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Cardiovascular risk among a group of patients with chronic kidney disease: An experience of a comparative study from a Low Middle Income Country.

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Abstract

Introduction: Chronic kidney disease (CKD) is a risk factor for cardiovascular disease (CVD). It is evident that traditional risk factors as well as uraemia related non-traditional risk factors are responsible for the increased CVD risk in CKD patients.

Objective: The objective of this study was to compare the prevalence of selected cardiovascular risk factors among patients with end stage renal disease with controls.

Method: Fifty (men=38) consecutive patients with ESRD, awaiting kidney transplant at Teaching Hospitals, Karapitiya and Kandy were included in the study. The control group included 50 age and sex-matched healthy individuals. Data were collected using a questionnaire followed by anthropometric and blood pressure measurements. Fasting plasma glucose (FPG) serum total cholesterol (TCh), triglyceride (TG), high–density lipoprotein cholesterol (HDL-Ch), phosphorous (SPho), corrected calcium (SCCa), creatinine (SCr), albumin (SAl), high-sensitivity C-reactive protein (Hs-CRP), interleukin-6 (IL-6), vitamin D (vit.D) concentrations and blood glycated haemoglobin (HbA_{1c}) were measured. The mean age of the patient group was 44(10) years.

Results: Compared to controls, mean TCh ($p<0.001$), LDL ($p<0.001$), SCCa ($p<0.001$) and S.Al ($p<0.001$) levels were significantly lower among patients. HbA_{1c} ($p=0.053$), SPho ($p=0.001$) and SCr ($p<0.001$) levels were significantly higher among patients with CKD compared to controls. In patients' median serum vit.D ($p=0.001$) level was significantly lower while serum Hs-CRP ($p=0.001$) and IL-6 ($p=0.003$) levels were significantly higher, compared to controls.

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Conclusion: Traditional and non-traditional risk factors of cardiovascular disease are prevalent among patients with end stage renal disease, despite the treatment and renal replacement therapy.

Keywords: *Chronic Kidney Disease, Cardiovascular Disease, Risk Factors*

INTRODUCTION

Chronic kidney disease (CKD) is a risk factor for cardiovascular disease (CVD) and it directly enhances the CVD risk [1]. CVD accounts for 22.7% of deaths in CKD patients on haemodialysis [2]. According to previous studies cardiovascular events are responsible for nearly half of the deaths occurring among patients with CKD on routine haemodialysis [3, 4]. Though, declined glomerular filtration rate (GFR) is a risk factor for CVD among CKD patients [5], how it is linked with increased CVD outcomes is still unclear [6].

The risk factors of CVD among CKD patients differ from those of general population [7]. The CVD risk among patients with CKD cannot be fully explained by the traditional CVD risk factors such as hypertension, hyperlipidaemia, diabetes mellitus, sedentary life style, smoking and obesity. Patients with the lowest risk level based on above factors reported the poorest outcome, leading to a phenomenon of 'reverse epidemiology' in patients with CKD [8]. Moreover, medications which are proven to reduce CVD risk among non-CKD patients, such as statins and renin-angiotensin aldosterone system (RAAS) inhibitors did not show the same efficacy in patients with CKD [9, 10].

It is plausible that uraemia related non-traditional risk factors may be responsible for the enhanced atherosclerosis in CKD. Hyperhomocysteinaemia, high check this: lipoprotein a, hyperfibrinogenaemia, oxidative stress and chronic inflammation are among the non-traditional CV risk factors, postulated in CKD [11, 12]. Furthermore, conditions linked with end stage renal disease (ESRD) such as anaemia, hyperparathyroidism, calcium-phosphorous disorders, malnutrition [13], bone mineral disease, valvular calcification and hypervolaemia are also considered as non-traditional risk factors of CVD in CKD [10].

A survey conducted in selected ten CKD prevalent districts in Sri Lanka, in 2018 revealed that approximately 15.4% houses had at least one person with CKD between 2008 to 2018 [14]. Another recent study reported a point prevalence of CKD/CKDu (Chronic Kidney Disease of unknown origin) ranging from 1.52% to 3.35% in Anuradhapura and 0.67% to 1.25% in Polonnaruwa districts [15]. According to a recent survey done by Ruwanpathirana et al, in Anuradhapura district, it was revealed that 12% of the population had eGFR<60 [16]. Although CKD is an emerging health problem in Sri Lanka, we could not find any published local literature which examines the CVD risk among CKD patients with age and sex matched controls.

Therefore, the objective of this study was to compare the prevalence of selected traditional and non-traditional cardiovascular risk factors among patients with ESRD with age and sex- matched controls.

METHODOLOGY

Fifty (men=38) consecutive patients with CKD, in the age range of 25 to 64 years, awaiting kidney transplant at Teaching Hospitals, Karapitiya or Kandy were included in the study after obtaining informed written consent. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Review Committee of the Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka (Reference Number;09.03.2016: 3.13).

The control group included fifty (50) age matched (within five years) and sex-matched individuals with normal serum creatinine at the time of recruitment. They were not following special diet plans or on long-term medications (for more than three months). They were selected from the neighbourhood of the CKD patients after a detailed

history and physical examination done by a senior physician.

Data on socio-demography, life style and clinical information were collected using an interviewer – administered, pre-tested questionnaire and data (drug usage, medical and surgical history and duration of dialysis, co-morbidities) were collected by interviewing patients and their caregivers and from medical records. The time of diagnosis to the time of interview was taken as the duration of the disease and duration of dialysis was taken as the time between the first dialysis to the last session in months.

Study subjects were categorized according to their smoking status and alcohol consumption. Practice of smoking was categorized as non-smoker (never smoked), ex-smoker or current smoker. Same categorization (non-alcohol user, ex-alcohol user or current alcohol user) was used for alcohol consumption as well.

Anthropometric measurements were obtained adhering to standard protocols. Height was measured to the nearest 1 cm, using a portable stadiometer, without wearing footwear. A beam balance was used to measure weight to the nearest 0.1 kg, wearing only light clothes and without wearing footwear. A non-stretchable tape was used to measure waist and hip circumferences to the nearest 1 cm and waist-to-hip ratio was obtained by dividing waist circumference by hip circumference.

Blood pressure (BP) was measured using a sphygmomanometer (Matsuoka Meditech corp., Tokyo, Japan) after allowing study subjects to rest for 15 minutes. In patients on haemodialysis, blood pressure was measured before three consecutive dialysis sessions. The average of the three consecutive measurements obtained was considered as the blood pressure of the study participants. The study subjects were considered to have hypertension if they had systolic BP (SBP) >140 mmHg or diastolic BP (DBP) > 90mmHg, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines or were on antihypertensive drugs [17].

A sample of venous blood (10 mL) was collected to a plain tube and to an EDTA tube. Glycated haemoglobin (HbA_{1c}) percentage was estimated using high performance liquid chromatography technique. Serum total cholesterol (TC), triglyceride (TG), high–density lipoprotein cholesterol (HDL-Ch), phosphorous (Pho), calcium (Ca), creatinine (Cr), albumin (Al) and fasting plasma glucose (FPG) were estimated using spectrophotometry (Hitachi company, Japan). Serum high-sensitivity C-reactive protein (Hs-CRP), interleukin-6 (IL-6) and vitamin D (vit.D) were estimated using ELISA kits (DRG Instruments GmbH, Germany).

Dyslipidaemia was diagnosed when serum TC > 200 mg/dL, TG level > 150 mg/dL, HDL-Ch level < 40 mg/dL in males or < 50 mg/dL in females or LDL – Ch level >100 mg/dL, according to the National Cholesterol Education Programme (NCEP) guidelines [18] or when they were on lipid lowering drugs. Diabetes mellitus (DM) was defined using the American Diabetes Association (ADA) guidelines; FPG of $\geq$126 mg/dL or HbA_{1c} level of $\geq$ 6.5 or long-term use of hypoglycaemic agents. Serum Pho level > 4.5 mg/dL was considered as hyperphosphataemia and serum creatinine $\geq$ 1.2 mg/dL was used to define impaired renal function. Hypoalbuminaemia was defined when serum albumin was less than 40 g/dL.

Statistical Analyses

Baseline categorical data were summarized as proportions and frequencies. Normally distributed data were presented as means and standard deviations (SD) while skewed data were presented as median and inter quartile range (IQR). The associations were tested using Pearson correlations. The independent sample t-test was used to compare patients and controls if the data were normally distributed while Mann-Whitney U test was used if the distribution was skewed. $p<0.05$ was considered as statistically significant.

RESULTS

A higher proportion of controls had studied up to G.C.E. advanced level and University level compared to patients with CKD and controls had higher income (Table 1).

Table 1: Comparison of age, anthropometric variables and blood pressure between the groups

	CKD group	Control group	P value
Education			
University	04 (8%)	08 (16%)	0.357
Advanced Level	14 (28%)	19 (38%)	0.395
Ordinary Level	23 (46%)	10 (20%)	0.010
Grade> 5 – 11	07 (14%)	09 (18%)	0.786
Grade 1-5	02 (4%)	03 (6%)	1.000
Not schooled	00 (0%)	01 (2%)	-
Monthly Income (United States Dollars)			
>135 - <325	16 (32%)	32 (64%)	0.003
≥54 - <135	17 (34%)	13 (26%)	0.513
≥27 - <54	03 (6%)	04 (8%)	1.000
≥5 - <27	12 (24%)	00 (0%)	-
No regular income	13 (26%)	01 (2%)	0.001
Unable to say	01 (2%)	00 (0%)	-
Presence of reported comorbidities at the time of enrolment			
Ischemic heart disease	03 (6%)	00 (0%)	-
Hypertension	47 (94%)	00 (0%)	-
Diabetes mellitus	23 (46%)	00 (0%)	-
Peripheral vascular disease	02 (4%)	00 (0%)	-
Stroke	00 (0%)	00 (0%)	-
Hypercholesterolaemia	15 (30%)	00 (0%)	-
Smoking status			
Non smoker	27 (54%)	25 (50%)	0.841
Ex-smoker	23 (46%)	12 (24%)	0.035
Current smoker	00 (0%)	13 (26%)	<0.001
Alcohol Status			
Non-alcohol users	24 (48%)	14 (28%)	0.063
Past-alcohol users	26 (52%)	00 (0%)	-
Current-alcohol users	00 (0%)	36 (72%)	-
Drug Usage			
Anti-hypertensive drugs	47 (94%)	00 (0%)	-
Hypoglycaemic agents	23 (46%)	00 (0%)	-
Statin treatment	19 (38%)	00 (0%)	-

The majority of patients were on antihypertensives, anti-diabetic drugs and lipid lowering medication. Though there were no current smokers or alcohol consumers among patients, compared to controls, significant number of patients was ex-smokers (46%) or alcohol users in the past (52%). A significant number of controls were current alcohol consumers (72%) (Table 1). The median (interquartile range) durations of CKD and dialysis were 24 (24) and 8 (9) months, respectively. Of the fifty patients with CKD, 41 were on haemodialysis (HD), three were on continuous ambulatory peritoneal dialysis (CAPD) and six were awaiting the first dialysis.

The patients and controls were not different with regard to height, weight and waist circumference. BMI ($p = 0.010$) and hip circumference ($p = 0.008$) were significantly lower and waist- to- hip ratio ($p = 0.002$) and systolic ($p < 0.001$) and diastolic blood pressure ($p < 0.001$) were significantly higher among patients with CKD compared to controls (Table 2).

Table 2: Comparison of age, anthropometric variables and blood pressure between the groups

Measurement	CKD Group (n=50) Mean (SD)	Control Group (n=50) Mean (SD)	P value
Age (years)	44.5(10.3)	44.04(10.1)	0.822
Height (m)	1.62(0.09)	1.61(0.08)	0.691
Weight (kg)	57.9(12.2)	62.3(11.1)	0.062
WC (cm)	82.5(10.5)	80.7(13.7)	0.462
HC (cm)	89.5(8.3)	93.8(7.6)	0.008
WHR	0.92(0.06)	0.86(0.12)	0.002
BMI (kg/m^2)	21.9(3.7)	23.9(3.7)	0.010
SBP (mmHg)	163.6(27.2)	119.8(13.9)	<0.001
DBP (mmHg)	97.4(14.5)	79.6(11.9)	<0.001

Abbreviations: BMI, body mass index; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure

Compared to controls, mean TC, LDL, SCCa and S.Al levels were significantly lower among patients. HbA_{1c}, SPho and SCr levels were significantly higher among patients with CKD compared to controls (Table 3).

Among patients with ESRD median serum vitamin D level was lower while serum Hs-CRP and IL-6 levels were significantly higher, compared to controls (Table 3).

Table 3: Comparison of biochemical parameters between two groups

Biochemical Parameter	CKD Group(n=50) Mean (SD)	Control Group (n=50) Mean (SD)	P value
TC (mg/dL)	151 (51.7)	187.4 (39.8)	<0.001
TGs (mg/dL)	98.3 (70.0)	86.2 (39.2)	0.288
HDL (mg/dL)	41.3 (9.7)	40.1 (10.2)	0.564
LDL (mg/dL)	90 (45.4)	130 (38.7)	<0.001
SPho (mg/dL)	4.5 (2.2)	3.4 (0.8)	0.001
SCr (mg/dL)	7.0 (2.3)	0.9 (0.2)	<0.001
FBS (mg/dL)	105.2 (93.6)	89.7 (20.3)	0.257
HbA_{1C} (%)	6.4 (1.9)	5.8 (1.2)	0.053
SAl (mg/dL)	4.43(0.6)	4.8 (0.5)	<0.001
SCCa (mg/dL)	8.9(0.5)	9.6(0.3)	<0.001
Vit. D (pg/mL) (Median (IQR))	17.4 (24.3)	27.7 (22.95)	0.001
Hs-CRP (pg/mL) (Median (IQR))	2.1 (3.53)	0.85 (1.62)	0.001
IL-6 (ng/mL) (Median (IQR))	25.3 (65.4)	7.25 (26.52)	0.003

*non normally distributed variables are reported as median and inter quartile range

Abbreviations: TC, total cholesterol; TGs, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein, SPho, serum phosphorous; SCr, serum creatinine; FBS, fasting blood sugar; $HbA_{1C,}$ glycated haemoglobin; SAl, serum albumin; SCCa, serum corrected calcium, VitD, serum vitamin D; Hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6

Number of patients with higher-than-normal SBP, DBP, SPho was significantly higher compared to controls. Number of CKD patients with hypocalcaemia and hypoalbuminemia was also significantly higher than controls as expected (Table 4).

Table 4: Comparison of cardiovascular risk factors between the groups

Variable	CKD Group (n=50)	Control Group (n=50)	Chi-square statistic (X^2)	P value
Hypertension				
SBP >140 mmHg	41/50	6/50	49.2	<0.001
DBP > 90 mmHg	36/50	13/50	21.2	<0.001
Glycaemic control				
FPG $\geq$ 126 mg/dL	8/50	3/50	2.3	0.13
$HbA_{1C} \geq 6.5$ %	8/50	8/50	0	1
Serum Lipids				
TC > 200 mg/dL	10/50	18/50	3.2	0.07
TGs > 150 mg/dL	3/50	4/50	0.2	0.69
HDL < 40 mg/dL men and < 50 mg/dL for women	28/50	30/50	0.2	0.69
LDL >100 mg/dL	16/50	35/50	14.4	<0.001
Hyperphosphatemia				
Spho > 4.5 mg/dL	21/50	5/50	13.3	<0.001
Hypoalbuminemia				
SAl < 4 mg/dL	12/50	2/50	8.3	<0.01
Hypocalcaemia				
SCa < 8.4 mg/dL	18/50	0/50	-	-

Discussion

Despite being on antihypertensive drugs (94%), 82% of patients with ESRD had a SBP of >140 mmHg and 72% of patients had DBP of > 90 mmHg. Only a few patients had the BP control of $\leq$ 130/80 mmHg. This difference in treatment targets and clinical reality is consistent with the previous findings [19], which showed the difficulty in achieving BP targets in patients with ESRD. This uncontrolled hypertension may be a major contributor to the increased CVD burden among patients with ESRD. According to a study by Lascasas et al, it was evident that men with diabetes mellitus (DM) had the poorest BP control compared to female counterparts [20]. In this study majority of CKD patients were men and nearly half (46%) of the patients had DM and this may explain why blood pressure target was not achieved.

The prevalence of DM among our patients (46%) was similar to a previous study conducted in the National Hospital, Sri Lanka in which 44% study participants had diabetes [21]. Another study done at the same centre, diabetic nephropathy was identified as the leading cause of CKD with a prevalence of 30.6% [22]. A recent study conducted by Lascasas et al, showed that in Portugal the prevalence of DM among CKD patients as 50%. However, the prevalence of DM in our patient group was marginally higher than that reported in other larger European CKD cohorts (German GCKD: 35% [19]; Spanish MERENA: 41% [23] Italian CARHES: 28% [24], even after adjusting for age.

Smoking is a well-known risk factor for CVD in general population [25]. There were no current smokers among patients with CKD, however, 46% of patients had smoked previously. Some studies have examined the effect of smoking on overall mortality of ESRD patients. Foley, et al., found that current smoking is associated with increased risk of mortality compared to life-long non-smoking and past smoking [26]. Another study on patients with ESRD showed that mortality was significantly higher among current and former smokers than non-smokers [27]. A longitudinal study conducted on a large group of patients on dialysis revealed that current smokers have a 59% and 37% increased risk for new heart failure and death,

respectively compared to non-smokers. However, there was no significant excess risk for ischemic heart disease or cerebrovascular disease [26]. Further, it was evident that smoking is associated with increased risk of CVD in a large longitudinal study conducted among patients with CKD [28].

We observed that serum TC and LDL-Ch were significantly lower in patients with ESRD compared to controls. However, no significant difference was observed between patients and controls with regard to TG and HDL-Ch. The majority of patients with ESRD were on statin which may explain the lower serum TC and LDL-Ch among them. Further, it is known that low levels of LDL-Ch is associated with inflammation and malnutrition seen in patients with ESRD on dialysis [29].

According to our study, SPho level was significantly higher among patients with CKD compared to the controls and 21(42%) patients had SPho levels more than 4.5mg/dL. Increased serum phosphate is associated with high CVD risk in CKD patients [30]. High calcium and phosphate products lead to accelerated atherosclerosis and vascular calcification [31]. In a big study with 14,000 patients on routine dialysis, a greater CVD risk was observed in patients with elevated serum phosphate. In this analysis, the CVD risk was 25% higher in the highest quintile compared to the lowest [32]. In a study conducted on a large cohort of American patients on haemodialysis (n= 40,538), high serum phosphate was associated with a greater risk of CVD related hospital admissions [33]. According to another study conducted among 3490 patients, a 35% higher risk of acute myocardial infarction (MI) for each one-unit increase in SPho was observed even after adjustment for eGFR and conventional risk factors [34]. However, there are controversies regarding interventions to lower SPho levels in patients with CKD. The recent update of Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD guideline emphasized the deficiency of trial data to prove the improved outcome in CKD patients [35]. Currently, there are two randomized control trials (RCT) in progress to determine the efficacy of phosphate binders in reducing the CVD risk of CKD patients. They are COMBINE (CKD Optimal Management with Binders and NicotinamidE) study for stages 3-4 and IMPROVE-CKD (Impact of phosphate reduction on vascular end-points in Chronic Kidney Disease) study for the early stages of CKD [36].

Low serum albumin (SAl) is a non-conventional risk factor of CVD in patients with CKD and it is associated with CVD irrespective of traditional risk factors [37]. Moreover, positive associations were observed between low SAl and risk of CVD and mortality related to CVD in ESRD patients [38].

A recent study conducted by Yamaguchi, et al., revealed that true hypocalcaemia denoted by serum ionized calcium is a risk factor for all-cause mortality and cardiovascular events in patients undergoing haemodialysis. However, they did not find an association with serum corrected calcium [39]. It is evident that serum corrected Ca level increases with the initiation of the haemodialysis due to positive calcium balance, vitamin D treatment and/or calcium-based phosphate binders [40, 41]. In another study, serum corrected and uncorrected serum Ca less than 7.5 mg/dL was associated with an increased mortality among patients with serum albumin higher than 3.8 g/dL [42]. Hypocalcaemia leads to heart failure and arrhythmia in patients with CKD. In addition, hypocalcaemia with a positive net balance in dialysis is linked with myocardial infarction [43]. Among our study subjects, 18 out of 50 (36%) patients were hypocalcaemic (corrected SCa levels less than the 8.4 mg/dL) according to KDOQI clinical practice guidelines recommendations [44].

Chronic inflammation is another non-traditional risk factor of CVD in CKD patients [45]. Advanced CKD is associated with a state of chronic inflammation evident by increased pro-inflammatory cytokines like IL-1β, IL-6 and TNF-ά and acute phase proteins like CRP [46, 47]. Chronic inflammation is also predictive of cardiovascular and all-cause mortality in patients with CKD on regular haemodialysis [48]. It is evident that, compared to the lowest quartile of Hs-CRP and IL-6, the highest quartile showed twice a risk for sudden cardiac death among CKD patients [49]. Mechanisms underlying chronic inflammatory state linked with uremia among patients with CKD are still not clearly understood [50]. Although, number of dialysis-associated factors results in chronic low-grade inflammation, the presence of increased inflammatory markers at the initial stages of CKD suggests that the inflammation is related to loss of kidney function and not merely

due to dialysis [50]. Our results are in par with the findings of previous studies as both serum IL-6 and Hs-CRP levels were significantly increased among patients with ESRD compared to age and sex-matched controls.

Previous studies indicate that the majority of patients on haemodialysis suffer from Vitamin D deficiency [51]. Vitamin D deficiency is associated with all-cause and cardiovascular mortality not only among CKD and ESRD patients, but also among general population [52]. Studies on animal models have suggested that association between Vitamin D deficiency and CVD is not only due to atherosclerosis but also due to vascular calcification [53]. Vitamin D deficiency among patients with CKD was underrated until a significant association was found between Vitamin D treatment and survival of patients on routine haemodialysis [54]. However, protective effects on vitamin D therapy on CKD patients are still controversial. An association between vitamin D treatment and improved survival of patients on dialysis as well as with CKD has been shown [55, 56] while some have reported adverse effects of such therapy in the CKD patients [54]. Vitamin D is significantly lower among patients with ESRD compared to controls, despite the treatments, making the patients more vulnerable for CVD according our findings.

Although CKD is not categorized under inflammatory diseases, an enhanced inflammatory state is seen in patients with CKD. This abnormality is considered a reason for many adverse health outcomes of CKD patients. Further studies are needed to examine this complex interaction of CKD, CVD and inflammatory state and the current study provides a platform for future research in this area. The outcome of this study can be used in planning future research especially in the calculation of sample size etc. The current study has many limitations. Small sample size, lack of data on albuminuria which is an independent predictor of CVD risk and markers of vascular calcification such as magnesium are definite limitations. Further the controls were relatively healthier than general population and this may have affected our results and we expect the readers to consider these limitations in interpreting this study.

CONCLUSION

Traditional and non-traditional risk factors of cardiovascular disease are prevalent among patients with ESRD, despite the treatment and renal replacement therapy. The biochemical abnormalities and the markers of systemic inflammation need further studies and the contribution of each risk factor to the clinical endpoints needs to be assessed. It is possible that risk factors interact with each other and the net effect may be different from the individual contributions.

Author declaration

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Author Contribution

EHS contributed for the data collection**.** EHS, CM and SL contributed for the study design, conceptualization, data analysis, interpretation and planning the manuscript. All authors reviewed the manuscript and approval was granted for publication.

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Availability of data and materials

Raw data of the study will be made available upon request.

Ethics approval and consent to participate

Ethical clearance for the study was obtained from Ethics Review Committee, Faculty of Medicine, University of Ruhuna. Study participants were enrolled in the study only after informed written consent.

Competing interests

All the authors have no conflict of interest to share.

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