Abstract

Objectives: **A)** to investigate the prognostic value of circulating levels of cell-free DNA in patients with sepsis in the intensive care setting regarding the clinical course and final outcome. Moreover, to compare this prognostic value of circulating cell-free DNA levels with other commonly used biochemical markers for prognosis of sepsis (CRP and Procalcitonin) and with the APACHE II and SOFA scoring systems. **B)** we tried to describe the gastric mucosal morphologic abnormalities occurring in the septic settings, then we attempted to correlate these findings with clinical course, prognosis and mortality of septic patients.

Design: A prospective, randomized, single center study. ***Setting:*** Critical Care Department (medical/surgical ICU), Cairo University Hospitals.

Patients: 30 critically ill patients admitted to the Critical Care Department, Cairo University Hospitals with a diagnosis of sepsis. ***Intervention:*** All included septic patients were subjected to the upper GIT endoscope, which was performed at ICU admission and once again during ICU stay (approximately one week later) to obtain a gastric mucosal biopsy for histopathological microscopic examination. ***Measurements:*** Cell-free plasma DNA concentrations (measured by real-time polymerase chain reaction assay for the ß- globin gene), CRP levels and Procalcitonin concentrations were all measured on admission to the ICU. APACHE II score was calculated once (in the first 24h of ICU admission) and SOFA score was calculated at baseline and subsequently thereafter everyday until ICU discharge or death or up to a total of 28 days. Clinical outcome (duration of stay in the ICU, need for mechanical ventilation, need for inotropic/vasopressor support, need for haemodialysis, and final outcome of survival/mortality rates) were recorded for all patients.

Results: The median plasma DNA concentration in critically ill septic patients was 186.5 ng/ml and this was significantly (approximately 7-fold) higher than the median DNA concentration in healthy subjects 26 ng/ml, **($P < 0.001$).** The patients who required mechanical ventilation had significantly higher median DNA concentration compared to those who did not require it (208.9 ng/ml versus 65.5 ng/ml; **$P = 0.001$**). The patients who were on inotropic/vasopressor support had significantly higher DNA concentrations compared to non-supported patients (235 ng/ml versus 114.6 ng/ml; **$P < 0.001$**). The median plasma DNA level was significantly higher in patients who required haemodialysis (244.2 ng/ml versus 169.1 ng/ml; **$P = 0.011$**). DNA concentration demonstrated a significant correlation with C-reactine protein (CRP) concentration **($r = 0.656$, $P < 0.001$)**, procalcitonin concentration (PCT) **($r = 0.835$, $P < 0.001$)**, and Sepsis-related Organ Failure Assessment (SOFA) score **($r = 0.860$, $P < 0.001$)**, but not with Acute Physiology And Chronic Health Evaluation (APACHE II) score **($r = 0.273$, $P = 0.145$)**, DNA concentration demonstrated insignificant negative correlation with length of ICU stay **($r = -0.044$, $P = 0.818$).** The median plasma DNA concentration in nonsurvivors was 240 ng/ml, and this was significantly (approximately 2-fold) higher than that in survivors 114.6 ng/ml, **($P < 0.001$)**. ROC analysis of the data indicated a sensitivity of 100% and a specificity of 100% when DNA concentration of 186.5 ng/ml was taken as a predictor of ICU mortality. The 1st gastric mucosal biopsies showed 5 different gastric mucosal changes and the2nd biopsies revealed 9 (5 were also previously detected in the 1st biopsies and 4 newly described in the 2nd biopsies) different gastric mucosal morphologic abnormalities (with varying degrees of severity from superficial gastritis to superficial erosions). Patients with septic shock at their ICU admission had a significant increase in superficial erosions and a significant decrease in superficial gastritis in their 2nd gastric mucosal biopsies when compared to non-septic shock patients **($P = 0.033$, $P = 0.032$** respectively).There was also a trend toward increased frequency of superficial erosions in nonsurvivors versus survivors in their 2nd biopsies **($P = 0.065$).**

Conclusion: Circulating DNA concentrations were elevated early in patients who were admitted to the ICU with sepsis when compared to healthy controls, cell-free plasma DNA concentrations were significantly higher in patients who needed organ supportive measures (mechanical ventilation, inotropic/vasopressor support and haemodialysis) during their ICU stay, cell free plasma DNA levels were significantly higher in ICU nonsurvivors than in survivors. Circulating DNA concentrations demonstrated a significant correlation with CRP, PCT concentrations and SOFA score, but not with APACHE II score or length of ICU stay. These findings indicate that plasma cell-free DNA might be used as a potential useful marker for evaluation of septic patients when admitted to ICU and for prediction of their adverse outcomes. Patients with septic shock at ICU admission demonstrated a significant increase in superficial erosions and a significant decrease in superficial gastritis in their 2nd gastric mucosal biopsies when compared to non-septic shock patients. In addition, there was a trend toward icreased superficial erosions in non-survivors in their 2nd biopsies **($P = 0.065$)** when compared to survivors. These findings indicate that more severe gastric mucosal lesions were detected in septic shock patients and nonsurvivors.

Key words: sepsis; plasma DNA; prognostic marker; cell necrosis; apoptosis; CRP; procalcitonin; APACHE II score; SOFA score; clinical outcome; gastric mucosal biopsy.