Urinary albumin-to-creatinine ratio in decompensated liver cirrhosis among elderly Egyptian patients: a single-center experience

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Abstract

Background: Hepatitis C virus and nonalcoholic steatohepatitis (NASH) are the most common causes of liver cirrhosis in Egypt. Increasing aging population is a worldwide issue, and societies are facing various problems, including long-term care for populations with a high prevalence of chronic conditions; hence, comprehensive geriatric assessment is important for determining patients' mental health, functional capacity, and social circumstances. Normally, a small amount of protein (normal urinary albumin-to-creatinine ratio [UACR] < 30 mg/g) excreted in daily urine and excess amounts warrant further examination. The present study aims to evaluate the relationship between UACR and the severity of liver cirrhosis among 47 elderly patients (more than 65 years old) and 47 adult patients (control group) admitted to the hospital as well as the relationship between UACR and geriatric cognitive functions, functional capacity, depression, and nutritional status.

Results: The present study showed that the cognitive, functional, and nutritional status of patients aged 65 years old or more were significantly affected by the severity of liver disease. The investigators also reported a significant relationship between UACR and Child–Pugh score in the elderly patient group. No significant relationship was found between UACR and the cognitive, functional, mood, or nutritional status of the elderly age group.

Conclusion: Overall, UACR was correlated to the severity of liver disease among elderly patients compared with adult patients with liver cirrhosis.

Keywords: Urinary albumin-to-creatinine ratio, Liver cirrhosis, Comprehensive geriatric assessment, Egypt

Background

Egypt has high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. According to the 2015 Egyptian Health Issues Survey, it has the highest prevalence of hepatitis C virus infection globally [1]. Moreover, the elderly population is increasing in our country, and, according to the latest estimate of the Central Agency for Public

Mobilization and Statistics, the Egyptian elderly (above 65 years) represented 6.7% of the population in the year 2019 and the senior citizens were approximately 6.5 million (3.5 million males and 3 million females). Hence, special considerations have to be taken in managing different complications of liver cirrhosis in those populations [2]. Although the Child–Pugh scoring system was designed to predict the severity and mortality of patients with cirrhosis, its use has limitations because ascites and encephalopathy require a subjective assessment. Because of these limitations, it is difficult for us to differentiate

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adequately between the severity stages based [3] only on the Child–Pugh scores. The model of end-stage liver disease (MELD) scoring system also has some limitations. Marked variations in the measurement of serum creatinine, which give a rough estimation of the renal function, interlaboratory variations in the measurement of international normalized ratio (INR), which lead to significantly different MELD scores, and the exclusion of hepatic encephalopathy were also a problem [4]. Chronic kidney disease can be diagnosed when proteinuria persists for more than 3 months, even with normal creatinine levels. Moreover, proteinuria with evident diffuse endothelial cell dysfunction is related to the development of extensive vascular disease and closely related to cardiovascular and kidney disease progression. Urine albumin creatinine ratio (UACR) correlates well with 24-h urinary protein level in diagnosis and follow-up of different diseases, besides its simplicity to test [5, 6]. A previous study done by Cholongitas et al. had shown that proteinuria worsens the prognosis of decompensated cirrhosis. A UACR of ≥30 mg/g was associated with more severe liver disease, as well as lower glomerular filtration rate (GFR) and worse survival in patients with decompensated cirrhosis [7]. Thus, the relationship between UACR and liver cirrhosis severity in elderly Egyptian patients must be investigated, which is the primary aim of the present study. Comprehensive geriatric assessment is an organized approach to assessment designed to determine an older person's medical conditions, mental health, functional capacity, and social circumstances. Hence, the National Clinical Program for Older People recommends that all older adults identified as being frail or at risk of frailty should have a timely comprehensive geriatric assessment performed and documented in their permanent health record [8]. In this study, the elderly patients were screened for cognitive impairment using the mini-mental state examination (MMSE) test [9], depression using the 4-item geriatric depression scale [10], functional capacity using Barthel index (BI) [11, 12], and malnutrition using the mini nutritional assessment (MNA) scale [13]. Depression in the elderly population is a serious health problem resulting in poor functional performance and exhausting healthcare resources. Compared with younger adults, malnutrition more frequently occurs in elderly patients with a greater impact on their functional and health status. Nutritional status can be screened using the MNA tool comprising a specific dietary questionnaire and a series of body measurements.

Liver cirrhosis is significantly associated with more errors of intrusions in the auditory, verbal, and learning tests, memory, and attention/calculation, even in patients with minimal hepatic encephalopathy [14]. This cognitive impairment may also persist after treatment of overt hepatic encephalopathy [15]. A meta-analysis done by Deckers et al. found enough evidence between albuminuria and cognitive impairment as 35% of the cases showed a significant increased risk of cognitive dysfunction [16]. In this line of concept, the presence of liver cirrhosis and albuminuria in elderly patients may significantly worsen their cognitive function. In the present study, the correlation between the UACR among elderly patients and their cognitive functions, functional capacity, depression, and nutritional status was also assessed.

This study aims to evaluate the relationship between UACR and the severity of liver cirrhosis (Child–Pugh and MELD scores) among elderly cirrhotic patients as well as the relationship between UACR and geriatric cognitive functions, functional capacity, depression, and nutritional status.

Methods

This cross-sectional analytic study included 94 Egyptian patients with decompensated liver cirrhosis admitted to the hospital for the management of jaundice, ascites, hepatic encephalopathy, or variceal hemorrhage from February 2019 to August 2020. Liver cirrhosis was diagnosed via laboratory tests and ultrasound, and the patients were categorized into two groups: 47 elderly patients aged ≥65 years and 47 adult patients aged <65 years (control group). The patients who were admitted with renal impairment (eGFR < 60 ml/min/m^2) were excluded from the study as well as those with diabetes and hypertension and administered with ACE-I or ARBs drugs. Written informed consent was obtained from all participants or a responsible caregiver for those who were incapable to give consent, and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki. It was revised and accepted by the faculty ethical committee. The severity of liver disease was evaluated based on the Child–Pugh score and MELD scores [17]. The following were measured for all patients: hemoglobin, total leucocyte count, platelet count, serum creatinine, urea, uric acid, sodium, potassium, serum total bilirubin, albumin, AST, ALT, INR, and fasting blood glucose. Random urine samples were obtained to measure UACR. The elderly patients were screened for cognitive impairment using MMSE, a screening test for cognitive impairment, assessing the different domains of cognitive function with a total score of 30. It is an 11-item questionnaire that evaluates the five areas of

Table 1 Demographic data, Child and MELD scores of all study population

		Control group		Geriatric group		P value
		Mean	SD	Mean	SD	
Age (years)		51.40	11.63	67.30	3.62	<0.001
Sex	**Male**	31	66.0%	26	55.3%	0.291
	Female	16	34.0%	21	44.7%	
Child score		8.57	2.33	8.64	2.21	0.828
MELD score		14.96	6.16	14.26	6.19	0.575

Child-Pugh and Model of end stage liver disease scores (P < 0.05 significant)

cognitive function: orientation, registration, attention and calculation, recall, and language. MMSE was used to measure attention, executive functioning, agnosia, language, memory, orientation, praxis, prosody, thought content, thought processes, and visuospatial proficiency [18]. Depression, which was measured using the 4-item geriatric depression scale, can be screened with simple questions: "Do you feel down or hopeless?" and "Are you bothered by loss of interest in doing your daily activities?" Functional capacity was assessed using the BI at three different levels: basic activities (e.g., bathing, toileting dressing, and feeding), intermediate activities (e.g., using telephone and shopping for groceries), and advanced activities (e.g., using the internet) [19]. Malnutrition assessment was measured using the MNA tool, a rapid and simple tool composed of brief questions that can be completed in approximately 10 min to identify people at risk for malnutrition [20].

Statistical methods
Data were coded and entered using the Statistical Package for the Social Sciences version 26 (IBM Corp., Armonk, NY, USA). Moreover, data were summarized using mean, standard deviation, median, minimum, and maximum for quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. The comparisons between the quantitative variables were performed using the nonparametric Kruskal–Wallis and Mann–Whitney U tests (Chan, 2003a). For comparing categorical data, the chi-square (X^2) test was performed. Fisher's exact test was used instead when the

expected frequency was less than 5 (Chan, 2003b). The correlations between the quantitative variables were performed using the Spearman correlation coefficient (Chan, 2003c). P values of less than 0.05 were considered statistically significant.
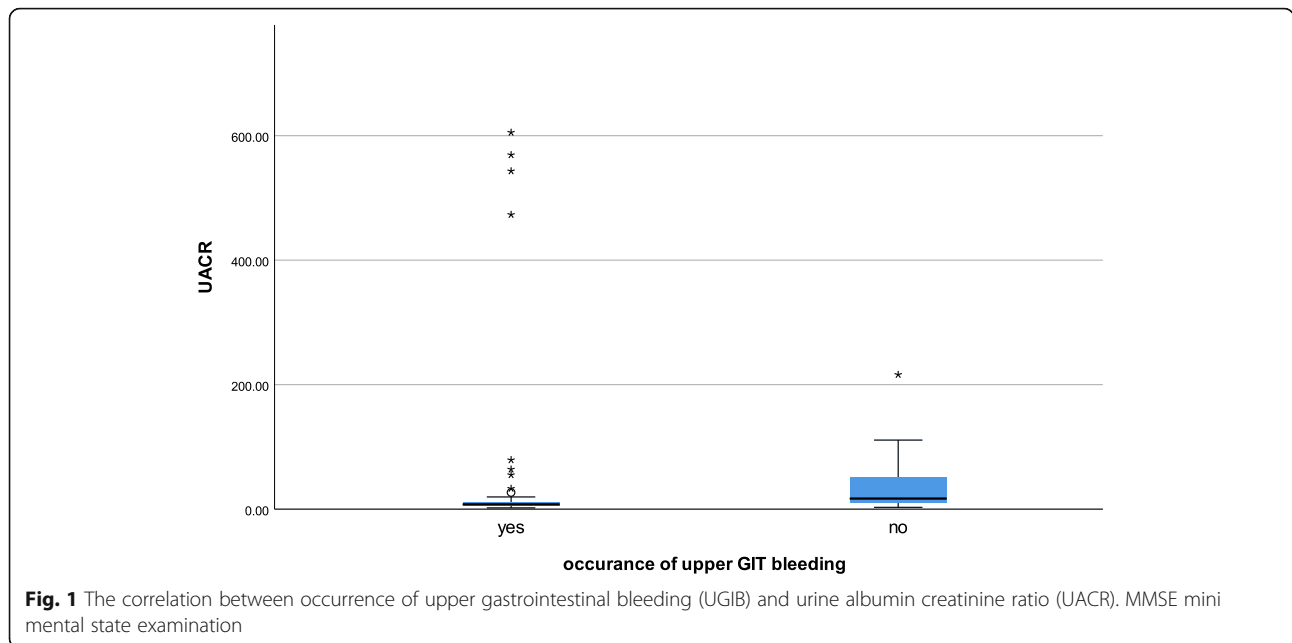
Results
Table 1 shows the demographic data of the studied groups. The majority of patients in both groups (58 patients, 61.7%) were admitted to the hospital because of upper gastrointestinal bleeding (UGIB). No significant difference in the Child–Pugh and MELD scores was found between the two studied groups. However, UACR was significantly correlated with the Child–Pugh scores in the elderly group ($P = 0.030$) but not with those in the control group (Table 2). A significant correlation was observed between UACR and the nonoccurrence of UGIB. The patients who did not experience UGIB before (22 patients) had higher levels of UACR than those who presented with or had a previous history of UGIB (72 patients) ($P \leq 0.001$) as shown in Fig. 1. Table 3 shows the comprehensive geriatric assessment tools used. Based on the results of the cognitive assessment, 48.9% of the cases had no cognitive impairment, whereas 14.8% had minor cognitive disorders and 36.1% had major cognitive disorders. Functional assessment using the BI revealed that 76.6% of the patients were independent, whereas 2.1% were totally dependent. Nutritional assessment showed that 31.9% of the patients were at risk for malnutrition and 21.3% were malnourished. Screening for depression using the 4-item geriatric depression scale showed that 34% of the elderly patients were depressed, whereas 40.4% of the patients had no signs of depression. UACR was not related to the cognitive, functional, mood, or nutritional status of the elderly patient group (Table 4).

Child–Pugh score was found to be significantly affecting the MMSE scores (as demonstrated in Fig. 2), functional capacity (BI), and nutritional status (MNA) in the elderly population with a correlation coefficient of 0.337, 0.397, and 0.353, respectively, and a P value of 0.022, 0.006, and 0.015, respectively). The MELD score was found to be significantly

Table 2 Correlation between urine albumin creatinine ration, Child and MELD scores

	UACR			
	Control		Geriatric	
	Correlation coefficient	P value	Correlation coefficient	P value
Child score	−0.196-	0.186	0.317	0.030
MELD score	−0.108-	0.470	0.053	0.724

UACR urine albumin creatinine ratio, MELD Model for End-Stage Liver Disease (P < 0.05 significant)

Fig. 1 The correlation between occurrence of upper gastrointestinal bleeding (UGIB) and urine albumin creatinine ratio (UACR). MMSE mini mental state examination

correlated with functional capacity (BI) with a correlation coefficient of 0.329 and a *P* value of 0.024 as shown in Fig. 3.

Discussion

Several studies had investigated the relationship between proteinuria and the severity of liver cirrhosis [7, 21] and had results similar to ours. These previous studies as well as the present study found that UACR significantly correlated with the Child–Pugh scores. The present study differs from the others because it focused on elderly patients. Moreover, a study done by Cholongitas et al. did not exclude the patients with elevated serum creatinine levels, low GFR, or hypertension, and this may be a confounding factor that affected their results, although no clear explanation can be proposed for the relationship between UACR and the severity of liver cirrhosis. It can be postulated that UACR may reflect greater inflammation as a result of bacterial translocation from the gut [7].

Table 3 Description of geriatric assessment tests

		Count	%
MMSE	No cognitive impairment	23	48.9
	Minor neurocognitive disorder	7	14.8
	Major neurocognitive disorder	17	36.1
BI	Independent	36	76.6
	Minimally dependent	3	6.4
	Partially dependent	2	4.3
	Very dependent	5	10.6
	Totally dependent	1	2.1
MNA	Normal	22	46.8
	Risky for malnutrition	15	31.9
	Malnourished	10	21.3
4 Question Geriatric Depression Scale	Depressed	16	34.0
	Not certain	12	25.5
	Not depressed	19	40.4

MMSE mini mental state examination, *BI* Barthel index, *MNA* mini nutritional assessment

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Table 4 The relation between UACR and MMSE, BI, depression, and MNA in geriatric population

	UACR	
	Correlation coefficient	***P* value**
MMSE	−0.140-	0.353
BI	−0.205-	0.167
Depression	0.025	0.868
MNA	0.008	0.957

UACR urine albumin creatinine ratio, *MMSE* mini mental state examination, *BI* Barthel index, *MNA* mini nutritional assessment (*P* < 0.05 significant)

The present study found that the severity of liver cirrhosis significantly affects cognitive function, functional capacity, and nutritional status in the elderly population. Patients with hepatic cirrhosis may have altered the blood–brain barrier accompanied by astrocyte degeneration responsible for metabolizing neurotoxic substances, including ammonia and manganese, which may contribute to the development of hepatic encephalopathy and other neurocognitive disorders [22]. The Child–Pugh scores were found to be significantly affecting the MMSE scores, whereas the MELD scores were found to be significantly correlated with functional capacity (BI). Although microalbuminuria is considered an early indicator of endothelial disease and associated with qualitative and quantitative cerebral white matter hyperintensity grade and volume abnormalities, respectively [23], no significant relationship between UACR and the results of the MMSE, BI, and MNA or mood was found in the present study. A prospective study in Taiwan on 136 patients investigated the relationship between proteinuria (dipstick) and premorbid, in-hospital, and discharge functional status in elderly patients. Moreover, functional status was assessed using premorbid BI (1 month before admission), on the first day of admission and on discharge, the investigators found no significant relationship between proteinuria and age or sex but a significant relationship between proteinuria and dementia and parkinsonism (*P* = 0.03) [24].

In the present study, nutritional assessment was performed in 47 elderly patients, and we found that 46.8% of the patients had normal nutritional status, 31.9% were at risk for malnutrition, and 21.3% were malnourished, which is higher than the prevalence of malnutrition in the Egyptian patients who did not have end-stage liver disease [25]. Another study done by Sweed et al. found that among the 200 Egyptian participants living in elderly care centers, 8.5% of them were malnourished, 48% were at risk of malnutrition, and 43.5% were well nourished [26]. The MMSE score was altered in patients with liver cirrhosis as shown in the present study. These patients had impaired orientation (spatial and time), attention, concentration, calculation, immediate and short-term memory, and visuospatial orientation, subclinical psychomotor retardation, and cognitive deficits that are typically present in minimal hepatic encephalopathy [27]. Special care should be directed to elderly patients, considering the differences in physiology, pathogenesis, and response to medications between adult and elderly age groups. Furthermore, comprehensive geriatric assessment is mandatory for the
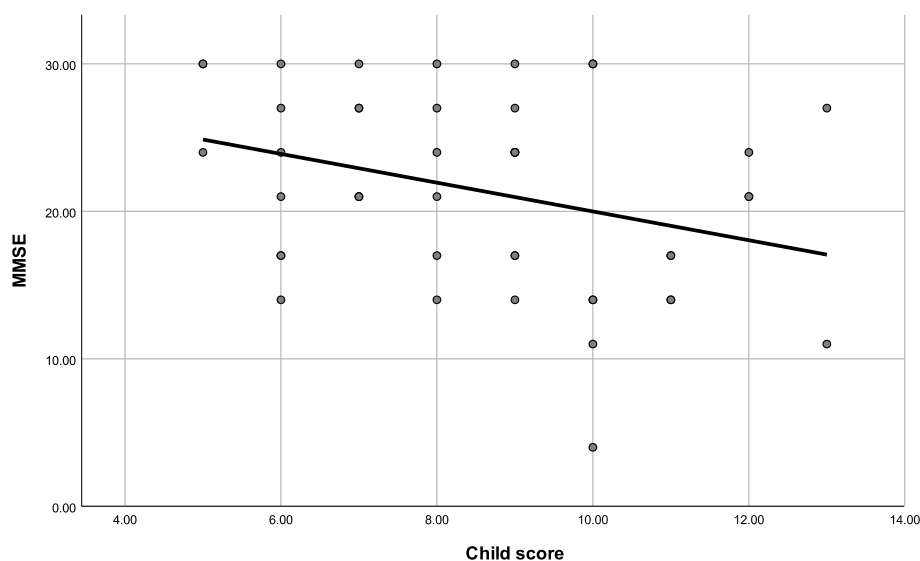
Fig. 2 The correlation between MMSE and Child score. BI Barthel index, MELD Model for End-Stage Liver Disease

Fig. 3 The correlation between BI and MELD score
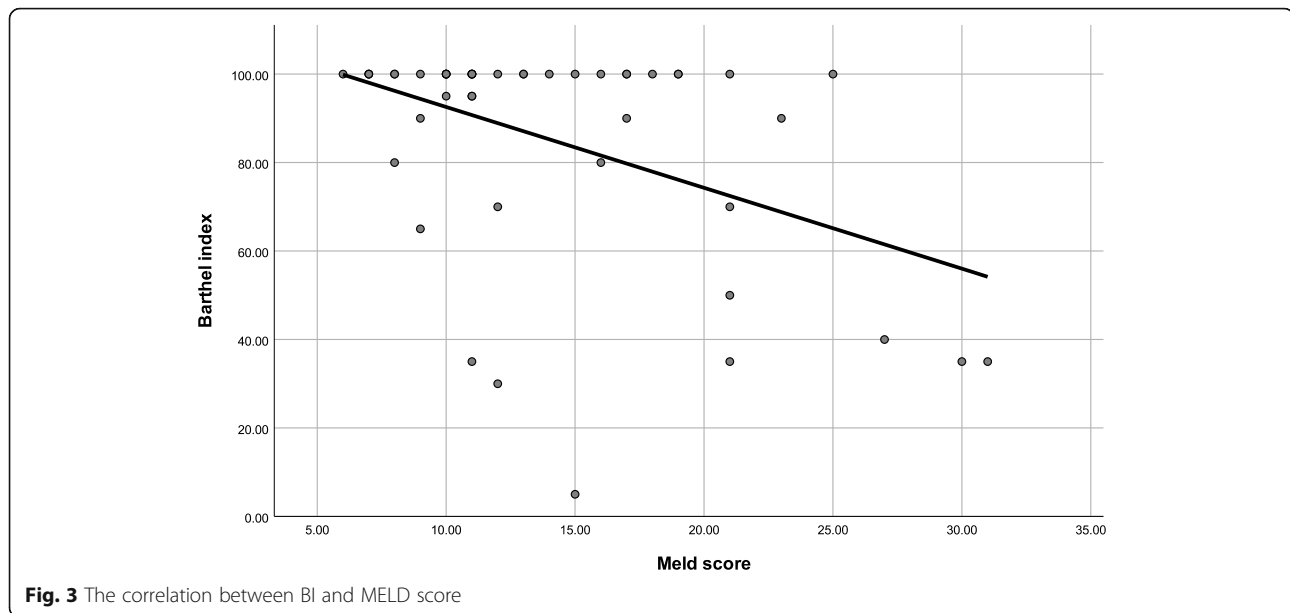
prediction of morbidity and mortality in elderly cirrhotic patients.

Conclusions

Overall, a significant relationship between UACR and Child–Pugh score was observed in elderly patients with liver cirrhosis, whereas no significant relationship between UACR and MELD score was observed in both groups. Cognitive, functional, and nutritional status were found to be significantly affected by the severity of liver disease (Child–Pugh and MELD scores) among elderly patients. Furthermore, no significant relationship was found between UACR and the cognitive, functional, mood, or nutritional status of the elderly group.

Abbreviations
ACE-i: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; BI: Barthel Index; GFR: Glomerular filtration rate; INR: International normalized ratio; MELD: Model for end-stage liver disease; MMSE: Mini-mental state examination; MNA: Mini nutritional assessment; NASH: Nonalcoholic fatty liver disease; UACR: Urinary albumin-to-creatinine ratio

Submission declaration
This work has not been published previously and is not under consideration for publication elsewhere, and its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out and, if accepted, will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright holder.

Authors' contributions
MH and AG analyzed and interpreted the patient data regarding the comprehensive geriatric assessment. RM and OM performed the study design and analysis of the results and was a major contributor in writing the manuscript, SE collected patients' data, and RM and AG supervised patient data collection validation and wrote the manuscript. The authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from all patients or a responsible care giver for those who were not able to give consent, the study protocol conformed to ethical guidelines of the 1975 declaration of Helesinki, approved by the Internal Medicine department Research Ethics Committee, Faculty of Medicine, Cairo University number: MS-331 -2019.

Consent for publication
Written consent for publication was obtained from patients or their care givers for patients who are unable to give consent.

Competing interests
Authors declare any financial and non-financial competing interests.

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