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CHILD-TURCOTTE-PUGH /ALBUMINURIA AS A PREDICTOR OF ACUTE KIDNEY INJURY AMONG HOSPITALIZED PATIENTS WITH LIVER CIRRHOSIS

By

Othman Mohammed Ahmed Othman*, Mohammad Sad Al-Den Radwan, Sadek Mostafa Sadek* and Ashraf Mohammed El-Bahrawy***

Departments of *Internal Medicine and **Clinical Pathology, Faculty of Medicine, Al-Azhar University

Corresponding author: Othman Mohammed Ahmed Othman

E-mail: doctorosmanmahmedosman@gmail.com

ABSTRACT

Background: The incidence of acute kidney injury (AKI) in cirrhotic patients about fifteen percent of hospitalized cirrhotic patient, Prediction of AKI indicated in all patients with liver cirrhosis. Albuminuria in cirrhotic patient can predict AKI.

Objective: To assess the role of Child-Turcotte Pugh/Albuminuria (CTP-Alb), in prediction of AKI among hospitalized patients with liver cirrhosis.

Patients and Methods: After departmental ethics committee approval and patient consents were obtained, 60 patients with liver cirrhosis screened for AKI during hospital admission at hepatogastroenterology unit, Department of Internal Medicine in Al-Hussein Hospital, Al-Azhar University, and The study was carried out during the period from September 2019 and September 2020, The diagnosis of liver cirrhosis based on clinical, biochemical and ultrasonography findings. Patients with Fib-4 $\geq$ 3.5 in the absence of liver decomposition were categorized as compensated liver cirrhosis. Severity of liver disease was assessed using the CTP score, model for end stage liver disease (MELD) score and CTP-Alb score. Diagnosis of acute kidney injury was based on the changes in serum creatinine. The baseline renal assessment at first day of hospital admission was included serum creatinine, estimated glomerular filtration rate (eGFR), albumin/creatinine ratio, and abdominal ultrasonography. AKI was categorized as hepatorenal syndrome (HRS), pre-renal azotemia, post-renal azotemia or intrinsic acute kidney injury.

Results: A total of 60 patients included. They were 40 (66.66%) males and 20 (33.34%) females. Their mean age was 50 ± 33 years, of them 8 (13.33%) patients developed AKI during hospital admission with their mean age was 60.6 ± 10.9 years. They were 5 (62.5%) males and 3 (37.5%) females, Hypoalbuminemia, Child score at admission and Child-albuminuria score at admission were identified as independent risk factors for AKI by multivariate analysis ($p < 0.05$).

Conclusion: Thirteen percent of cirrhotic patients developed AKI during hospital admission according to our results. The majority of patients were child C in our series; CTP/Albuminuria score, Hypoalbuminemia and ACLF has promising sensitivity, specificity and accuracy in prediction of AKI in hospitalized cirrhotic patient.

Key words: AKI, CTP/Albuminuria score, Hypoalbuminemia and ACLF.

INTRODUCTION

Renal dysfunction is a common complication of liver cirrhosis. This may be related to the abnormal hemodynamics of systemic and splanchnic arterial vasodilation and extra-hepatic vasoconstriction peculiar to advanced cirrhosis *(Wong, 2012)*.

Regardless of the cause, the development of AKI has a profound impact on survival. This is particularly true in those with AKI who then progress to persistent kidney injury, where the 30-day mortality rate is nearly 10-fold higher *(Belcher et al., 2013)*.

The diagnosis of AKI in cirrhosis has undergone dramatic changes in recent years, partly related to better understanding of the pathophysiology of AKI, and partly related to the need to institute earlier treatment, so to improve the prognosis of these patients. The IAC proposed changes in the definition and diagnostic criteria for AKI in cirrhosis is the first step towards better identification of these patients. Once validated, these diagnostic criteria will help to contribute to an improved prognosis of these patients. The use of biomarkers in the future will certainly further enhance the diagnostic accuracy of AKI for the patients *(Wong, 2016)*.

The renal dysfunction is not represented in CTP score. Diagnostic information is contained in the renal function in cirrhotic patients which could add much to the standard CTP score. The addition of serum creatinine to the CTP score did not significantly improve its predictive ability *(Amathieu et al., 2017)*.

The present work aimed to assess the role of Child-Turcotte-Pugh/albuminuria (CTP-Alb), in prediction of AKI among hospitalized patients with liver cirrhosis.

PATIENTS AND METHODS

This was a cross sectional study conducted on 60 adult patients with liver cirrhosis admitted to hospital. Patients were admitted to the Gastroenterology and Hepatology Unit, Department of Internal Medicine, Al-Azhar University, Cairo, Egypt. Approval of the medical ethics committee of Al-Azhar Faculty of Medicine had been taken. An informed consent from patient or patients' next of kin had been taken before enrollment to the study.

Inclusion criteria:

Patients with liver cirrhosis aged between (17-83) years included.

Exclusion criteria:

Severe cardiopulmonary disease, history of renal disease, had previous liver transplantation, nephrotoxic drugs or NSAIDs use in the last 4 weeks or diabetes mellitus.

The diagnosis of decompensated liver cirrhosis based on combination of clinical, biochemical and ultrasonography findings. Patients with Fib-4 $\geq$ 3.5 in the absence of liver decomposition were categorized as compensated liver cirrhosis. Severity of liver disease was assessed using the CTP score, MELD score, and CTP-Alb score. Diagnosis of acute kidney injury based on the changes in serum creatinine. The baseline renal assessment at first day of hospital admission included serum creatinine, eGFR, albumin/creatinine ratio, and abdominal ultrasonography. The

cause of AKI was categorized as HRS, pre-renal azotemia, post-renal azotemia or intrinsic acute kidney injury. The primary study outcome was occurrence of AKI during hospitalization and the secondary outcome was in hospital mortality.

Statistical analysis:

Data were analyzed using Statistical Pachage for Social Science (SPSS) version 24. Quantitative data were expressed as mean± standard deviation (SD) and median. Qualitative data were expressed as frequency and percentage.

Independent-samples t-test of significance was used when comparing between two means (for normal distributed data). Mann–Whitney U test: was used when comparing between two means (for abnormal distributed data). P-value < 0.05 was considered significant.

RESULTS

Among 60 patients with liver cirrhosis, they were 40 (66.66%) males and 20 (33.34%) females, their mean age was 50 ± 33 years, of them 8 (13.33%) patients developed AKI during hospital admission. their mean age was 60.6 ± 10.9 years. They were 5 (62.5%) males and 3 (37.5%) females.

There was a significant relationship between cirrhotic patient with AKI and hypoalbuminemia, as p values were 0.042, while no significant relationship between cirrhotic patient with AKI and other laboratory parameters **(Table 1)**.

Table (1): Comparisons of laboratory tests as regard AKI

AKI / Parameters		No (n = 52)	Yes (n = 8)	P-value
Hb (g/dl)	**Mean ±SD**	10.5 ± 2.4	9.2 ± 1.6	0.162
	Median	10.5	9.4	
PLTs (x10³/ul)	**Mean ±SD**	102.6 ± 70.1	102.1 ± 45.4	0.557
	Median	81	86	
TLC (x10³/ul)	**Mean ±SD**	6.5 ± 3.9	6.1 ± 1.9	0.777
	Median	5.8	6.5	
AST (U/L)	**Mean ±SD**	45.3 ± 32.1	43.3 ± 21.9	0.720
	Median	31.5	40.5	
ALT (U/L)	**Mean ±SD**	28.6 ± 26.9	21.1 ± 6.1	0.819
	Median	20.5	22.5	
ALB (g/dl)	**Mean ±SD**	3.6 ± 0.6	3.01 ± 0.6	**0.042**
	Median	3.6	3.3	
T. Bilirubin (mg/dl)	**Mean ±SD**	2.2 ± 2.8	2.7 ± 2.8	0.609
	Median	1.3	1.5	
D. Bilirubin (mg/dl)	**Mean ±SD**	1.08 ± 2.2	1.45 ± 1.7	0.177
	Median	0.4	0.8	
INR	**Mean ±SD**	1.5 ± 0.5	1.6 ± 0.3	0.071
	Median	1.3	1.6	

Child score at admission, Child-albuminuria score at admission and acute on top of chronic liver failure (ACLF) were identified as independent risk factors for AKI by multivariate analysis ($p < 0.05$), (Table 2).

Table (2): Predictors of AKI in hospitalized cirrhotic patients by multivariate analysis

	B	SE	p-value	95% CL	
(Constant)	- 3.1	2	0.116		
Age	0.02	0.033	0.509	0.95	1.08
Sex	0.21	0.78	0.789	0.26	5.8
Abdominal Pain	1.2	0.78	0.123	0.7	15.4
Abdominal Distension	**2.8**	**1.3**	**0.029**	**1.33**	**216.6**
Hematemesis	0.6	0.9	0.502	0.31	10.7
Melena	-19.5	14210	0.999	----	-----
Jaundice	19.4	40192	1.0	----	-----
Dyspnea	19.3	23205	0.999	----	-----
Weight loss	19.4	40192	1.0	----	-----
Poly-arthralgia	19.4	40192	1.0	----	-----
Easy Fatigability	19.4	40192	1.0	----	-----
SBP	- 0.074	0.067	0.271	0.814	1.06
DBP	- 0.035	0.77	0.649	0.830	1.12
Temp	0.52	0.76	0.488	0.381	7.5
Jaundice (Clinical)	0.33	0.88	0.705	0.24	7.9
Ascites	1.56	0.86	0.07	0.88	26.1
HE	23.2	40192	1.0	----	-----
Lower limb Edema	1.14	0.78	0.145	0.67	14.7
HB	- 0.23	0.17	0.167	0.56	1.1
PLT	0.0	0.006	0.986	0.98	1.01
TLC	- 0.02	0.112	0.803	0.78	1.2
AST	- 0.002	0.013	0.859	0.97	1.02
ALT	- 0.019	0.024	0.435	0.93	1.02
ALB	**- 1.3**	**0.65**	**0.003**	**0.069**	**0.89**
T. Bilirubin	0.058	0.11	0.622	0.84	1.3
D. Bilirubin	0.069	0.15	0.644	0.79	1.43
INR	0.36	0.66	0.587	0.38	5.3
Creat (Basal)	- 2.09	1.9	0.280	0.003	5.5
HBs Ag	19.4	40192	1.0	----	-----
HCV Ag	19.6	11602	0.999	----	-----
ALB/Creat ratio	- 0.003	0.005	0.558	0.98	1.007
Urine Pus	1.98	1.47	0.177	0.4	130.07
	B	**SE**	**p-value**	**95% CL**	
Urine Crystals	1.27	1.29	0.324	0.28	44.7
Paracentesis Pus	23.2	40192	1.0	---	----
Plural effusion	1.7	0.86	0.049	1.005	30.3
Splenomegaly	19.5	16408	0.999	----	-----
Ascites (US)	0.7	0.86	0.412	0.37	11.05
HFL	0.3	0.79	0.704	0.28	6.3
PVT	- 0.085	1.14	0.914	0.098	8.6
Nephropathic	- 19.3	28420	0.999	----	-----
OV	- 19.3	28420	0.999	----	-----
PHG	- 19.3	28420	0.999	----	-----
CHILD (Admission)	**2.6**	**1.2**	**0.026**	**1.37**	**156.9**
CTP	**0.44**	**0.193**	**0.02**	**1.07**	**2.28**
MELD (Admission)	0.09	0.061	0.138	0.97	1.23
GFR (Admission)	- 0.017	0.017	0.318	0.95	1.01
FIB4 Score	- 0.041	0.069	0.552	0.83	1.09
ACLF	**1.97**	**0.89**	**0.028**	**1.24**	**41.7**

DISCUSSION

The exact mechanisms implicated in the pathogenesis of microalbuminuria in cirrhotic patient remain unclear, liver cirrhosis is considered a systemic disease affecting the function of several extra-hepatic organs as a result of bacterial translocation from the gut and the development of hyperdynamic circulation. Thus, patients with liver cirrhosis especially decompensated cirrhosis (DC) have decreased effective arterial blood volume leading to renal hypoperfusion, deterioration of GFR and simultaneous compensatory activation of the endogenous sympathetic system and renal vasoconstrictor systems, such as renin angiotensen aldosterone system (RAAS). In fact, in patients with DC, greater activation of RAAS correlates with the severity of renal dysfunction. Taken together, these all mechanisms may explain the pathogenesis of microalbuminuria in cirrhotic patient, explained by *Cholongitas et al. (2014)*.

In the current study, we found that 13.3% of cirrhotic patient developed AKI during hospital admission. Hypoalbuminemia, child/Albuminuria score and ACLF at admission were independent predictors of AKI in hospitalized patients with liver cirrhosis. Going with this result .albuminuria was significantly higher in cirrhotic patients adjudicated with acute tubular necrosis (ATN) versus non-ATN *(Belcher et al., 2014)*.

In our study, we firstly found that CTP/Albuminuria score can discriminate between patients with AKI and patients without AKI at a cutoff level of > 10.5, with 50% sensitivity, 88.5% specificity, 81.3% PPV and 63.9% NPV. This hints that albuminuria can be predicted early before deterioration of serum creatinine and can segregate cirrhotic patients with risk of AKI.

Moreau et al. (2013) mentioned that the renal dysfunction or failure is universally presented in patients with ACLF, according to the definition by the European association for the study of the liver disease –chronic liver failure (EASL-CLIF) consortium. In agreement with this concept in the current study, we demonstrated that the ACLF is independent predictor of AKI in cirrhotic patients.

Mi-yeon et al. (2017) reported that the hypoalbuminemia at admission predicts the development of acute kidney injury in hospitalized patients and replacement of albumin after development of AKI may contribute to renal recovery. In addition, *Wiedermann et al. (2010)* showed that the lower serum albumin was significant independent predictor of AKI development in chronic liver disease patients.

Going with these results, our findings indicate that Hypoalbuminemia can be used to discriminate between patients with AKI and patients without AKI at a cutoff level of < 3.2, with 50% sensitivity, 75% specificity, 66.7% PPV and 60% NPV.

CONCLUSION

CTP/Albuminuria score, hypoalbuminemia and ACLF have promising sensitivity, specificity and accuracy in prediction of AKI in hospitalized cirrhotic patient.

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دور معامل شيلد مضافا إليه كمية تسرب الزلال بالبول فى التنبوء بحدوث خلل حاد بوظائف الكلى بين مرضى الشمع الكبدى أثناء تواجدهم بالمستشفى

عثمان محمد أحمد عثمان*، محمد سعد الدين رضوان، صادق مصطفى صادق*، أشرف محمد البحراوي***

قسمي الأمراض الباطنة*، والباثولوجيا الاكلينيكيه، كلية الطب، جامعة الأزهر**

خلفيـــة البحـــث: هنـــاك نســبة حـــدوث خلـــل حـــاد بوظـــائف الكلـــي فـــي مرضـــى التشـــمع الكبـــدي المحجـــوزين فـــى المستشـــفى حـــوالى خمســـة عشـــر بالمائـــه. يشـــار الـــى التنبـــؤ بحـــدوث خلـــل حـــاد بوظـــائف الكلـــي فـــي حميـــع مرضـــى التشـــمع الكبـــدي. وقـــد وجـــدت البيانـــات الحديثـــه أن تســـرب الـــزلال بـــالبول فـــي مرضـــى التشـــمع الكبـــدي يمكـــن ان يتنبـــأ بحدوث خلل حاد بوظائف الكلي.

الهـــدف مـــن البحـــث: تقيـــيم دور معامـــل شـــيلد مضـــافا إليـــه كميـــة تســـرب الـــزلال بـــالبول فـــي التنبـــؤ بحـــدوث خلـــل حـــاد بوظـــائف الكلـــي فـــي مرضـــى التشـــمع الكبـــدي أثنـــاء تواجدهم بالمستشفى.

المرضـــي وطـــرق البحـــث: أجريـــت هـــذه الدراســـة علـــي ســـتين مريضـــا يعـــانون مـــن التشـــمع الكبـــدي بحثـــا عـــن وجـــود قصـــور حـــاد بوظـــائف الكلـــي اثنـــاء تواجـــدهم بالمستشـــفي .وقـــد تـــم تشـــخيص التشـــمع الكبـــدى بنـــاءا علـــي الفحـــص الاكلينيكـــى والمعـــاملات الكيميائيـــة الحيويـــة والتصـــوير بالموجـــات فـــوق الصـــوتيه. وقـــد تـــم تصـــنيف المرضـــي حســـب تقيـــيم معـــدل التليـــف لـــديهم (Fib-4) اكثـــر مـــن ثلاثـــه ونصـــف فـــى حالـــة عـــدم وجـــود كبـــد متكـــافئ علـــي انهـــم مرضـــى تشـــمع كبـــدى. كمـــا تـــم تقيـــيم شـــدة إعـــتلال الكبـــد باســـتخدام درجـــة شـــيلد (CTP) ودرجـــة (MELD) وهـــو تصـــور لتقيـــيم إعـــتلال الكبد المتاخر.

وقـــد اســـتند تشـــخيص الخلـــل الحـــاد بوظـــائف الكلـــى علـــى التغيـــرات فـــى مصـــل الكريـــاتينين, وشـــمل تقيـــيم الكلـــي الأساســـى فـــى اليـــوم الأول مـــن دخـــول المستشـــفى كـــلا مـــن مصـــل الكريـــاتينين ومعـــدل ترشـــيح كبيبـــات الكلـــى, (GFR) ونســـبة الألبـــومين إلـــى الكريـــاتينين فـــي البـــول والتصـــوير بالموجـــات فـــوق الصـــوتيه علـــى الـــبطن, ويصـــنف

سبب القصور الحاد في وظائف الكلى الى أزوت الدم ماقبل الكلوى وأزوت الدم مابعد الكلوى ومتلازمة القصور الكبدى الكلوى وإصابة الكلى الحادة الداخلية.

نتائج البحث: أجريت هذه الدراسة علي ستين (60) مريضا, حيث كانوا أربعين (40) من الذكور (66.66%) وعشرين من الاناث (33.34%) وكان متوسط أعمارهم 50 ± 33سنه, ثمانية منهم (13.33%) أصيبوا بخلل حاد بوظائف الكلى أثناء تواجدهم بالمستشفى وكان متوسط أعمارهم 60.6 ± 10.9 سنه, وكانوا خمسة رجال (62.5%) وثلاث سيدات (37.5%).

وقد تم تحديد نقص البومين الدم ودرجة شيلد (CTP) ولاول مرة درجة معامل شيلد مضافا اليه كمية تسرب الزلال بالبول وكذلك حدوث خلل حاد في مرضى القصور الكبدى المزمن كعوامل خطر مستقله للتنبوء بحدوث خلل حاد بوظائف الكلي عن طريق التحليل متعدد التغيرات ($p<0.05$).

الإستنتاج: أصيب ثلاثة عشر بالمائه من مرضى التشمع الكبدى بخلل حاد بوظائف الكلى اثناء تواجدهم بالمستشفى. كان غالبية المرضى من الدرجه الثالثه في تقييم شيلد.قد يكون لنتيجة درجة معامل شيلد مضافا اليه كمية تسرب الذلال بالبول وكذلك حدوث خلل حاد في مرضى القصور الكبدى المزمن ونقص البومين الدم دور واعد في التنبؤ بحدوث خلل حاد بوظائف الكلي في مرضى التشمع الكبدى اثناء تواجدهم بالمستشفى.