

**Abstract Type : Oral**

**Abstract Submission No. : OR-1067**

**Plasma circulating tumor necrosis factor  $\alpha$  receptor 1 can predict the outcomes of severe acute kidney injury**

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**Objectives:**

While circulating tumor necrosis factor receptors (cTNFRs) are known to predict the long-term outcome in chronic kidney disease, their association with acute kidney injury (AKI) was not well documented. Here, we investigated how cTNFR levels could be a prognostic biomarker in severe AKI patients requiring continuous renal replacement therapy (CRRT).

**Methods:** A total of 136 patients participating in VENUS (VolumE maNagement Under body composition monitoring in critically ill patientS on CRRT) trial were enrolled from seven hospitals from 2017 to 2019. cTNFR1 and cTNFR2 levels were measured using plasma samples collected at day 0, 2 and 7 (D0, D2, and D7).

**Results:** Patients were divided into high- and low-cTNFR groups based on their D0 cTNFR concentrations. D0 concentrations of cTNFR1 and cTNFR2 were positively correlated with each other ( $R^2=0.37$ ,  $P < 0.001$ ). The high-cTNFR1 group displayed a higher in-hospital mortality rate than the low-TNFR1 group ( $P = 0.002$ ). Also, the mortality rate was significantly higher in the high-TNFR1 group than in the low-TNFR1 group after adjusting for age, sex and APACHE II score (hazard ratio [HR] 1.81,  $P = 0.025$ ). The D2 and D7 cTNFR1 levels were also associated with in-hospital mortality. However, cTNFR2 levels were not associated with in-hospital mortality. When patients were divided into tertiles according to change in cTNFR levels from D0 to D2 ( $\Delta$ cTNFR), the bottom tertile had a lower mortality rate than the others ( $P = 0.030$  and  $0.019$  for  $\Delta$ cTNFR1 and  $\Delta$ cTNFR2, respectively). After adjusting for age, sex, APACHE II score and CCI, the top  $\Delta$ cTNFR tertile had a higher mortality rate than the others (HR 2.37,  $P = 0.018$  for  $\Delta$ cTNFR1; HR 1.98,  $P = 0.049$  for  $\Delta$ cTNFR2).

**Conclusions:** Plasma cTNFR1 concentrations at CRRT initiation and changes of cTNFR1 and 2 levels immediately following CRRT initiation are significant biomarkers in predicting outcomes of severe AKI.

The risk of death for circulating TNFR1 (A) D0 (B) D2 (C) D7

