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

Ahmed Abdelghani, Maha Hosam El-Din Ibrahim, Osama Mohamady Mohamed, Sobhi Eid Rizk and Rabab Mahmoud Ahmed

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...
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/m²) 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
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 ($\chi^2$) 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 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)

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

|                      | UACR          |                     | Geriatric |                     |
|----------------------|---------------|---------------------|-----------|---------------------|
|                      | Control       | $P$ value           | Geriatric | $P$ value           |
|                      | Correlation coefficient |             | Correlation coefficient |             |
| 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)
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

| Assessment Test                  | 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*
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

| 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 \((P < 0.05 \text{ significant})\)
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.

**Funding**
No funding was obtained for this study.

**Availability of data and materials**
All raw data used in this study is available.

**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 Helsinki, 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.

Received: 7 May 2021 Accepted: 29 June 2021
Published online: 01 October 2021

**References**
1. Kandeel A, Genedy M, el-Refai S, Funk AL, Fontanet A, Talaat M (2017) The prevalence of HCV infection in Egypt 2015: implications for future policy on prevention and treatment. Liver Int. 37(1):45–53. https://doi.org/10.1111/liv.13186
2. Kenya K. et al. Considerations of elderly factors to manage the complication of liver cirrhosis in elderly patients World J Gastroenterol 2019;25(15):1817–1827.
3. Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK (2005) Systematic review: the model for end-stage liver disease—should it replace Child-Pugh’s classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther. 22(11-12):1079–1089. https://doi.org/10.1111/j.1365-2036.2005.02691.x
4. Gotthardt D, Weiss KH, Baumgartner M, Zahn A, Stremmel W, Schmidt J, Bruckner T, Bauer P (2009) Limitations of the MELD score in predicting mortality or need for removal from waiting list in patients awaiting liver transplantation. BMC Gastroenterol. 9(1):22. https://doi.org/10.1186/1471-230X-9-22
5. Visram A, Al Saleh AS, Parmar H, McDonald JS, Lieske JC, Vaxman I, Muchtar E, Hobbs M, Fonder A, Hwa YL, Buadi FK (2020) Correlation between urine ACR and 24-h proteinuria in a real-world cohort of systemic AL amyloidosis patients. Blood Cancer J 10(12):124. https://doi.org/10.1038/s41408-020-00391-2

6. Heerspink HJ, Garonne R, Brenner BM, Cooper ME, Parving HH, Shakhnfar S, de Zeeuw D (2010) Comparison of different measures of urinary protein excretion for prediction of renal events. J Am Soc Nephrol. 21(8):1355–1360. https://doi.org/10.1681/ASN.2010010063

7. Cholongitas E, Goulios I, Soulaipoulos S, Chalekas P, Alaviadis E (2017) Urine albumin-to-creatinine ratio is associated with the severity of liver disease, renal function and survival in patients with decompensated cirrhosis. Hepatol Int. 11(3):306–314. https://doi.org/10.1007/s12072-016-9755-9

8. NHS. (2014) Safe, compassionate care for frail older people using an integrated care pathway: practical guidance for commissioners, providers and nursing, medical and allied health professional leaders. Available at: http://www.england.nhs.uk/wp-content/uploads/2014/02/safe-comp-care.pdf

9. Folstein F, Susan E (1975) Folstein et al.

10. Arroll B, Khin N, Kerse N (2003) Screening for depression in primary care with two verbally asked questions: cross sectional study. BMJ. 327(7424):1144–1146. https://doi.org/10.1136/bmj.327.7424.1144

11. Mahoney, R. and DW, B., 1965. Barthel index (BI). Surya Shah, PhD, OTD, Professor Neurorehabilitation, University of Tennessee Health Sciences Centre, 950(1).

12. Collin C, Wade DT, Davies S, Home V (1988) The Barthel ADL index: a reliability study. Int Disabil Stud. 10(2):61–63. https://doi.org/10.3109/0963888890164103

13. Charlton KE, Kolbe-Alexander TL, Nel HJ (2007) The mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res. 12(3):189–198. https://doi.org/10.1016/j.jpsychires.2007.00074.x

14. Ciećko-Michalska I, Wójcik J, Senderecka M, Wyczesany M, Binder M, Szwczak J, Dziedzic T, Slowik A, Mach T (2013) Cognitive functions in patients with liver cirrhosis: a tendency to commit more memory errors. Med Sci Monit. 19:283–288. https://doi.org/10.12659/MSM.883890

15. Bajaj JS, Schubert CM, Heuman DM, Wade JB, Gibson DP, Topaz A, Saieen K, Hafeezullah M, Bell DE, Sterling RK, Stravitz RT (2010) Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology 138(7):2332–2340. https://doi.org/10.1053/j.gastro.2010.02.015

16. Deckers K, Camerino I, van Boxtel MP, Verhey FR, Irving K, Brayne C, Kivipelto M, Stark JM, Yaffe K, de Leeuw PW, Köhler S (2017) Dementia risk in renal dysfunction. A systematic review and meta-analysis of prospective studies. Neurology. 88(2):198–208

17. Tsoris A, Marlar CA. Use of the Child Pugh score in liver disease. [Updated 2020 Feb 17]. In: StatPearls. Treasure Island: StatPearls Publishing; 2020 Jan

18. Norris D, Clark MS, Shipley S (2016) The mental status examination. Am Fam Physician. 94(8):635–641. PMID: 27929229

19. Hartigan I (2007) A comparative review of the Katz ADL and the Barthel index in assessing the activities of daily living of older people. Int J Older People Nurs. 2(3):204–212. https://doi.org/10.1111/j.1748-3744.2007.00074.x

20. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahmou D, Lauque S, Allardele JD (1999) The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition. 15(2):116–122. https://doi.org/10.1016/S0899-9007(98)00171-3

21. Chen Y-C et al (2014) Proteinuria can predict short-term prognosis in critically ill cirrhotic patients. J Clin Gastroenterol. 48:377–382

22. Bruskiew SW (2002) Hyperammonemic encephalopathy. Medicine. 81(3):240–249. https://doi.org/10.1097/00055792-200205000-00007

23. Weiner DE, Bartolomei K, Scott T, Price LL, Griffith JL, Rosenberg L, Levey AS, Folsom MF, Samak MJ (2009) Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. Ann J Kidney Dis. 53(3):438–447. https://doi.org/10.1053/j.ajkd.2008.08.022

24. Chao CT, Tsai HB, Chang CK, Huong JW, Hung KY (2017) Dipstick proteinuria level is significantly associated with pre-morbid and in-hospital functional status among hospitalized older adults: a preliminary study. Sci Rep. 7(1):42030. https://doi.org/10.1038/srep42030

25. Hassan Elghazally NW, Saeid S (2019) Nutritional Assessment of the Elderly: A Comparative study of residents of Geriatric Homes versus Community living Population, Tanta, Egypt. Egyptian Family Med J. 3(1):1–16

26. Saeed HS, Mabrouk RR, Kamel HY, Jamil MA (2017) Malnutrition and its relation to food system among elderly home male residents in Cairo, Egypt. Egypt J Geriatrics Gerontol 4(1):15–18

27. Bajaj JS, Wade JB, Sanyal AJ (2009) Spectrum of neurocognitive impairment in cirrhosis: implications for the assessment of hepatic encephalopathy. Hepatology. 50(6):2014–2021. https://doi.org/10.1002/hep.23216

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.