Plasma Nectin-4 increase in alcohol dependent patients is correlated with severity of brain damage and drinking compulsivity improvement during detoxification period

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Background
Nectin-4 molecule is an adhesion protein responsible for cell-cell integrity. In our previous studies of heroin and ketamine dependent patients, plasma Nectin-4 of extracellular domain fragment re-lease into blood stream showed significantly increase and related to dependent symptoms.

Aims & Objectives
The aims of this study are to estimate the role of plasma Nectin-4 extracellular fragment level in active alcohol use of alcohol dependent (AD) patients and its role during two weeks of withdrawal (also called detoxification) period.

Methods
A total of 170 AD patients and 119 non-AD controls were recruited and taken blood after their consent for further plasma Nectin-4 analysis. The plasma Nectin-4 extracellular domain fragment (R&D Systems Inc, Minneapolis, MN) and neurofilament light chain (NFL) levels (Aviva Systems Biology, San Diego, CA) were measured by enzyme-linked immunosorbent assay (ELISA) ac-cording to the manufacture guidelines. The clinical assessment for AD included the biochemical analysis of serum creatinine, obsessive compulsive drinking scale (OCDS), Penn Alcohol Craving Score (PACS), and Beck Anxiety Inventory score (BAI) from the basal and during the withdrawal period of week1 and week2.

Results
In age-and gender-match comparisons between AD patients and non-AD controls, plasma Nectin-4 extracellular domain fragment levels were significantly higher in AD patients than in controls, and this elevation were continually higher than controls throughout the detoxification period of week 1 and week 2 ($P<=0.007$). The receiver operating characteristics (ROC) curve analysis showed that plasma Nectin-4 level was not an indicator for AD (AUC=0.59, P=0.007). Further analyses of ma-jor factors correlating with the plasma Nectin-4 levels in AD patients using multivariate regres-sion analyses revealed that NFL (partial r2=0.11, P=0.002) and creatinine (partial r2=0.14, P=0.00002) had strong positive correlations with plasma Nectin-4 levels at basal week 0. Increase in plasma Nectin-4 levels during withdrawal period of week 1 and week 2 was correlated with plasma NFL levels (r=0.162, P=0.040), with reductions in alcohol drinking compulsivity rated by OCDS (r= -0.2, P=0.008) especially the OCDS subscale of thought (r= -0.218, P=0.004), with re-duction of anxiety rated by BAI (r=-0.181, P=0.018), and with reduction of craving rated by PACS (r=-0.162, P=0.035).

Discussion & Conclusion
Alcohol dependence may have a traumatic influence toward the brain indicated by the release of peripheral plasma neurofilament light chain (NFL) levels. This damage may be partially due to the disruption of brain cell-cell integrity which were indicated by the correlation between NFL levels and plasma adhesion molecule Nectin-4 extracellular fragment levels. Plasma Nectin-4 level also were correlated with kidney functional parameter creatinine suggested this elevation may also contributed partially from the cell-cell disruption in kidney. The elevated plasma Nec-tin-4 levels correlated with improvement of alcohol drinking compulsivity rated by OCDS, with the improvement of anxiety rated by BAI, and with the reduction of craving rated by PACS. The extracellular domain of Nectin-4 might be serve an indicator for the improvement of alcohol drinking compulsivity, anxiety and craving improvement during detoxification period.