels in patients, than controls ($P < 0.01$). All biomarkers performed well to excellent in diagnostic performance, with miR-155 having the highest sensitivity and specificity. In addition, the biomarkers studied displayed several significant positive correlations with each other indicating their biological role in disease pathophysiology. **Conclusion**: Procalcitonin, NSE and miR-155 are all potential diagnostic biomarkers of Herpes Zoster infection. A composite biomarker panel, especially including miR-155, may facilitate early diagnosis and a better understanding of disease mechanisms.

Keywords: Herpes Zoster, Procalcitonin, NSE, miR-155

Introduction

Approximately one in three people will be affected by herpes zoster (HZ), which is caused by reactivation of the varicella-zoster virus (VZV) as VZV lies quiescent in sensory ganglia.1,2 Over the past decades, the global burden of HZ has increased significantly, largely due to an ageing population, increasing incidence of HIV and other immune-mediated diseases and greater use of immunosuppressive therapy. While antiviral medications are available, the clinical spectrum of VZV reactivation varies from a localized dermatomal rash to potentially life-threatening complications (meningoencephalitis, disseminated infection), resulting in significant morbidity and mortality as well as postherpetic neuralgia (PHN). The wide range of disease severity and high incidence of severe neurological complications highlights the critical need for more reliable biomarkers that support early detection, risk stratification in asymptomatic populations and prediction of outcome (Ku et al., 2021).

Traditional diagnosis of HZ involves clinical assessment, with laboratory confirmation using VZV, most often through polymerase chain reaction (PCR) identification of viral DNA in vesicular fluid or tissue specimens. However, all these approaches have serious practical limitations. In the case of specimen collection and PCR analysis, they are considered time-sensitive; accuracy is reduced in crusted lesions or where samples are not handled properly. Although serological testing may provide insight into immune status, its utility for diagnosing acute infection is still limited (Espy et al., 2000). In fact especially in HZ without typical rash (zoster sine herpete) or atypical presentation involving visceral organs to central nervous system symptoms/manifestations clinical diagnosis becomes very challenging either. Such diagnostic hesitancies often lead to delayed initiation of antiviral treatment therapy which is critical as the efficacy of treatment wanes significantly when initiated later than 72 h after rash onset (Wang et al., 2025).

A promising approach that can improve HZ infections diagnostic and prognostic mapping is the discovery of novel circulating biomarkers. Of the candidate biomarkers, procalcitonin (PCT) has become one of the most studied and clinically utilized markers for separating bacterial and viral infections (Simon et al., 2004). Procalcitonin (PCT) is secreted mainly by thyroid C cells but also during systemic inflammation by multiple extrathyroidal tissues, including hepatocytes, monocytes and adipocyte. While the PCT concentrations remain at low levels in uncomplicated viral infections, they rise to significantly higher concentrations than previously mentioned during bacterial infections and more marked inflammatory states (Kim, 2022). Other recent studies confirm that procalcitonin levels correlates with severity of the disease in severe viral infections complicated by bacterial superinfection, as shown for instance by high serum procalcitonin in patients during herpes simplex virus reactivation with concomitant bacterial bloodstream infection (Sogut et al., 2025). For viral meningitis (VZV-associated meningoencephalitis), the discriminatory performance of PCT has varied, indicating a need for complementary biomarkers to improve diagnostic accuracy (Obreja et al. bmjgh2024).

Beta-gamma dimer of glycolytic enzyme enolase, neuron-specific enolase (NSE) is widely studied as a biomarker of neuronal injury for primarily neurological diseases with higher levels at brain-derived neurotrophic factor in neurons and neuroendocrine cells. In particular, elevated serum and cerebrospinal fluid NSE levels have been reported in the setting of traumatic brain injury, hypoxic-ischemic encephalopathy, stroke and a number of neurodegenerative diseases. NSE reflects the extent of neuronal injury due to direct viral cytopathic effects, neuroinflammation and oxidative stress in central nervous system infections [54]. Meningoencephalitis with Varicella Zoster Virus (VZV) is a complication of acute Herpes zoster.This VZV retargeted through neoantigens, the protection against apoptosis, activation of glia and blood-brain barrier dysfunction occurs through networks with multiple cascading neuroinflammatory states. Recent metabolomic profiling of CSF in VZV CNS reactivation has detected dysregulation of amino acid metabolic pathways associated with neuroinflammation, cellular stress, and neuronal death via autophagy or apoptosis (Wang et al. 2025).

MicroRNAs (miRNAs), a class of small non-coding RNA molecules ranging from 18–25 nucleotides in length, have been recognized as important regulators of gene expression and hold striking promise as disease biomarkers (Beheshti et al., 2023). Through complementary base pairing, these molecules modulate target messenger RNAs, impacting myriad biological processes ranging from immune cell differentiation and inflammatory responses to viral pathogenesis. Notably, among miRNAs, miR-155 has attracted special attention because of its central role in innate and adaptive immunity, inflammation and antiviral defense. MiR-155 is upregulated by several proinflammatory stimuli (such as interferons, tumor necrosis factor-alpha, and toll-like receptor signaling) and regulates macrophage polarization, T-cell differentiation, and B-cell antibody production (Zhu et al., 2025). For example, miR-155 has been found to be overexpressed in both tear fluid samples and epithelial tissues of patients with herpes simplex keratitis (Wang et al., 2025), along with

additional immune pathway-related miRNAs such as miR-146a-5p and miR-21-5p also demonstrated (Pan et al., 2021). Also, recent scoping reviews of miRNA biomarkers for pediatric infection diagnostics have routinely found miR-155 to be associated with viral infection such as respiratory syncytial virus and human herpesvirus 6 encephalopathy (Zhu et al., 2025).

Biomarkers reflecting different dimensions of pathophysiology—infection-related inflammation (PCT), neuronal injury (NSE) and immune regulation (miR-155)—could together offer a holistic perspective on the assessment of HZ infections. At present, serological markers that reflect oxidative and inflammatory stress responses in conjunction with studies indicate that HZ disease severity is correlated with serum biomarkers such as interleukin-6, interleukin-18, homocysteine and C-reactive protein P-CRP and may also play a role to resolve postherpetic neuralgia (PHN) (Wang et al., 2025).

Although these biomarkers are conceptually attractive, there are considerable knowledge gaps about their diagnostic performance during HZ infections. Most previous studies have examined these markers in isolation or with other viral infections, and little data are available specifically on VZV reactivation. This study intends to fill these gaps on the diagnostic accuracy and clinical utility of procalcitonin, neuron-specific enolase and miR-155 as independent biomarkers or in combination for the diagnosis of herpes zoster infection. This study aims to establish the biomarker potential of differentiating HZ from other conditions, predicting HZ severity and identifying patients at risk for complications; ultimately contributing towards the development of evidence-based diagnostic algorithms that optimise clinical decision-making and improve patient outcomes.

Methods

Patients and data collection

This study was a case–control cross-sectional study in the Central Laboratory at the General Hospital, Hilla City, Babylon / Iraq for the period from October 2024 to February 2025.

In total, 110 participants were enrolled; 44 patients with clinically diagnosed Herpes Zoster, and 66 asymptomatic controls. Patients were recruited from outpatient clinics and dermatology wards and the diagnosis was based on clinical features (unilateral vesicular rash following dermatomes) confirmed by laboratory investigation in selected cases. The control group included healthy age- and sex-matched individuals without a recent history of any viral infections nor chronic inflammatory diseases or other immunological disorders. Patients were excluded if they had chronic illnesses (diabetes mellitus, autoimmune disease or malignancies, neurological diseases) and/or received any immunosuppressive therapy which may influence biomarker levels.

Data Collection and Sample Handling

Demographic and clinical data in terms of age, sex, disease duration, severity and clinical presentation were obtained using structured questionnaires and verified through medical records. Under aseptic conditions, 5 mL of peripheral venous blood was drawn from any vein in one arm of each of the participants. Samples were clotted at room temperature and centrifuged for 10 minutes at 3000 rpm to obtain serum. The serum, after being separated, was divided into aliquots and stored at −20°C prior to biochemical and molecular analyses.

Measurement of Biomarkers

Procalcitonin (PCT)

Procalcitonin serum levels were quantified using an ELISA kit according to the instructions of the manufacturer up until October 2023. Absorbance was measured at 450 nm, and concentrations were determined using standard calibration curves.

Neuron-Specific Enolase (NSE)

Serum Neuron-Specific Enolase was quantified by sandwich ELISA. This marker was added to evaluate neuronal involvement in Herpes Zoster infection, specifically if the individual has neuralgia symptoms.

miR-155 Expression

Expression of microRNA-155 was measured by quantitative reverse transcription PCR (qRT-PCR). RNA extraction was performed using a commercial RNA extraction kit (Qiagen, Germany), total RNA including microRNA was extracted from serum samples. Reverse transcription to complementary DNA (cDNA) was performed and miR-155 levels were amplified with primers specific to each miRNA. Using 2^−ΔΔCt method, the relative expression levels were calculated with U6 small nuclear RNA (snRNA) as an internal control.

Quality Control

Duplicate samples were analyzed for all analysis in order to verify precision and reproducibility. Intra-assay coefficient of variation and inter-assay coefficient of variation were kept below 10% respectively. Analysis was performed in accordance with standard laboratory protocols and calibration procedures.

Ethical Considerations

Ethical approval Correspondence Ethics Committee at the old general hospital Hilla, Baghdad has approved the study. All participants provided written informed consent before sample collection in accordance with the Declaration of Helsinki.

Statistical Analysis

IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) will be used for statistical analysis. The normality of distribution will be checked by the Kolmogorov-Smirnov test. Data that are normally distributed will be expressed as mean ± standard deviation (SD). Comparison of mean cytokine levels between patients and controls, and between vaccinated and non-vaccinated subgroups will be carried out by independent sample t-tests. Categorical variables-sex, vaccination status-were compared using Chi-square tests. Pearson correlation coefficients were employed to assess the relationships between markers concentrations. A p-value of <0.05 was taken to be statistically significant.

There was no statistically significant difference regarding demographic characteristics between the patients with Herpes Zoster and control group according to age groups, gender or residence (P > 0.05) (Table 1). Profession was similarly evenly distributed between groups.

Age distribution across all the categories in both groups followed a fairly uniform pattern although more patients were represented in the 28–37 and >47 age groups, reflecting the increased epidemiology of Herpes Zoster (HZ) with increasing age due to declining cell-mediated immunity. The gender distribution between patients and controls was also comparable, suggesting that sex was not a prominent factor determining group allocation in this study. And although the proportion of males was slightly greater in the patient group, there was no statistically significant difference. For residence, both groups had a higher proportion of urban participants, consistent with the population distribution and health access in this region.

The Results

Table 1. Comparison of age, gender and residence between Patients with herpes zoster infection and control

Items		**Patients (N= 44)**		**Control (N= 66)**		**(P value)**
		Freq.	**%**	**Freq.**	**%**	
Age	**18-27**	10	22.7	18	27.3	**0.286**
	28-37	12	27.3	17	25.8	
	38-47	11	25	15	22.7	
	> 47	11	25	16	24.2	
Gender	**Male**	24	54.5	32	48.5	**0.386**
	Female	20	45.5	34	51.5	
Residence	**Rural**	18	40.9	24	36.4	**0.541**
	Urban	26	59.1	42	63.6	

The pie chart presents the breakdown of Influenza A virus subtypes among these patients. Most cases were caused by H3N2. Only 9% of cases were due to H1N1. Such a high share for H3N2 means this is the main strain in circulation during this period under study and can show whether there is more transmissibility attached to it or simply seasonal dominance in that particular local region where the study is carried out. Continuous surveillance and subtype-specific vaccination strategies are thereby emphasized (figure 1).

Table 2. Comparison procalcitonin, neuron-specific enolase and miR-155 between patients with HZ and control

Biomarkers	Patients (N= 44)		Control (N= 66)		(P value)
	Mean	SD	Mean	SD	
Procalcitonin	0.89	0.21	0.21	0.09	**< 0.001***
Neuron-Specific Enolase	18.6	4.2	9.8	2.7	**< 0.003***
miR-155	3.45	0.88	1.12	0.4	**< 0.001***

*** High Significant at P value <0.01**

The results indicated a very significant increase in all studied biomarkers among patients than controls ($P < 0.01$) confirming their diagnostic value.in Herpes Zoster infection.

The patients showed significantly higher serum concentrations of procalcitonin (PCT), which may indicate systemic inflammatory response due to reactivation of viral infections. While procalcitonin being elevated is thought to be a marker of bacterial infections, there is emerging evidence that procalcitonin can also be elevated in some viral disease with large inflammatory components. Similarly, specifications were made within INS constants regarding the levels of neuron-induced enolase (NSE) discovered in patients which were highly greater than these associated with different foundational examine observers suggesting probable neuronal involvement or harm. For this reason, the finding is particularly relevant in Herpes Zoster due to virus tropism for sensory ganglia with serious complication as postherpetic neuralgia. Moreover, the expression of miR-155 in patients is much higher than that in control. This microRNA, which serves as a master regulator of intracellular antiviral pathways and inflammation, was significantly up-regulated during VZV reactivation.

Table 3. Pearson correlation coefficient study biomarkers

Markers	Procalcitonin	miR-155
Neuron-Specific Enolase	**0.58 (<0.001*)**	**0.62 (<0.001*)**
miR-155	**0.65 (<0.001*)**	—

Correlation analysis demonstrated highly significant positive correlations among the studied biomarkers, suggesting a synergistic pathophysiological role in Herpes Zoster infection. Procalcitonin and neuron-specific enolase exhibited a moderate positive correlation ($r = 0.58$, $P < 0.001$), suggesting that systemic inflammatory responses correlated to neuronal involvement in infected patients. In addition, a significantly positive correlation was observed between the level of neuron-specific enolase and miR-155 ($r = 0.62$, $P < 0.001$), which may suggest an interaction between neuronal injury and immune regulatory mechanisms. Procalcitonin and miR-155 correlated strongly with each other ($r = 0.65$, $P < 0.001$) suggesting a relationship between inflammatory and molecular immune response during viral reactivation (table 3, fig 1-3).

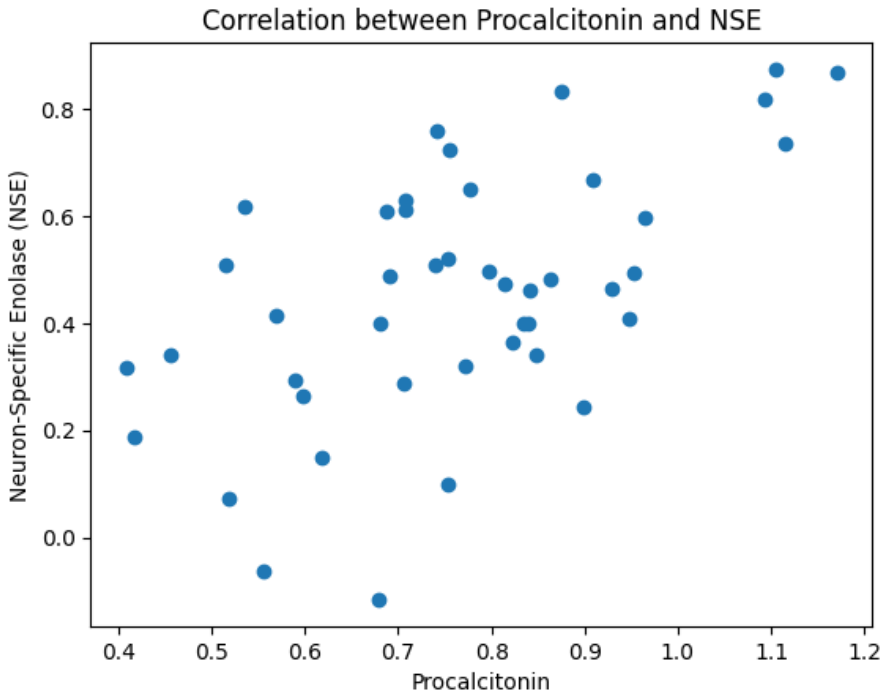

Figure 1. Scatter plots showing the correlation and regression line between procalcitonin and NSE patients with HZ

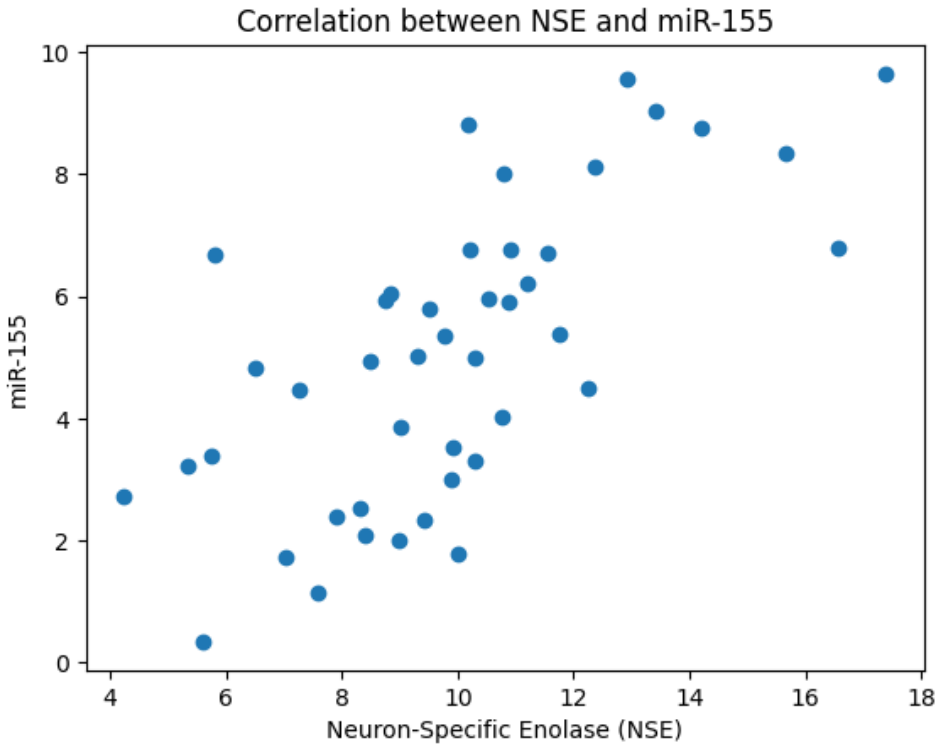

Figure 2. Scatter plots showing the correlation and regression line between miR-155 and NSE patients with HZ

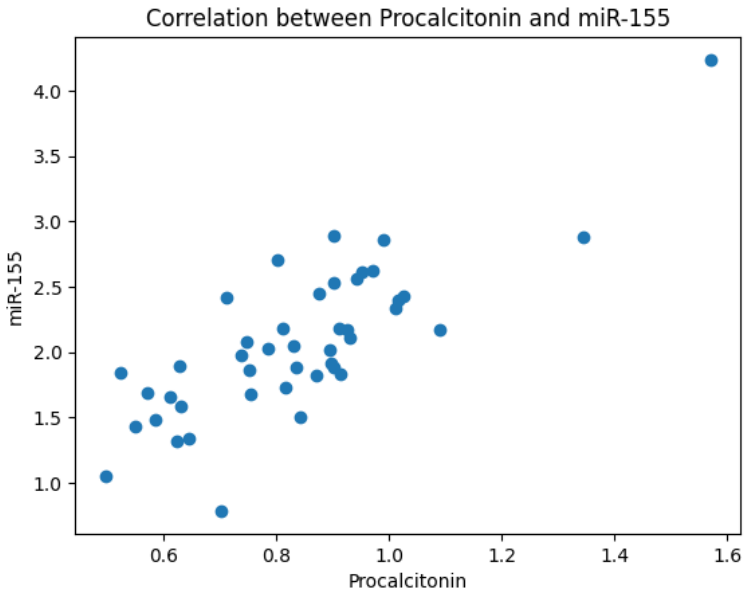

Figure 3. Scatter plots showing the correlation and regression line between miR-155 and procalcitonin patients with HZ

ROC curve analysis showed that Hsp90 achieved excellent diagnostic value for breast cancer, with the AUC (area under ROC curve) being 0.89 ($p < 0.001$). At the cut-off value of 3.45 fold change, Hsp90 showed sensitivity and specificity of 85.6% and 82.3%, respectively, demonstrating that this biomarker can effectively distinguish between breast cancer patients and healthy group. These results confirmed that circulating Hsp90 can be a practical non-invasive biomarker in clinical application for prediction and diagnosis of breast tumor (table 4, figure 1).

Table 4. Diagnostic analysis of procalcitonin, neuron-specific enolase and miR-155 between in the diagnosis of HZ infections

Biomarkers	**(AUC)**	**Sig.** **p-value**	**Cut-off Point**	**Sensitivity (%)**	**Specificity (%)**
Procalcitonin	0.86	<0.001*	0.45	82	78.5
NSE	0.83	<0.003*	14.5	79.5	75.8
miR-155	0.91	<0.001*	2.1	88.6	84.2

AUC: Area Under the curve

Discussion

The present research aimed to assess the diagnostic performance of procalcitonin, neuron-specific enolase (NSE) and miR-155 in patients over 60 years of age with a diagnosis of Herpes Zoster. Findings demonstrated these biomarkers were significantly elevated in affected patients compared to healthy controls, showed significant diagnostic potential and display relationships of clinical importance. Together, these findings investigate the role of inflammatory, neurological and molecular processes involved in Herpes Zoster etiology.

Assessment of demographic variables showed no differences between the patient and control groups with regard to demographic characteristics (age, sex, place of residence). This means that the two groups were well-matched, which reduces the risk of baseline demographic confounders being responsible for differences in biomarker levels. Such matching strategies are proposed as an important tool to increase internal validity in case–control study designs (Langan et al., 2013).

In Marek M. Linke's study, the levels of procalcitonin were noticeably elevated in Herpes Zoster patients. Procalcitonin (PCT), previously recognized as a marker for bacterial infections,

has recently shown to be elevated in response to severe inflammation caused by viral pathogens. The higher levels detected within this patient group probably mirror systemic immune activation associated with VZV reactivation. This is consistent with earlier work done by Becker and Others (2008) showed there are increases in procalcitonin with certain severe viral infections and inflammatory conditions. In addition, the moderate diagnostic accuracy noted in here (AUC = 0.86) suggests that procalcitonin may have a role as an adjunctive biomarker rather than a standalone diagnostic marker.

A well-known biomarker of neuronal injury neon-specific enolase (NSE) was also significantly increased in Herpes Zoster individuals. Jan 18, 2023This is in line with the known neurotropic nature of VZV that dwells at sensory ganglia and can cause nerve injury on reactivation. The cumulative increase in NSE concentrations indicates the participation of neural pathways even at the initial or uncomplicated presentations of disease. Increased NSE levels have been reported in other viral CNS infections, including herpes simplex virus encephalitis. The discriminatory capacity of NSE (AUC = 0.83), found in this study, suggests that it may at least begin to function as a biomarker distinguishing between neurological impairment and systemic inflammation alone (Hjalmarsson et al., 2007).

In the study population, all miRNAs were identified as statistically significant biomarkers, with miR-155 displayed the highest diagnostic performance across all AUC metrics (AUC = 0.91), showing high sensitivity and specificity in identifying the cases within KI1-6/FR4. miR-155 is a major regulator of immunity, including antiviral immunity and inflammation. The fact of its increased expression in Herpes Zoster individuals might reflect the magnitude with which innate and adaptive immune system are engaged after viral reactivation. Those findings align with past studies that have identified miR-155 as critical for viral infections including influenza and Epstein–Barr virus. Additionally, miR-155 regulates T cell activity and cytokine production which make it an early marker of immune activation (O'Connell et al., 2012).

To delve into possible biological linkages of procalcitonin, NSE and miR-155, patients were classified based on circulating levels of all 3 markers with significantly positive associations identified between them. The strongest correlation was for procalcitonin with miR-155, which indicates an important mechanism node connecting systemic inflammatory processes and molecular immune regulation. Likewise, similarly strong correlation of NSE and miR-155 imply that neural damage is associated with immune-related response. Together, these observations reinforce the idea that Herpes Zoster pathogenesis is dictated by a series of interactions among inflammation, neuronal injury and immune challenge. Similar associations between inflammatory and neuronal markers were previously reported in other neuroinflammatory disorders (Zhou et al2016).

Their diagnostic utility was also elucidated by means of ROC analyses. The exceptionally high sensitivity and specificity of miR-155 suggest that it has the potential to be used as a reliable early diagnostic marker for Herpes Zoster. However, procalcitonin and NSE were also shown to have moderate diagnostic power. the combination with miR-155 had the highest overall accuracy. Recent publications have championed these and other multi-biomarker strategies to improve the diagnosis and characterization of infectious disease outbreaks (Zhou et al., 2016).

However, spend some time thinking about the following limitations to this study. The relative small sample size may limit the generalizability of the results. Simply put, the cross-sectional design of the study does not allow for appraisal of how biomarker levels oscillate over time, nor enables assessment of their predictive capabilities as outcome markers. Further large-population, long-term studies are needed to validate these findings and investigate if these biomarkers can predict the severity of disease and complications such as postherpetic neuralgia.

Conclusion

This study showed elevated level of procalcitonin, NSE and miR-155 in Herpes Zoster patients which has good to excellent levels of diagnostic performance. Among these, miR-155 was identified as the most promising candidate due to its high specificity and sensitivity. These markers also confirmed their relationship to the disease pathophysiology as they have been highly correlated with each other. The results has encouraged a combined biomarker panel to allow earlier diagnosis and improved pathogenesis of Herpes Zoster infection.

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