学位論文内容の要旨
（Summary of dissertation）

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学 位 論 文 題 名
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Predictive and Monitoring Markers in Systemic Lupus Erythematosus
（全身性エリテマトーデスにおける疾患予測・活動性評価のためのマーカー研究）

Systemic lupus erythematosus (SLE) is an autoimmune disease that presents with diverse clinical symptoms, requiring early detection and careful monitoring for diagnosis and treatment. SLE can affect multiple organs including joints, skin, kidneys, and the nervous system, potentially causing significant deterioration in patients' quality of life. Despite recent advances in understanding the underlying pathophysiology, the field lacks robust biomarkers for disease monitoring. Here we focused on IgG anti-phosphatidylserine/prothrombin antibodies (aPS/PT) as novel biomarkers and clarified their clinical significance.

[Background and Objectives] Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL) in the blood, leading to arterial thrombosis, venous thrombosis, and pregnancy complications. Autoimmune diseases are complex disorders characterized by immune system dysfunction, where the body's defense mechanisms incorrectly target its own tissues. Among these conditions, APS and systemic lupus erythematosus (SLE) represent significant challenges in both diagnosis and management. Primary APS (PAPS) is defined as APS without coexisting other autoimmune disorders. Although PAPS is distinct from SLE, the two conditions share clinical features and susceptibility genes. Progression from PAPS to SLE is well-recognized. However, risk factors for this transition are poorly understood. We aimed to identify predictors of progression to SLE in patients with PAPS.
[Methods] A longitudinal single-center study was conducted at Hokkaido University Hospital from 1990 to 2021. Baseline characteristics including clinical features, laboratory data, aPL profiles were compared between patients who progressed to SLE (SLE group) and those who did not (non-SLE group).
[Results] Among 64 patients diagnosed with PAPS at the baseline, nine (13.8%) progressed to SLE over a mean follow-up of 9 years (incidence rate, 1.61 per 100 person-years). At the diagnosis of PAPS, the SLE group had a higher prevalence of anti-phosphatidylserine/ prothrombin antibodies (aPS/PT) and anti-dsDNA antibodies compared to the non-SLE group. Other clinical findings, autoantibody profiles, and serum complement levels were similar between the two groups. Multivariate Cox analysis showed that IgG aPS/PT was significantly associated with SLE development (Hazard ratio: 10.3, 95%CI: 1.13-92.6, p=0.04).
[Discussion] In this longitudinal investigation of primary antiphospholipid syndrome (PAPS), we demonstrate that IgG anti-phosphatidylserine/prothrombin antibodies (aPS/PT IgG) serve as a novel predictor for systemic lupus erythematosus (SLE) development. While PAPS-to-SLE progression rates aligned with established literature, the identification of aPS/PT IgG as a predictive marker represents a significant advance in understanding disease trajectory. Although previously recognized for its association with thrombotic manifestations, aPS/PT IgG's capacity to forecast SLE development was previously unrecognized. These findings reveal aPS/PT IgG potentially enabling targeted surveillance and timely therapeutic intervention in high-risk populations.
[Conclusion] IgG aPS/PT may be a predictive factor for new-onset SLE in patients with PAPS, suggesting its utility in monitoring strategies for these patients.

Supplementary：Urin-Presepsin Levels in Patients with Lupus Nephritis

[Background and Objectives] Presepsin (PSEP) is a 13kDa glycoprotein containing amino acid sequence 1-64 of CD14, discovered in Japan in 2002 as a marker that shows elevated levels in sepsis patients. It is a CD14 fragment product released when monocytes and neutrophils containing elastase phagocytose bacteria and antigens under inflammatory stress. It is currently measured at the general clinical level as a diagnostic and treatment marker for sepsis. Additionally, elevated plasma PSEP (P-PSEP) levels have been reported in hemophagocytic syndrome,

where abnormal monocyte activation is the main pathological feature. Lupus nephritis (LN) remains one of the most important manifestations of SLE, significantly impacting patient outcomes and quality of life. Despite advances in therapeutic approaches, the assessment of disease activity and prediction of prognosis continue to rely heavily on renal biopsy, which serves as the gold standard for diagnosis, evaluation of disease activity, and treatment decision-making. Additionally, since kidney biopsies are invasive for patients, it is difficult to regularly check their disease progression or treatment response. Therefore, the development of reliable urinary biomarkers is required as a critical advancement in LN management. We previously showed that the P-PSEP in patients with SLE are elevated in association with disease activity of SLE. However, no data is available on urinary levels of PSEP (U-PSEP) in LN. The aim of this study is to clarify whether U-PSEP is high in LN as a potential urinary biomarker.

[Methods] We conducted cross-sectional study, including LN, SLE without LN, and other autoimmune diseases admitted to our department from August 2013 to September 2020. Urinary and P-PSEP levels were measured by CLEIA system. U-PSEP levels were compared between LN and non-LN. In addition, sub analysis was performed using each PSEP data compared among the following three groups [1. Active LN, 2. Inactive LN, 3. SLE without LN]. Active LN is defined as clinical and laboratory manifestations that meet ACR criteria (persistent proteinuria > 0.5g/gCre or active urinary sediment).

[Results] A total of 82 patients were enrolled in this study, including 36 patients with SLE [11 active LN patients, 8 inactive LN, 17 without LN] and 46 patients with other autoimmune diseases. There was no statistically significant difference in U-PSEP levels in between the SLE group and other immune disease group (average (SD): 461.5 (1312.9) VS 584.39 (1221.17), $P = 0.3285$). In sub analysis of SLE groups, U-PSEP levels of SLE with LN is higher than SLE without LN (161±1761.3 vs 56±289.5, $p < 0.0001$). The analysis revealed a statistically significant difference between the SLE with active LN group and SLE with inactive LN group (average (SD):1280(2209). VS 48(52.9), $P < 0.001$), SLE with active LN group and SLE without LN (average (SD):1280(2209). VS 127(14), $P < 0.001$).

[Discussion] Our results suggest that while U-PSEP levels show some association with lupus nephritis, several limitations need to be carefully considered. Although we observed differences in U-PSEP levels between active and inactive LN groups, U-PSEP elevation is not specific to LN, as similar elevations can be seen in various inflammatory conditions affecting the kidney. The presence of CD14-positive cells in urine, while mechanistically plausible, may reflect general inflammation rather than LN-specific pathology. Additionally, factors such as infection, medication use, and other comorbidities could potentially confound U-PSEP measurements, making interpretation challenging in clinical practice.

[Conclusion] We could detect U-PSEP in patients with active LN. Additional markers are needed for showing the specificity and further experiment should be needed.