

1 **Original Article**

2 A slight decrease in serum albumin level is associated with rapid progression of
3 kidney dysfunction even within the normal range: The Yuport Health Checkup
4 Center Cohort Study

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1 **Abstract (225 words)**

2

3 **Objective:** A low-normal albumin level is associated with a high risk of
4 cardiovascular disease and mortality in the general population. However, the
5 relationship between serum albumin level and future decline of kidney function is
6 unclear. We aimed to clarify the effect of serum albumin level on the decline of
7 kidney function in the general population.

8 **Methods:** The data used were from 11,000 participants of a voluntary health
9 checkup program between 1998 and 2006 conducted in Japan. The primary
10 outcome for kidney function was a difference in estimated glomerular filtration
11 rate ($\Delta eGFR$) of ≥ 3 mL/min/1.73 m²/year. The association of the risk of
12 decreased kidney function with albumin level was determined using a logistic
13 regression analysis. We fit separate multivariable logistic regressions for serum
14 albumin levels (g/dL) as a continuous variable and as categorical data, classified
15 as ≤ 4.3 (n=2,530), 4.4– 4.6 (n=5,427), and ≥ 4.7 (n=3,043).

16 **Results:** Of 11,000 participants, 346 had a $\Delta eGFR$ /year of ≥ 3 . As compared
17 with the participants with albumin levels of ≥ 4.7 g/dL, the risk of decline in kidney
18 function was higher not only in those with albumin levels of ≤ 4.3 g/dL (adjusted

1 OR = 2.29, 95% CI: 1.65–3.18) but also in 4.4–4.6 g/dL (adjusted OR = 1.60, 95%

2 CI: 1.20–2.14).

3 **Conclusion:** Decreased albumin level is an independent risk factor for rapid

4 decline in kidney function even within the normal range.

5

6 **Key words:** chronic kidney disease, kidney dysfunction, general population,

7 albumin, Yuport

1 INTRODUCTION

2

3 The number of patients with chronic kidney disease (CKD) has been increasing
4 in most parts of the world, and the disease is estimated to affect 200 million
5 individuals worldwide [1]. Furthermore, the increase in the number of patients
6 with CKD is expected to accelerate. CKD creates a large burden and is
7 recognized as an important problem for both individuals and the society as a
8 whole. First, CKD is a risk factor for not only end-stage kidney disease (ESKD)
9 but also cardiovascular disease (CVD), which is the main cause of death
10 worldwide [2-5]. Second, the worldwide medical expenses associated with
11 hemodialysis due to ESKD is estimated to increase to a 1000 billion USD within
12 the next 10 years [6]. For these reasons, establishment of an effective measure
13 for CKD prevention is vital; in fact, this is one of the most important issues in
14 public and national health.

15 While accumulating evidence shows that some metabolic and lifestyle risk
16 factors of CKD, such as hypertension, dyslipidemia, and diabetes mellitus were
17 addressed [7-13], the effective measure for CKD prevention has not been
18 established yet. Therefore, risk factors other than the “conventional” risk factors

1 of CKD should be considered.

2 Previous studies suggested that a lower albumin level, even that within the
3 clinical normal range, is associated with high risks of CVD and mortality in the
4 general population [14,15]. However, studies that investigate the relationship
5 between the albumin level and decline of kidney function are completely lacking.

6 The aim of this study was to evaluate the effect of serum albumin level on the
7 decline of kidney function in the general population by using a large retrospective
8 cohort data set of the Japanese population.

1 **METHODS**

2

3 *Study design and study population*

4 This was a retrospective cohort study, and we used a dataset derived from the
5 health screening program performed by the Yuport Medical Checkup Center in
6 Tokyo. In this study, we set the 4-year baseline period to be between April 1998
7 and March 2002, and the 4-year follow-up period between April 2002 and March
8 2006. During the baseline period, 21,885 persons underwent checkups at least
9 once during this period when, in total, 47,995 checkups were performed (Fig. 1).
10 If the subjects underwent more than one checkup during the baseline period, the
11 initial checkup data were used. During the follow-up period, 23,547 persons
12 underwent checkups at least once for 49,390 checkups. If the subjects
13 underwent more than one checkup during the follow-up period, all the data were
14 used to identify incident diabetes. Follow-up data were merged with baseline data,
15 yielding 11,129 persons who had been examined during both time periods. Of
16 these patients, 129 with known diabetes at baseline were excluded, leaving
17 11,000 persons.

18 In accordance with the Private Information Protection Law, information that

1 might identify subjects was kept private by the center. Informed consent for
2 anonymous participation in epidemiological research was obtained at every
3 checkup.

4

5 *Measurements*

6 Serum albumin level was determined using the bromocresol green method
7 (reagents supplied by Denka Seiken, Tokyo, Japan) [16]. Other laboratory
8 values were measured using the standard laboratory technique. All the checkup
9 procedures were performed in the same manner, both during the baseline and
10 follow-up periods, including blood measurements. Height and weight were
11 measured to calculate body mass index (BMI), which was defined as weight
12 divided by height squared (kg/m^2). Blood pressure was measured by trained
13 nurses using a sphygmomanometer.

14

15 *Kidney function*

16 Kidney function was expressed as an estimated glomerular filtration rate (eGFR)
17 using the CKD Epidemiology Collaboration (CKD-EPI) modified for Japanese [17].
18 GFR estimated by the coefficient-modified CKD-EPI equation was more closely

1 related to CVD incidence than that estimated by the Japanese GFR equation [18].

2 The coefficient-modified CKD-EPI equation is as follows.

3 Estimated GFR (mL/min/1.73 m²) = 141 x min (Cr/ κ , 1) ^{α} x max (Cr/ κ , 1)^{-1.209} x

4 0.993^{Age} x 1.018 (if female) x 0.813 (Japanese coefficient).

5 (κ : 0.7 in females and 0.9 in males, α : -0.329 in females and -0.411 in males.)

6 In general, kidney function decreases with age: A previous study showed that
7 the rate of GFR decline was 0.36 ml/min/1.73 m²/year on average among
8 120,727 individuals aged \geq 40 years [19]. Therefore, the clinical kidney disease
9 outcome in this study was assessed as an abnormal annual decline of kidney
10 function in each participant. An abnormal annual decline of kidney function was
11 defined as a difference in eGFR (Δ eGFR) of \geq 3 mL/min/1.73 m²/year. This
12 cutoff value for an “abnormal decline,” represents a magnitude of change that is
13 $>$ 3 times the rate previously described in studies of normal aging, and this change
14 is known to be associated with clinically deleterious outcomes [20, 21]. To
15 ensure the accuracy of evaluated trend, we also performed a sensitivity analysis
16 in which a Δ eGFR of \geq 5 mL/min/1.73 m²/year was regarded as an abnormal
17 decline [22].

18

1 *Statistical analyses*

2 Continuous data were expressed as mean \pm standard deviation or median within
3 the 25th and 75th percentiles, and categorical data were expressed as
4 percentages. Baseline characteristics were compared between those who met
5 the criteria for abnormal decline in kidney function and those who did not, and
6 independent variables were assessed using the chi-square test in the case of
7 categorical variables and the t-test or Mann-Whitney U test in the case of
8 continuous variables. Analysis for trend was evaluated using Cochran-Armitage
9 test. Regarding the relationship between two values, the Pearson correlation
10 coefficient was employed.

11 Abnormal decline in kidney function and odds ratios (ORs) were estimated
12 from the logistic regression model. Multiple analyses were used to calculate the
13 OR for abnormal decline in kidney function after adjusting for age, sex, BMI,
14 systolic blood pressure (SBP), eGFR at baseline, serum alanine
15 aminotransferase level, serum uric acid level, high-density lipoprotein (HDL) level,
16 HbA1c level, C-reactive protein level, history of cardiovascular disease (stroke or
17 ischemic heart disease, or both). Inclusion of variables in the models was based
18 on our existing knowledge regarding the risk factors of kidney function decline.

1 We fit separate multivariable logistic regressions for both serum albumin level as
2 a continuous variable and categorical data, which were classified as ≤ 4.3 , 4.4–
3 4.6, and ≥ 4.7 g/dL.

4 Differences with a P value of <0.05 were considered statistically significant.

5 All statistical analyses were performed using EZR Version 1.33 (Saitama Medical
6 Center, Jichi Medical University, Saitama, Japan), which is a graphical user
7 interface for R (The R Foundation for Statistical Computing, Vienna, Austria).
8 More precisely, it is a modified version of R commander, which is designed to
9 add statistical functions frequently used in biostatistics [23].

10

11 *Ethics issues*

12 This study was conducted in accordance with the principles of the Declaration of
13 Helsinki. The study was approved by the review board of Teikyo University
14 (approval No. 15-205). The participants' written informed consent for
15 anonymous participation in epidemiological research was obtained at every
16 evaluation.

1 **RESULTS**

2

3 The baseline characteristics of the participants according to abnormal decline in
4 kidney function status are shown in Table 1. Of the participants, 346 had an
5 abnormal decline in kidney function. Among the patients with abnormal decline
6 in kidney function, higher SBP values and lower levels of albumin and HDL-C
7 were observed. The relationship between baseline serum albumin level and the
8 change in eGFR is shown in Fig. 2.

9 Next, we evaluated the unadjusted and adjusted ORs and 95% confidence
10 intervals (CIs) for abnormal decline of kidney function according to albumin level.
11 In the continuous variable evaluation, the albumin levels (per 0.1 g/dL) were
12 negatively associated with the risk of abnormal decline in kidney function in both
13 the crude (OR = 0.89, 95% CI: 0.84–0.93) and adjusted models (OR = 0.86, 95%
14 CI: 0.82–0.91). Same trends were also observed in sensitivity analysis in both
15 the crude (OR = 0.88, 95% CI: 0.81–0.97) and adjusted models (OR = 0.85, 95%
16 CI: 0.77–0.94).

17 In the categorical variable evaluation, as compared with the participants with
18 albumin levels of ≥ 4.7 g/dL, the risk of abnormal decline in kidney function was

1 significantly higher not only in those with albumin levels of ≤ 4.3 g/dL but also in
2 those with 4.4-4.6 g/dL (Fig. 3A): This result means that lower serum albumin
3 level, even within the normal range, is related to rapid kidney function decline.
4 The results of the sensitivity analysis, in which a $\Delta eGFR$ of ≥ 5 mL/min/1.73
5 m²/year was regarded as an abnormal decline in kidney function, are shown in
6 Fig. 3B: Similar trends were observed.

1 **DISCUSSION**

2

3 In this retrospective, population-based, cohort study, the relationship between
4 albumin level and decline in kidney function over time was investigated. A
5 decrease in albumin level was found to be the primary risk factor of abnormal
6 decline in kidney function. More importantly, our study suggests that even within
7 the normal range, those with albumin levels of ≤ 4.6 g/dL had a risk of decline in
8 kidney function.

9 Our study could not reveal the reason why relatively low but within normal limit
10 level of albumin read to early decline of kidney function. Slight decline of serum
11 albumin might reflect some confounding risk factor such as slight undernutrition
12 [24], slight albuminuria, or profound liver dysfunction. Another explanation is
13 that relatively lower level of serum albumin *per se* caused rapid decline of kidney
14 function. Serum albumin, which epithet is “multi-functional protein” [25], has
15 various functions as follows: maintenance of osmotic pressure, buffering of the
16 acid-base balance, supply of amino acid to tissues, binding and transporting of
17 numerous compounds, elastase activity, and antioxidative activity. In fact,
18 serum albumin level is the most abundant, thus most important, antioxidant of the

1 extracellular space [26]. We reported that the decrease in serum albumin
2 fraction, which has an antioxidative property, correlated with kidney dysfunction
3 [27, 28] and that such decrease in serum albumin fraction was directly related to
4 cardiovascular incidence in the population with advanced CKD [29, 30].
5 Therefore, theoretically and actually, lower serum albumin level can induce
6 undesirable outcomes such as mortality [14], cardiovascular incidence [15], and
7 rapid decline in kidney function as shown in the present study.

8

9

10 Most previous studies used abnormally lower albumin levels as an indicator
11 of malnutrition status for research [15,31]. However, our study showed that
12 even within the normal range, albumin levels of ≤ 4.6 g/dL are associated with a
13 risk of decline in kidney function. Only a few studies showed that lower albumin
14 levels within the normal range affect kidney function. Among 2,535 subjects
15 aged 40–69 years, in the multivariable analyses, the CKD hazard ratios (95% CI)
16 for the highest and lowest quartiles of serum albumin levels were 0.69 (0.40–
17 1.17) for men and 0.42 (0.28–0.64) for women [32]. While these results were
18 similar to ours, the number of subjects was small. To overcome this limitation,

1 in our study, we included almost five times more subjects than that in the previous
2 study.

3 Our study showed that decreased albumin level was significantly associated
4 with abnormal decline in kidney function and patients with albumin levels of ≤ 4.6
5 g/dL had a risk of decline in kidney function. This indicated that a slight
6 decrease within the normal range of albumin level might be a risk for kidney
7 function deterioration. This is consistent with the results of a previous study that
8 reported that lower albumin level within the normal range was predictive of CKD
9 in women [32]. Together with a previous observational study, our findings
10 suggested that the risk of reduced kidney function might increase with decreased
11 albumin levels even within the normal range. These findings might be
12 therapeutic target from the viewpoint of public health.

13 This study has some limitations. First, the findings cannot be generalized to
14 other ethnic or age groups, as the study participants might be healthier than the
15 general population and their risk of developing medical complications was lower,
16 as the study subjects were participants in a health checkup program. Second,
17 the albumin levels were measured only at baseline; the changes in albumin levels
18 during the follow up period that might have an independent effect on kidney

1 outcome were not evaluated. Third, the eGFR was evaluated only twice; this
2 parameter is known to show day-to-day variations. Fourth, present study lacks
3 data regarding urinary finding: the level of urinary albumin might relate to the
4 serum albumin level. Lastly, further studies are needed to assess whether other
5 confounders such as smoking history and serum calcium/phosphate levels may
6 affect kidney function. Future prospective studies on these relationships should
7 be conducted to provide more insight.

8 In conclusion, our study showed that decreased serum albumin level is an
9 independent risk factor of abnormal decline in kidney function in the general
10 population and that a slight decrease in albumin level, even within the normal
11 range, may be a risk factor of decline in kidney function.

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1 **Figure legends**

2

3 **Figure 1. Flowchart of the study population.**

4

5 **Figure 2. The relationship between baseline serum albumin level and the**
6 **yearly decline in kidney function.**

7 A weak but significant relationship was observed ($R = -0.0830$, $P = 2.92 \times 10^{-18}$):

8 Lower serum albumin level was related to greater decline in estimated glomerular
9 filtration rate.

10

11 **Figure 3. Association between albumin level at baseline and renal outcome.**

12 A: main analysis in which renal outcome is $\Delta eGFR/year \geq 3 \text{ mL/min/1.73 m}^2$, B:

13 sensitivity analysis in which renal outcome is $\Delta eGFR/year \geq 5 \text{ mL/min/1.73 m}^2$.

14 In both analyses, similar trends were observed: Namely, the risk of kidney
15 impairment was increased in correlation with lowering of serum albumin even
16 within normal range (P-value; <0.0001 in A and $=0.0249$ in B, Cochran-Armitage
17 test).

18 Adjusted for age, sex, body mass index, systolic blood pressure, eGFR at

- 1 baseline, serum alanine aminotransferase level, serum uric acid, high-density
- 2 lipoprotein cholesterol, HbA1c level, C-reactive protein level, history of
- 3 cardiovascular disease.
- 4 Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration.
- 5

	All	$\Delta eGFR/\text{year} < 3$ mL/min/1.73 m ² (n = 10,654)	$\Delta eGFR/\text{year} \geq 3$ mL/min/1.73 m ² (n = 346)	P value
Age (years)	53.2 (11.6)	53.2 (11.6)	52.2 (13.4)	0.104
Sex (male), n (%)	5248 (48)	5101 (48)	147 (43)	0.049
Body mass index (kg/m ²)	23.0 (3.0)	23.0 (3.0)	23.1 (3.2)	0.387
Systolic blood pressure (mmHg)	124.1 (17.9)	124.0 (17.9)	126.5 (18.7)	0.011
Diastolic blood pressure (mmHg)	75.0 (11.0)	74.9 (11.0)	77.5 (11.4)	<0.001
Laboratory data				
Hemoglobin (g/dL)	13.9 (1.4)	13.9 (1.4)	13.9 (1.6)	0.460
Serum albumin (g/dL)	4.52 (0.23)	4.52 (0.23)	4.46 (0.23)	<0.001
Aspartate aminotransferase (U/L)	22.9 (16.7)	22.8 (16.7)	22.2 (16.1)	0.476
Alanine aminotransferase (U/L)	22.7 (9.3)	22.69 (9.35)	22.25 (8.70)	0.393
Lactate dehydrogenase (U/L)	298.2 (55.3)	298.1 (55.2)	299.29 (57.5)	0.701
Blood urea nitrogen (mg/dl)	14.9 (3.5)	14.9 (3.5)	14.9 (3.8)	0.989
Serum creatinine (mg/dL)	0.7 (0.2)	0.72 (0.16)	0.73 (0.2)	0.191
Estimated glomerular filtration rate (mL/min/1.73 m ²)	82.9 (10.3)	82.4 (10.2)	83.8 (13.3)	0.090
Serum uric acid (mg/dL)	5.4 (1.4)	5.4 (1.4)	5.4 (1.5)	0.951
Total cholesterol (mg/dL)	203.3 (35.0)	203.4 (34.9)	201.0 (36.8)	0.206
High-density lipoprotein cholesterol (mg/dL)	58.5 (15.2)	58.6 (15.2)	55.7 (14.2)	<0.001
Triglyceride (mg/dL)	97.0 [70.0, 140.0]	97.0 [69.0, 140.0]	97.5 [73.0, 143.0]	0.308
HbA1c (% , NGSP)	5.1 (0.7)	5.1 (0.7)	5.1 (1.0)	0.770
C reactive protein (mg/dL)	0.10 [0.01, 0.10]	0.10 [0.01, 0.10]	0.10 [0.01, 0.10]	0.092
History of complications				
Stroke (+, %)	20 (0.2)	19 (0.2)	1 (0.3)	0.473
Angina pectoris (+, %)	36 (1.2)	32 (0.3)	4 (1.2)	0.026
Myocardial infarction (+, %)	10 (0.1)	10 (0.1)	0 (0)	0.999
Observation period (years)	5.4 (1.6)			
Data are expressed as mean and standard deviation, or percentage and number or median with 25th and 75th percentiles. Abbreviations: NGSP, National Glycohemoglobin Standardization Program				
Table 1. Participants' characteristics at baseline according to decline in kidney function				

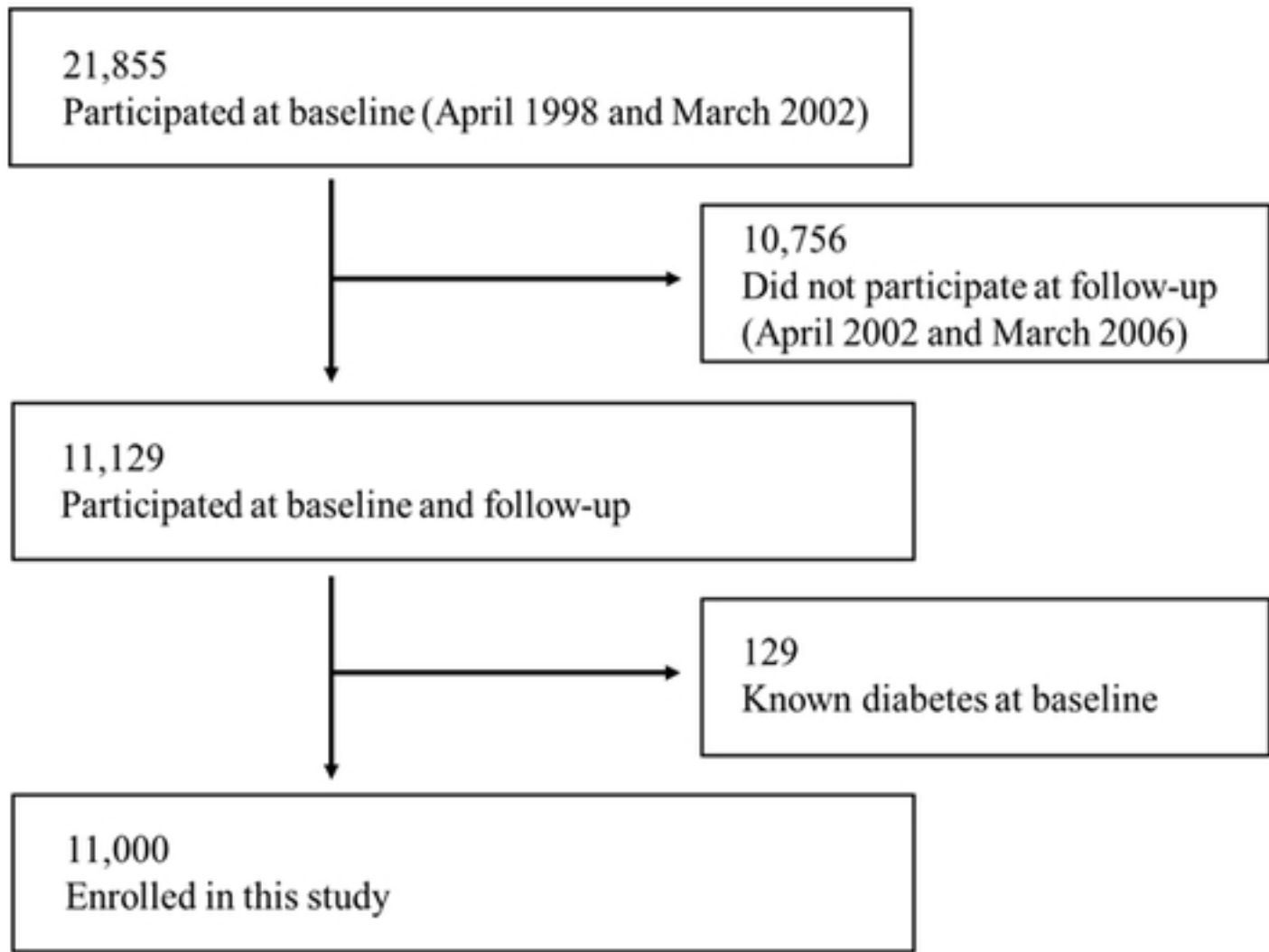


Figure 1

Figure 1

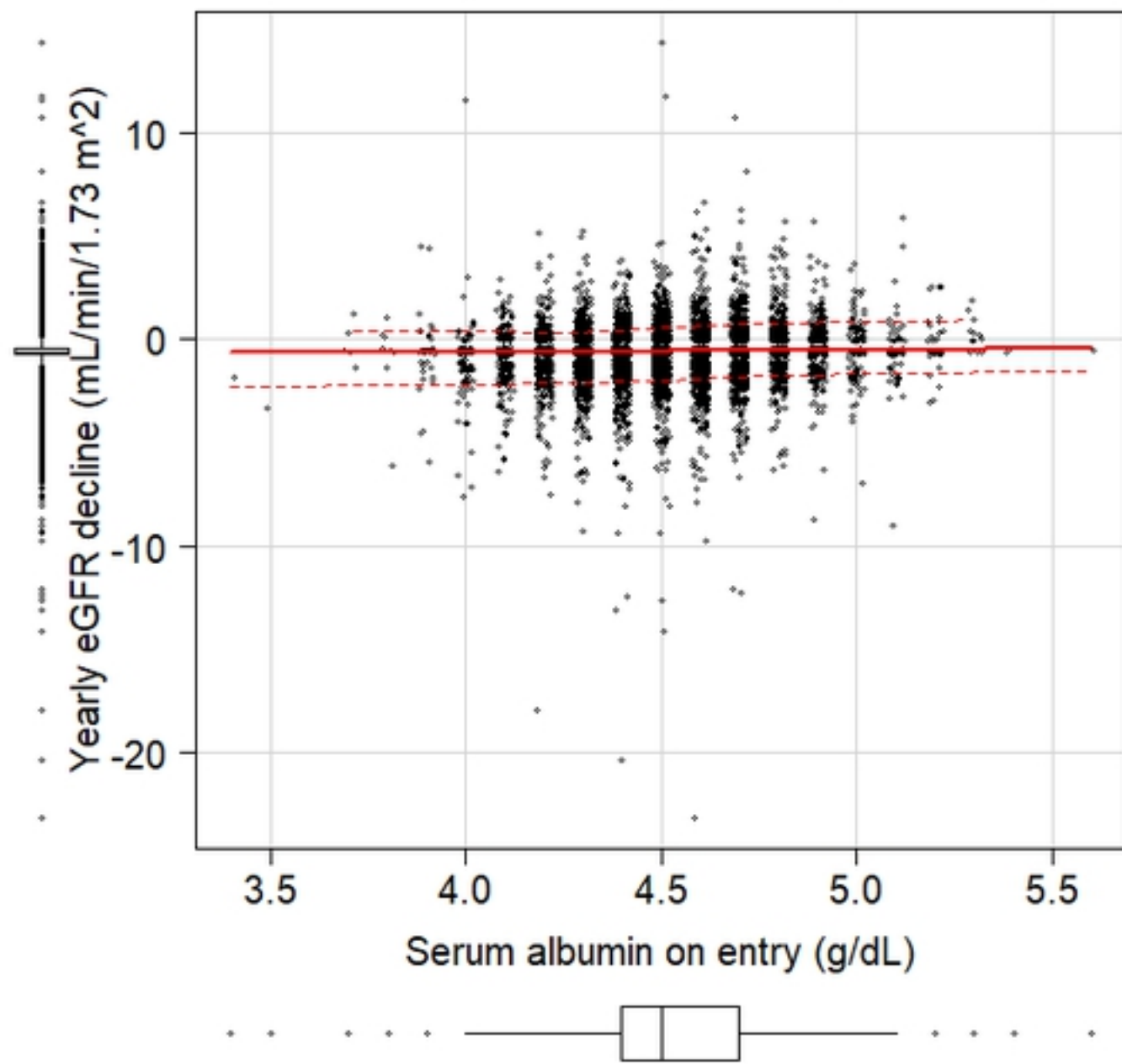
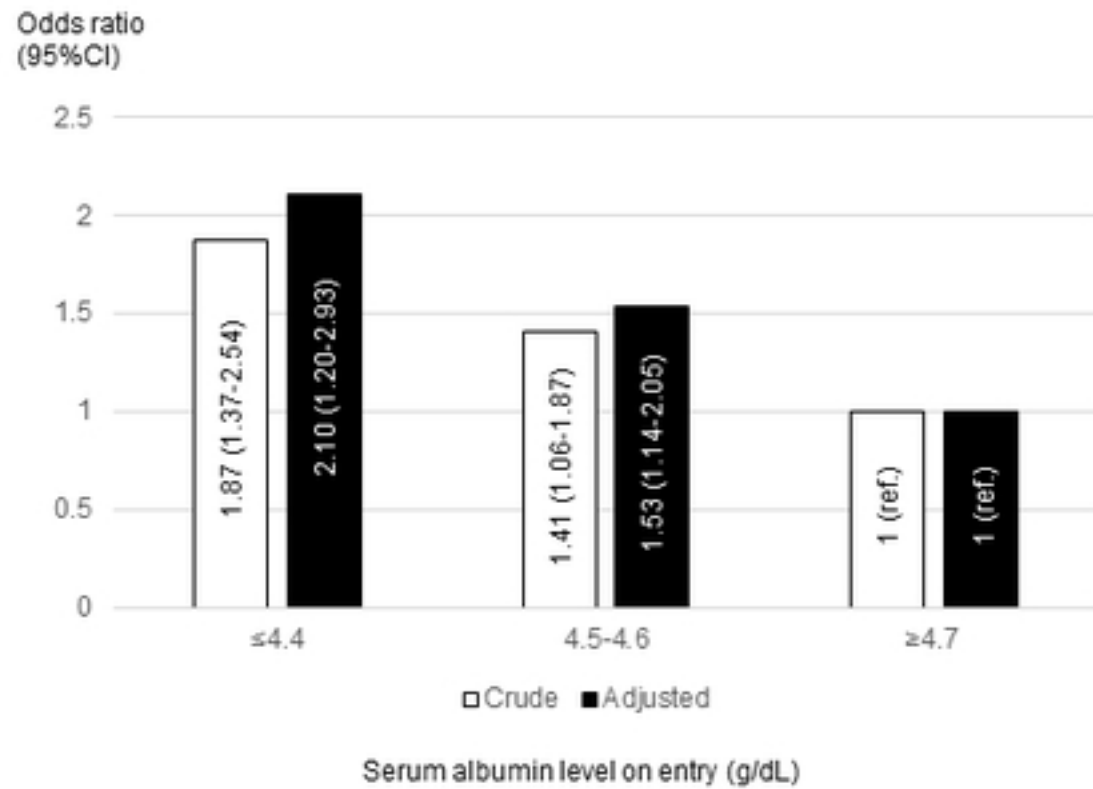


Figure 2

Figure 2

A



B

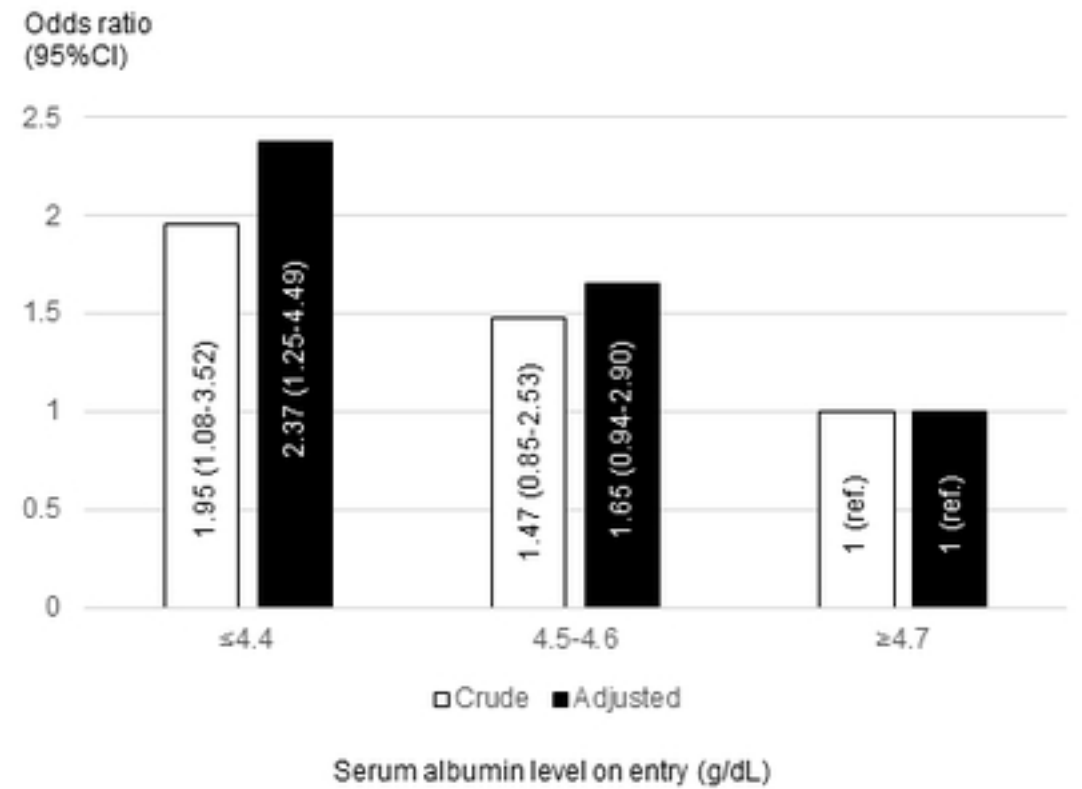


Figure 3