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Calreticulin and GRP78 as Bioindicators for the Diagnosis of COVID-19 Pneumonia

COVID-19 Pnömonisi Tanısında Biyoindikatör Olarak Calreticulin ve GRP78

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) has been reported by the World Health Organization as a global health issue, leading to severe respiratory infections in humans. Recent studies have shown that endoplasmic reticulum stress can contribute to both the development and increased severity of many diseases, such as viral infections. In our study, we evaluated the diagnostic adequacy of the ER stress markers glucose-regulated protein 78 (GRP78) and calreticulin for diagnosing COVID-19 pneumonia and predicting mortality.

Materials and Methods: Our study included patients who presented to the emergency department, were over 18 years of age, had at least two clinical symptoms compatible with COVID-19 pneumonia, and whose diagnosis was confirmed by polymerase chain reaction testing, and had typical findings compatible with COVID-19 pneumonia on radiological imaging. GRP78 and calreticulin levels were statistically compared between patient (n=44) and control (n=44) groups, and between patient groups (survivors and non-survivors).

Results: GRP78 levels were found to be significantly greater in patients with COVID-19 pneumonia than in controls. The calreticulin levels were significantly lower. However, no significant difference was observed between the two groups in terms of survival. The sensitivity and specificity of GRP78 were 52.27% and 93.18%, respectively, when the cut-off value for GRP78 was >1.61 [area under the curve (AUC): 0.697, p<0.001]. The sensitivity and specificity were 81.82% and 72.73%, respectively, when the calreticulin cut-off was <3.96 (AUC: 0.816, p<0.001).

Conclusion: Our results showed that both GRP78 and calreticulin may be good bioindicators for COVID-19 pneumonia.

Keywords: COVID-19, pneumonia, endoplasmic reticulum stress, calreticulin, GRP78

ÖZ

Amaç: Koronavirüs Hastalığı 2019 (COVID-19), Dünya Sağlık Örgütü tarafından insanlarda ciddi solunum yolu enfeksiyonlarına yol açan küresel bir sağlık sorunu olarak bildirmiştir. Son çalışmalar endoplazmik retikulum stresinin, enflamatuvar bozukluklar ve viral enfeksiyonlar da dahil olmak üzere çeşitli hastalıkların patogenezine katkıda bulunduğunu ve bu olayların şiddetini artırabileceğini göstermektedir. Çalışmamızda endoplazmik retikulum stres belirteçlerinden glukoz düzenleyici protein 78 (GRP78) ve kalretikulinin COVID-19 pnomonisinin teşhisi ve mortaliteyi öngörmede tanısal yeterliliğini değerlendirmeyi planladık.

Gereç ve Yöntemler: Çalışmamızda acil tıp kliniğine başvuran 18 yaş üzeri ve COVID-19 pnomonisi ile uyumlu en az iki klinik semptomu bulunan gerçek zamanlı ters transkriptaz polimeraz zincir reaksiyonu testi ile tanısı doğrulanan ve radyolojik görüntülemede COVID-19 pnomonisi ile uyumlu tipik bulguları olan hastalar dahil edildi. GRP78 ve kalretikulin düzeyleri hem hasta (n=44) hem de kontrol (n=44) gruplarında istatistiksel olarak karşılaştırıldı.

Bulgular: GRP78 düzeylerinin COVID-19 pnomonisi saptanan hastalarda kontrol grubuna göre anlamlı olarak yüksek olduğu tespit edildi. Kalretikulin seviyeleri ise anlamlı olarak düşüktü. Ancak sağkalım açısından değerlendirildiğinde her iki grup arasında anlamlı bir fark görülmedi. GRP78'in kesim değeri >1,61 [eğri altındaki alan (AUC): 0,697, p<0,001] olduğunda duyarlılığı %52,27, özgüllüğü %93,18 olarak tespit edilmiştir. Kalretikulinin kesim değeri <3,96 (AUC: 0,816, p<0,001) olduğunda duyarlılığı %81,82, özgüllüğü %72,73 olarak tespit edilmiştir.

Sonuç: Sonuçlarımız, hem GRP78 hem de kalretikulinin COVID-19 pnömonisi için iyi biyoindikatörler olabileceğini göstermiştir.

Anahtar Kelimeler: COVID-19, pnömoni, endoplazmik retikulum stresi, kalretikulin, GRP78

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Introduction

Coronavirus Disease 2019 (COVID-19) is a multisystemic disease with a clinical presentation ranging from mild flu-like symptoms to severe pneumonia. Understanding the pathogenesis of this disease is necessary to reduce hospitalization and mortality rates, predict the development of pneumonia, and identify patients at risk (1).

Endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of many respiratory diseases (2). Excessive accumulation of unfolded proteins in the lumen of the ER leads to activation of the signaling pathway known as the unfolded protein response (UPR). Protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 alpha (IRE1α) are transmembrane proteins that mediate the UPR (3). The UPR is part of the cellular stress response that can be exploited by respiratory viruses to fight against the host's immune system. In coronavirus (CoV) infection, it has been suggested that the possible mechanism responsible for the induction of the UPR may involve excessive synthesis, modification, and folding of viral proteins (4). Although PERK is most commonly associated with CoV infections, there is evidence that IRE1 and ATF6 are also involved (5).

Glucose-regulated protein 78 (GRP78) is the major chaperone protein of the UPR in the ER. GRP78, a member of the heat shock protein 70 (HSP70) family, is localized to the ER membrane of all eukaryotic cells. Forces cause unfolded proteins to undergo refolding or degradation via cellular degradation mechanisms (6). The amino-terminal region of the GRP78 protein is known as the ATP binding domain, and the carboxy-terminal region is known as the substrate binding domain. GRP78 normally binds PERK, IRE1α, and ATF6 and keeps these proteins inactive. When the UPR is increased and the folding capacity of the ER is exceeded, these proteins dissociate from GRP78 and become activated (7). In this case, the cell may resort to protein refolding or inhibition of protein synthesis. In studies, GRP78 has been associated with viral infections. It is thought to be involved in the synthesis of envelope proteins in some viruses. GRP78 may be one of the proteins that mediates the entry of some viruses into the cell by binding to cell surface proteins. Overexpression of GRP78 may cause its translocation from the ER to the cell membrane and mediate the entry of some viruses into the cell through its substrate binding site (7,8).

Calreticulin is an ER chaperone protein that plays an important role in regulating intracellular calcium homeostasis and proper protein folding in the ER. It binds, stores, and translocates Ca2+ ions in the lumen of the ER (9). Calreticulin consists of three parts: an N domain, a P domain, and a C domain (10). The N-domain is a spherical structure with internal folding, a highly conserved amino acid sequence, and the ability to bind Zn2+. It can interact with other chaperone molecules (11). The P domain has a high affinity for Ca2+ but a low Ca2+-binding capacity. The C-domain binds Ca2+ with low affinity and high capacity due to its acidic structure and thus plays a role in Ca2+ storage and homeostasis in the ER lumen (12). Loss of calreticulin function in cells may cause the onset of ER stress (9,13). The UPR has been shown to increase in viral infections. Therefore, it is important to evaluate the function of calreticulin in viral infections. However, to our knowledge, there are little data in the literature on the role of calreticulin, an ER stress indicator, in COVID-19 pneumonia.

Biomarkers are becoming increasingly important in areas such as predicting disease progression and monitoring treatment. They also help to better understand the pathogenesis of the disease. In this study, we evaluated the diagnostic adequacy of GRP78 and calreticulin as biomarkers for the diagnosis of COVID-19 pneumonia and the prediction of mortality.

Materials and Methods

Study Design

Our study was conducted between March 2021 and June 2021. Patients who presented to the emergency medicine clinic were over 18 years of age, had at least two clinical symptoms compatible with COVID-19 pneumonia (shortness of breath, cough, sputum, pleuritic chest pain, fever of 38 °C and above), had a diagnosis confirmed by real-time reverse transcriptase polymerase chain reaction test, and had typical findings compatible with COVID-19 pneumonia on radiological imaging (unilateral or bilateral ground-glass appearance, subpleural consolidation, paving stone appearance). These patients were included in our study. People who did not have clinical, laboratory, or radiological suspicion of COVID-19 infection and who were informed about the study and agreed to participate were included in the control group. Written informed consent was obtained from patients without consciousness disorder who were mentally healthy enough to sign, and from the first-degree relatives of patients with a consciousness disorder or who were not mentally healthy enough to sign. Patients under 18 years of age, pregnant women, cancer patients, immunosuppressed patients, those with impaired consciousness, sepsis, multiorgan failure, respiratory failure, and hemodynamically unstable conditions for any reason other than COVID-19 pneumonia were excluded from the study.

All patients included in the study were grouped into survivors and non-survivors. GRP78 and calreticulin levels

were statistically compared between the patient (n=44) and control (n=44) groups,and within the patient group (survivors and non-survivors). Approval was received from the Ethics Committee of Kocaeli University Non-interventional Clinical Trials (KÜ GOKAEK-2021/7.01, dated: 01.04.2021).

Biochemical Analyses

Blood samples collected at enrollment were analyzed for white blood cell count, neutrophil count, lymphocyte count, D-dimer level, and C-reactive protein (CRP) level. Blood samples from the patient and control groups were centrifuged at 1500 g for at least 15 minutes. The serum obtained was stored at -80 °C until analysis of GRP78 and calreticulin levels. GRP78 and calreticulin levels in these samples were analyzed by sandwich enzyme-linked immunosorbent assay (ELABSCIENCE-E-EL-H5586 and ELABSCIENCE-E-EL-H0627, respectively). The sensitivities of these assays were 0.38 ng/mL and 0.10 ng/mL, respectively. The intra-assay and inter-assay coefficients of variation (%) of both assays were less than 10%. Within 24 hours of diagnosis, 10 mL of venous blood was collected in EDTA tubes for hematological analysis. Complete blood count was performed on a Sysmex XN-1000 automated hematology analyzer (Sysmex Europe SE, Norderstedt, Germany).

Statistical Analysis

The IBM SPSS 29.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. The Shapiro-Wilk test was used to assess the normality of the data. Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Categorical variables are presented as numbers and percentages. Independent sample t-tests were used for normally distributed variables and Mann-Whitney U tests were used for non-normally distributed variables. The chi-square test was used to investigate the relationships between categorical variables. Receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC), sensitivity, specificity, and cut-off values. A p-value <0.05 was considered statistically significant. According to the power analysis result, the minimum sample size required to find a significant difference using this test was determined to be 84 in total, 42 in each group; the type 1 error amount (alpha) was 0.001; the power of the test (1-beta) was 0.90; the effect size was 0.76; and the alternative hypothesis (H1) was two-sided.

Results

There were 88 participants in the study, 44 in the control group and 44 in the patient group. The patients were divided into survivors (n=32) and non-survivors (n=12). The mean age of the patients was 65 years (male, 63.6%; female, 36.4%) and the mean age of the controls was 65.5 years (male, 52.3%; female, 47.7%). Oxygen saturation was significantly lower in the non-survivor group (p=0.011). However, no significant difference was observed between the two groups in terms of temperature, heart rate, or systolic or diastolic blood pressure. CRP was also significantly lower in the survivor groups than in the non-survivor groups (46.7, 108.4; mg/L p=0.015). GRP78 and calreticulin levels were not significantly different between the survivors and non-survivors groups (1.49, 2.15; 1.90, 3.23, ng/mL, respectively). Table 1 shows the data for the groups.

Table 2 shows the comparison of GRP78 and calreticulin levels, as well as age and sex, between the patient group and the control group. GRP78 levels were significantly greater (p=0.001) and calreticulin levels were significantly lower (p<0.001) in the patient group than in the control group.

ROC analysis of GRP78 and calreticulin levels in the patient and control groups is shown in Figures 1 and 2. The cut-off and AUC values of GRP78 and calreticulin are given in Table 3. When the cut-off value of GRP78 was >1.61 (AUC: 0.697, 95% CI: 0.590-0.791, p<0.001), the sensitivity was 52.27%, and the specificity was 93.18%. When the cut-off value of calreticulin was <3.96 (AUC: 0.816, 95% CI: 0.719-0.890, p<0.001), the sensitivity was 81.82%, and the specificity was 72.73%.

Discussion

In viral infections, especially during the replication cycle, a high level of viral protein accumulates in the ER and exceeds its folding capacity. This situation therefore triggers the UPR (14). CoV infections are also among the infections that can activate the UPR (15). Understanding the relationship between COVID-19 and ER stress is important for comprehending the pathogenesis of COVID-19. In our study, the level of GRP78, an ER chaperone protein, was significantly greater in patients with COVID-19 pneumonia than in the controls (p=0.001). There was significantly less calreticulin in the patient group than in the control group (p<0.001). In addition, when ROC analysis of GRP78 and calreticulin was performed, the AUC values calculated for both indicators were 0.697 for the patient group and 0.816 for the control group.

GRP78 functions as a major chaperone that maintains protein homeostasis within the ER. It has also been shown in many studies to participate in various processes, such as cellular signaling, the inflammatory response, apoptosis, and the development of viral infection (16,17). In autopsies of COVID-19 patients, increased expression of GRP78 was found in both pneumocytes and lung macrophages (18). Overexpression of GRP78 may increase the likelihood of

Table 1. Basic characteristics of the patients

Variables	All Patiens (n=44)	Survivors (n=32)	Non-survivors (n=12)	p-value
Age[a]	65.00 (50.75-70.75)	65 (50.75-71.75)	65 (49.75-69.75)	0.711
Gender, n (%)[b] Male Female	 28 (63.6) 16 (36.4)	 20 (62.5) 12 (37.5)	 8 (66.7) 4 (33.3)	1.00
Fevera	36.7(36.5-37.2)	36.7 (36.5-37.4)	36.7 (36.5-37.1)	0.886
Heart rate (min.)[c]	94.25±17.3	92.97±16.9	97.6±18.6	0.431
Sistolic pressurea	120 (110-130)	120 (110-130)	120 (100-140)	0.745
Diastolik pressurea	70 (62.5-80)	70 (70-80)	80 (60-80)	0.507
Saturation, (%)[a]	96 (9.5-97)	96 (93-97.75)	89 (81.75-96.50)	0.011
WBC, (10^3/mL)[a]	5.1 (3.95-7.05)	5.1 (4.12-6.82)	5.65 (3.4-10)	0.726
Neutrofil, (10^3/mL)[a]	3.40 (2.60-4.57)	3.35 (2.60-4.20)	3.90 (2.40-7.32)	0.474
Lymphocyte, (10^3/mL)[a]	1.20 (0.80-1.40)	1.30 (0.82-1.47)	1 (0.80-1.37)	0.507
CRP, (mg/L)[a]	2.70 (2.20-4.40)	46.7 (11.10-81.10)	108.4 (54.12-173.15)	0.015
D-dimer, (ug/mL)[a]	0.62 (0.44-1.43)	0.57 (0.41-1.18)	0.97 (0.57-2.13)	0.112
GRP78, (ng/mL)[a]	1.66 (1.01-2.82)	1.49 (0.98-2.28)	2.15 (1.01-3.27)	0.397
Calreticulin, (ng/mL)[a]	2.33 (1.35-3.76)	1.90 (1.32-3.51)	3.23 (1.76-5.38)	0.089
Lenght of stay in hospital, (day)[a]	9 (5.75-14)	9 (6-12)	10 (2-17)	0.504

[a]Data are presented as the median (IQR), [b]Data are presented as the n (%), [c]Data are presented as the mean ± standard deviation, IQR: Interquartile range, WBC: White blood cell, CRP: C-reactive protein, GRP78: Glucose-regulated protein 78

Table 2. Comparison of GRP78 and calreticulin levels between the patient and control groups

	Patient (n=44)	Control (n=44)	p-value
Age[a]	65 (50.75-70.75)	65.50 (46.25-72.50)	0.917
Gender[b] Male Female	 28 (63.6) 16 (36.4)	 23 (52.3) 21 (47.7)	0.388
GRP78 (ng/mL)[a]	1.66 (1.01-2.82)	1.11 (0.79-1.29)	0.001
Calreticulin (ng/mL)[a]	2.33 (1.35-3.76)	6.23 (3.63- 8.32)	<0.001

[a]Data are presented as the median (IQR), [b]Data are presented as the n (%), IQR: Interquartile range, GRP78: Glucose-regulated protein 78

Table 3. Predictive value of GRP78 and calreticulin for the patient and control groups

	AUC	95% CI Lover/Upper limit	Cut-off	Sensitivity (%)	Specificity (%)	p-value
GRP78 (ng/mL)	0.697	0.590/0.791	>1.61	52.27	93.18	<0.001
Calreticulin (ng/mL)	0.816	0.719/0.890	<3.96	81.82	72.73	<0.001

AUC: Area under the ROC curve, ROC: Receiver operating characteristic, CI: Confidence interval, GRP78: Glucose-regulated protein 78

GRP78 translocation from the ER to the cell membrane. Once GRP78 is translocated to the cell membrane, the cell becomes more susceptible and can mediate virus entry (7). The frequency of CD45+GRP78+ cells increased significantly in patients with severe COVID-19 (17). In their prospective case-control study, Sabirli et al. (19) reported that the level of GRP78 in serum samples from COVID-19 (+) patients was significantly greater than that in both the control group and the COVID-19 (-) pneumonia group. They suggested that the high level of GRP78 in patients with computed tomography-negative COVID-19 infection may increase ER stress and cause upregulation of GRP78 expression even before Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) triggers pneumonia. Our study results support these findings. In our study, we found that the serum GRP78 level was greater in patients with COVID-19 pneumonia than in controls (p<0.001). In addition, when the cut-off value of GRP78 exceeded

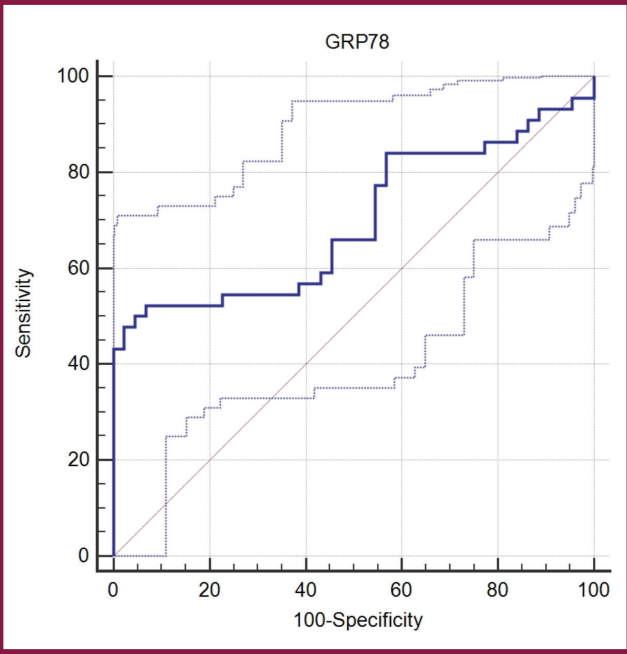

Figure 1. Receiver operating characteristic analysis of the best cut-off values for GRP78 levels in the patient and control groups
GRP78: Glucose-regulated protein 78

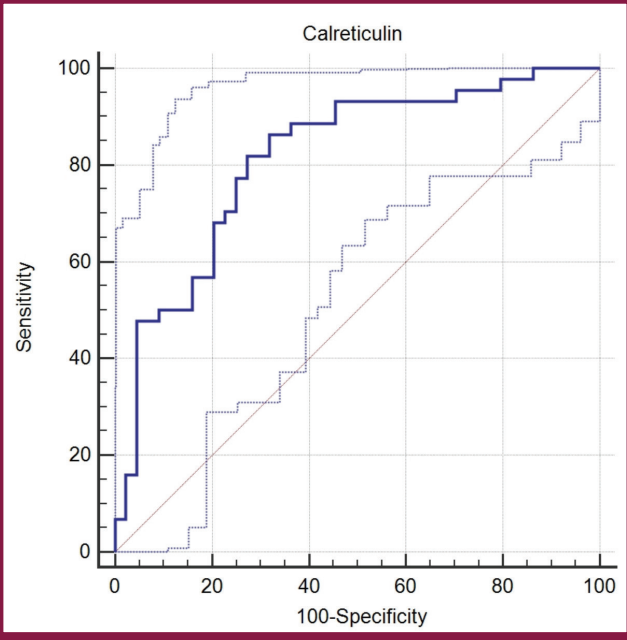

Figure 2. Receiver operating characteristic analysis of the best cut-off values for calreticulin levels in the patient and control groups

1.61 (AUC: 0.697, 95% CI: 0.590-0.710), its sensitivity and specificity were 52.27% and 93.18%, respectively. Our statistical analyses revealed that it was not a significant predictor of mortality.

Loss of calreticulin function in cells may cause the onset of ER stress (9). Calreticulin gene deletion has been found to cause the accumulation of unfolded proteins (20). The UPR is activated by a significant increase in GRP78, Ire1α, and PERK levels (9). Rahimi et al. (21) also reported that the absence of calreticulin in SARS-CoV-2-infected cells causes the spike protein to escape lysosome-mediated degradation. Therefore, they emphasized that shRNA-mediated knockdown of calreticulin may increase the severity of SARS-CoV-2 infection. In our study, serum calreticulin levels were significantly lower in the COVID-19 patient group than in the control group ($p<0.001$). However, no significant difference was found between the survivor and non-survivor groups.

Decreased calreticulin levels in COVID-19 patients may impair Ca+2 homeostasis in the ER. It can also induce ER stress by causing the UPR to increase. Our data confirm this finding. In addition, calreticulin was used as an indicator of COVID-19, with a sensitivity of 81.82% and specificity of 72.73% when the calreticulin cut-off was <3.96 ng/mL (AUC: 0.816, 95% CI: 0.719-0.890, $p<0.001$).

Increases in CRP and D-dimer during COVID-19 pneumonia are indicators of an increased inflammatory response. These parameters were also correlated with the severity of the disease (22,23). In addition, parameters such as interleukin-6, ferritin, and the neutrophil-to-lymphocyte ratio have been shown to be effective in predicting mortality. However, D-dimer did not show similar results in the same study (24).

Study Limitations

Our study is the first to investigate the diagnostic value of GRP78 and calreticulin in COVID-19 pneumonia, informed by our open-source literature searches. The limitation of this study was the insufficient data and limited sample size regarding GRP78 and calreticulin's ability to predict mortality. In addition, many factors, such as existing diseases, medications used by patients before hospitalization, and biodiversity, may have influenced the measurement results.

Conclusion

ROC curve analysis revealed that both GRP78 and calreticulin may be good indicators of COVID-19 pneumonia. Calreticulin appears to be more accurate and sensitive than GRP78 for detecting COVID-19 pneumonia. However, using both parameters together may be more promising.

Ethics

Ethics Committee Approval: Approval was received from the Ethics Committee of Kocaeli University Non-interventional Clinical Trials (KÜ GOKAEK-2021/7.01, dated: 01.04.2021).

Informed Consent: Written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.K., Concept: B.Ö., Design: B.Ö., Ş.K., Data Collection or Processing: Ş.K., Analysis or Interpretation: B.Ö., Literature Search: Ş.K., Writing: B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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