Application of RIFLE criteria in Chinese patients with ANCA-associated renal vasculitis

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Abstract

Background

Antineutrophil cytoplasmic autoantibody (ANCA) associated small vessel vasculitis (AASV) constitutes a group of life-threatening diseases and renal involvement is its most severe and common manifestation. Acute kidney injury (AKI) is common in patients with AASV but the value of RIFLE criteria is still unclear in those patients.

Methods

We performed a retrospective study on patients with AASV in Shanghai Ruijin Hospital from 1997 to 2008.

Results

A total of 147 ANCA-associated renal vasculitis patients were studied and 92 developed AKI at diagnosis. According to RIFLE classification, 8 (8/147, 5.44%) patients had AKI-R, 15 (15/147, 10.20%) had AKI-I and 69 (69/147, 46.94%) had AKI-F. Our results demonstrated that more hypertensive patients and higher BVAS were found in patients with AKI-F than those in other groups ($p<0.01$ and $p<0.01$, respectively). Survival rate was significantly lower among patients with advanced RIFLE categories during remission-induction therapy ($p<0.05$). Survival rate of 1 year and total survival rate were significantly lower among patients with advanced RIFLE categories ($p<0.01$, $p=0.001$, respectively). Cox regression analysis demonstrated that advanced RIFLE categories were associated with a worse prognosis of the patients (OR=1.706, 95%CI: 1.262–2.307, $p<0.01$). The area under the ROC curve for mortality was 0.718 (95% CI: 0.63–0.81, $p<0.001$).

Conclusion

The RILFE criteria is a valid measurement of both prognosis and progression in patients with AASV.

Key words

ANCA, antineutrophil cytoplasmic autoantibody, CKD, chronic kidney disease, RIFLE, AKI, acute kidney injury, vasculitis

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Introduction

Antineutrophil cytoplasmic autoantibody (ANCA) associated small vessel vasculitis (AASV) constitutes a group of life-threatening diseases which include Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) and their localised forms (1). Renal involvement is the most common and severe manifestation of AASV and could be presented in more than 50% of patients at diagnosis (2-4). Acute kidney injury (AKI) is a critical condition which is defined as deterioration of renal function within a short interval of time and is a common manifestation in patients with AASV (5, 6). In our previous study, we demonstrated that renal function at disease onset was important to patients' prognosis (7). In this sense, evaluating renal impairment at presentation could provide us with important information to stratify treatment according to probable outcome.

Risk-Injury-Failure-Loss-End-stage renal disease (RIFLE) classification (8) is now widely used to evaluate clinical situations of patients with AKI. However, the clinical value of RIFLE has not been fully evaluated in vasculitic patients. We therefore carried out the current study to investigate RIFLE classification in AASV patients with AKI so as to further assess its clinical values.

Patients and methods

Patients

From 1997 to 2008, patients with newly onset ANCA-associated vasculitis from Ruijin Hospital were studied. Only patients with renal involvement were enrolled in the current study. The diagnosis was made according to Chapel Hill Consensus Conference (CHCC) and American College of Rheumatology (ACR) criteria (1, 9, 10). Renal involvement was defined as renal insufficiency attributable to the disease, proteinuria with protein >300 mg/day, or microscopic hematuria with >10 erythrocytes/high-power field on two separate occasions in the absence of urinary infection. Patients with anti-glomerular basement membrane disease or secondary causes of vasculitis were excluded.

RIFLE classification

RIFLE criteria classify levels of renal dysfunction into three severity categories (Risk, Injury and Failure) and two clinical outcome categories (Loss and End-stage renal disease). The patients were assigned to their worst RIFLE category according to serum creatinine. The baseline creatinine was defined in two ways. For patients who had recorded serum creatinine, the baseline serum creatinine was defined as last recorded value before disease onset. For patients without recorded serum creatinine, the simplified "modification of diet in renal disease" (MDRD) formula was used to estimate the glomerular filtration rate (GFR), as recommended by the ADQI workgroup (8).

ANCA analysis

All the patients were tested for ANCA by indirect immunoflurescence (IIF; Euroimmun, Lübeck, Germany) as well as antigen-specific enzyme-linked immunosorbent assay (ELISA, Euroimmun, Lübeck, Germany) for myeloperoxidase (MPO) and proteinase 3 (PR3) as we previously described (7, 11).

Treatment protocols

The patients were treated with pulsed intravenous cyclophosphamide (CTX) in combination with corticosteroids in a tapering schedule for remission induction therapy. Oral prednisone was given at an initial dosage of 0.8–1.0 mg/kg/day for 1–2 months tapering to 20 mg/d by 3–6 months. Pulsed intravenous CTX was given at $0.5 g/m^2$ every month and adjusted according to the patients' leukocyte count. Dose reduction of CTX was made for those older than 65 years or leukocyte count less than $4\times10^{9}/l$. Pulse methyl prednisolone or plasma exchange were added to those patients with severe renal involvement or alveolar haemorrhage. For the remission maintenance therapy, patients were treated with low dose oral prednisone together with mycophenolate mofetil (MMF) or CTX after 3–6 months of remission induction therapy. Cotrimoxazole was added to patients with WG for *Pneumocystis carinii* (PC) prophylaxis while receiving remission induction therapy.

Table I. Demographic features of patients.

	No AKI	AKI-R	AKI-I	AKI-F
n. of patients	55	8	15	69
Age at presentation, yr (mean)	55.8 ± 17.6	53.9 ± 19.7	57.7 ± 16.4	61.5 ± 13.6
Male/female	24/31	4/4	5/10	39/30
ANCA at presentation (n, %)				
P-/MPO-ANCA	37 (67.3%)	7 (87.5%)	13 (86.7%)	59 (85.5%)
C-/PR3-ANCA	18 (32.7%)	1 (12.5%)	2 (13.3%)	10 (14.5%)
Diagnosis of patients (n, %)				
Microscopic polyangiitis	33 (60.0%)	6 (75.0%)	12 (80.0%)	53 (76.8%)
Wegener's granulomatosis	11 (20.0%)	0	2 (13.3%)	9 (13.0%)
Churg-Strauss syndrome	3 (5.5%)	1 (12.5%)	0	0
Renal limited vasculitis	8 (14.5%)	1 (12.5%)	1 (6.7%)	7 (10.1%)

Statistics

SPSS 11.0 (SSPS Inc., Chicago, IL., USA) was used for statistical analysis. Data were presented as mean ±SD or otherwise indicated. The differences in qualitative results were compared using the χ^2 test or Fisher's exact tests. Differences in quantitative parameters between groups were performed with the *t*-test (for normally distributed data) or non-parametric test (for non-normally distributed data). Kaplan-Meier curves were used to analyse survival. Cox regression analysis was used to assess the association of the RIFLE classification with prognosis. Model fit was assessed by the goodness of fit test, and discrimination was assessed by the area under receiver operator characteristic (Au-ROC) curve. $P<0.05$ was considered statistically significant.

Results

Demographic features

A total of 147 ANCA-associated renal vasculitis patients were admitted during the study period and 92 developed AKI at diagnosis. According to RIFLE classification, 8 (8/147, 5.44%) patients had AKI-R, 15 (15/147, 10.20%) had AKI-I and 69 (69/147, 46.94%) had AKI-F. Details are summarised in Table I.

We compared the clinical and laboratory data of patients with AKI and without AKI at presentation (Table II). Our results demonstrated that more hypertensive patients and higher BVAS were found in patients with AKI-F than those in other groups (both $p<0.01$). Our results also found that more patients with AKI-I had neurological system involvement than those without. No other clinical manifestations were found significantly different among the patients.

Clinical course of AKI and outcome

The clinical course of patients with AKI are demonstrated in Figure 1. For the cumulative survival rate, our results found that the survival rate was significantly different among patients with different RIFLE categories during remission-induction therapy ($p<0.05$). Further analysis also demonstrated that survival rate of one year and total survival rate were significantly different ($p<0.01$, $p=0.001$ respectively) among patients by different RIFLE categories. In all, our results showed that more advanced RIFLE category was associated with worse survival rate (Fig. 2).

For renal outcome, our study showed that more patients with AKI-F developed ESRD than those in other groups (AKI-F *vs*. AKI-R: $p<0.01$; AKI-F *vs*. AKI-I $p<0.01$). And patients with AKI-F had a lower percentage of renal recovery (AKI-F *vs*. AKI-R: $p<0.01$; AKI-F *vs*. AKI-I $p<0.01$). Details are summarised in Figure 3.

To investigate the relationship between RIFLE categories and outcome of the patients, we analysed the data by Cox regression analysis. Our results suggested that advanced RIFLE categories were associated with worse prognosis (OR=1.706, 95%CI: 1.262–2.307; $p<0.01$). The ROC curve model presents the true-positive and false-positive rates for mortality of the patients, and the area under the ROC curve for mortality was 0.718 (95% CI: 0.63–0.81, $p<0.001$) (Fig. 4)

Discussion

ANCA-associated vasculitis is a multisystem autoimmune syndrome which affects small-to-medium-size blood

Table II. Comparison of clinical features at presentation between patients with AKI by RIFLE classification and patients without AKI.

	No AKI (n=55)	AKI-R (n=8)	No AKI *vs*. AKI-R, *p*	AKI-I (n=15)	No AKI *vs*. AKI-I, *p*	AKI-F (n=69)	No. AKI *vs*. AKI-F, *p*
Hypertension, n (%)	27 (49.1%)	4 (50.0%)	NS	10 (66.7%)	NS	50 (72.5%)	<0.01
Fever, n (%)	26 (47.3%)	3 (37.5%)	NS	11 (73.3%)	NS	34 (49.3%)	NS
BVAS at presentation (median)	20	20.5	NS	21	NS	25	<0.01
Renal involvement (mean)							
Serum creatinine, μmol/L	140.7 ± 77.0	152.3 ± 56.9	NS	213.1 ± 49.4	$p<0.05$	648.9 ± 294.8	$p<0.001$
Proteinuria, mg/d	1190.1 ± 1062.8	1485.3 ± 1686.5	NS	2010.5 ± 1656.6	$p<0.05$	1783.6 ± 1775.9	NS
eGFR, ml/min	51.9 ± 30.8	38.9 ± 17.3	NS	23.7 ± 6.8	$p<0.05$	7.8 ± 4.1	$p<0.001$
Extra-renal involvement, n (%)							
Pulmonary	32 (58.2%)	5 (62.5%)	NS	12 (80.0%)	NS	51 (73.9%)	NS
Skin	7 (12.7%)	1 (12.5%)	NS	3 (20.0%)	NS	5 (7.2%)	NS
ENT	16 (29.1%)	3 (37.5%)	NS	4 (26.7%)	NS	19 (27.5%)	NS
Gastrointestinal tract	3 (5.5%)	1 (12.5%)	NS	1 (6.7%)	NS	9 (13.0%)	NS
Neurological system	14 (25.5%)	2 (25.0%)	NS	0	$p<0.05$	15 (21.7%)	NS
Cardiovascular	1 (1.8%)	0	NS	0	NS	3 (4.3%)	NS

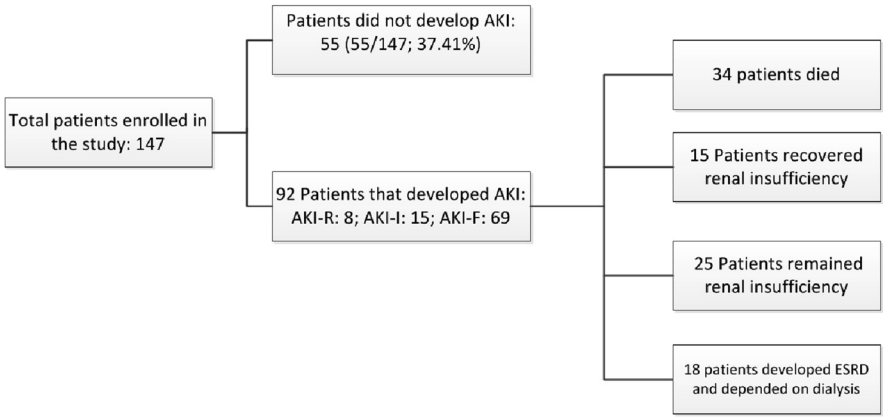

Fig. 1. Flow chart of the clinical course and follow-up of the patients enrolled in the current study. Data expressed as patient numbers who were identified at each level; AKI: acute kidney injury.

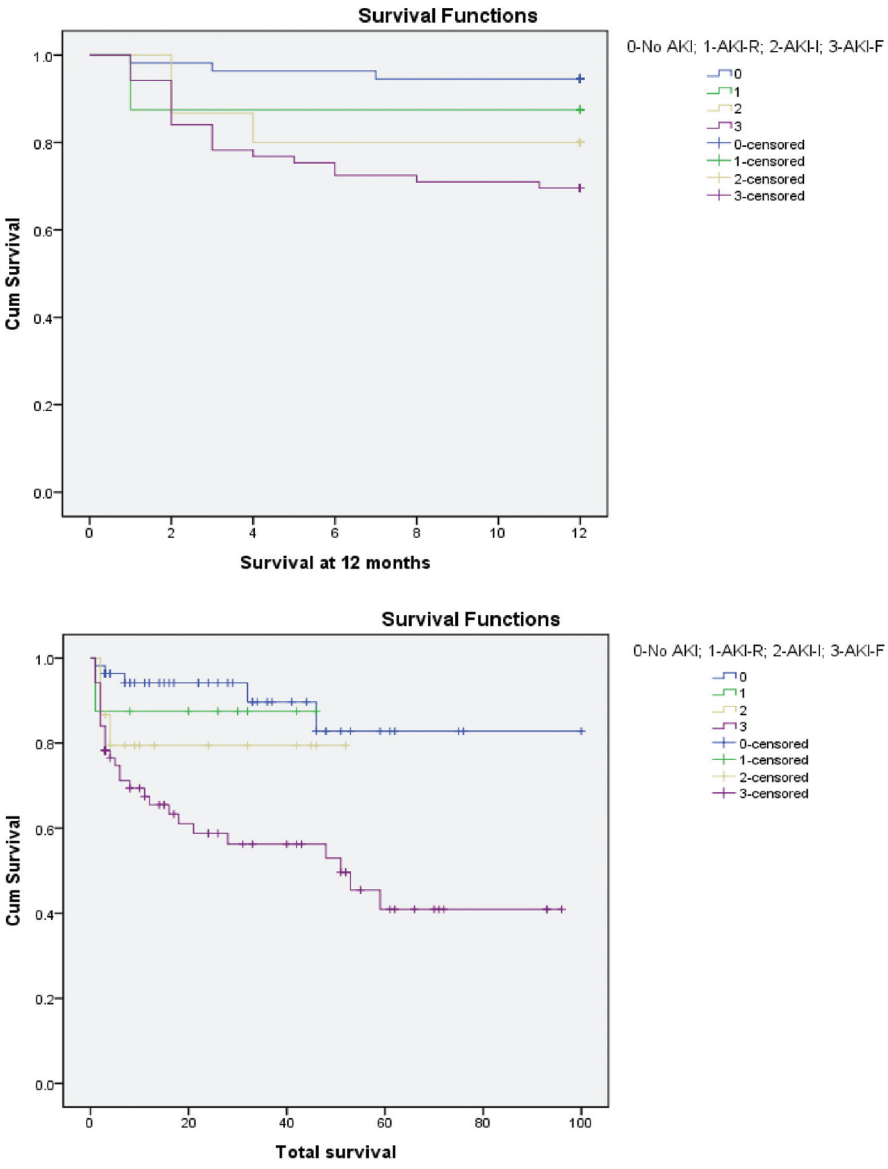

Fig. 2. Survival of the patients by RIFLE category.
We analysed survival by Kaplan-Meier curves. The results suggested that a one-year survival rate was significantly different among patients with different RIFLE categories (p<0.01). Further analysis suggested that total survival rate was significantly different among those patients (p=0.001).

vessels and is closely associated with high mortality (12, 13). Patients with AASV could present with multi-organ involvement, including renal involvement, pulmonary involvement, CNS involvement and others at disease onset (14-16). Renal involvement occurs in more than half of the patients at presentation and could present as RPGN as well as acute kidney failure (ARF) (4, 6, 17). In 2004, Acute Dialysis Quality Initiative (ADQI) Group proposed to use Acute kidney injury (AKI) to reflect the entire spectrum of ARF. The definition of AKI also encompasses the whole spectrum of the syndrome from minor changes in renal function to requirement for renal replacement therapy (8, 18-20). RIFLE classification was thus created to evaluate patients who are critically ill and has been widely used in clinical practice nowadays; however, its value in AKI caused by secondary renal diseases is seldom studied.

In the present study, there were more patients in the AKI-F groups than those in other groups. The difference suggests that renal involvement might be severe even at disease onset in patients with AASV. Similar results were also found by Harper and colleagues (21) in their elderly patients whose median creatinine was >400 μmol/L at diagnosis. Furthermore, there were more hypertensive patients in AKI-F group (No AKI *vs*. AKI-F, p<0.01). Those findings are consistent with different distribution of patients by RIFLE classifications because blood pressure is known to be associated with impairment of renal function. Our results thus urge the necessity to evaluate and stratify the severity of renal impairment of vasculitic patients at disease onset.

Our results also suggest that more advanced RIFLE classification was associated with worse clinical outcome. Patients with AKI-F had a higher mortality and lower recovery rate of kidney impairment in comparison with patients with other RIFLE classifications. Furthermore, Cox regression analysis suggested advanced RIFLE classification was associated with poor prognosis of the patients. Our results suggest that evaluating and stratifying renal injury

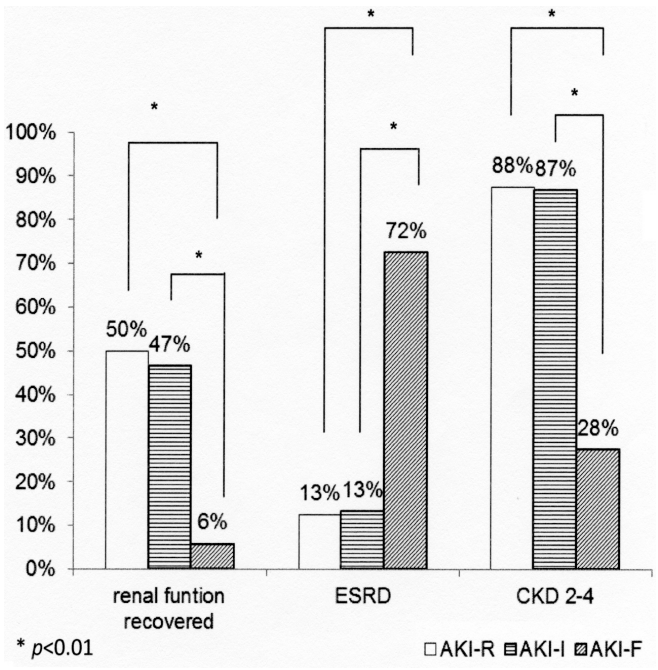

Fig. 3. Outcome of patients with AKI by RIFLE classification.

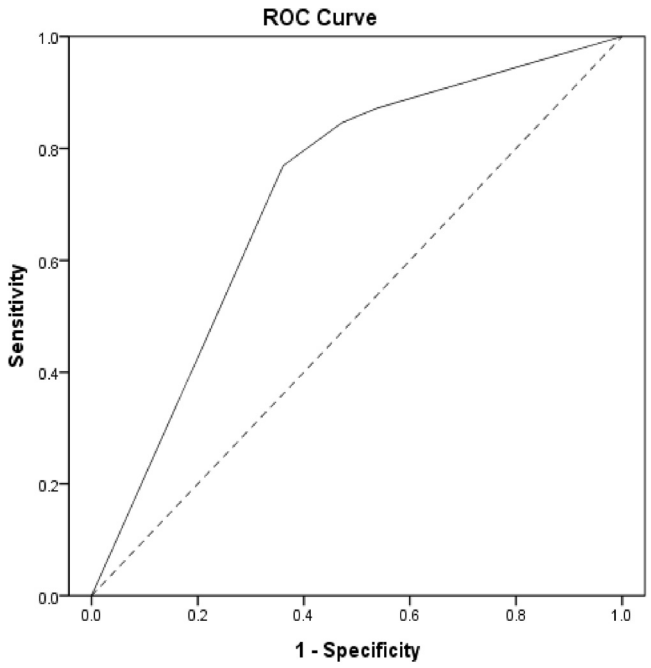

Fig. 4. ROC curves for RIFLE classification.

at disease onset using RILFE classification might be helpful to predict the outcome of the patients with AASV.

BVAS is a standard assessment tool for scoring disease activity in ANCA associated vasculitis (22). It uses several categories of clinical manifestations and laboratory data to score the disease activity. Renal abnormality in BVAS was defined as hypertension, proteinuria, haematuria and creatinine abnormality (details might differ in different versions) (22, 23). Though the studies pointed out that BVAS were reliable and replicable (24), its definition of renal abnormality might not fully take into account the severity of creatinine change and GFR loss when AKI was present, especially in patients with acute-on-chronic kidney diseases. Moreover, the change in creatinine or GFR in BVAS could not stratify patients with different severity of renal impairment. In this sense, RIFLE classification could be used as a compensatory tool to BVAS to predict outcome of AASV patients with AKI. Our results support the notion that RIFLE classification is also useful for measuring disease severity and prognosis of patients with secondary renal diseases (25).

Although RIFLE has been demonstrated to be reliable and applicable in clinical practice, there are still limitations and imperfections in the classification (18, 26, 27). One of the limitations is how best to determine the RIFLE category when the baseline serum creatinine is not known (26, 27). ADQI suggested that the MDRD formula could be used to estimate baseline creatinine, but it might not fully represent the exact baseline creatinine of the patients. Závada *et al*. (28) compared three methods to estimate baseline creatinine for RILFE classification, the results showed that recorded creatinine values should be used as a reference of baseline whenever possible. The use of an MDRD equation might not estimate the risk of AKI accurately in some occasions, but it is unlikely to misclassify patients in AKI-Injury or AKI-Failure. A similar result was also found by Pickering *et al*. (29) which suggested measured creatinine should be used for baseline creatinine value. In this study, we used recent recorded serum creatinine values as baseline creatinine whenever possible to minimise the bias caused by the MDRD formula to estimate baseline values. Since there were several limitations in RIFLE classification, AKIN classification was then created but there were still imperfections in the classification scheme. One crucial point is that AKIN requires the 48-hr timeframe within which the diagnosis of AKI is made (18). This timeframe prevented AKIN from being applied in many retrospective studies, in which every-other-day creatinine values were not available. For this reason, it might be plausible to believe that AKIN would be used prospectively while RIFLE would be used retrospectively (26, 30). Another study pointed out that such a limitation might also result in under-recognising AKI (26). Some studies demonstrated that the RIFLE criteria are more sensitive for AKI diagnosis and more precise for predicting outcome than AKIN, while the AKIN criteria is not much better than the RIFLE criteria (19, 27, 31-33). Therefore, applying different AKI classification according to clinical situations and studying purposes might be one good strategy to evaluate patients with AKI.

Urine output is another criteria for RILFE classification apart from GFR criteria. Recent studies point out that serum creatinine level and urine output criteria should not be given equal weighting while evaluating patients with AKI because urine output is often affected by diuretic treatment, many cases of AKI might be nonoliguric in

nature and patients with oliguric AKI have a worse outcome than nonoliguric AKI (27, 34-36). Though RIFLE classification has been refined, this issue has not been fully resolved by AKIN classification as diagnosis of AKI is still based on clinical parameters and diagnosis could be considered to be pathophysiologically late (26). In our retrospective study, we did not use urine output criteria because the data of urine output change were not available in some patients. In a retrospective study which only 24-hr urine output was available, Bagshaw *et al*. (28) tried to resolve this issues by using modified criteria of urine output to define AKI stages. Though the study provided interesting and valuable findings, some authors were still uncertain about such modifications (26). In this sense, further study is necessary to improve urine output criteria in RIFLE/AKIN classifications; perhaps a combination of urine output, GFR and other AKI biomarkers including neutrophil gelatinase-associated lipocalin (NGAL) (37, 38), kidney injury molecule-1(KIM-1) (39), cystatin C(40), interleukin-18 (IL-18) (41, 42), cysteine-rich protein 61(CCN1) (43) and spermidine/spermine N(1)-acetyltransferase (SSAT) (44) would be a rational way to improve the classification.

In conclusion, the present study has shown that the more advanced RIFLE classification is associated with worse outcome in vasulitic patients with AKI. Further analysis suggested that RIFLE and BVAS could both be predicative indicators for outcome of AASV patients with AKI

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