THU-159-YI

Development and validation of dimethylarginines (DAS) as a novel biomarker to identify pre-ACLF and predict outcomes following acute decompensation of cirrhosis in two prospective multicentre european cohorts

Kohilan Gananandan[1], Peter Holland-Fischer[2], Karen Louise Thomsen[3], Konstatin Kazankov[4], Rohit Sawhney[5], Olivia Greenham[1], Steven Masson[6], Guruprasad Aithal[7], Daniel Forton[8], Kathryn L. Nash[9], Graham R. Foster[10], Carolyn Hyde[11], Cristina Sanchez[12], Agustín Albillos[13], Wim Laleman[14], Salvatore Piano[15], Javier Fernández[16], Paolo Caraceni[17], Thierry Gustot[18], Carlo Alessandria[19], Joan Claria[20], Richard Moreau[12], Paolo Angeli[21], Vicente Arroyo[12], Jonel Trebicka[22], Rajiv Jalan[23], Rajeshwar Prosad Mookerjee[24]. *[1]Liver Failure Group, University College London, London, United Kingdom; [2]Aalborg University Hospital, Aalborg, Denmark; [3]Aarhus University Hospital, Liver Failure Group, University College London, Aarhus, Denmark; [4]Aarhus University Hospital, Aarhus, Denmark; [5]Eastern Health and Monash University, Melborne, Australia; [6]Freeman Hospital, Newcastole, United Kingdom; [7]Queens Medical Centre, Nottingham, United Kingdom; [8]St George's Hospital, London, United Kingdom; [9]Southampton General Hospital, Southampton, United Kingdom; [10]Queen Mary University, London, United Kingdom; [11]Bio-Analysis Centre, London, United Kingdom; [12]European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain; [13]Hospital Ramon y Cajal, Madrid, Spain; [14]Department of Gastroenterology and Hepatology, University Hospitals, KU Leuven, Leuven, Belgium; [15]University and Hospital of Padova, Padova, Italy; [16]Hospital Clinic, European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain; [17]University of Bologna, Bologna, Italy; [18]Universite Libre De Bruxelles, Brussels, Belgium; [19]University of Turin, Turin, Italy; [20]Hospital Clinic, Barcelona, European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain; [21]University and Hospital of Padova, European Foundation for the Study of Chronic Liver Failure, Padova, Italy; [22]Munster University Hospital, European Foundation for the Study of Chronic Liver Failure, Munster, Germany; [23]Liver Failure Group, University College London, European Foundation for the Study of Chronic Liver Failure, London, United Kingdom; [24]Liver Failure Group, University College London, Aarhus University Hospital, London, United Kingdom*
Email: k.gananandan1@nhs.net

Background and aims: Cirrhosis patients hospitalized with acute decompensation (AD) have a high 90-day mortality. Asymmetric dimethylarginine (ADMA) and its stereoisomer symmetric dimethy-larginine (SDMA) reduce nitric oxide generation, cause endothelial cell dysfunction and play a role in driving portal hypertension and liver-related mortality. This study aimed to develop and validate a new scoring system termed DAS, combining these 2 biomarkers, in predicting liver-related events following AD.

Method: The derivation cohort encompassed patients from the DASIMAR study (n = 247), a prospective, observational, UK study recruiting patients admitted non-electively with AD cirrhosis. The validation cohort was from the PREDICT study (n = 409) which was a multicentre European trial with a similar design. ADMA and SDMA analysis were performed by liquid chromatography- tandem mass spectrometry at baseline (T0) and a second time point within 7 days (T1).

Results: Both cohorts exhibited similar baseline characteristics. With regards to inpatient transplant-free mortality in the DASIMAR cohort, T0 DAS was significantly higher in those who died (13%) compared to survivors (6.7 vs 4.1 umol/L, p < 0.001). Indeed, T0 DAS remained a predictor of inpatient mortality in multivariate analysis (OR 1.3 [95%CI 1.1–1.5], p = 0.002) and was superior to the baseline CLIF-C AD score (OR 1.1 [95% CI 1.0–1.2], p = 0.003). When assessing 90-day mortality, T0 DAS was also significantly higher in those who died (n = 56) compared to survivors (5.7 vs 4.1 umol/L, p < 0.001). Whilst both T0 and T1 DAS were significant predictors in univariate analysis, only T1 DAS remained significant in multivariate analysis (OR 1.48 [95% CI 1.18–1.86], p = 0.001). When assessing 90-day mortality in the PREDICT cohort a similar signal was demonstrated with significantly higher T0 DAS scores in those who died (5.5 vs 4.2 umol/L, p = 0.033). Significantly higher T0 DAS scores were noted in the DASIMAR cohort in the pre-ACLF patients (5.3 vs 3.6 umol/L, p < 0.001). This was confirmed in the PREDICT cohort where T0 DAS was an independent predictor of ACLF development in multivariate analysis (OR 1.13 [95%CI 1.01–1.25], p = 0.027). With respect to renal dysfunction in the DASIMAR population, T0 DAS scores were significantly higher in those who developed an acute kidney injury (AKI) during admission compared to those who did not (5.2 vs 3.5 umol/L, p < 0.001). This was shown in multivariate analysis (OR 1.3 (1.1–1.5, p < 0.001) and replicated in the PREDICT cohort where T0 DAS also predicted renal failure in multivariate analysis (OR 1.2 [95% CI 1.0–1.3, p = 0.025).

Conclusion: This study demonstrates that the novel DAS score can predict liver-related events including mortality, ACLF development and renal dysfunction. With further validation, DAS could be translated for clinical use in identifying patients with pre-ACLF and those at high risk of mortality.