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Impact of Constipation on Progression of Chronic Kidney Disease (CKD) in Association with The Incidence of Cardio-Vascular Events of CKD Patients and The Role of Dietary Habits and Activities on Constipation

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Abstract

This study investigated the effect of constipation on Chronic kidney disease (CKD) progression, cardio-vascular (CV) events, and the role of dietary and lifestyle factors. A total of 482 individuals were screened, of whom 459 CKD patients were enrolled. Based on ROME IV criteria, 285 patients with constipation formed the constipation group, while 174 without constipation served as controls. This prospective, open-label, single-centre, observational study recorded demographic data, comorbidities, medications, Estimated Glomerular Filtration Rate (eGFR), cardiovascular events, dietary habits, and physical activity. Constipation severity was assessed using the Constipation Scoring System. The primary outcome was eGFR decline, while secondary outcomes were incidence of cardiovascular events and associations with diet and lifestyle. Constipation was significantly associated with faster CKD progression. In patients aged 55 - 75 years, prolonged constipation duration and reliance on medications or assistance for defecation were linked to reduced eGFR. Regarding cardiovascular outcomes, incomplete evacuation and need for medication/assistance were independently associated with higher risk of cardiovascular events ($p<0.05$). Nutritional analysis indicated protein intake positively correlated with constipation risk, whereas fibre intake had a protective effect. Physical activity showed a favourable influence on constipation, though varying with CKD stage. Longer duration and severity of constipation markedly increased the likelihood of both accelerated renal decline and CV complications. Constipation in CKD is more than a discomfort. It is a

predictor of renal deterioration, cardiovascular risk, and poor nutritional outcomes. Early recognition and multifactorial interventions, including dietary fibre, lifestyle modification, and targeted therapies, may improve patient outcomes and reduce complications.

Keywords: Chronic Kidney Disease, Constipation, Cardiovascular Risk, Diet and Lifestyle

Introduction

Chronic kidney disease (CKD) affects millions worldwide and is often accompanied by gastrointestinal disorders, among which constipation is common and debilitating, significantly reducing patients' quality of life[1]. Although its exact mechanisms are unclear, constipation in CKD is linked to decreased gut motility, fluid and electrolyte imbalance, and medication side effects. While constipation affects about 30% of the general population, especially elderly and women[2], its incidence is notably higher in advanced CKD, ranking as the third most common symptom in end-stage renal disease (ESRD)[3]. Constipation has been associated with an increased risk of cardiovascular diseases (CVD)[4], CKD progression[5], colorectal cancer, and mortality[6]. Sedentary lifestyle and comorbidities such as diabetes further contribute to this burden[7]. In advanced CKD, elevated uremic toxins and altered gut microbiota[8] aggravate constipation, creating a kidney- gut axis vicious cycle. Fluid overload, intestinal wall edema, reduced dietary fibre intake, and medications like phosphate binders and iron supplements worsen intestinal dysbiosis[9]. Often overlooked, constipation serves as an indicator of gut dysbiosis and a potential risk factor for CKD progression. It also contributes to anorexia and malnutrition, which are strongly linked to hospitalization and mortality in dialysis patients[10]. Despite its prevalence and impact, constipation in CKD remains underdiagnosed and poorly managed, with limited literature available.

Therefore, the present study aimed to (i) understand the impact of constipation on CKD progression; (ii) estimate of cardiovascular (CV) risk in constipated, and (iii) evaluate the influence of dietary habits and activities on constipation and its association with quality of life (QOL) in this population.

Patient and Method

Study Population

This research study recruited eligible CKD patients from the outpatient Nephrology Department of ILS Hospital, Kolkata, West Bengal, India, over 12 months. Of 482 individuals screened, 23 were excluded due to non-fulfilment of inclusion criteria or refusal to participate. The final study population consisted of 459 patients, including 285 with constipation (constipation group) and 174 without constipation (control group) (Figure 1).

Study Design

This was a prospective, open-label, single-centre observational study comparing CKD progression between constipated and non-constipated patients. Constipation was identified based on the ROME IV criteria[11]. Demographic data (sex, age, diet, CKD stage, duration, medication, cardiovascular (CV) events, and comorbidities) were recorded at baseline along with eGFR values and constipation scores, which subsequently assessed during follow-up visits. All questionnaires were handled by a single coordinator to maintain consistency.

The eGFR value was the main response variable, while the constipation score served as the independent variable. Confounding factors include:

- Daily protein intake
- Dietary type (vegan/non-vegan)

- Blood pressure control (uncontrolled if >140/90 mmHg in ≥4/6 visits)
- Medications affecting eGFR value (ACE/ARB, Diuretics, Proton Pump Inhibitors (PPI), Acetylcysteine, and Probiotics).
- Medications causing constipation.

Selection of the study population

The subjects were screened based on the selection criteria mentioned below:

Inclusion Criteria

- CKD patients aged 17-80 years
- Patient with CKD III to CKD V (not on dialysis) under conservative treatment.
- Patients having constipation per ROME IV criteria[11]
- CKD patients without constipation (control group).

Exclusion criteria

- ESRD patients on hemodialysis or post-transplant.
- Intestinal obstruction, piles, fissures, anal fistula, IBS, inflammatory disease
- Malignancy, major surgery, gastrointestinal tuberculosis
- Patients with collagen vascularis

Tools for identifying constipation:

Constipation was assessed using the Constipation Scoring System (eight questions; Table 1). Appetite scores were calculated following[12].

Statistical analysis

a) Two groups were considered in the statistical analysis. A patient after their consent, was evaluated based on the constipation scoring system as soon as a patient is allocated to any of the two study arms.

b) Statistical approach

The study focused on (i) the impact of constipation on CKD progression, (ii) the risk of CV events in constipated CKD patients, and (iii) the influence of dietary habits and physical activities on constipation.

1. Constipation on the progression of CKD

A linear model was performed with the raw eGFR values, the possible confounding variables and the significant independent variables to select the correct set of confounding factors. The confounding variables were represented as follows: protein intake day^{-1} (pd), vegan or non- vegan (v), blood pressure in control or not (bp), ACE/ARB (ace), diuretic (dir), probiotic (pr), proton pump inhibitor (ppi), Acetyl cysteine (actc), Iron (fe) supplements, Calcium (ca) or vitamin D (vitd) and Phosphate binder (pb). A homoscadastic linear model was performed to identify the significant confounding variables in relation to constipation. To investigate how the eight constipation scores affected the 6 responsive variables or eGFR value another homoscadastic linear mixed-effects models were constructed using each of the constipation scores (QL).

For studying the relationship between constipation and the progression of CKD, the generalized linear mixed effect models were constructed using two types of data, raw eGFR value, and the rate of change of eGFR values over 12 months.

In order to investigate any underlying association of constipation with CKD progression a sub-group analysis was followed according to age and CKD stages (Table 2). A statistical model considering each constipation score individually was analysed for different age groups. In case of the first age group (< 40 years), the sample size was very small (n<10). Hence further analyses would be restricted to the rest of the three age groups. For each of the concerned age groups, F-test was carried out for question coefficients and p-values were plotted.

CKD stage grouping also yields a similar model as age grouping involving all of the questions together. For each of the concerned CKD stage groups, F-test for question coefficients was carried out.

2. Risk of CV events in CKD patients with constipation.

In this study, sex and incidence of cardiovascular events (CV) were considered as categorical variables and age, CKD duration, CKD stage and responses to eight questions mentioned before were considered as numeric variables. To evaluate the effect of constipation on CV events in CKD patients GLMM (generalized linear mixed model) using logit link function were performed.

3. Impact of dietary habits and different modes of activities on constipation

In the case of the impact of dietary habits and different modes of activities on constipation, a generalized linear model was used. The four different types of dietary explanatory variables considered in this study were:

1. Food type (vegan or non-vegan)
2. Fibre intake
3. Protein intake
4. Fluid intake

Food habit 1 was for vegetarians and food habit 2 was for non-vegetarians.

The 4 types of different activities' explanatory variables were-

1. Performs normal activities
2. Performs restricted activities
3. Performs household task
4. Almost bedbound

The data for different aspects were collected in the form of scoring. To check the effect of fluid intake, food habits, and physical activities on constipation Chi-Square Tests were performed. Generalized linear model analysis (Logistic model) was performed with the independent variables (Fibre Intake, Protein Intake, Food habit, Fluid intake, Normal activity, restricted activity, and household) as the response. The responses were again considered as ordered data i.e. higher the score the data represents more value or worse cases and the question 1 to question 8 (Constipation score) were used as response data to fit an ordered logistic regression model against explanatory variables such as fibre intake, protein intake, fluid intake, food habit, normal activity, restricted activity, and household activity. After fitting the logistic model the significant variables for each question were tested for significance.

Results and Discussion

1. The effect of constipation on the progression of CKD

All the confounding variables except PPI and Acetyle cysteine were reported to be significant in this study and incorporated into the further analysis. The patients of different ages and in different CKD stages, constipation was found to affect eGFR value differently. The eGFR value was found to be decreased with increasing the duration of constipation (Q1) and increasing assistance or medication (Q8) in the 3rd age group (55-75 years) of CKD patients (Figure 1A). These findings suggest that specific dimensions of constipation may contribute differently to CKD progression depending on patient age. The stronger association observed in older patients may be attributed to age-related reductions in gastrointestinal motility, a higher burden of comorbidities, polypharmacy, and increased susceptibility to gut dysbiosis.

When analysed according to CKD stage, all the *p*-values corresponding to the 1st group of stages (CKD stage 1 and CKD stage 2) were greater than 0.1. Therefore, the *p*-values for each question corresponding to 2nd group of stages (CKD Stages 3 and 4) and 3rd group of stages (CKD stage 5) were plotted which depicted an association of constipation with the progression of CKD only in 3rd group (CKD stage 5). An increased score of not feeling complete evacuation while facing bowel

movement decreased the value of eGFR indicating the progression of CKD in stage 5 CKD patients (Figure 1B). However, the other 7 questions related to constipation were found insignificant to show any association of constipation with CKD progression.

These observations are biologically plausible because advanced CKD is frequently accompanied by profound alterations in the gut microbiota and increased retention of gut-derived uremic toxins. As CKD progresses, podocyte and proximal tubular cell injury contribute to proteinuria and declining renal function[13]. Furthermore, gut-derived toxins such as indoxyl sulfate and p-cresyl sulfate, which are inadequately cleared due to protein binding, induce oxidative stress and pro-inflammatory responses that accelerate both renal and cardiovascular damage[14]. Prolonged intestinal transit and incomplete evacuation may further enhance the generation and absorption of these toxins, thereby contributing to CKD progression.

2. Risk of CV events in CKD patients with constipation.

Among the constipation-related variables, the feelings of complete evacuation while facing bowel movement (Q3) and the requirement for assistance or medication (Q8) during defecation were significantly associated with cardiovascular events ($p < 0.05$). Higher scores for these parameters corresponded to an increased risk of cardiovascular events in CKD patients (Table 1).

Although constipation is often regarded as a non-life-threatening condition, several cohort studies have demonstrated its association with increased mortality and cardiovascular morbidity in the general population[15]. Honkura et al.[4] reported that lower defecation frequency significantly increases cardiovascular mortality, while individuals with constipation exhibit a higher incidence of coronary heart disease and ischemic stroke than those without constipation[5].

The association between constipation and cardiovascular disease may be mediated through alterations in the intestinal microbiota. Gut dysbiosis has been linked with hypertension, atherosclerosis progression, and cardiovascular disease[16-18], and similar microbiome alterations have been observed in CKD patients. In the present study, increasing severity of incomplete evacuation and greater dependence on medication or assistance for defecation were associated with higher cardiovascular risk. Repeated straining during defecation may contribute to transient elevations in blood pressure; previous studies have reported increases of approximately 30 mmHg during defecation, and sustained increases in blood pressure are known to substantially increase cardiovascular risk[19]. Moreover, constipation and laxative use have been associated with a higher risk of coronary heart disease and ischemic stroke[4,5]. Increased serotonin release observed in constipated individuals may further contribute to vasoconstriction, thrombus formation, and atherosclerotic plaque development[20,21]. Emerging evidence also suggests that gut dysbiosis and sympathetic nervous system activation promote chronic inflammation and adverse cardiorenal outcomes in CKD[18,22], providing a potential mechanistic explanation for the observed findings.

3. The impact of dietary habits and different modes of activities on constipation

Generalized linear model analysis demonstrated that fibre and protein intake significantly influenced constipation status (Table 3). The regression coefficient for protein intake was positive, whereas that for fibre intake was negative, indicating that higher protein intake was

associated with a greater probability of constipation while higher fibre intake was protective.

The ordered logistic regression model further revealed that most constipation-related parameters were significantly influenced by fibre intake, protein intake, fluid intake, normal physical activity, and household activity. In contrast, dietary pattern (vegan versus non-vegan) and restricted activity were largely insignificant. Increased fibre intake improved nearly all aspects of constipation except the frequency of sitting on the toilet for successful bowel movement. Similarly, increased fluid intake improved several constipation-related symptoms, including incomplete evacuation, pain during defecation, and the need for assistance or medication. Normal physical activity and household activity were also associated with improvements in multiple constipation parameters.

These findings are consistent with the multifactorial nature of constipation in CKD. Reduced fibre and fluid intake, sedentary lifestyle, concomitant medications, and multiple comorbidities are recognised contributors to constipation in this population. In agreement with previous reports, fibre intake among constipated individuals in the present study was lower than that of controls, and reduced fibre intake significantly increased constipation risk. Nevertheless, fibre-rich fruits and vegetables are often restricted in advanced CKD because of concerns regarding hyperkalaemia[23], creating a therapeutic challenge.

Similarly, increased fluid intake was associated with a lower probability of constipation, while higher protein intake increased constipation risk. This observation may partly reflect the lower fibre content of protein-rich diets. In addition, high dietary protein intake has been associated with glomerular hyperfiltration and accelerated kidney injury[24], whereas protein restriction has been shown to reduce proteinuria and cardiovascular risk in CKD patients[25].

No significant relationship was observed between dietary preference (vegan or non-vegan) and constipation. However, normal physical activity significantly reduced constipation severity. Patients with limited mobility were more likely to require digital assistance, laxatives, or manual evacuation for successful defecation. These findings support previous reports linking reduced physical activity with constipation[2]. Johansen et al.[26] and Zamojska et al.[27] similarly reported lower physical activity levels among dialysis patients, particularly older individuals.

Importantly, the requirement for assistance or medication was reduced among patients with higher fibre intake and greater physical and household activity. Given the risk of hypermagnesemia associated with magnesium-containing laxatives in CKD patients[28], alternative strategies such as dietary optimisation, increased physical activity, bulk-forming laxatives, and polyethylene glycol may represent safer approaches for constipation management[29].

Overall, the present findings suggest that constipation is not merely a gastrointestinal complaint but may contribute to CKD progression and cardiovascular risk. Further studies are warranted to elucidate the underlying mechanisms and determine whether targeted interventions, including exercise programmes, dietary modification, probiotics, and safer laxative strategies, can improve both gastrointestinal and cardiorenal outcomes in CKD patients.

Conclusion

The present study showed that the longer duration of constipation in CKD patients increased the risk further. Due to potential involvement of CKD-related gut dysbiosis in constipation, this complication is frequently untreatable because of its complex pathophysiology,

especially in CKD patients. In this study different statistical models proposed that pharmacological, nutritional, and lifestyle-based methods are applicable for its treatment. Further investigations on the relationship between CKD-related gut dysbiosis and constipation are important for the development of novel treatment options for constipation, which may also exert favourable effects on CKD and CVD.

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Legend Tables and Figures

Table 1: Constipation Scoring System consisting of eight questions based on ROME IV criteria asked to the patients and the effect of these questions related to constipation on cardio vascular event using mixed-effect models

Variables (Constipation Question)	Questions	Scores	Estimate	Std. error	Pr (> | z |)
Q1	Duration	0-4	0.33	0.34	0.35
Q2	Frequency of bowel movements	0-2	0.73	0.52	0.16
Q3	Feeling of complete evacuation	0-4	1.23	0.17	8.20×10^{-13}***
Q4	Time spent for defecation	0-4	0.05	0.27	0.85
Q5	Number of times to sit per day	0-4	-0.77	0.40	0.05.
Q6	Abdominal pain during defecation	0-3	-0.56	0.30	0.07.
Q7	Pain in rectum while defecation	0-3	0.33	0.29	0.26
Q8	Assistance during defecation	0-2	1.46	0.39	0.00***

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 2: Sub-groups according to age and CKD stages

Factors for grouping		Groups
	Age group 1	< 40
	Age group 2	40 - 55
	Age group 3	55 -75
	Age group 4	> 75
CKD stages		
	Stage group 1	CKD Stage 1 + CKD stage 2
	Stage group 2	CKD Stage 3 + CKD stage 4
	Stage group 3	CKD stage 5

Table 3: Effect of different variables on different aspects (questions, Q) of constipation

	Covariate coefficient (Q1)	P value	Covariate coefficient (Q2)	P value	Covariate coefficient (Q3)	P value	Covariate coefficient (Q4)	P value	Covariate coefficient (Q5)	P value	Covariate coefficient (Q6)	P value	Covariate coefficient (Q7)	P value	Covariate coefficient (Q8)	P value
Fibre	-0.14	$7.78e^{-09}$	-0.16	$2.61e^{-13}$	-0.13	$1.50e^{-10}$	-0.04	$3.03e^{-02}$	0.13	$7.05e^{-04}$	-0.05	0.02	-	NS	-0.16	$4.11e^{-10}$
protein	0.05	$1.23e^{-06}$	0.04	$3.92e^{-06}$	0.06	$1.41e^{-07}$	-	NS	-0.07	$2.93e^{-03}$	-	NS	-	NS	0.08	$1.46e^{-11}$
Fluid	-	NS	-	NS	-0.25	$4.95e^{-02}$	-	NS	-	NS	-0.39	0.002	-	NS		
Normal activity	-0.90	$1.87e^{-05}$	-	NS	-0.85	$6.69e^{-06}$	-0.72	$2.24e^{-04}$	1.14	$1.11e^{-03}$	-0.72	0.003	-	NS	-0.41	$5.80e^{-02}$
Household activity	-	NS	-	NS	-0.94	$1.28e^{-02}$	-	NS	-	NS	-	NS	-	NS	-1.39	$5.36e^{-03}$

Note: NS, not significant at 5% level of confidence; The positive sign implies higher chances of constipation whereas the −ve sign of the coefficients corresponds that a larger value of the covariates corresponds to a smaller probability of constipation and vice versa.

Figure 1: Study design

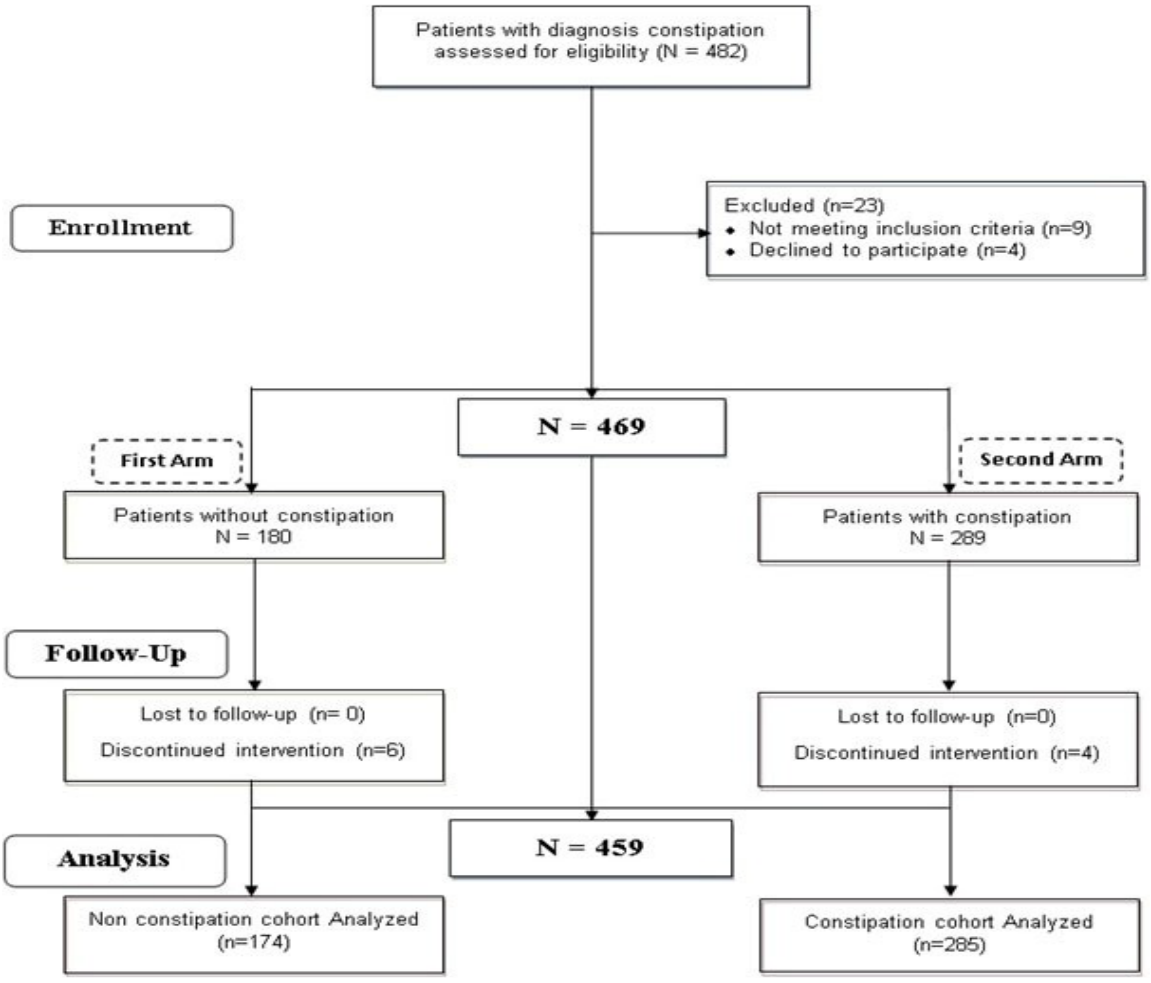
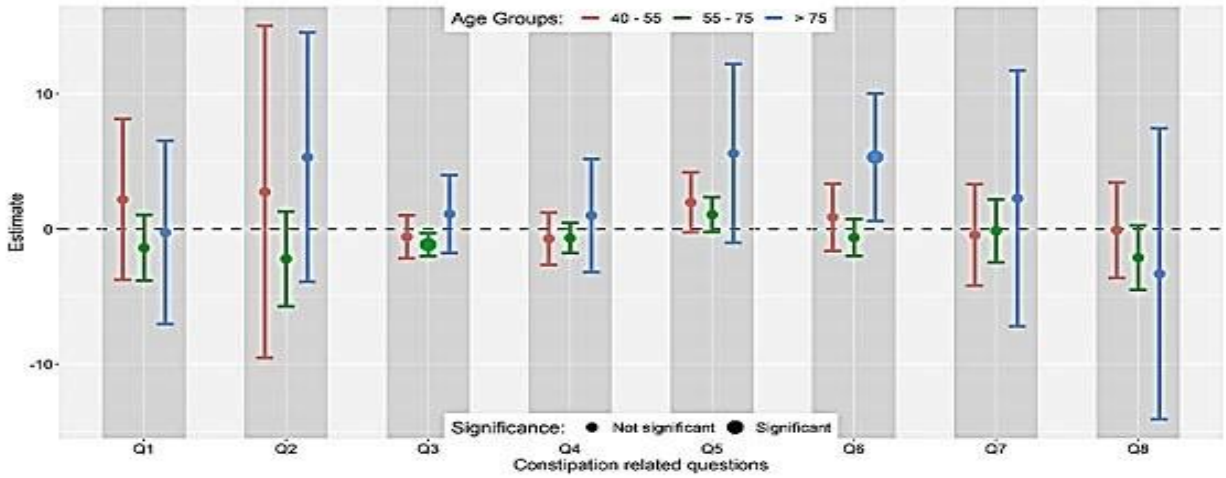
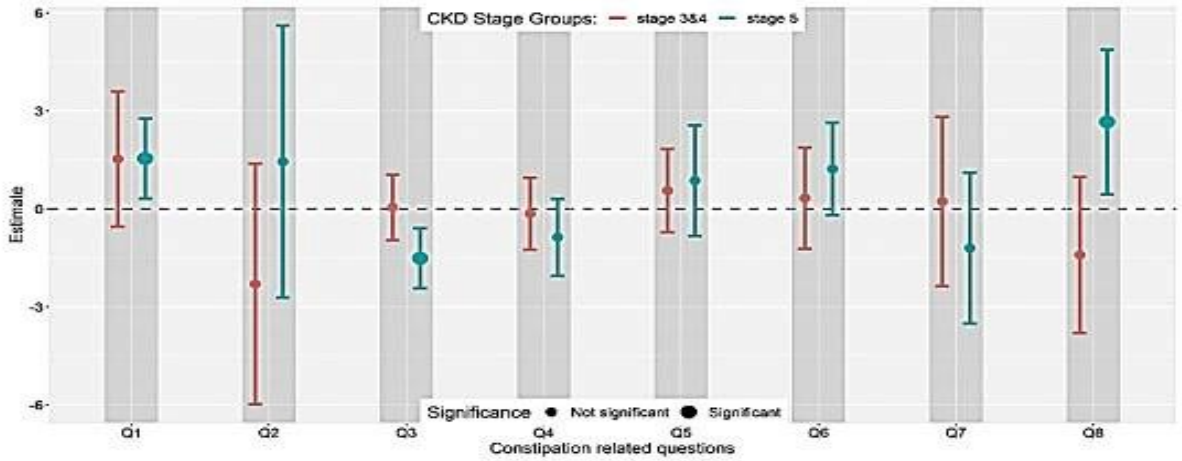


Figure 2: Error bar plot showing the level of significance for eight different aspects of constipation in the progression of CKD at different age groups (A) and at different CKD stages (B)



(A)



(B)