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PD-1/PD-L1 immune checkpoint dysregulation and immunological biomarkers in systemic lupus erythematosus patients with chronic renal failure

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Abstract
Background: Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by immune dysregulation and autoantibody production. Renal involvement represents one of its most severe complications, significantly affecting prognosis. This study investigated the association between programmed cell death protein-1 (PD-1) and its ligand (PD-L1) immune checkpoint markers, immunological parameters, and renal involvement in SLE patients.
Methods: A case–control study enrolled 100 SLE patients and 100 age- and sex-matched healthy controls (December 2025–February 2026). Anti-nuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) were quantified by ELISA; complement factors C3 and C4 by nephelometry; thymosin β4 and vitamin D3 by ELISA; and renal biomarkers (cystatin C, urea, uric acid, creatinine) by standard biochemical methods. PD-1/PD-L1 expression was evaluated at the cellular level by flow cytometry and at the soluble serum level by ELISA.
Results: SLE patients exhibited significantly elevated ANA (147.31 ± 33.90 vs. 13.90 ± 3.70 IU/mL; $p<0.001$) and anti-dsDNA levels (109.73 ± 23.42 vs. 7.20 ± 3.51 IU/mL; $p<0.001$), with markedly reduced C3 (68.5 ± 12.20 vs. 110.3 ± 15.40 mg/dL) and C4 (12.4 ± 4.10 vs. 28.7 ± 5.20 mg/dL; $p<0.001$). Flow cytometry revealed significantly elevated PD-1+ T cells (34.50 ± 8.20% vs. 12.30 ± 4.10%) and PD-L1+ monocytes (28.70 ± 7.40% vs. 10.50 ± 3.50%), most pronounced in lupus nephritis (LN) subgroup. Soluble sPD-1 (3.42 ± 0.89 ng/mL) and sPD-L1 (2.97± 0.76 ng/mL) were significantly higher than controls. Thymosin β4 (15.30 ± 4.51 vs. 28.70 ± 5.10 ng/mL) and vitamin D3 (12.80 ± 3.23 vs. 31.20 ± 6.00 ng/mL) were markedly decreased. Cystatin C was found to be most correlated with PD-1 expression and severity of the disease ($p<0.001$).
Conclusion: PD-1/PD-L1 immune checkpoint dysregulation, in combination with conventional immunological and renal biomarkers, offers a holistic strategy of determining disease activity and renal involvement in SLE, with the potential of these biomarkers to serve as prognostic biomarkers and therapeutic targets.

Keywords: Systemic lupus erythematosus, chronic renal failure, pd-1/pd-l1, immune checkpoint, autoantibodies, cystatin C

Introduction

Systemic lupus erythematosus (SLE) is a severe, chronic, multisystem autoimmune disease with dysregulatory immune response, loss of self-tolerance, and autoantibodies against nuclear, cytoplasmic and cell-surface antigens [1] with a wide clinical spectrum of manifestation: mild cutaneous and musculoskeletal to life-threatening organ injury of Lupus nephritis (LN) is one of the most severe complications and, at about 4060 percent of SLE cases, it is a significant cause of morbidity and mortality in the world [2, 3].

SLE is a multifactorial immunopathogenesis that includes genetic predisposition, epigenetic alterations, environmental stimuli and hormonal factors. It is immunologically maintained by hyperactivity of B and T lymphocytes, malfunction of clearance of apoptotic debris, and development of pathogenic immune complexes, which activate complement and cause systemic inflammation [4]. Serological hallmarks consist of anti-nuclear antibodies (ANA) and anti-double stranded DNA antibodies (anti-dsDNA) which are commonly used as diagnostic markers and disease activity indices. The degree of systemic and renal inflammation is also indicated by dysregulation of the complement system, especially the loss of C3 and C4 following the immune complex consumption [5].

An important aspect of SLE pathophysiology is a breakdown of peripheral immune tolerance. PD-1 is an inhibitory immune checkpoint molecule that involves both the programmed cell death protein-1 (PD-1) and its ligand, PD-L1, which is expressed on T cells and B cells during activation, and on antigen-presenting cells (APCs) to suppress overactivation of immunity and peripheral self-tolerance. Aberrant PD-1/PD-L1 signalling has been shown to promote the survival of autoreactive lymphocytes, long term inflammation, and progressive tissue destruction in autoimmune diseases such as SLE [8, 9]. LN in LN, a defect of PD-1/PD-L1 immunoregulation may provoke the deposition of immune complexes in the glomeruli, impair the role of regulatory T cells (Treg), and promote renal fibrosis and functional failure [10].

In addition to immune checkpoint interactions, a number of immunomodulatory molecules also control the immune environment in SLE. Thymosin β4 is a pleiotropic peptide that is involved in actin polymerisation, cell migration, tissue repair, and inhibition of inflammatory cascades, whereas vitamin D3 has far-reaching effects on innate and adaptive immunity, promoting Treg differentiation and inhibiting the production of pro-inflammatory cytokines [11]. Both molecules are often lost in SLE patients with active nephritis, which shows a cumulative immunoregulatory defect that can enhance the PD-1/PD-L1 dysregulation [12].

In nephroprotective terms, cystatin C has proven a better indicator of glomerular filtration rate (GFR) than the traditional creatinine-based measures, and is more sensitive in identifying early renal impairment in autoimmune settings [13]. A combination of immune checkpoint analysis with conventional serological parameters (ANA, anti-dsDNA, C3, C4) and renal biomarkers (cystatin C, urea,

creatinine) can thus be a more effective and dynamic indicator of disease severity and organ involvement in SLE [14].

Despite advances in SLE research, the mechanistic links between PD-1/PD-L1 checkpoint dysregulation and renal biomarker profiles remain incompletely characterised, particularly in populations with established chronic renal failure. This study aims to bridge that gap by providing a comprehensive immunological profiling of SLE patients with and without renal involvement, with the objective of identifying candidate prognostic biomarkers and potential immunotherapeutic targets [15, 16].

Materials and Methods

Study Design and Participants

This case–control study enrolled 100 patients with confirmed SLE and 100 age- and sex-matched healthy controls. Participants were recruited between December 2025 and February 2026. SLE diagnosis was established according to the 2019 European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria [17]. Exclusion criteria encompassed concurrent autoimmune disorders, active infections, malignancy, pregnancy, or receipt of immunosuppressive therapy within four weeks preceding enrolment. Of the SLE cohort, 48 patients had biopsy-confirmed lupus nephritis (LN subgroup) and 52 had non-renal SLE (SLE-NR subgroup). All participants provided written informed consent, and the study received institutional ethical approval.

Sample Collection and Processing

The peripheral venous blood (~10 mL per participant) was taken under standardised aseptic conditions. Samples assays were done using samples drawn into ethylenediaminetetraacetic acid (EDTA) anticoagulated tubes and biochemical and serological tests using samples drawn into plain serum separator tubes. Centrifugation to obtain serum was done at 3,000 rpm at 10 minutes at 4°C and kept at −80°C until the batch analysis.

Immunological Assays

Autoantibodies (ANA, anti-dsDNA): The ANA and anti-dsDNA serum concentrations were quantified with commercial ELISA kits according to the manufacturer protocols. The optical density was taken at 450 nm and the concentrations were obtained using four-parameter logistic standard curves.

Complement factors (C3, C4): Serum C3, C4 concentration was measured by immunonephelometry, and the reference intervals were considered based on the laboratory-validated normal ranges.

Thymosin β4 and vitamin D3: Sandwich ELISA was used to determine the concentration of thymosin β4 and 25-hydroxyvitamin D3 in the serum. The outcomes were presented in ng/mL and categorised in relative to the known deficiency levels.

Renal Function Biomarkers

Cystatin C was quantified by using the particle-enhanced immunonephelometry. Serum urea, uric acid, and creatinine were assessed by standard enzymatic and colorimetric methods on an automated biochemical analyser. All assays were performed in triplicate, and results were expressed as mg/dL or mg/L as appropriate.

PD-1/PD-L1 Immune Checkpoint Analysis

Flow cytometry: Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Paque density gradient centrifugation. Cells were washed, enumerated, and stained with fluorochrome-conjugated monoclonal antibodies against PD-1 (CD279) and PD-L1 (CD274) in combination with appropriate lineage markers. Data acquisition was performed on a BD FACSCanto II cytometer and analysed using FlowJo v10 software. The percentage of PD-1+ T cells and PD-L1+ monocytes and mean fluorescence intensity (MFI) values were recorded.

Soluble PD-1/PD-L1 (ELISA): Serum levels of soluble PD-1 (sPD-1) and soluble PD-L1 (sPD-L1) were measured using commercial sandwich ELISA kits. Absorbance was read at 450 nm, and concentrations were interpolated from standard curves and expressed in ng/mL.

Statistical Analysis

IBM SPSS statistics version 26 was used to analyse the data. Mean and standard deviation (SD) are used to show continuous variables. Comparison of the two groups was done with independent samples t-tests where the variables were normally distributed and Mann-Whitney U test where variables were not normally distributed. Pearson or Spearman correlation coefficients were used to determine correlations between immune checkpoint markers, renal biomarkers and disease activity indices. The p-value was taken to be statistically significant at p-value <0.05

Results

Demographic and Clinical Characteristics

The study comprised 100 SLE patients (92% female; mean age 35.8 ± 1.4 years; range 8–65 years; mean disease duration 7.5 ± 3.2 years) and 100 healthy controls (90% female; mean age 34.9 ± 1.2 years). Forty-eight patients (48%) had biopsy-confirmed lupus nephritis. No significant differences in age or sex distribution were observed between the two groups ($p = 0.42$ and $p = 0.65$, respectively; Table 1).

Table 1: Demographic and clinical characteristics of study participants

Parameter	SLE Patients (n=100)	Healthy Controls (n=100)	p-value
Age (years), mean ± SD	35.8 ± 1.4	34.9 ± 1.2	0.42
Female, n (%)	92 (92%)	90 (90%)	0.65
Disease duration (years)	7.5 ± 3.2	—	—
Lupus nephritis, n (%)	48 (48%)	—	—

Immunological Parameters

SLE patients had significantly higher ANA (147.31 ± 33.90 IU/mL) and anti-dsDNA antibody levels (109.73 ± 23.42 IU/mL) compared to healthy controls (13.90 ± 3.70 and 7.20 ± 3.51 IU/mL, respectively; $p<0.001$ for both). Within the SLE cohort, LN patients demonstrated higher autoantibody titres than non-renal SLE patients ($p<0.01$). Serum C3 (68.5 ± 12.20 mg/dL) and C4 (12.4 ± 4.10 mg/dL) levels were

markedly reduced compared to controls (110.3 ± 15.40 and 28.7 ± 5.20 mg/dL, respectively; p<0.001), with the most pronounced complement depletion observed in the LN subgroup (Table 2).

Table 2: Autoantibody and complement levels in SLE patients and healthy controls

Marker	SLE Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
ANA (IU/mL)	147.31 ± 33.90	13.90 ± 3.70	<0.001
Anti-dsDNA (IU/mL)	109.73 ± 23.42	7.20 ± 3.51	<0.001
C3 (mg/dL)	68.5 ± 12.20	110.3 ± 15.40	<0.001
C4 (mg/dL)	12.4 ± 4.10	28.7 ± 5.20	<0.001

PD-1/PD-L1 Immune Checkpoint Markers

Flow cytometry demonstrated significantly elevated proportions of PD-1+ T cells (34.50 ± 8.20% vs. 12.30 ± 4.10%; p<0.001) and PD-L1+ monocytes (28.70 ± 7.40% vs. 10.50 ± 3.50%; p<0.001) in SLE patients compared to controls. The LN subgroup exhibited the highest expression levels of both markers among all patient subgroups. Serum sPD-1 (3.42 ± 0.89 ng/mL) and sPD-L1 (2.97 ± 0.76 ng/mL) were markedly elevated compared to controls (0.85 ± 0.24 and 0.62 ± 0.18 ng/mL, respectively; p<0.001; Table 3). Representative flow cytometry histograms are presented in Figure 1.

Table 3: PD-1 and PD-L1 expression by flow cytometry and ELISA in SLE patients and controls

Marker	SLE Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
PD-1+ T cells (%)	34.50 ± 8.20	12.30 ± 4.10	<0.001
PD-L1+ Monocytes (%)	28.70 ± 7.40	10.50 ± 3.50	<0.001
sPD-1 (ng/mL)	3.42 ± 0.89	0.85 ± 0.24	<0.001
sPD-L1 (ng/mL)	2.97 ± 0.76	0.62 ± 0.18	<0.001

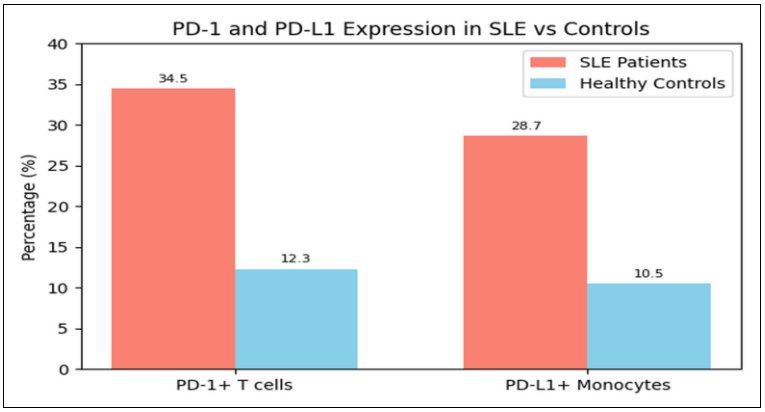

Fig 1: Representative flow cytometry histograms depicting PD-1 and PD-L1 expression in SLE patients compared to healthy controls. Filled histograms (grey) represent isotype controls; coloured histograms represent specific staining.

Thymosin β4 and Vitamin D3 Levels

Serum thymosin β4 and vitamin D3 concentrations were significantly lower in SLE patients than in controls (15.30 ± 4.51 vs. 28.70 ± 5.10 ng/mL and 12.80 ± 3.23 vs. 31.20 ± 6.00 ng/mL, respectively; p<0.001 for both). The most pronounced deficiencies were identified in the LN subgroup, which evidences the relation between renal involvement and the decline of immunomodulatory capacity (Table 4 and Figure 2).

Table 4: Serum thymosin β4 and vitamin D3 levels in SLE patients and healthy controls

Marker	SLE Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
Thymosin β4 (ng/mL)	15.30 ± 4.51	28.70 ± 5.10	<0.001
Vitamin D3 (ng/mL)	12.80 ± 3.23	31.20 ± 6.00	<0.001

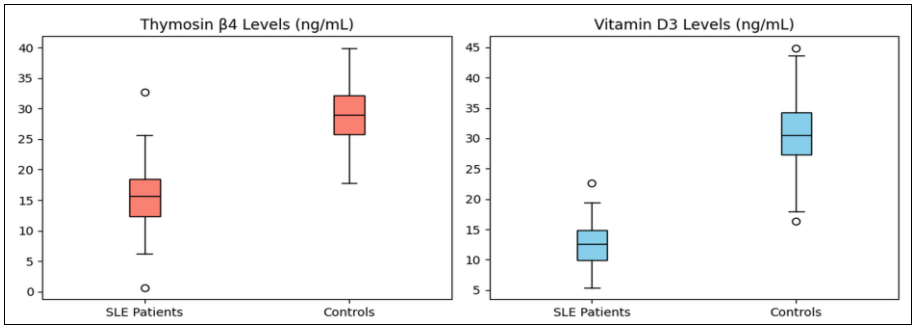

Fig 2: Box plots showing serum thymosin β4 and vitamin D3 levels in SLE patients versus controls. Medians, interquartile ranges, and 1.5×IQR whiskers are displayed; ***p<0.001 indicates significance.

Renal Function Biomarkers and Correlation with PD-1/PD-L1

The LN subgroup showed high levels of cystatin C, urea and creatinine compared to the non-renal SLE and controls ($p<0.001$). Cystatin C reached 2.95 ± 0.74 mg/L in LN patients versus 1.21 ± 0.32 mg/L in non-renal SLE and 0.84 ± 0.21 mg/L in controls. Correlation analysis found that cystatin C had the highest positive correlation with the percentage of T cells with PD-1+ ($r = 0.74$; $p<0.001$) compared to urea and creatinine as an index of immune checkpoint-mediated renal injury. This relationship can be observed in the scatter plot in Figure 3 (Table 5).

Table 5: Renal function biomarkers across patient subgroups and healthy controls

Marker	SLE-NR (Mean ± SD)	SLE-LN (Mean ± SD)	Controls (Mean ± SD)	p-value
Cystatin C (mg/L)	1.21 ± 0.32	2.95 ± 0.74	0.84 ± 0.21	<0.001
Urea (mg/dL)	35.60 ± 7.80	62.30 ± 15.10	28.90 ± 6.40	<0.001
Creatinine (mg/dL)	0.92 ± 0.23	1.78 ± 0.41	0.84 ± 0.18	<0.001

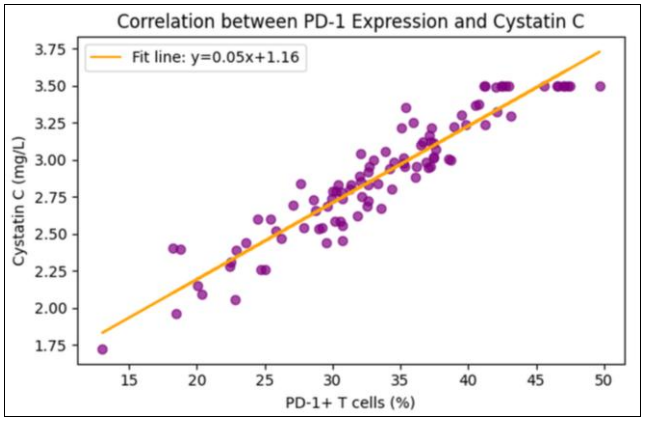

Fig 3: Scatter plot demonstrating the positive correlation between PD-1+ T cell percentage (%) and serum cystatin C concentration (mg/L) in SLE patients. The line represents linear regression fit ($r = 0.74$; $p<0.001$).

Discussion

The current research paper offers an in-depth immunological characterisation of SLE patients having chronic renal failure that combines the PD-1/PD-L1 immune checkpoint monitoring with well-established serological and biochemical biomarkers. Our data shows that there is a consistent trend of immune malregulation whereby high autoantibody titres, depletion of complement, upregulation of PD-1/PD-L1, and decreases in thymosin β4 and vitamin D3 all characterise a pathogenic milieu which is most evident in lupus nephritis patients.

Immune Checkpoint Dysregulation* in *SLE

Overexpression of PD-1 + T cells and PD-L1 + monocytes in SLE patients, especially renal involvement, supports the growing evidence of central immune checkpoint pathways in autoimmune diseases. PD-1 is traditionally considered as a negative regulator of T cell activation, but its overexpression under the conditions of chronic autoreactive stimulation can paradoxically lead to the stimulation of immune fatigue, Treg dysfunction, and the maintenance of the pathogenic immune complex formation [18]. These data, together with the fact that PD-1 expression on peripheral T lymphocytes is directly correlated with disease activity in SLE, support our findings of elevated PD-1 levels in the LN group, and are supported by the observations of other authors [19].

Autoantibodies* and *Complement* in *LN

The high levels of ANA and anti-dsDNA antibodies and concomitant decreases in C3 and C4 of the LN subgroup recapitulate the classical serological features of active lupus nephritis. Complement consumption secondary to immune complex deposition in glomerular capillaries is a well-established mechanism of renal injury in SLE. [20] Our findings support the idea that these traditional markers are still strong in their ability to discriminate against renal involvement and further highlight the informational increment of PD-1/PD-L1 analysis. Similar results were reported by Li *et al*, who indicated that PD-L1 levels in renal tissue are proportional to the extent of histological damage in LN biopsies [21]. Adding serology indexes with markers on checkpoints could thus enhance risk stratification more than each of these categories can deliver alone.

Immunomodulatory Molecules: Thymosin β4* and *Vitamin D3

The significant decreases in thymosin β4 and vitamin D3 in our SLE cohort, which are most significant in the LN subgroup, suggests an exacerbating immunoregulatory deficit which probably enhances PD-1/PD-L1 dysregulation. Thymosin β4 facilitates tissue regeneration, regulates actin cytoskeletal dynamics and inhibits NF- 0B-mediated inflammatory signalling, deficiency of which can consequently hinder resolution of glomerular inflammation [22]. Vitamin D3 has an extensive immunomodulatory effect, such as Treg differentiation and Th17 and Th1 suppression. Our results are in line with those of Cavalletti *et al*, who found that the lack of vitamin D in active LN is linked to impaired immune response and more aggressive clinical progression, [23] and to those of others. These findings indicate that supplementation approaches to address both molecules can be adjunctive treatment options in SLE.

Cystatin C* as a *Marker of Immune-Mediated Renal Injury

Cystatin C, one of the renal biomarkers tested, showed a higher correlation with PD-1 expression ($r = 0.74$; $p<0.001$) than the traditional creatinine-based measurements. This aligns with previously established superiority of cystatin C as a marker of early GFR deterioration, especially in inflammatory conditions in which tubular secretion of creatinine can be disturbed. The predictive value of cystatin C in renal injury caused by autoimmune processes was earlier determined by Ercan *et al*. [24] and our results further verify this conclusion by directly relating the activation of the checkpoints to the increase of cystatin C. The hypothesis that PD-1/PD-L1-mediated immune dysregulation is a mechanistic pathway in the disintegration of the glomerular filtration barrier is confirmed by this association, which offers a new functional relationship between systemic immune checkpoints and nephropathological outcomes.

Contrasting Evidence and Study Limitations

Not every published data are entirely in agreement with our findings. Heterogeneous PD-1 expression pattern was reported in different disease subsets in SLE with reports of some patients with mild disease having lower PD-1 expression, [25] indicating that checkpoint dynamics may be different depending on the phase of the disease, tissue compartment, and whether patients are treated or not. Huang *et al*. did not find any significant correlation between soluble PD-L1 and renal involvement in a smaller group of SLE, [26] which might be because of methodological variation or ethnicity-disproportionate immune response. These discrepancies highlight the intricacy of immune checkpoint control in autoimmune diseases and the need of multicentre studies that follow-up. The cross-sectional nature of our study, which does not allow causality, and lack of histopathological correlation of all LN cases are also limitations of our study. To enable causal relationships to be established, longitudinal checkpoint profiling, renal biopsy data and mechanistic studies should be included in the future.

***Clinical* and *Therapeutic* Implications**

Our findings have significant clinical implications. The regular connection of high PD-1/PD-L1 with LN severity indicates that these checkpoint molecules may be utilized as non-invasive serum biomarkers to track the renal progression and make therapeutic choices in patients who have renal biopsy intolerable risks. Moreover, therapeutic value of checkpoint modulation in SLE is a developing field; close adjustments of PD-1/PD-L1 inhibitory versus stimulatory programs will be needed to prevent the enhancement of autoimmunity and to restore immunohomeostasis. The combination of cystatin C, thymosin β4, and vitamin D3 with regular SLE monitoring panel could improve the ability to identify cases of renal dysfunction early and help to tailor treatment therapies.

Conclusion

This current study demonstrates shows that the immune checkpoint dysregulation of PD-1/PD-L1 is strongly linked with involvement of kidneys in SLE as indicated by significantly high cellular and soluble checkpoint markers in the lupus nephritis subgroup. High autoantibodies, low levels of complement, low levels of thymosin β4 and vitamin D3, and high levels of cystatin C are characteristic of an immunoregulatory environment that is disrupted and supports the development of progressive renal damage. Cystatin C also became the most strongly correlated renal biomarker with the checkpoint dysregulation, which highlights the significance of its application as a sensitive marker of immune-mediated glomerular damage. A PD-1/PD-L1 analysis combined with standard immunological and renal biomarker panels offers a holistic system of disease monitoring and prognostication and the checkpoint molecules are potential targets of immunotherapeutic intervention in the future in SLE-related chronic renal failure.

Ethical approval: Approved by the Institutional Review Board of Ibn Sina University of Medical and Pharmaceutical Sciences. All participants provided written informed consent.

Conflicts of interest: None

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