Clinical, Laboratory Characteristics, Comorbidity and Function in Elderly patients with Rheumatoid Arthritis

Eman Abdel Ghani Sayed[a*], Anna Abou-Raya[a], Magdy El-Bordiny [b], Kareem Yehia[a]
[a]Department of Internal Medicine (Division of Rheumatology and Clinical Immunology), Faculty of Medicine, Alexandria University, Alexandria, Egypt.
[b]Clinical and Chemical Pathology , Faculty of Medicine, Alexandria University, Alexandria, Egypt.

Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease affects several body systems as well as the synovial tissue. RA decreasing the health related quality of life (QoL) and functional abilities. Many challenges in the management of elderly RA because of the presence of "geriatric syndromes" as frailty, mobility, risk of falls, fractures and polypharmacy, all of which have an effect on the disease course and treatment.

Objectives: To evaluate the clinical, laboratory and comorbid characteristics of elderly RA patients and its impact on function and quality of life.

Patients and methods: Sixty elderly RA of both sexes aged ≥ 60 years fulfilling the 2010 EULAR/ACR classification criteria.

Comprehensive geriatric assessment (CGA), CBC, FBS, 2hr PP, thyroid function tests, lipid profile, ESR, CRP, ACPA, RF, liver and kidney function, uric acid, BMI, DAS28-CRP, VAS and HAQ score.

Results: Significant reduction in health QoL regarding mobility, fall risk, depression scale, significant elevated levels of ACPA, RF, ANA, high disease activity score -28 CRP (> 5.1).

Significant association with disease comorbidity factors; hypertension (p=0.632), cerebrovascular (p <0.001), cardiovascular (p < 0.001), diabetes (p < 0.001), respiratory disease (p < 0.001) and methotrexate treatment.

Conclusion: Elderly RA patients showed impaired function and lowered health QoL. Comorbidity and markers of disease activity were higher in elderly RA therefore, when treating elderly RA careful attention is needed to associated comorbidities, treatment should aimed at achieving adequate control and clarifying the complex interrelationship between elderly RA and their associated "geriatric syndromes".

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***Correspondence**: eman96abdelghani@gmail.com
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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that may cause joint destruction and dysfunction due to synovitis and bone erosion **(Shourt et al., 2022).** RA is more common between 40 and 60 years **(Rasch et al., 2003)**, and treatment response to methotrexate (MTX) and biologics is comparable among younger and older patients with RA **(Koller et al., 2023)**.Older patients with RA are more difficult to treat due to associated high disease activity **(Sokka et al., 2007; Burmester et al., 2023).** Previous reports have shown that rheumatoid patients with comorbidities have higher disease activity and worse outcomes than patients without comorbidities **(Treharne et al., 2007; Jung et al., 2018)**, but, few reviews have examined the relationship between specific comorbidities and disease activity in RA **(Ranganath et al., 2013 ; Crepaldi et al., 2016).**

Comparing RA patients to the overall population, their life expectancy is shortened. Death rates are higher in cases when the disease is more severe, reduced radiologic damage and a worse functional state. Therapy has been shown to affect disease outcomes, despite the fact that comorbidities and socioeconomic, educational, and marital status have been associated with a higher risk of mortality **(Symmons et al., 2015; Almoallim et al., 2021).** An early onset of immunological breakdown that happens with aging and is irrespective of disease duration, is the inappropriately accelerated immunosenescence which is a unique characteristic **(Roubille et al., 2014 ; Tokuda et al., 2017).**

Elderly RA patients also more likely to experience chronic disease-associated anemia, which exacerbates functional impairment, cognitive dysfunction and results in greater disability and a propensity towards depression among these individuals **(Chen et al., 2019).** Autoantibodies against citrullinated protein (ACPAs) and the presence of rheumatoid factor (RF) are two RA indicators. There are many challenges in the management of RA in the elderly because of the presence of "geriatric syndromes" such as frailty, mobility, risk of falls, fractures and polypharmacy, all of which can have an effect on the disease course and treatment **(Isik et al., 2017).** Consequently, malnutrition aggravates GS in elderly RA patients, aggravating RA symptoms and functional outcomes. It follows that older RA patients would benefit more from effective RA treatment in terms of both their physical and psychological outcomes **(Ruban et al., 2016).**

Our study aims to evaluate the clinical, laboratory and comorbid characteristics of elderly RA patients and its impact on function and quality of life.

Patients and methods

Type of the study: Prospective observational study.

Setting: The study was conducted on 60 patients aged above 65 years old recruited from the Rheumatology Clinics of Alexandria Main University and from Internal Medicine department.

Ethical consideration: An informed written consent from all patients was obtained according to the declaration of Helsinki.The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Alexandria University (EC serial number: 0106551)(IRB NO: 00012098-FWA NO: 00018699).

Inclusion criteria: Sixty elderly patients with RA of both sexes aged ≥ 60 years fulfilling the 2010 EULAR/ACR classification criteria **(Aletaha et al., 2010 ; Aggarwal et al., 2015).**

Exclusion criteria: Concomitant other autoimmune diseases, severe life threatening diseases as severe dementia, past history of cancer or active viral hepatitis.

Methods

1-Full medical history taking with specific stress on duration of mourning stiffness, number of swollen and tender joints, previous joint surgery, arthroplasty, history of falls and fractures.

2-Complete physical examination was performed with specific stress on examination of musculoskeletal system.

3-Medication history especially use of methotrexate, hydroxychloroquine, sulphasalazine, leflunomide, glucocorticoids and NSAIDs.

4-General examination for detection of extra-articular disease manifestations: as subcutaneous nodules, anaemia, sicca syndrome (dry eyes, dry mouth), interstitial lung disease (ILD), serositis, scleritis

,episcleritis, vasculitis and peripheral neuropathy.

5-Co-morbidity assessment: detection of hypertension, cerebrovascular disease, cardiovascular disease, renal disease, liver disease, non-alcoholic steatohepatitis (NASH), diabetes mellitus, hypothyroidism, gout, osteoarthritis, osteoporosis and associated infections (COVID-19).

6-Comprehensive geriatric assessment involving functional assessment using Katz activities of daily living (ADLs) **(Prevoo et al., 1995)**, mobility assessment using (timed Get up and Go test), cognitive assessment using mini mental examination (MMSE) **(Koh et al., 1998)**, depression assessment using Geriatric Depression Scale (GDS-15)**(Carlsson et al.,1983)**,fall risk assessment using the Fall Risk Checklist, nutritional assessment using the mini nutritional scale (MNA)**(Katz et al., 1970)**, assessment of frailty using Frailty index measurement **(Pangman et al., 2000).**

7-Functional assessment scores using (DAS-28-CRP) **(Yesavage et al., 1982)**,Visual analogue pain scale (VAS) **(Vellas et al., 1999)**, Functional and Quality of Life (QoL) assessment scores using Health Assessment Questionnaire (HAQ) score **(Fried et al., 2001; Brain 2010).**

8-Laboratory tests:complete blood count and differential count **(Johnston et al., 1999)**, fasting and 2 hrs postprandial blood glucose, blood urea, serum creatinine **(Tippins et al., 2000)**, ESR, CRP mg/dl **(Gabay et al., 1999)**, SGPT,SPOT **(Hermann et al., 1996).** 9-Immunological Profile: Rheumatoid Factor (RF) titre **(Detrick et al., 2006)**, Antinuclear antibody (ANA) and Anticitrullinated Protein Antibody (Anti-CCP Abs) using ELISA technique **(Montes et al., 2016).**

10-Body Mass Index (BMI) assessment according to the WHO criteria and categorized as normal, overweight and obese **(Hales et al., 2018).**

Statistical analysis

Data were entered into a computer system and subsequently analyzed using the IBM SPSS version 20.0 software package.(Armonk, NY: IBM Corp).

Normality was tested using the Kolmogorov-Smirnov test. Quantitative data were analyzed using minimum, maximum, mean and standard deviation, median and interquartile range (IQR).

Qualitative data were evaluated using the Chi-square test.An independent t-test was used for comparison between groups. Multivariate correlations between study variables were calculated using odd ratio (OR) and confidence interval (CI). Pooled results were evaluated for statistical significance at the 5% significance level. Values < 0.05 were considered statistically significant

(Kotz et al., 2006 ; Kirkpatrick et al., 2015).

Results

Distribution of elderly rheumatoid cases according to demographic data.**Table1.** Distribution of the study cases based on signs and symptoms.**Table 2.**

Table 1.Demographic data of the studied group, (n=60)

Variables	No.	%
Sex		
male	26	43.3
female	34	56.7
age(years)		
Min-Max.	65-73	
Mean±SD	68.4±2.3	
Median(IQR)	68(66.0-71.0)	
Smoking Status		
Non Smoker	45	74.0
Smoker	15	25.0
BMI Classification		
Normal(18.5-24.9)	15	25.0
Pre obesity(25-29.9)	25	41.7
Class I obesity(30-34.9)	18	30.0
Class II obesity(35-39.9)	2	3.3

BMI(kg/m^2)		
Min-Max	21-35	
Mean±SD	27.18±4.09	
Median(IQR)	27(24.25-30.0)	
Educational Level		
Illiterate	8	13.3
Primary	1	1.7
Preparatory	1	1.7
Secondary	26	43.3
University	24	40.0

SD: standard deviation; IQR: interquartile range

Table 2. Signs and symptoms of the studied group,(n=60)

Variables	**No.**	**%**
Joint pain		
Present	60	100.0
Joint erosions		
Absent	8	13.3
Present	52	86.7
Fatigue		
Absent	46	76.7
Present	14	23.3
Joint stiffness		
Present	60	100.0
Mourning stiffness		
Min-Max.	0.25-1.50	
Mean±SD	0.58±0.36	
Median(IQR)	0.43(0.25-0.43)	
Duration of stiffness		
Morning	60	100.0
Pallor		
Absent	60	100.0
Xanthelasma		
Absent	55	91.7
Present	5	8.3
Hyperpigmentation		
Absent	51	85.0
Present	9	15.0
Skin rash		
Absent	55	91.7
Present	5	8.3

SD: standard deviation; IQR: interquartile range

Distribution of the study cases based on (DAS28-CRP); most of the patients (41 patients; 68.3%) showed high disease activity (>5.1), while 18 patients (30%) showed moderate disease activity (>3.2 to 5.1) and only one patient (1.7%) showed low disease activity (>2.6 to 3.2), (**Table.3).**

Table 3. DAS28-CRP in the studied group, (n=60)

Disease activity score of 28 joints (DAS-28-CRP)	**No.**	**%**
High disease activity(>5.1)	41	68.3
Moderate disease activity(>3.2 to 5.1)	18	30
Low disease activity(>2.6 to 3.2)	1	1.7
Min-Max	3.02-5.90	
Mean±SD	4.35±0.90	
Median(IQR)	4.34(3.57-5.08)	

SD: standard deviation ; IQR:interquartile range

Distribution of the study cases according to Katz assessment, MMSE, Mobility, MNA, and GDS scores; among the studied cases, the Katz score (ADL) (out of 12) ranged from 3 to 6 with a median (IQR) of 5 (4.0-6.0), MMSE that was used to check for cognitive impairment (out of 30), ranged from 23 to29 with a median (IQR) of 26 (24.0-27.75); more than half of the cases showed good scores (26-30), representing 53.3% while 46.7% showed mild impairment; motility assessment score ranged from 15 to 20 with a median (IQR) of 18.0 (16.0-19.0); according to the motility assessment, all patients had a risk of falling (>12); elderly patient's nutritional status was graded using the MNA, ranged from 8 to 13 with a median (IQR) of 10.0 (9.0-11.0); according to the MNA, all patients were malnourished (<17); (GDS) ranged from 4 to 12 with a median (IQR) of 9.0 (7.0-11.0) ; more than half of the patients were suggested to be depressed (score >5) (31 patients; 51.7%),while 20 patients (33.3%) had obvious depression (score >10), and 9 patients (15%) showed normal scores, indicating no depression, (**Table. 4).**

Table 4. Katz assessment, MMSE, Mobility, MNA, and GD scores in the studied group (n=60).

Katz Activity of Daily Living (out of 12)		
Min-Max.	3.0 – 6.0	
Mean±SD	4.55 ± 1.12	
Median(IQR)	5.0 (4.0 – 6.0)	
Mini Mental State Exam (MMSE) (out of 30)		
Min-Max	23.0-29.0	
Mean±SD	25.83±1.95	
Median(IQR)	26.0(24.0-27.75)	
	No.	%
Questionably significant (26-30)	32	53.3
Mild (21-25)	28	46.7
Moderate(10-20)	0	0.0
Mobility Assessment Score (get and go)		
Min-Max.	15.0-20.0	
Mean±SD.	17.53±1.59	
Median(IQR)	18.0(16.0-19.0)	
	No.	%
<12 (no risk of falling)	0	0.0
>12 (risk of falling)	60	100.0
Mini Nutritional Assessment (MNA)		
Min-Max.	8.0-13.0	
Mean±SD.	10.17±1.64	
Median(IQR)	10.0 (9.0-11.0)	
	No.	%
Normal(24-30)	0	0.0
Risk of malnutrition(17-23.5)	0	0.0
Malnourished(<17)	60	100.0
Geriatric Depression Score (GDS)		
Min-Max.	4.0-12.0	
Mean±SD.	8.70±2.5	
Median(IQR)	9.0 (7.0-11.0)	
	No.	%
Score<5	9	15.0

Suggest depression>5	31	51.7
Indicative of depression>10	20	33.3

SD:standard deviation ; IQR:interquartile range

Distribution of the study involved patients according to blood pressure, (**Table 5).** Distribution of the examined cases according to neurological, chest, liver, kidney and thyroid examination. **Table 6.**

Table 5. Blood pressure in the studied group (n=60)

Systolic blood pressure (mmHg)	
Min-Max	110-160
Mean±SD	133.67±13.40
Median(IQR)	130(121.25-145)
Diastolic blood pressure (mmHg)	
Min-Max	70-105
Mean±SD	86.42±9.87
Median(IQR)	85(80-100)

SD: standard deviation; IQR:interquartile range

Table 6. Neurological, chest, liver, kidney and thyroid examination in the studied group (n=60)

Variables	**No.**	**%**
Neurological abnormality		
Absent	48	80.0
Present	12	20.0
Numbness of one side of the body		
None	53	88.3
Left	4	6.7
Right	3	5.0
Lower limb numbness		
Absent	57	95.0
Present	3	5.0
History of stroke		
Absent	50	83.3
Present	10	16.7
Side weakness		
None	57	95.0
Left	1	1.7
Right	2	3.3
Chest fine crepitation		
Absent	60	100.0
Tachycardia		
Absent	60	100.0
Palpitations		
Absent	55	91.7
Present	5	8.3
LVH		
Absent	60	100.0
Dyspnea on exertion		
Absent	55	91.7
Present	5	8.3
COPD		
Absent	60	100.0
Thyroid examination		
Normal	60	100.0
Liver examination		
Normal	60	100.0
Kidney examination		
Normal	60	100.0

SD:standard deviation; IQR:interquartile range; LVH: left ventricular hypertrophy

Distribution of the study group based on their medications review, (**Table.7).** Distribution of the studied cases according to Immunological findings; sixty patients were ACPA positive (100.0%); (56 patients;

93.33%) were RF positive ; (54 patients; 90%); were ANA positive, (**Table.8).**

Table7. Medications review in the studied group (n=60)

Variables	No.	%
Metformin		
No	55	91.7
Yes	5	8.3
Gliclazide		
No	59	98.3
Yes	1	1.7
Insulin Therapy		
No	59	98.3
Yes	1	1.7
Levothyroxine		
No	59	98.3
Yes	1	1.7
Amlodipine		
No	55	91.7
Yes	5	8.3
Hydroxychloroquine		
Yes	59	98.3
No	1	1.7
Atorvastatin		
No	38	63.3
Yes	22	36.7
Omeprazole		
Yes	57	95.0
No	3	5.0
Leflunomide		
No	19	31.7
Yes	41	68.3
NSAIDs		
No	44	73.3
Yes	16	26.7
Corticosteroids		
No	57	95.0
Yes	3	5.0
Sulfasalazine		
No	28	46.7
Yes	32	53.3
Methotrexate		
No	45	75.0
Yes	15	25.0

SD:standard deviation; IQR:interquartile range

Table 8.Immunological findings in the studied group (n=60)

Variables	No.	%
ACPA		
Absent	0	0.0
Present	60	100.0
RF		
Absent	4	6.67
Present	56	93.33
ANA		
Absent	6	10.0
Present	54	90.0

SD:standard deviation; IQR:interquartile range; RF:rheumatoid factor; ACPA: citrullinated protein antibody;ANA:antinuclear antibody.

Study distribution included patients based on comorbidities; Diabetes was found in 28 patients (46.7%), hypothyroidism in one patient (1.7%), aortic stenosis in one patient (1.7%), (LVH) in one patient (1.7%), sinus tachycardia in one patient (1.7%),congestive heart failure (CHF) in four patients (6.7%), osteoporosis in (60 patients; 100.0%), COVID-19 infection in (5 patients; 8.3%), (**Table 9).** Distribution of patients in the study based on the results of radiological examination; using ECG, two

patients (3.3%) were diagnosed with LVH and three patients (5%) showed sinus tachycardia, (**Table.10).**

Table 9.Comorbidities in the studied group (n=60)

Variables	No.	%
Diabetes		
No	32	53.3
Yes	28	46.7
Hypothyroidism		
No	59	98.3
Yes	1	1.7
Chronic kidney disease		
No	60	100.0
Lung disease		
No	60	100.0
Aortic stenosis		
No	59	98.3
Yes	1	1.7
Myocardial infarction		
No	60	100
Left ventricular hypertrophy		
No	59	98.3
Yes	1	1.7
Sinus tachycardia		
No	59	98.3
Yes	1	1.7
Congestive heart failure		
No	56	93.3
Yes	4	6.7
Osteoporosis		
Yes	60	100.0
COVID-19		
No	55	91.7
Yes	5	8.3

SD:standard deviation; IQR:interquartile range

Table 10. Radiological examination in the studied group (n=60)

Variables	No.	%
Plain chest x-ray		
Normal	60	100.0
CT chest		
Normal	60	100.0
Echocardiography and ECG		
Normal	55	91.7
Left ventricular hypertrophy	2	3.3
Sinus tachycardia	3	5.0
U/S abdomen		
Normal	60	100.0

SD:standard deviation ; IQR:interquartile range

On conduction of multivariate regression analysis for impacting variables, statistically significant predictive risk of diabetes (OR=1.297)(p<0.001),COPD (OR=1.427)(p<0.001), neurological abnormality (OR=1.862) (p<0.001) and LVH (OR=1.517) (p<0.001) was found in elderly patients with rheumatoid arthritis, (**Table 11).**

Table 11.Multivariate regression analysis of elderly rheumatoid patients adjusted for age, sex, ACPA and associated diseases (n=60)

Variables	OR	CI	P value
Age	1.005	0.993- 1.083	0.403
Sex	1.779	1.151- 2.626	0.054
Duration of the disease	0.979	0.965- 0.993	0.041
ACPA	1.008	1.001- 1.016	0.021
Methotrexate	1.030	0.707- 1.402	0.836
Hypertension	1.069	0.768- 1.513	0.632
Diabetes	1.297	0.772- 2.135	<0.001
COPD	1.427	0.921- 2.146	<0.001
Neurological abnormality	1.862	1.042- 3.647	<0.001
LVH	1.517	0.819- 2.545	<0.001
Renal disease	1.197	0.829- 1.720	0.349

OR:odd's ratio; CI: confidence interval; ACPA: citrullinated protein antibody; LVH: left ventricular hypertrophy

Discussion

RA is a chronic inflammatory disease that affects several body systems as well as the synovial tissue. It causes joint degeneration and damage. RA commonly affects patients aged 30-50 years old **(Olofsson et al., 2017)**, while in patients over 60 years of age, the disease is called elderly RA (EORA), accounting for approximately 10-33% of RA cases in elderly patients **(Deal et al., 1985 ; Krams et al., 2016).** Recently, special attention has been paid to the novelty of EORA in terms of its genetic predisposition, clinical features, and therapeutic options **(Kobak et al., 2018).** Elderly patients have different clinical and laboratory signs, they also appear more often with aggressive forms of the disease and more systemic damage **(Turkcapar et al., 2006 ; Serhal et al., 2020).**

The aim of the study was to evaluate the clinical, laboratory and comorbid characteristics of elderly RA patients and there impact on function and quality of life.

Sixty elderly rheumatoid arthritis patients of both sexes aged ≥ 60 years meeting the 2010 EULAR/ACR classification criteria.

The mean patients age involved within the current study was 68.4±2.3 years, in accordance to our study, **(Jung et al., 2018)** mentioned that the mean age of elderly RA patients was 70.3±4.2 years.

(Tanski et al., 2021) who were concerned with the association between malnutrition and QoL in elderly RA patients, mentioned that the mean age RA diagnosed elderly patients was 72.6±6.5 years.

In the current study BMI was 27.18±4.09 kg/m^2, according to BMI classification, the majority of patients were preobese (41.7%), followed by obesity class I (30%), normal weight (25%), and obesity class II (3.3%).Our findings indicated that the majority of our patients were preobese and not cachectic.

Similarly, **(Bąk et al., 2020)** stated that elderly RA patients in their study were preobese with a mean BMI of 26.89 kg/m^2. As regards presenting manifestations, all patients suffered from joint pain and a duration of stiffness ranging from 0.25 to 1.5 hours with a mean of 0.58±0.36.

(Ke et al.,2021) found more than 80% of elderly RA patients (EORA and eYORA) suffered from joint pain and joint stiffness in the morning.

(Albayrak G et al., 2017) concluded that in elderly RA, pain and fatigue significantly worsen with age, leading to poor health related quality of life.

Because inflammatory markers are affected by the aging process and inflammation, we found increased systemic markers of inflammation (ESR with a mean of 68.47±26.43 mm/hr and CRP with a mean of 39.38±12.31 mg/dl, a finding similar to that reported by **(El-Labban et al., 2010)** and **(Spinel B et al., 2013).**

Therapy planning for RA may become more difficult if an aged patient has polypharmacy, a frequent issue brought on by a higher frequency of comorbid disorders. If RA is not identified and treated promptly in older adults, it can have detrimental effect , physical reliance and functional impairment. A patient's comorbid conditions, medication compliance and tolerance risk are all important

considerations in treatment planning because efficient care lowers morbidity and death **(Erdem et al., 2021).**

Contrary to our findings, **(Tian Z et al. 2021)** did not observe high diabetes rate of incidents among elderly RA patients. However, their study showed diabetes was an independent bone destruction risk factor among the elderly population.

On the other hand, they agreed with our findings regarding the other comorbidities as they observed low rates of cerebrovascular disease, hypertension, and thyroid diseases among elderly RA patients.

According to the DAS28, the majority of patients (41; 68.3%) had high activity of disease (>5.1), followed by 18 (30%) with moderate disease activity (>3.2 to 5.1), and only one (1.7%) with low disease activity (>2.6 to 3.2). Among all patients, DAS-28-CRP ranged from 3.02 to 5.90 with a mean of 4.35± 0.90.

(Marloes et al., 2020) found an age-related elevation in ESR and DAS-28 scores without a relevant corresponding increase in the number of tender joints 28 and the Patient Global Assessment (PTGA) might suggest that age-related processes contribute to a higher DAS-28 scores in elderly patients.

All laboratory results, including lipid profile, liver and kidney function tests, were increased over the established normal range for this age group. According to immunological profile ACPA antibodies were positive in 60 (100.0%) patients, 56 (93.33%) patients were RF positive and 54 (90.0%) patients were positive for ANA.

Furthermore, **(Takanashi et al., 2016)** reported that after the age of thirty, the RF positivity rates and anti-CCP titers declined almost linearly with the increase in age. Following a multivariable analysis, they discovered that age is an independent factor contributing to seronegative RA in females who were non smokers and showing a normal body mass index .

Limitations of the study: Future research needs to focus on elderly RA patients with higher rates of comorbidity and disability, as these management beliefs may differ from those of the patients included in our study.

Conclusions

Elderly patients with RA showed impaired function and reduced quality of health. Aging comorbidity and markers of disease activity were higher in older RA patients. Therefore, when treating RA in elderly patients, we must pay careful attention to associated comorbidities, treatment should be aimed at achieving adequate control, clarify the complex interrelationship between elderly RA and "geriatric syndromes".

Conflicts of interest: No conflicts of interest.

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