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The effects of chronic kidney disease stages on dyslipidemia, cardiovascular disease prevalence and mortality

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ABSTRACT

OBJECTIVE: Cardiovascular disease (CVD) is the most common cause of death in chronic kidney disease (CKD) patients. The prevalence of CVD is significantly increased in CKD patients, and the frequency of CVD increases as the CKD stage worsens. Although atherosclerosis is more common in CKD patients, the lipid profile may change as the CKD stage changes. Many mechanisms cause this. Also, mortality is more common in patients with advanced CKD. In this study, we aim to emphasize the incidence of cardiovascular diseases and dyslipidemia in patients with CKD at different stages and the effect of these variable conditions on patient mortality.

METHODS: Patients who applied to the internal medicine outpatient clinic and were diagnosed with chronic kidney disease were examined. Mortality and complications were followed up for one year. A total of 1323 patients with a diagnosis of CKD between stages 3a-5 were included in the study. The relationships between kidney functions and lipid profiles, biochemical values, and prognosis of the patients were evaluated.

RESULTS: Non-survivors had lower glomerular filtration rate (GFR) and higher C-reactive protein (CRP) levels. High-density lipoprotein (HDL), low-density lipoprotein (LDL), and albumin values decreased, and CRP increased as the disease stage progressed. More survivors had CKD and hyperlipidemia than non-survivors. It was observed that the stage remained the same in patients with hyperlipidemia at a higher rate. In contrast, the stage worsened or remained at stage 5 more in patients with cardiovascular disease or diabetes mellitus. Declining CKD stage and increasing CRP were influential risk factors that affect mortality.

CONCLUSION: It is essential to closely monitor the changes in laboratory parameters at baseline and follow-up in CKD patients to predict or prevent comorbidities, mortality, and deterioration in patients' renal functions.

Keywords: Cardiovascular diseases; chronic kidney disease; dyslipidemia; mortality.

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Cardiovascular disease (CVD) is the most common cause of death in chronic kidney disease (CKD) patients [1]. Although the prevalence of CVD is significantly increased in early-stage CKD patients, the prevalence is also higher in advanced-stage patients compared to the average population. Pathophysiological mechanisms for CVD developing in patients with CKD are the widespread and possibly accelerated formation of atherosclerotic plaques due to hyperlipidemia, uremic toxins, inflammation, oxidative stress, and endothelial dysfunc-

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tion [2]. Increased triglyceride levels are expected due to decreased lipoprotein lipase and hepatic triglyceride lipase activities in CKD patients. Although low-density lipoprotein (LDL) levels are increased in patients with nephrotic syndrome, they remain the same or may be found to be lower than in the average patient population, especially in patients with advanced CKD, due to the prolongation or decrease in LDL clearance accompanying the decrease in LDL production and malnutrition [3–5]. It is crucial to understand the correlation between chronic kidney disease and dyslipidemia and their impact on cardiovascular disease and mortality. The different stages of chronic kidney disease can have varying effects on these factors, making it essential to stay informed and aware. By delving into this topic, we can gain valuable insights that will help us better manage and prevent these conditions. In this study, we aim to emphasize the incidence of cardiovascular diseases and dyslipidemia in patients with CKD at different stages and the effect of these variable conditions on mortality in patients admitted to our hospital's outpatient clinics.

Highlight key points

- As the CKD stage worsens, the incidence of mortality increases. Therefore, patients diagnosed with CKD should be followed closely in terms of stage change.
- LDL levels may decrease as the CKD stage worsens due to malnutrition and decreased LDL production. However, patients with advanced CKD have a more atherogenic environment.
- The incidence of cardiovascular diseases is increased in patients with advanced CKD, but this is not a risk factor affecting mortality.

MATERIALS AND METHODS

This retrospective cohort study used the Haseki Training and Research Hospital database. The Ethics Review Board of the Haseki Training and Research Hospital reviewed and approved the study protocol (reference number 63-2021, date: 14.07.2021). Our study was conducted to be compatible with the principles of good clinical practice and the Declaration of Helsinki. The medical records of the patients who applied to the internal medicine outpatient clinic in the first six months of 2019 and were diagnosed with chronic kidney disease were examined. Mortality and complications were followed up for one year. The data of 8120 patients diagnosed with chronic kidney disease were analyzed. Patients with missing data, patients on routine dialysis programs, patients under 18, patients with conditions that may cause kidney disease (such as excessive non-steroid anti-inflammatory drug usage, postrenal causes, contrast nephropathy), and those with acute kidney injury or CKD stage 1/stage 2 were excluded from the study. Patients with familial dyslipidemia, who were followed up with a diagnosis of malignancy, and patients with collagen tissue disease were also excluded from the study. To examine the relationship between changes in laboratory parameters and CKD stages in the follow-ups and mortality/comorbidities, the control laboratory values of the patients within one year were also examined. For this reason, patients who were examined only once in 2019 were not included in the study. Comorbidities of the patients were evaluated by reviewing the patients' declaration, medication reports, and laboratory data (such as HbA1c, fasting blood glucose for diabetes mellitus, and LDL, triglyceride for hyperlipidemia). A total of 1323 patients with a diagnosis of CKD between stages 3a-5 (according to the CKD criteria determined by the Kidney Disease Improving Global Outcomes (KDIGO) working group) were included in the study. The patients' initial and follow-up blood values were examined and divided into groups according to their GFR values and CKD stages. The relationships between kidney functions and lipid profiles, biochemical values, drugs used, and prognosis of these groups were evaluated. Kidney function tests are performed with Roche Cobas Analyzer system device, Creatinine Jaffe Gen. 2 kit (inter-assay coefficient: 2.5%, intra-assay coefficient: 2.2%).

Statistical Analysis

All data obtained in the study were evaluated using IBM SPSS (Statistical Package for Social Sciences) Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. program. In descriptive statistics, continuous variables were expressed as mean, and standard deviation and categorical variables were expressed as percentages. Their distribution was evaluated with the Kolmogorow-Smirnow test. Normally distributed numerical data were assessed using Student's t-test to compare two groups. If the distribution was abnormal, the Mann-Whitney U test was used for pairwise comparisons of numerical data. Comparisons of numerical variables in more than two groups were made using the One Way Anova test when the normal distribution condition was met, and the Kruskal Wallis test when it was not. Categorical variables were evaluated with the chi-square test. Mortality and surviv-

Table 1. Distribution of age, gender and laboratory values according to stages

Initial values	Stage 3a	Stage 3b	Stage 4	Stage 5	Overall	p
Age (min–max.)	68.2±11.5 (20–95)	69.8±12.9 (22–95)	68.5±13.5 (26–96)	62.6±14.9 (22–91)	68.3±12.6 (20–96)	<**0.001**
Sex (F/M), (n)	287/283	217/172	160/102	57/45	721/602	0.031
HDL (mg/dl)	45.9±11.2 (>40)	45.0±11.7 (>40)	43.6±11.6 (>40)	41.0±12.0 (>40)	44.8±11.6 (>40)	<**0.001**
LDL (mg/dl)	125±44.6 (<100)	125.7±45.2 (<100)	121.1±46.5 (<100)	108.7±39.5 (<100)	123.4±44.9 (<100)	**0.003**
Triglyceride (mg/dl)	191.1±145.0 (<200)	188.5±114.7 (<200)	174.9±103.8 (<200)	167.5±78.3 (<200)	185.3±124.8 (<200)	0.145
CRP (mg/dl)	15.6±29.2 (0–5)	19.0±47.4 (0–5)	24.9±46.2 (0–5)	36.3±53.4 (0–5)	20.2±41.5 (0–5)	<**0.001**
Albumin (g/dl)	4.1±0.6 (3.5–5.2)	4.0±0.7 (3.5-5.2)	4.0±1.2 (3.5–5.2)	3.8±0.7 (3.5–5.2)	4.0±0.8 (3.5–5.2)	<**0.001**

Min: Minimum; Max: Maximum; F: Female; M: Male; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein. Reference ranges for laboratory tests are shown in parentheses.

ing patients were determined, and Cox regression analysis was performed as a surveillance analysis in light of the data. $p<0.05$ or 95% confidence interval was considered statistically significant.

RESULTS

The mean age of these 1323 patients was 68.3 (minimum 20, maximum 96). The age distribution and lowest/highest ages in CKD stages were similar (Table 1). 602 (45.5%) were male, and 721 (54.5%) were female. Of the patients, 570 were identified as stage 3a, 389 as stage 3b, 262 as stage 4, and 102 as stage 5 CKD (Fig. 1). Among the female patients, 287 had stage 3a, 217 had stage 3b, 160 had stage 4, and 57 had stage 5 CKD. Among the male patients, 283 had stage 3a, 172 had stage 3b, 102 had stage 4, and 45 had stage 5 CKD.

Out of 1323 patients, 1048 survived, and 275 did not. Non-survivors tended to be older and had higher creatinine and lower GFR, elevated urea, and C-reactive protein (CRP) levels, and lower albumin levels. Survivors had higher LDL levels. Other laboratory findings were similar between the two groups (Table 2). It was observed that high-density lipoprotein (HDL), LDL, and albumin values decreased, and CRP increased as the disease stage progressed (Table 1).

The incidence of hyperlipidemia in the survivor group was higher than in the non-survivor group (75.9% vs. 62.9%). The difference between incidences was significant ($p<0.001$). There was no significant difference between survivors and non-survivors in the incidence of CKD combined with hypertension, diabetes mellitus, or cardiovascular diseases (Table 3).

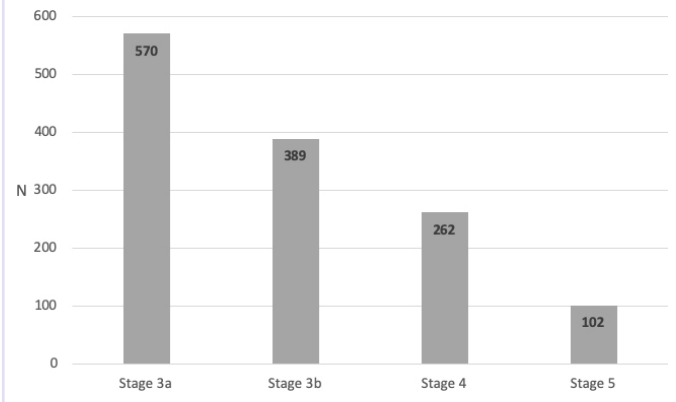

Figure 1. Distribution of patients by stage (N).

In our study, the CKD stage of 510 patients remained the same, while the stage of 303 patients improved, and the stage of 510 patients worsened or remained as stage 5. When the relationship between stage changes and comorbidities was examined, it was observed that the stage remained the same at a higher rate in patients with hyperlipidemia. In contrast, the stage worsened or remained at stage 5 more in patients with cardiovascular disease or diabetes mellitus. It was observed that the stage changes did not create a statistically significant difference in patients with and without hypertension (Table 4).

In the Cox regression model, which is composed of variables affecting the worsening of the CKD stage and remaining in stage 5, an increase in CRP ($p<0.001$, OR=1.491), an increase in triglycerides ($p=0.038$, OR=0.780), and increase in HbA1c ($p=0.031$, OR=0.765) were found to be the most influential factors (Table 5). In the Cox regression model, which was formed from the variables thought to affect mortality,

Table 2. The relationship between demographic/laboratory findings and mortality

Demographic/laboratory findings	Survivor (n=1048)	Non–survivor (n=275)	p
Age (years), (min–max)	67.1±12.9 (20–95)	72.9±10.7 (35–96)	<**0.001**
Sex (F/M), (n)	581/467	140/135	0.190
Creatinine (mg/dl)	1.9±1.3 (0.7–1.2)	2.1±1.5 (0.7–1.2)	**0.006**
GFR (mg/dl)	40.0±14.4 (>60)	34.0±14.8 (>60)	<**0.001**
Urea (mg/dl)	66.6±34.2 (17.1–46.6)	78.9±39.8 (17.1–46.6)	<**0.001**
LDL (mg/dl)	125.0±44.7 (<100)	117.2±45.4 (<100)	**0.010**
Triglyceride (mg/dl)	188.5±126.5 (<200)	173.1±117.2 (<200)	0.069
CRP (mg/l)	18.2±41.5 (0–5)	27.8±40.7 (0–5)	**0.001**
HbA1c (%)	6.9±1.7 (4–6)	7.1±2.0 (4–6)	0.159
Albumin (g/dl)	4.0±0.5 (3.5–5.2)	3.7±0.5 (3.5–5.2)	<**0.001**
TSH (mU/l)	2.8±4.6 (0.27–4.2)	2.6±4.0 (0.27–4.2)	0.637
AST (U/l)	23.5±22.2 (<32)	27.5±47.5 (<32)	0.171
ALT (U/l)	19.4±1.4 (<33)	19.9±26.8 (<33)	0.743
GGT (U/l)	36.6±65.9 (6–42)	54.2±117.0 (6–42)	**0.020**
ALP (U/l)	98.7±48.5 (35–104)	1089.6±55.2 (35–104)	**0.003**

Min: Minimum; Max: Maximum; F: Female; M: Male; GFR: Glomerular filtration rate; LDL: Low-density lipoprotein; CRP: C-reactive protein; TSH: Thyroid stimulating hormone; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferas; ALP: Alkaline phosphatase. Reference ranges for laboratory tests are shown in parentheses.

stage 4 compared to stage 3a (p=0.001, OR=1.981), stage 5 compared to stage 3a (p<0.001, OR=3.092), increase in CRP (p<0.001, OR=1.880), increase in triglyceride (p=0.019, OR=0.661) and increase in HbA1c (p=0.004, OR=0.589) were the most influential factors (Table 6).

DISCUSSION

Cardiovascular disease and mortality increase as kidney functions deteriorate [6]. It has been determined that the parameters used to calculate the risk of cardiovascular disease vary in the group of patients with CKD, and the differing lipid profile in patients with CKD is one of these changes [7].

Age was associated with mortality (p<0.001). We thought that the reason for this relationship was the increase in the duration of exposure to the disease, as well as inflammation and malnutrition, and the severity of the disease with increasing age. The study of Hallan et al. [8] showed that increasing age in the CKD patient population increases the risk of mortality. In a study on CKD patients in the predialysis stage, mortality was higher in men [9]. The reason for this was thought to be the protective effect of estrogen, the harmful effects of testosterone, and the unhealthy lifestyle of men. Similarly, in our study, 135 (22.4%) of 602 male patients and 140 (19.4%) of 721 female patients died (p=0.190). The mortality rate was higher in male patients than in female patients, but this difference was insignificant.

Table 3. The relationship between comorbidities and mortality

Comorbidities	Survivor (n=1048) (%)	Non-survivor (n=275) (%)	p
CKD + Hyperlipidemia	75.9	62.9	<**0.001**
CKD + Cardiovascular diseases	21.4	21.5	1.000
CKD + Hypertension	77.9	73.1	0.095
CKD + Diabetes mellitus	61.3	60.4	0.786

CKD: Chronic kidney disease.

We found a significant correlation between baseline creatinine and GFR values and mortality. This indicates that mortality in CKD patients is directly proportional to disease severity at the beginning of follow-up. Studies have shown that the initial GFR level and increased creatinine values are associated with mortality [8, 10, 11].

Table 4. Comorbidities and changes in chronic kidney disease stages

Comorbidities	Patients with improving stage (%)	Patients remained at the same stage (%)	Patients with worsening stage or stage 5 (%)	p
Hyperlipidemia				**0.010**
+ (N: 968, F: 534, M: 434)	68.6	68.6	71.4	
- (N: 355, F: 187, M: 168)	31.4	31.4	28.6	
Cardiovascu-lar diseases				**0.027**
+ (N: 283, F:126, M: 157)	16.2	16.2	24.1	
- (N: 1040, F: 595, M: 445)	83.8	83.8	75.9	
Hypertension				0.303
+ (N: 1017, F: 569, M: 448)	73.6	73.6	78.0	
- (N: 306, F: 152, M: 154)	26.4	26.4	22.0	
Diabetes Mellitus				**0.033**
+ (N: 808, F: 472, M: 336)	55.1	55.1	64.3	
- (N: 515 F: 249, M: 266)	44.9	44.9	35.7	

N: Number of patients; F: Female patients; M: Male patients; +: Present; -: Absent.

Table 5. Cox regression analysis of factors affecting worsening in CKD stage

	HR 95% CI (Lower–Upper)	p
Age	0.993 (0.984–1.003)	0.193
Increasing CRP	1.491 (1.198–1.856)	**<0.001**
Increasing LDL	0.993 (0.786–1.255)	0.952
Decreasing HDL	1.176 (0.939–1.473)	0.157
Increasing triglyceride	0.780 (0.617–0.987)	**0.038**
Increasing HbA1c	0.765 (0.599–0.975)	**0.031**

HR: Hazard ratio; CI: Confidence interval; CRP: C-reactive protein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; HbA1c: Hemoglobin A1c.

Table 6. Cox regression analysis of factors affecting mortality

	HR 95% CI (Lower–Upper)	p
Age	1.032 (1.017–1.046)	**<0.001**
Initial CKD stage		**<0.001**
Stage 3b vs. 3a	1.348 (0.928–1.958)	0.117
Stage 4 vs. 3a	1.981 (1.327–2.957)	**0.001**
Stage 5 vs. 3a	3.092 (1.868–5.116)	**<0.001**
Increasing CRP	1.880 (1.398–2.528)	**<0.001**
Increasing LDL	0.802 (0.575–1.119)	0.194
Decreasing HDL	0.830 (0.611–1.127)	0.233
Increasing Triglyceride	0.661 (0.468–0.933)	**0.019**
Increasing HbA1c	0.589 (0.412–0.843)	**0.004**

HR: Hazard ratio; CI: Confidence interval; CKD: Chronic kidney disease; CRP: C-reactive protein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; HbA1c: Hemoglobin A1c.

Patients with CKD generally have lower plasma HDL levels compared to non-uremic individuals. Due to the low apolipoprotein A1 (apo-A1) levels and decreased lecithin cholesterol acyl transferase (LCAT) activity, the esterification of free cholesterol and, thus, the conversion of HDL3 to HDL2 is reduced in uremic patients. Another critical component of HDL is paraoxonase, an enzyme that inhibits the oxidation of LDL. Plasma paraoxonase activity is reduced in patients with CKD, thus predisposing LDL and HDL particles to oxidation [12]. In addition, inflammation associated with infection or uremia can convert HDL from an antioxidant to a pro-oxidant particle [13, 14]. All of these may contribute to atherogenesis in CKD. The article published by Kwan et al. [15] showed that HDL levels decrease as kidney functions deteriorate. In a study conducted with 120 patients in Japan, it was suggested that decreased HDL levels are associated with CKD progression [16]. Our research also found that HDL levels decreased as the stage progressed. However, our Cox regression analysis observed that decreased HDL levels were not among the factors affecting CKD progression and mortality.

There are different interpretations of the relationship between GFR progression and LDL. While some studies indicate that LDL will increase as kidney function deteriorates, most studies have found a decrease in LDL [17, 18]. When we looked at the relationship between the first LDL measurements and GFR values, we observed that LDL decreased as the CKD stage progressed. The study by Kasiske B. [19] showed that LDL levels increased in CKD patients with nephrotic syndrome and LDL decreased in those without nephrotic syndrome. Patients not on dialysis and without nephrotic syndrome have low HDL and LDL cholesterol, high triglycerides, and even low total cholesterol.

As reported in several studies, as the CKD stage worsens, patients develop malnutrition, which leads to a decrease in their LDL levels. For this reason, hyperlipidemia may be less common in advanced-stage CKD patients. Since patients who develop mortality are mostly cachectic patients with worse nutritional status, LDL levels in these patients may be lower than in others. Nevertheless, within this range, there exists a profile that is more atherogenic, which consists of high levels of apolipoprotein B (apoB), lipoprotein a, intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), as well as small, dense LDL particles [20]. In addition, in patients with progressive CKD, LDL and HDL particles are altered by the oxidative process, which increases the formation of oxidized LDL, which is more atherogenic [21, 22]. As the stage of CKD progresses, LDL cholesterol levels decrease in patients due to malnutrition, whereas mortality increases due to increased inflammation, malnutrition-related factors, and the atherogenic changes mentioned earlier [23, 24]. Elevated LDL cholesterol levels and hyperlipidemia are seen in patients with better nutritional status, and both CKD stages and prognosis are better in these patients. This may be the reason for our study's lower mortality rate in CKD patients with hyperlipidemia. In addition, our Cox regression analysis found that increased LDL values were not among the factors affecting mortality.

While there are some studies showing that triglyceride levels have an inverse relationship with mortality in CKD patients, some studies also show that increased triglyceride levels are related to increasing all-cause mortality and CKD progression [25, 26]. We found that baseline triglyceride value was not associated with mortality or CKD stages. However, in our study, when we evaluated the factors affecting CKD progression during follow-up with regression analysis, it was observed that an increase in triglycerides reduced the risk of progression (OR=0.780). When the factors affecting mortality were evaluated, it was concluded that the rise in triglycerides lowers the mortality risk (OR=0.661). It was thought this was due to decreased triglyceride values as the CKD stage progressed, as in LDL.

Chronic renal failure is a significant risk factor for cardiovascular disease. It has been reported that CKD patients have a 20–30% higher prevalence of atheromatous plaques compared to patients with normal renal function, and this rate increases as kidney function deteriorates. A cohort study by Tonelli et al. [27] showed that the risk of cardiovascular events (especially myocardial infarction) is increased by 1.4 times in patients with CKD. Our study found that the frequency of cardiovascular diseases increased as kidney functions deteriorated.

In some studies, it has been observed that CRP increases as kidney functions deteriorate in patients in the predialysis stage [28]. In our research, when we looked at the relationship between the first CRP measurements and the CKD stages, we found that the CRP increased as the stage progressed. In the study of Stenvinkel et al. [29], CRP levels were higher in CKD patients than in the average population. This increase in CRP is thought to be due to increased inflammation and uremic environment as kidney functions deteriorate. Our regression analysis showed that increased CRP levels during follow-up were among the risk factors affecting worsening and mortality in the CKD stage.

The decrease in LDL, triglyceride, and HDL levels and the increase in CRP levels, which are more common in patients with worsening stages, can be explained by malnutrition-inflammation complex syndrome (MICS). Protein-energy malnutrition (PEM) and inflammation are common and can be seen together in patients with advanced stages of CKD and patients on dialysis. Decreased appetite and hypercatabolic metabolism are standard in these patients. Possible causes of MICS include comorbid disorders, oxidative stress, anorexia and reduced food intake, uremic toxins, decreased clearance of inflammatory cytokines, and volume overload. MICS is thought to cause reduced effect of erythropoietin, increased cardiovascular atherosclerotic diseases, decreased quality of life, and increased mortality [30, 31]. Although increased body mass index and high serum cholesterol and creatinine levels are considered risk factors in the general population, they are evaluated as protective factors from mortality in dialysis patients [32, 33]. The increased mortality seen in patients with both

LDL and triglyceride levels below our cut-off values can be explained by the MICS stage. Studies on this subject are primarily conducted with hemodialysis patients, and there need to be more studies on CKD patients at the predialysis stage. The difference in our study is that it includes data from many CKD patients who are not on dialysis. Therefore, the findings of our study in patients with renal failure who were not on a dialysis program could be an example for future studies.

Conclusion

CKD is associated with comorbidities and is a factor that increases mortality. Malnutrition should be remembered when evaluating the lipid profile during chronic kidney disease. It was observed that the patients' hyperlipidemia and CVD diagnoses were associated with worsening in the CKD stage. It would be appropriate to follow these patients more closely. It is essential to closely monitor the changes in laboratory parameters at baseline and follow-up in CKD patients to predict or prevent both mortality and deterioration in the renal function of patients.

Ethics Committee Approval: The Haseki Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 14.07.2021, number: 63-2021).

Authorship Contributions: Concept – EH, HEA; Design – EH, HBM; Supervision – SA, HEA; Data collection and/or processing – EH, ACK; Analysis and/or interpretation – HBM, HEA; Literature review – EH, ACK; Writing – EH, HBM; Critical review – SA, ACK.

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